ORGANIC ELECTROCHEMISTRY

Fourth Edition, Revised and Expanded

edited by
Henning Lund
Ole Hammerich

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Preface

Organic electrochemistry is concerned with the reduction and oxidation of organic molecules at electrodes. Although the electrochemical community has just celebrated the 200th anniversary of the discovery of the Volta pile, it wasn't until 1830–1850 that the investigation of organic electrochemical processes, pioneered by Faraday and Kolbe, was established as a research area in its own right. Toward the end of the 19th century, investigators such as Tafel and Haber made significant contributions to the knowledge of organic electrode processes. Haber, for instance, in his now famous paper on the reduction of nitrobenzene (*Z Elektrochem* 4:506, 1898), recognized the significance of the electrode potential in the following words: "Oxydations- und Reduktionsprozesse hängen in erster Linie von dem Potential der Elektrode ab, an welcher sie ablaufen, und Stromdichte, Stromdauer und Elektrodenmaterial sind nur insofern bedeutsam, als sie das Elektrodenpotential und seine Änderungen im Gang der Elektrolyse bestimmen." The application of electrolysis as a means of preparing organic compounds continued in the first half of the 20th century.

The results were summarized by Fichter in his useful book *Organische Elektrochemie* in 1942. This development took place along with the invention of new electroanalytical techniques for the study of electrode processes, for instance, polarography at the dropping mercury electrode introduced by Heyrovsky in the early 1920s. Other important contributions were made by Lingane, Kolthoff, Laitinen, and Delahay.

Most of the work reported before the Second World War was carried out in aqueous electrolyte solutions. Since 1945 the focus has shifted to include the application of nonaqueous solvents. This has allowed for the detection of the primary intermediates, typically radical anions and radical cations, and for the study of their reactions. The theoretical foundations, for the analysis of kinetics and mechanisms by, for instance, cyclic voltammetry and related techniques were mostly published in the 1960s and 1970s. The application of such techniques has resulted in a steadily increasing understanding of the kinetics and mechanisms of organic electrochemical processes. The current trend is to return to water-like conditions reflecting the need to substitute organic solvents with environmentally friendlier electrolyte systems.

Given that thousands of organic electrochemical processes are now known, it is amusing (or depressing, depending on one's outlook) to notice that most often the only electrochemical reaction to be mentioned in a typical organic chemistry textbook is the oxidation of an organic carboxylic acid R–COOH to the dimeric alkane R–R and CO_2, published by Kolbe in 1849. Also, it is usually overlooked that, for example, dissolving metals reductions involving radical anions as intermediates and cathodic reductions are intimately related. And most frequently, radical cations are not mentioned at all, except, of course, in the context of mass spectroscopy! The difficulties that organic electrochemistry has had in penetrating into the organic chemistry curriculum was pointed out in the preface to the first edition of this book. Unfortanetely, not much has changed in the nearly 30 years since.

Although the knowledge of organic electrochemistry was still accumulating rapidly in the 1960s and 1970s, the field had at that time matured to the point where the time was ripe for the first edition of *Organic Electrochemistry* which appeared in 1973. The editor was Manuel M. Baizer, well known for his contributions to preparative organic electrochemistry, his foremost achievement being the

development of the electrohydrodimerization of acrylonitrile into a highly successful industrial process for the manufacture of adiponitrile. Baizer set the standards for the book, which was organized to include chapters both on the electrochemical reduction and oxidation of specific classes of compounds and on specific types of electrode processes. This approach obviously led to some overlap, a problem that Baizer touched on: "It has become routine, at least for reviewers, to point out that in a multi-authored book there is overlap of material, nonuniformity of style, repetition, etc. This book was not hastily assembled, and there was adequately time to achieve uniformity if that had been desired. But the material was deliberately organized so that a given segment might appear in two or more contexts and, further, where unanimity of opinion does not exist, more than one current viewpoint might be expressed." The same basic philosophy was followed in the organization of the second (1983) and third editions (1991), and now in this fourth edition. Although it may sound pretentious, we believe it is fair to say that *Organic Electrochemistry* has been established as *the* introduction to the field and numerous students of organic electrochemistry have been told by their supervisors to "look it up in Baizer" when information about a particular electrochemical reaction was needed.

The past ten years of progress in organic electrochemistry are reflected in this new edition. The basic mechanism of many important processes are now known and this has made possible more general presentations of the reaction details. In comparison with the third edition, the following major changes have been made: Two new chapters have been included: "The Electrochemistry of C_{60} and Related Compounds" by L. Echegoyen and L. E. Echegoyen and "Electroenzymatic Synthesis" by E. Steckhan. Approximately one-third of the chapters have been rewritten by new authors, including: "Carbonyl Compounds" by J. Grimshaw, "Anodic Oxidation of Oxygen-Containing Compounds" by G. W. Morrow, "Anodic Oxidation of Sulfur- and Selenium-Containing Compounds" by H. Viertler, J. Gruber, and V. L. Pardini, "Electrosynthesis of Bioactive Materials (formerly "Natural Products and Pharmaceuticals") by R. D. Little and P. Mikesell, "Organoelemental Compounds" by J. Yoshida and S. Suga, "Reductive Coupling" by M. F. Nielsen and J. H. P. Utley, "Electrochemical Partial Fluorination" by T. Fuchigami, "Electrogenerated Bases" by J. H. P. Utley and M. F. Nielsen, "Industrial Electroorganic Chemistry by H. Pütter, and "Conducting Polymers" by J. Heinze. All other chapters have been thoroughly revised or, rewritten, and topics of diminished relevance have been omitted.

Altogether, the fourth edition contains 32 chapters written by 29 authors. Two of the authors, Lennart Eberson and Eberhard Steckhan, most unexpectedly and untimely passed away in February 2000. In their deaths the electrochemical community has lost two great scientists and those who knew them well have lost two dear friends. We will remember their contributions to the present and previous editions of this book with respect.

The authors and the editors have strived to maintain the high standards of the previous editions; we hope that we have succeeded. We wish to thank the authors for the enthusiasm with which they have undertaken the enormous task of making this fourth edition possible.

Henning Lund
Ole Hammerich

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[†]Deceased.

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ORGANIC ELECTROCHEMISTRY

1
Basic Concepts

Christian Amatore
Ecole Normale Supérieure, Paris, France

A te convien tenere altro viaggio ...
Chè questa bestia, per la qual tu gride,
Non lascia altrui pasar per la sua via,
Ma tanto lo impedisce, che l'uccide ...
Dante, *Divina Commedia*

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II. Fundamental Aspects of Electron Transfer Reactions
  A. Oxidation-reduction reactions versus electron transfer reactions in organic chemistry and electrochemistry
  B. Standard potentials: What they mean and what they do not mean
  C. Mechanism and theory of outer sphere electron transfer reactions
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I. INTRODUCTION

Our objective in this chapter is to familiarize organic chemists with fundamental electrochemical concepts that support several aspects of organic electrochemistry elaborated in this book, as well as many important features of electron transfer reactions. In fact, although the term "electrochemistry" evokes for most readers the idea of chemistry at electrodes, in our opinion electron transfer chemistry constitutes a better definition when organic or organometallic electrochemistry is concerned. This is particularly obvious when one thinks of an

electrode as a macrosized molecule whose ability to provide or accept electrons may be precisely adjusted by fine-tuning of the electrode potential. Similarly, electrochemical reactions involving specific interactions with the electrode material are no more than the analogs of inner sphere, ion-pairing, or complexation reactions. Thus, in many respects, electrochemical reactions do not differ basically from their homogeneous counterparts. This is even more true insofar as it concerns the chemical reactivity of electrogenerated intermediates, since they evolve in conditions that a priori do not differ from those considered in homogeneous chemistry. Indeed, the extraordinarily large electric fields (of magnitude comparable to those at the origin of storm lightning) drop to negligible values within a few angstroms of the electrode surface, in contradiction to generally held ideas. Thus as soon as molecules have moved over a few molecular diameters from the electrode surface, they probe no special electrical effects associated with their electrochemical origin. This is an important point, although not well recognized or publicized, since it permits an easy transposition of electrochemical results to homogeneous situations, or vice versa.

Yet there are specific particularities of chemistry at electrodes. They both arise from the fact that electrodes supply and accept electrons to and from molecules dissolved in a solution. This has two important consequences dealing with mass transfer (i.e., transfer of the reagents from the homogeneous volumic space and to the heterogeneous two-dimensional surface) and with current transport across the solution.

Transport of the current through the solution requires that rather conductive media be used, at least when high currents are considered. This is an obvious disadvantage of electrochemical methods, although in our opinion it is fully compensated by the extraordinary advantage of a precise adjustment of the driving force via the electrode potential.

Mass transfer from a volumic homogeneous region, the bulk solution, to a two-dimensional surface results in a spatial structuring of solutions in the close vicinity of the electrode surface. Although such effects are not specific to electrochemistry,* they may be thought of at first, as additional difficulties to cope with in electrochemistry. However, these spatial structurings may be used with considerable advantage to control the chemical route followed by a given intermediate and force it into a pathway that would never be followed under homogeneous conditions. Indeed, this is used in most electrochemical reactions, especially in indirect reductions or oxidations, in which the proper choice of the electron transfer mediator or of the electrogenerated reagent precursor is crucial to the success of a particular reaction. In fact, the conscious (or even subconscious) use of spatial structuring of solutions is not a privilege of electrochemists: nature uses the same phenomenon in most of its reactions, as in the proton transfer "pump" crucial to ATP synthesis or in the photosynthetic chain.

From our experience the largest difficulty (or activation barrier) that "homogeneous chemists" encounter in trying to deal with the electrochemical literature is directly related to electrochemical jargon rather than to fundamental concepts. Although electrochemistry was born as a synthetic method (by Kolbe, Haber, and Fichter, among others), most electrochemical textbooks use an analytic approach to these fundamental concepts. As a result, mathematical formulations and jargon invade most of the presentations, which often results in an effect similar to the caveat at the entrance of Dante's Inferno:

*They intervene as soon as heterogeneous reactants or phase boundaries are involved in the reaction medium.

Per me si va nella città dolente,
Per me si va nell' eterno dolore
Per me si va tra la perduta gente ...
Lasciate ogni speranza, voi ch' entrate.
Dante Alighieri, *Divina Commedia*

Our point is not to criticize these necessary and worthwhile approaches that give to electrochemistry its ability to interpret and rationalize on a quantitative basis a large number of experimental facts that extend far beyond strictly electrochemical domains. Most of our published work (as well as the latter section of this chapter) advocates our belief in the usefulness of these physicomathematical approaches, yet we regret that they may be perceived by nonanalytical chemists as important obstacles in approaching electrochemistry. For this reason, in this chapter we take advantage of the fact that most of these precise approaches are extremely well exposed in popular electrochemical textbooks [1] to try to present most of the necessary electrochemical basis in words and concepts using as much as possible references (or antireferences) to analogous concepts of homogeneous chemistry. Thus we hope that this chapter may constitute both a whole and a guide to further and more specialized readings in electrochemistry. Yet there are three exceptions, each dealing with kinetic aspects, in which we had to break our resolution. The first two concern electron transfer theories, and the third relates to electrochemical kinetics in the presence of follow-up chemical reactions. Although these three points, and their pertinent derivations, are in our opinion very important for a fine understanding of electrochemical processes and capabilities, we suggest that the reader not interested in the mathematical body may skip the equations but nevertheless follow the corresponding text.

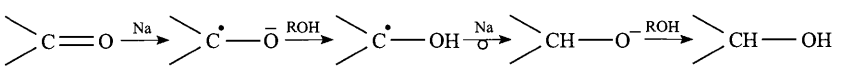
This chapter is divided into three parts. In the first, basic definitions and their consequences for homogeneous chemistry are presented. The second deals with the fundamental aspects of electrode phenomena, whereas the third discusses the problem of mass transfer at electrodes and its consequences for electrochemical kinetics. The particular problems and concepts associated with preparative-scale electrolysis are presented in a special chapter (Chapter 3).

II. FUNDAMENTAL ASPECTS OF ELECTRON TRANSFER REACTIONS

A. Oxidation-Reduction Reactions Versus Electron Transfer Reactions in Organic Chemistry and Electrochemistry

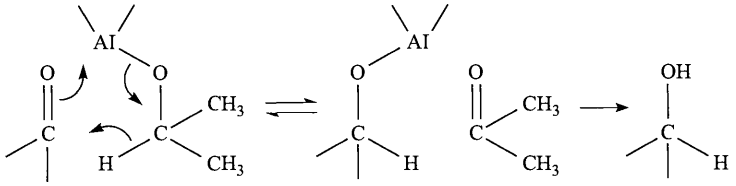
1. Oxidation-Reduction Versus Electron Transfer Reactions

In homogeneous chemistry, pure electron transfer reactions are seldom encountered. Indeed, with the exception of a few examples, electron transfers are often associated with atom or group transfers. This usually results in a confused notion of the nature of oxidation-reduction reactions. For example, the reaction of a ketone with sodium in alcohol to afford the corresponding alcohol, via the sequence in Eq. (1) [2],



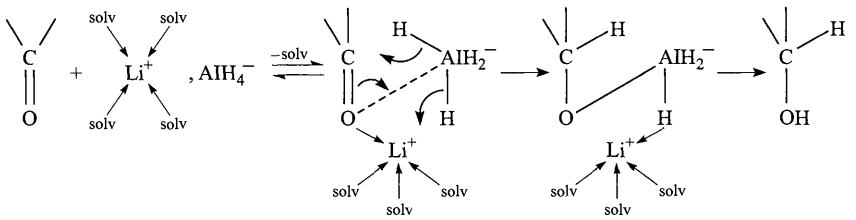
(1)

is termed a reduction. The same term is used for the Meerwein-Ponndorf-Verley reaction, which is supposed to involve a concerted cyclic transition state [Eq. (2)] [3,4]:



(2)

Similarly, reactions of metallic hydrides of aluminum or boron, in which hydride is transferred to the carbon [Eq. (3) [6] or (4) [7,8]], are also considered reductions [8]:



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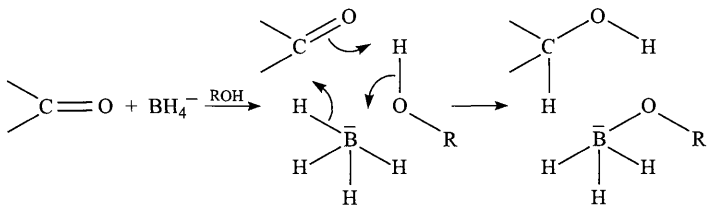


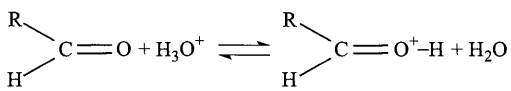
(4)

Although the preceding four reactions all obey the same stoichiometry for the carbonyl-alcohol transformation and thus involve the same variation in the oxidation state of the carbon atom, they are obviously different. Sodium reduction, in Eq. (1), involves single electron and proton transfers in a succession of separate steps; conversely, in reactions (2) through (4), groups or atoms are transferred.

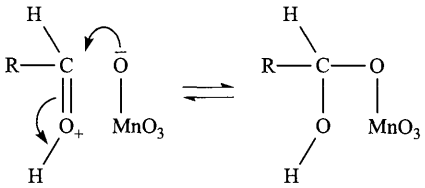
The same confused notions also exist for oxidation reactions, the problem being even more subtle. For example, permanganate is presented in most introductory textbooks as a typical oxidant corresponding to the half-reaction in Eq. (5):

$$MnO_4^- + 5e + 8H^+ \rightleftharpoons Mn^{2+} + 4H_2O \tag{5}$$

This, associated with the classic one-electron oxidation of ferrous to ferric salts by permanganate, for example, may lead to the implicit notion that permanganate actually accepts electrons in a similar way as the carbonyl group in Eq. (1). That this is not always the case in practice is clearly evidenced by the mechanism of alcohol or aldehyde oxidation by permanganate to ketones or carboxylic acids. Indeed, it is generally accepted that the mechanism of acidic oxidation of aldehydes by permanganate involves no electron transfer steps but rather atom transfers as in the sequence of Eqs. (6) through (8) (where B^- is one of the bases present in the reaction medium) to afford the carboxylic acid and an unstable manganese(V) moiety, which rapidly evolves to MnO_2 or Mn^{2+} according to the pH of the solution [9].



(6)



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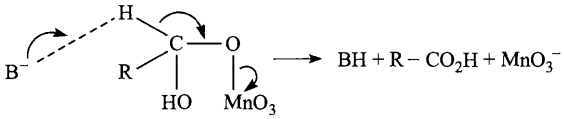
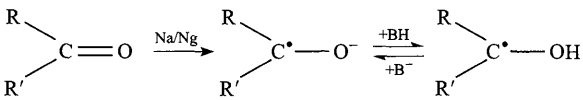
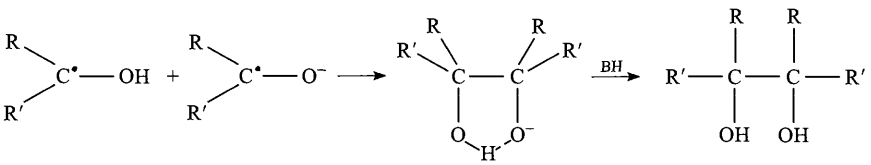


(8)

Similarly, a reaction proceeding through a sequence of one-electron transfers and chemical steps, such as pinacol formation from a ketone [Eqs. (9) and (10)],

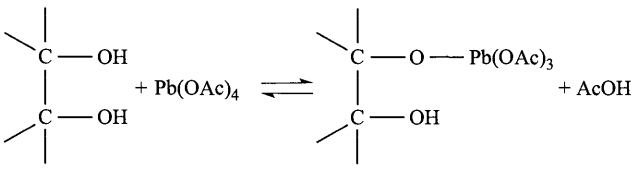


(9)

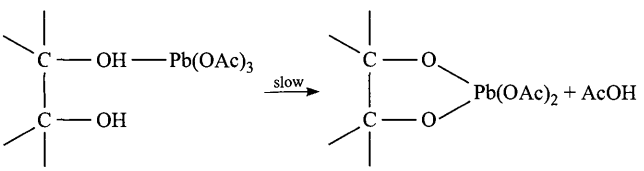


(10)

can be reversed via a sequence of steps involving atom transfers as in the classic glycol oxidation to ketones by lead tetraacetate in Eqs. (11) through (13) [10]:



(11)



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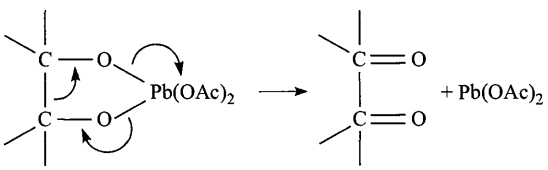


(13)

2. Outer Sphere and Inner Sphere Electron Transfers

The preceding examples, which were purposely restricted to well-known reactions of carbonyl and related functions, illustrate the large ambiguities associated with oxidation-reduction notions in organic chemistry. As suggested earlier, these ambiguities cer-

tainly stem from the fact that more attention is given to the overall transformation of one of the reactants (the substrate) than to the other(s). Indeed, in the ketone to alcohol reductions described, more interest is devoted to the ketone than to the coreactant [Na, $Al(OR)_3$, $Li^+AlH_4^-$, or BH_4^-]. If the complete stoichiometries are considered, it appears more clearly that all four reactions [Eqs. (1) through (4)] are totally different.

On the other hand, when one thinks in terms of electrochemical reductions or oxidations, special attention is devoted to the coreactant, that is, to the electrode that provides or accepts electrons. Thus, in order to discuss or compare electrochemical reactions with their organic analogs, it is of the utmost importance to use more precise terms than the so inaccurate reduction of oxidation notions. A similar problem has been addressed in the inorganic and organometallic fields. Indeed, it was early recognized that oxidation-reduction reactions at metal centers must be classified according to two types: *outer sphere* or *inner sphere* reactions. A typical example of this dichotomy is given in Eqs. (14) and (15), which relate to chromium (II) oxidations by cobalt (III) complexes.

Outer sphere (electron transfer) reaction [11]:

$$Cr^{2+} + Co^{(III)}(NH_3)_6^{3+} \longrightarrow Cr^{3+} + Co^{(II)}(NH_3)_6^{2+}, \ldots \tag{14}$$

Inner sphere (ligand transfer) reaction [11,12]:

$$Cr^{2+} + Co^{(III)}(NH_3)_5Cl^{2+} \longrightarrow Cr^{(III)}Cl^{2+} + Co^{(II)}(NH_3)_5^{2+}, \ldots \tag{15}$$

Besides their relatively close stoichiometries, that the fundamental nature of the reactions differs is evidenced by the acceleration by a factor of approximately 6×10^9 in the rate constant when a chlorine ligand is involved in the transition state of the process.

Outer sphere electron transfers correspond to situations in which an electron is transferred without the necessity of bond formation or bond cleavage between or within the reactants. The electron is then transferred when the partners are sufficiently close to allow orbitals of suitable geometries to overlap. The energetic stabilization required is of the order of 1 kcal/mol^{-1}, which is considerably smaller than that corresponding to any bond formation. The ketone reduction by sodium metal in Eq. (1a) is considered to belong to this class of electron transfer. Similarly, owing to the usual poor ability of electrodes in establishing bonds with the electroactive molecules, most of the electrochemical electron transfers pertain to this group. Interestingly, theories have been developed for outer sphere electron transfers that allow reasonable predictions of their rate constants and activation energies (see Secs. II.C and III.C).

Note that this definition does not imply that the products obtained upon electron transfer must be stable, but only that the electron transfer activation process does not imply any important molecular rearrangement. Indeed, one or both of the products may chemically evolve through fast follow-up reactions as in the reaction sequences (1) or (9) and (10).

Inner sphere reduction or oxidation is normally restricted to bond formation between the reactants in the transition state. For example, the chromium (II) oxidation in Eq. (15) has been shown to involve a chloride bridge between the chromium and cobalt centers as depicted in Eq. (16) [12]:

$$[Cr^{2+} \cdots Cl \cdots Co^{(III)}(NH_3)_5]^{\#} \tag{16}$$

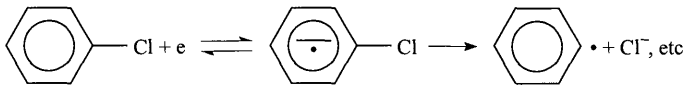
The organic chemical reduction-oxidations presented in the reaction sequences (2), (3), (4), (7), or (11) through (13) belong to this class. Obviously, because an electrode is considered

able only to supply or accept electrons, this class of reduction-oxidation reactions should not be observed in electrochemistry. Yet it must be recalled that this is not a very clear-cut problem since the existence of such group or atom transfer has been invoked to explain the role of chemical surfaces, or of additives, as in the Kolbe reaction [13].

In our opinion a third class of reduction-oxidation reactions exists, which is not clearly encompassed by one of the two just mentioned. It corresponds to the cases in which there really is an electron transfer (i.e., not a group or atom transfer) but the latter is concerted with bond breaking or formation within one of the reactants. We propose that the phrase "inner sphere electron transfer" be used to refer to such situations. A characteristic example of this class is given by the reduction of alkyl halides, represented in Eq. (17):

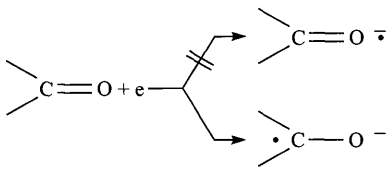
$$RR'R''C-X+e \longrightarrow RR'R''C^{\bullet}+X^{-} \tag{17}$$

Indeed, it is now considered that carbon-halide bond cleavage is concerted with electron uptake (see Ref. 14 and Chapter 8), that is, that there is no intermediacy of an anion radical, such as $[RR'R''C-X]^{-}$, during the electron transfer [15]. These cases must be contrasted with those, such as the aryl halide reduction in Eq. (18),



(18)

in which the electron is taken up (or lost) without drastic molecular rearrangement [14,16], to afford an anion radical (or a cation radical in oxidations), although the latter may be extremely short-lived. Formally, the carbonyl reduction in Eq. (1a) should fall in this class of reaction, since it is usually considered that the π-carbonyl bond is broken (2b) upon electron transfer to yield a ketyl anion radical [Eq. (20)].



(19)

(20)

Yet the nature of the bond cleaved, especially when the latter is involved in extended delocalizations as in aromatic ketones, and the fact that the skeleton of the molecule remains intact, may explain why these reductions are generally considered as belonging to the outer sphere class.

From Table 1, which summarizes this discussion, it is seen that outer sphere and inner sphere electron transfers have their exact analogs in both fields of organic chemistry and electrochemistry. The third class, that is, inner sphere group transfers, deals with the peculiar properties of special reactants in organic chemistry or with those of special electrode materials in electrochemistry.

At this point it should be emphasized that there is a larger body of outer sphere or inner sphere electron transfer reactions identified and used in electrochemistry, whereas this class of reactions is less developed in organic chemistry. Conversely, there is an extensive variety of chemicals designed for specific group or atom transfer in reduction-oxidation reactions in organic chemistry, but this is an area that is not very developed in electrochemistry. This certainly originates from the obvious fact that the reductive or oxidative strength of an electrode can be varied over a wide range and adjusted with considerable precision because of the easy control of the electrode potential. This advan-

Table 1 Chemical and Electrochemical Reductions or Oxidations in Organic Chemistry

Designation	Bond-breaking or formation in the transition state	Follow-up chemical reaction	Examples	
			Chemical	Electrochemical
Outer sphere electron transfer	No	No	$\text{Anthracene} \xrightarrow{\text{NA}} \text{Anthracene}^-$	$\text{Anthracene} + e \rightleftharpoons \text{Anthracene}^-$
		Yes	$ArCH_3 + Fe^{(III)} \rightleftharpoons ArCH_3^+ + Fe^{(II)}$	$ArCH_3 - e \rightleftharpoons ArCH_3^+$
			$ArCH_3^+ + \text{base} \longrightarrow ArCH_2^{\cdot}, \cdots$	$ArCH_3^+ + \text{base} \longrightarrow ArCH_2^{\cdot}, \cdots$
Inner sphere electron transfer	Within reactants	Frequent	Wurtz reaction	$RX + e \longrightarrow R^{\cdot} + X^-$
Group or atom transfer	Between reactants		Meerwein-Ponndorf reaction	Invoked to interpret the effect of additives or electrode surface states (as in the Kolbe reaction)

tage is not matched in homogenous organic chemistry owing to the discrete number of electron transfer reagents, particularly for reductions. On the contrary, surface modifications and reactivities, especially under the conditions of the large electrical fields encountered in electrochemistry (Sec. III.A.4), are not easy to design and control within the present state of the art, whereas owing to the extensive development of organic [8], inorganic, and organometallic [17] chemistry, a large variety of specific agents is made available. However, the apparent disadvantage of electrochemistry in the latter area exists only when the electrode is considered the main reactant effecting the sought reaction. Indeed, specific chemicals (catalytic or stoichiometric reactants) that effect the desired transformation on the substrate of interest may easily be electrochemically generated as discussed in Part VIII of this book [18].

B. Standard Potentials: What They Mean and What They Do Not Mean

1. Standard Potentials

When considering a reaction between a possible electron donor and a possible electron acceptor, it is important to decide a priori whether it will take place. This is usually answered by comparison of the standard (reduction) potentials E° pertinent to each reactant. Indeed, when one considers the possible reaction in Eq. (21),

$$A + D \rightleftharpoons A^- + D^+ \tag{21}$$

the corresponding equilibrium constant K is related to the difference between the standard (reduction) potentials $E^\circ_{A/A-}$ and $E^\circ_{D+/D}$ of the A/A^- and D^+/D couples, respectively. It follows from the expression of K,

$$K = e^{F(E^\circ_{A/A-} - E^\circ_{D+/D})/RT}$$

that at equilibrium Eq. (21) should be displaced toward the right-hand side when $E^\circ_{A/A-} \gg E^\circ_{D+/D}$ and to the left-hand side when the converse is true (however, see Sec. II.B.6). When the difference between the values of the two standard reduction potentials is small, the reactant(s) and product(s) equilibrium concentrations obviously depend on the potential difference but also greatly on the initial composition of the solution.

According to its definition, the standard (reduction) potential of the A/A^- couple is the standard electromotive force of a cell in which an A/A^- electrode (where the activities of A and A^- are made unity) is opposed to an NHE (normal hydrogen electrode) whose potential is assigned to zero by convention.

$$A + e \rightleftharpoons A^- \qquad (E^\circ) \tag{22}$$

Thus a standard reduction potential E° is ascribed to the "half-reaction" in Eq. (22).*

*Because of thermodynamic and electrochemical conventions, standard potentials are defined in the direction of reduction, independently of the respective chemical stabilities of the molecules involved. Thus for the oxidation of toluene to its cation radical, E^0 refers to the reduction of the highly unstable cation radical into the highly stable toluene. To overcome such a priori chemical nonsence, E^0 is frequently designated as the standard oxidation potential of toluene for example. However, such a term should not be accepted according to canonical rules because it formally implies that the cell now operates in a driven mode, that is, is connected to an external power supply [19]. Thus in this chapter we prefer to use the denomination *standard reduction potentials*, rather than the usual term "standard potential," as a reminder of the E^0 definition, although such as expression is basically a pleonasm.

When the activities of A and A^- are not unity, the potential of the A/A^- electrode is given by the Nernst equation,

$$E = E^\circ + \frac{RT}{F} \ln \frac{(A)}{(A^-)} \tag{23a}$$

as a function of these activities [20]. Note that in this discussion a "simple" or elementary electron transfer is considered. In actual practice the definition of E° may be extended to more complex situations (Sec. II.B.5) in which the half-reaction corresponds to a series of equilibria involving at least one electron transfer step. If the pertinent half-reaction is written

$$\alpha_1 O_1 + \alpha_2 O_2 + \cdots + ne \rightleftharpoons \beta_1 R_1 + \beta_2 R_2 + \cdots$$

the potential of the corresponding electrode is given by the Nernst equation,

$$E = E^\circ + \frac{RT}{nF} \ln \frac{(O_1)^{\alpha 1}(O_2)^{\alpha 2} \cdots}{(R_1)^{\beta 1}(R_2)^{\beta 2} \cdots} \tag{23b}$$

In practice there are several limitations to such measurement. Obviously it implies that both members of the half-reaction are sufficiently stable for a cell to be realized. This is a serious difficulty in organic chemistry owing to usual great reactivities of the species formed upon electron transfers. For the most frequent cases it is then impossible to rely on reversible thermodynamic transformations to determine experimental values of standard reduction potentials. However, these important figures, or at least very precisely approximated values, can be obtained from current intensity potential curves or transient electrochemical methods as is discussed in a later section.

2. Reference Electrodes and Liquid Junction Potentials

Potentials are not measurable on an absolute scale, yet relative scales are easily constructed from measurements of potential differences. This is a fortiori true for electrode potentials. Thus, as explained earlier, electrode potentials are given, by convention, as their potential difference versus the NHE. Yet there are several difficulties associated with the use of the NHE. The most obvious is that, although it may be approximated via extrapolations, a real NHE cannot be constructed according to the stipulations included in its definition. The other limitations directly follow from the fact that approximated NHE are almost impossible to use in real experiments. Thus, many other reference electrodes have been proposed and constructed [21]. Each of these electrodes is used by electrochemists according to historical or sentimental reasons or because a given reference electrode is more adequate for a given experimental situation owing to geometric factors or possible pollution of the solution under study.

To be considered a suitable reference electrode, an electrode must have a known and reproducible potential versus the NHE. This potential must be nearly an invariant of the current flowing through the electrode, which implies that the electrode reaction is extremely fast and the electrode reactants are extremely concentrated (see Secs. III.C.3 and IV.B.2). It should also have a small temperature coefficient and should be easily constructed in a reproducible way. A large variety of electrodes meeting these requirements to different degrees have been devised; Table 2 presents a few of the most frequently used.

Inspection of Table 2 shows that the solution composition of the electrode half-cell is critical. These solutions may differ considerably (nature of the solvent, nature and con-

Table 2 Potentials of Some Reference Electrodes

Reference Electrode		E°_{Ref}, V versus NHE[a]	
Half-cell[b]	Name	25°C	20°C
Hg/HgO, NaOH (1 N)		0.14[c]	
Ag/AgCl, KCl (s)		0.20[c]	
Ag/AgCl, KCl (1 M)		0.22[c]	0.22[c]
Hg/Hg_2Cl_2, NaCl (s)	SSCE	0.236[d]	
Hg/Hg_2Cl_2, KCl (s)	SCE	0.241[d]	0.245[d]
Hg/Hg_2Cl_2, KCl (1 M)	NCE	0.280[d]	0.281[d]
Hg/Hg_2Cl_2, KCl (0.1 M)		0.334[d]	
Hg/Hg_2SO_4, K_2SO_4 (s)		0.64[c]	
Hg/HgO, NaOH (0.1 M)		0.93[d]	

[a]For any O/R couple, E° (versus NHE) = E° (versus Ref) + E°_{Ref}.
[b]In aqueous solutions; (s) indicates saturation.
[c]From Ref. 21c.
[d]From Refs. 21a and 21b.
Source: From Refs. 21.

centrations of the electrolytes or ionic members of the half-reaction, and so on) from those used in organic or organometallic electrochemistry. The two solutions, that of the experimental system under study and that in the inner reference electrode compartment, then tend to equilibrate across their interface (the liquid junction) to reach a final state in which both solutions are identical. In practice, to avoid pollution of both solutions, a third solution is usually interposed, which acts as a buffer. This "bridge" then results in the creation of two liquid junctions. At each of these junctions the physical process of equilibration is controlled by the diffusion of the various components, that is, depends on their mobilities, which may be extremely different [22]. In the process of equilibration there is then a trend to break the electroneutrality on both sides of the junction. Indeed, the center of positive charges tends to separate from the center of negative charges because of intrinsic differences in the mobilities of the cations and anions. This results in the creation of an electrostatic potential difference E_j across the junction, which opposes the charge separation. The system reaches then a steady-state "equilibrium" so that the electrostatic energy exactly matches that resulting from differences in chemical composition across the liquid junction. For identical solvents on both sides of the junction, models have been developed to estimate the resulting junction potentials E_j, which may reach several tens of millivolts in practice [23]. Yet in most organic or organometallic experiments, different solvents are used on both sides of the liquid junctions. Other phenomena (e.g., solvent mixing, different abilities in wetting the physical interface, usually a sintered glass frit or a glass crack, and interfacial and capillary tensions [24]) are then involved. This makes the corresponding analysis intractable or totally irrelevant to real conditions, especially when one considers the difficult reproducibility of most of these phenomena from one experimental setup to another.

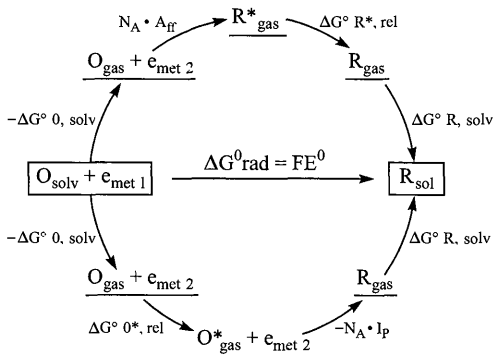
In practice it is advisable to use reference electrodes involving, when possible, a solvent identical to that used in the electrochemical cell. Yet this is not always possible, since other problems may arise from solubilities or temperature dependence, for example. In any case, when potential determinations are crucial, a way to overcome these difficulties is to calibrate the potential scale by measuring the potential of a reference compound in

the same solution, that is, introducing it in the investigated solution at the end of the experiment. Under such conditions, and provided that the solution composition remains invariant in the course of the experiment, a "floating reference electrode" may also be used. A silver wire of large surface area or a mercury pool, for example, constitutes such a floating reference electrode. Indeed, it keeps a constant, but unknown potential difference vis-à-vis the solution. Yet the resulting potential scales obtained from run to run need to be reconciled, via the calibration procedure explained earlier, since the floating reference potential is unknown and prone to vary as a function of the exact composition of the solution.

3. Standard Reduction Potentials Versus Ionization Potentials or Affinities

When one of the members of a given half-reaction is too unstable for measurement of the pertinent standard reduction potential, one frequently relies on the values of ionization potentials or affinities. However, one should be extremely cautious in the use of such data obtained from gas phase when applying them to reactions in solution [25].

Let us consider a simple half-reaction $O + e \rightleftharpoons R$, with a standard reduction potential E°. It must be realized that E° corresponds to (1) stable solvation states for O and R and (2) stable nuclear configurations for O and R. On the other hand, ionization potentials I_p or affinities A_{ff} correspond to nonsolvated O and R and radiative transitions (Sec. II.C), that is, to unstable nuclear configurations R^* or O^*, respectively, for R (affinities) or O (ionization potentials). The ensuing thermodynamic relationships between the three numbers E°, I_p, and A_{ff} are then derived from thermodynamic considerations based on the cycles in Scheme 1.†



Scheme 1

Thus it follows that

$$E^\circ = -A_{ff} + \frac{(\Delta G^\circ_O, \text{solv} - \Delta G^\circ_{R,\text{solv}}) - \Delta G^\circ_{R^*}, \text{rel}}{F} + \text{Cst} \tag{24}$$

and

† Note that no explicit attention to NHE or metal phases [26] has been given in the cycles, since these factors introduce a constant term Cst in Eq. (24) or (25), independent of the O/R couple.

$$E^\circ = I_p + \frac{(\Delta G^\circ_O, \text{solv} - \Delta G^\circ_{R,\text{solv}}) - \Delta G^\circ_{O^*}, \text{rel}}{F} + \text{Cst} \tag{25}$$

where E°, A_{ff}, and I_P are expressed in volts and electron-volts, whereas ΔG° is in joules and relative to molar quantities. From Eqs. (24) and (25), it is seen that E° and I_P (or E° and A_{ff}) should correlate linearly, with a slope of unity for an extended series of O/R couples, only when the terms in the fraction are reasonably constant within the series. In practice this condition is almost impossible to fulfill accurately but is approximated for large delocalized molecules belonging to an identical class [27,28]. Indeed, for such molecules the gain or loss of an electron introduces only small disturbances in the molecules. Similarly, there are nearly no specific solvation effects, the charge being largely delocalized. Then, provided the equivalent solvation radii are large or remain close within the series, the solvation differences are negligible [27]. Figure 1 shows that when these conditions are fulfilled, good correlations with slopes close to the unity are observed. Thus determination of E° for some of the compounds of the series allows good estimates of E° to be obtained from I_P or A_{ff} measurements. Yet it must be emphasized at this point that there should be virtually no special difficulties in the direct measurements of the unknown E° values for the O/R couples meeting all the requirements discussed here. Indeed, these conditions restrict the validity of the method to chemically reversible outer sphere electron transfers.

From this statement it is seen that the eventual practical interest of the method deals with series of redox couples that involve a too chemically unstable member for experimental E° to be determined easily. An example of such a case is given by the series of alkylbenzenes [29] presented in Fig. 2. Indeed, owing to the rather small size of the π system compared with the large aromatics in Fig. 1, as well as to the considerable variations in size with the number and nature of the alkyl substituent, it seems clear that the difference in solvation energies in Eq. (25) must vary within the series.

$$(\Delta G^\circ_{O,\text{solv}} - \Delta G^\circ_{R,\text{solv}}) + \Delta G^\circ_{O^*,\text{rel}} \approx -0.3FE^\circ$$

Interestingly, a good linear correlation is nevertheless observed in Fig. 2, yet with a slope of 0.7, instead of unity as in Fig. 1. From Eq. (25) it follows that the term on the left-hand

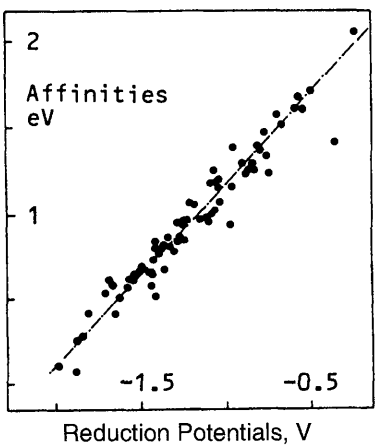


Figure 1. Correlation between affinities and reduction potentials for an extended series of polycyclic aromatic hydrocarbons. (Data from Ref. 28.)

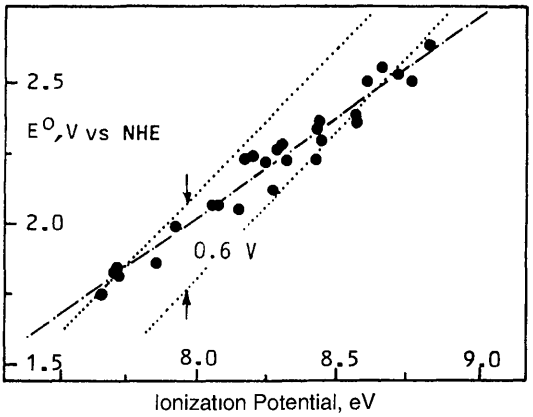


Figure 2. Correlation between ionization potentials and standard reduction potentials of the corresponding cation radicals for a series of alkylbenzenes. Two dotted lines, with slopes unity, are positioned at each end of the series to emphasize the deviations vis-à-vis the data in Fig. 1. (Data from Ref. 29.)

side also correlates with E°, a reasonable conclusion owing to the homogeneity in the series of substituents. Yet the correlation in Fig. 2 clearly shows the danger of the blind use of such correlations, that is, of the use of I_P or A_{ff} values instead of E°. Indeed, a difference larger than 0.5 V is introduced when extrapolating E° from I_p values and assuming a unity slope as in Fig. 1.

4. Comparison or Extrapolation Between Solvents

Owing to the extremely large variety of solvents used in organic or organometallic chemistry, it is unlikely that all the pertinent electrochemical data can be found for a particular system and a particular solvent [30]. Thus the problem of the transposition of data obtained for one solvent to another frequently arises. As discussed for I_p or A_{ff}, this should not be done without extreme precautions. Indeed, by substraction of the two equations, akin to Eq. (25), pertinent to each solvent, one obtains readily for a given O/R redox system

$$E^\circ_{solv1} - E^\circ_{solv2} = \frac{(\Delta G^\circ_{O,solv1} - \Delta G^\circ_{O,solv2}) - (\Delta G^\circ_{R,solv1} - \Delta G^\circ_{R,solv2})}{F} + C'$$

where C' is a constant term independent of the O/R couple. However, the numerator, which may include specific solvation terms for each solvent, may vary considerably from one redox couple to the other. Thus on an absolute basis, extrapolations between solvents are meaningless; however, they may be used with great caution. Evidently the same is a fortiori true for the utilization of HOMO or LUMO energies [31] or Hammett-Taft and related extrathermodynamic relationships [32].

5. Formal Reduction Potentials

It is usually difficult to determine or impose activities, since activation coefficients are nearly always unknown for the redox systems investigated in organic or organometallic chemistry. Thus formal reduction potentials $E^{o'}$ are measured, when feasible, rather than

E°. $E^{\circ'}$ corresponds to the electrode potential versus NHE when the concentration ratio C_O/C_R is made unity, rather than the ratio of the activities, as in the definition of E° [33]. Thus from Eq. (23), it follows that

$$E = E^{\circ} + \frac{RT}{F} \ln\frac{(O)}{(R)} = E^{\circ} + \frac{RT}{F} \ln\frac{f_O C_O}{f_R C_R}$$

that is,

$$E^{\circ'} = E^{\circ} + \frac{RT}{F} \ln\frac{f_O}{f_R} \tag{26}$$

where f_J is the activity coefficient of species J. The latter being affected by ionic strength and concentrations, for example, it is predicted that $E^{\circ'}$ values should vary from medium to medium. This is important to remember when $E^{\circ'}$ values, determined under the conditions of low concentration and large ionic strength usually met in electrochemistry, need to be utilized under the conditions of low ionic strength and high concentration frequently used in organic chemistry [34].

Formal potential may also include some constant or selected components of the medium that participate in the overall redox reaction. Thus pH, and concentrations of complexing reagents, for example, are often included in $E^{\circ'}$ [35] when the O and R molecules are not interconnected by a simple electron transfer. To explicate this point, let us discuss a typical example related to aldehyde oxidation. The stoichiometry of the reaction in Eq. (27) involves an overall transfer of two electrons and one oxygen atom.

$$R - CHO + 3H_2O \rightleftharpoons R - CO_2H + 2e + 2H_3O^+ \qquad (E_1^{\circ}) \tag{27}$$

Yet the acid may exist under two equivalent forms, the acid per se or its conjugated base. Thus, when the pH is such that the carboxylate anion is the stable form, Eq. (27) is better rewritten as in Eq. (28).

$$R - CHO + 4H_2O \rightleftharpoons R - CO_2^- + 2e + 3H_3O^+ \qquad (E_2^{\circ}) \tag{28}$$

From a preparative point of view, both reactions are nearly identical, since the acid and its conjugated base are two forms of the same chemical entity. From a thermodynamic point of view, however, they differ because of the involvement of the acid dissociation in Eq. (29),

$$R - CO_2H + H_2O \rightleftharpoons R - CO_2^- + H_3O^+ \qquad (K_a) \tag{29}$$

which thus corresponds to the definition of a second standard reduction potential E_2° in Eq. (28). Yet E_1° and E_2° are related because of the necessity of a unique potential for the solution. Indeed from Eq. (27), the potential is obtained as in Eq. (30), whereas it is expressed as in Eq. (31) from Eq. (28).

$$E = E_1^{\circ} + \frac{RT}{2F} \ln\frac{(RCO_2H)(H_3O^+)^2}{(RCHO)} \tag{30}$$

$$E = E_2^{\circ} + \frac{RT}{2F} \ln\frac{(RCO_2^-)(H_3O^+)^3}{(RCHO)} \tag{31}$$

Identification of both equations readily gives the relationship between E_1° and E_2° in Eq. (32), which shows that provided that K_a is known, knowledge of either E_1° or E_2° is sufficient.

$$E_2^\circ = E_1^\circ - \frac{RT}{2F} \ln K_a \tag{32}$$

On the other hand, owing to the involvement of proton activities in Eq. (30) or (31), it is expected that the acid-aldehyde reduction potential is extremely dependent on the pH. Thus it is more convenient to separate the pH-dependent terms from those corresponding to the degree of conversion. Similarly, it is more realistic to consider the sum of the acid and its conjugated base activities to represent the oxidation products. Thus, taking into account Eq. (29), Eq. (30) is rewritten as in Eq. (33),

$$E = E_1^\circ + \frac{RT}{F} \ln \frac{h^3}{h + K_a} + \frac{RT}{F} \ln \frac{(\text{acid})}{(\text{aldehyde})} \tag{33}$$

where the term "acid" represents the sum of its two forms and $h = (H_3O^+)$. Similarly, concentrations may be introduced for the acid and aldehyde, rather than activities:

$$E = E^{\circ'} + \frac{RT}{F} \ln \frac{[\text{acid}]}{[\text{aldehyde}]} \tag{34}$$

This allows finally the rewritting of Eq. (33) under the form in Eq. (34), which directly gives the conversion ratio as a function of the potential and of the pH-dependent formal potential $E^{\circ'}$ in Eq. (35), where $K_a' = K_a(f_{RCO_2H}/f_{RCO_2^-})$, and $E_1^{\circ'} = E_1^\circ + (RT/2F)\ln(f_{RCO_2H}/f_{RCO_2^-})$:

$$E^{\circ'} = E_1^{\circ'} + \frac{RT}{2F} \ln \left[\frac{h^3}{h + K_a'} \right] \tag{35}$$

It is seen from Eq. (34) that although it is not established on definitions as solid as those for E°, $E^{\circ'}$ nevertheless is of great practical interest since it is the reference parameter that controls the actual conversion ratio in a given situation. Indeed, at any pH or ionic strength, $E > E^{\circ'}$ requires that the acid is the major component in the system, whereas it is the aldehyde for $E < E^{\circ'}$. At $E = E^{\circ'}$, 50% of the aldehyde is oxidized. To decide which potential is needed at a given pH, or vice versa, it is then important to know the variations of $E^{\circ'}$ with pH. These variations are conveniently represented in the form of a "potential-pH" diagram and are derived from Eq. (35). Indeed, from the latter it is easily seen that $E^{\circ'}$ varies linearly with the pH as soon as the latter differs slightly from pK_a'; that is (at room temperature),

$$\text{pH} < \text{p}K_a' \qquad E^{\circ'} \approx E_1^{\circ'} - 0.06\ \text{pH}$$

$$\text{pH} = \text{p}K_a' \qquad E^{\circ'} \approx E_1^{\circ'} - 0.01 - 0.06\ \text{p}K_a'$$

$$\text{pH} > \text{p}K_a' \qquad E^{\circ'} \approx E_1^{\circ'} + 0.03\ \text{p}K_a' - 0.09\ \text{pH}$$

Such a diagram is represented in Fig. 3. The "acid" predominance zone corresponds to the upper part of the diagram, that is, to pH and potential conditions so that the point representing the system is above the $E^{\circ'}$ versus pH curve. Conversely, the aldehyde predominates when the system is located under this boundary. To illustrate the practical interest of these diagrams, let us refer to the classic test of the silver mirror, which corresponds to aldehydes oxidation by the silver nitrate-ammonia reagent.

The standard reduction potential for Ag^+/Ag is 0.80 V versus NHE. Comparison with the diagram in Fig. 3 shows that the silver ion is not able to oxidize aldehydes except under basic conditions. Yet under such conditions silver oxides are formed and precipitate.

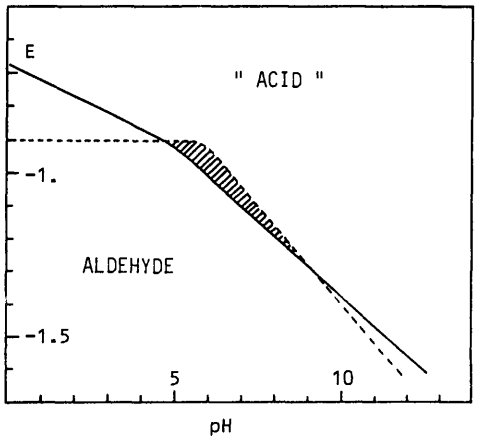


Figure 3. Potential-pH diagram for the aldehyde-acid transformation (solid line). The dashed line gives that for Ag/Ag^+ (0.1 M) when the pH is imposed by NH_3. The hatched zone corresponds to the only region where the silver mirror test can be performed.

$$Ag^+ + 2NH_3 \rightleftharpoons Ag(NH_3)^+ + NH_3 \rightleftharpoons Ag(NH_3)_2^+ \tag{36}$$

Thus a particular base, ammonia, which gives stable complexes with Ag^+ in Eqs. (36), is used to bring about the basic pH. However, because of the formation of complexes in Eqs. (36), the free Ag^+ concentration decreases, which tends to lower the oxidative strength of the solution ($E = E^\circ_{Ag^+} + 0.06 \ln (Ag^+)$). This implies that the ammonia concentration must be adjusted precisely: sufficient for the pH to be in the required range, but not too high in order to retain a sufficient oxidizing power of the silver ion solution. In practice the best concentration is that corresponding to the titration point of the silver ion, which explains the great caution used in the preparation of the reagent $Ag(NH_3)_2^+, NO_3^-$.

6. Relationships Between Thermodynamic Driving Force ΔE° and Feasibility of an Electron Transfer Reaction

According to thermodynamics, the feasibility of an electron transfer reaction depends on the free energy change ΔG associated with it.

$$\alpha_1 O_1 + \beta_2 R_2 \rightleftharpoons \beta_1 R_1 + \alpha_2 O_2 \tag{37}$$

For the electron transfer in Eq. (37), which involves the two half-reactions in Eq. (38),

$$\alpha_1 O_1 + ne \rightleftharpoons \beta_1 R_1 \qquad (E_1^\circ) \tag{38a}$$

$$\alpha_2 O_2 + ne \rightleftharpoons \beta_2 R_2 \qquad (E_2^\circ) \tag{38b}$$

the free energy change is given from basic thermodynamics by

$$\Delta G = \Delta G^\circ + RT \ln \left[\frac{(R_1)^{\beta 1} (O_2)^{\alpha 2}}{(O_1)^{\alpha 1} (R_2)^{\beta 2}} \right]_{in.}$$

where $\Delta G^\circ = nF(E_2^\circ - E_1^\circ)$ and the subscript in. means that the activities to be used in the bracketed term are those corresponding to the initial state of the system. A reaction is observed provided ΔG is negative or positive. The equilibrium point is then such that

$\Delta G = 0$; therefore, at equilibrium the activities are such as given in Eq. (39), where the subscript eq. indicates equilibrium:

$$\left[\frac{(R_1)^{\beta 1}(O_2)^{\alpha 2}}{(O_1)^{\alpha 1}(R_2)^{\beta 2}}\right]_{eq.} = e^{(nF/RT)(E_1^\circ - E_2^\circ)} \tag{39}$$

From Eq. (39) it is deduced that for the forward electron transfer in Eq. (37) to be realized to some extent, it is necessary that the term on the left-hand side of Eq. (39) is considerably larger than unity and thus that $E_1^\circ > E_2^\circ$. Conversely, $E_1^\circ < E_2^\circ$ should lead to the conclusion that the reaction in Eq. (37) is not possible. This conclusion may not be true, however, depending on the respective stabilities of the various species considered in Eq. (37).

When all reactants and products are stable, these conclusions are valid. However, when one or both produces are not stable, Eq. (37) is continuously displaced to the right, even when thermodynamics predicts that the equilibrium should lie to the left-hand side. This is a situation akin to that usually considered in equilibrium displacements by physical removal (e.g., distillation, precipitation, and complexation) of one of the products. Thus one may have $E_1^\circ < E_2^\circ$ and nevertheless observe a reaction between O_1 and R_2 in Eq. (37). Characteristic examples of such situations are given elsewhere in this book, particularly in Chapter 29, since this phenomenon is the basis of redox catalysis. In such a situation the validity of Eq. (39) is not altered, provided the equilibrium remains established. Yet since (R_1) or (O_2) approaches zero, because of the follow-up chemical reaction(s), (O_1) and (R_2) may be extremely small and the bracketed term on the left-hand side of Eq. (39) remains considerably smaller than unity, fulfilling the condition imposed by $E_1^\circ < E_2^\circ$.

$$\alpha_1 o_1 + \beta_2 R_2 \rightleftharpoons \beta_1 R_1 + \alpha_2 O_2 \longrightarrow \cdots \tag{40}$$

It is thus seen that a direct relationship exists between the thermodynamic driving force ΔE° and the feasibility of an electron transfer reaction only for those special cases in which all the products and reactants are stable within the time scale considered. Yet it must be pointed out that this is seldom encountered in usual practice, owing to the generally high reactivities of the species formed upon electron transfers.

This discussion may lead to the extreme conclusion that when the products of an electron transfer reaction are unstable, as in Eq. (40), thermodynamic figures, such as ΔE°, are irrelevant. From a simple point of view this is true. Yet in practice kinetic notions are implicitly involved in the discussion of the feasibility of any chemical reaction. Indeed, a possible reaction whose completion requires infinite time is not considered feasible. Amazingly, it is because of kinetics that thermodynamic figures recover an interest for situations like that featured in Eq. (40). To state this point exactly, let us present and discuss the case of the oxidation of methylbenzenes by tris-(1,10-phenantroline)-iron(III) complexes (FeL_3^{3+}) in the presence of pyridine bases [36].

From their standard reduction potentials, in the range of 1.35 V versus NHE [37], FeL_3^{3+} complexes should not be able to oxidize methylbenzenes, the standard potentials of which exceed 1.75 V versus NHE [29]. The reaction, however, proceeds easily in the presence of a pyridine base, according to the following stoichiometry:

$$ArCH_3 + 2FeL_3^{3+} + 2py \longrightarrow ArCH_2 - py^+ + pyH^+ + 2FeL_3^{2+}$$

and was shown [36,38,39] to involve an electron transfer between the iron and the arene centers, as outlined in Scheme 2. Two limiting kinetic situations are observed according to

$$ArCH_3 + Fe^{(III)} \rightleftharpoons ArCH_3^{+\cdot} + Fe^{(II)} \quad (k_f, k_b) \tag{41}$$

$$ArCH_3^{+\cdot} + py \rightarrow ArCH_2^{\cdot} + pyH^+ \quad (k_H) \tag{42}$$

$$ArCH_2^{+\cdot} + Fe^{(III)} \rightarrow ArCH_2^{\cdot} + Fe^{(II)} \quad \text{(fast)} \tag{43}$$

$$ArCH_2^{+\cdot} + py \rightarrow ArCH_2{-}py^+ \quad \text{(fast)} \tag{44}$$

Scheme 2

the respective rates of the proton transfer [Eq. (42)] or of the backward electron transfer [Eq. (41)]. When the latter is larger, the electron transfer in Eq. (41) acts as a rapid equilibrium, the proton transfer being the rate-determining step (RDS). Thus an apparent rate constant is determined, as in Eq. (45):

$$k^{ap} = k_H \frac{k_f}{k_b} \tag{45}$$

Conversely, when the proton transfer rate is considerably faster than the backward electron transfer, the RDS is the forward electron transfer and the observed rate constant is then k_f, as given in Eq. (46):

$$k^{ap} = k_f \tag{46}$$

It is thus seen that, in the first situation, although the thermodynamic interdiction has been overruled, thermodynamic figures control the apparent rate constant observed. Indeed, Eq. (45) may be rewritten as in Eq. (47):

$$k^{ap} = k_H e^{(F/RT)(E^\circ_{Fe} - E^\circ_{ArCH_3})} \tag{47}$$

Thus owing to the large magnitude of k_H($10^3 - 10^6\ M^{-1}\ s^{-1}$ [36b–c,38,40]), the rate constant in Eq. (47) remains appreciable even for largely endergonic electron transfers (for 1,2,4,5-tetramethylbenzene, $E^\circ_{Fe} - E^\circ_{ArCH_3} < -0.6$ V). Yet if the electron transfer is too endergonic, k^{ap} becomes too small for the reaction to proceed at a significant rate.

The involvement of thermodynamic figures when the forward electron transfer is the RDS is more subtle and arises because of linear or quadratic [41] relationships between activation free energies and thermodynamic driving force, which applies for outer sphere electron transfers like that in Eq. (41) (Sec. II.C.6).

C. Mechanism and Theory of Outer Sphere Electron Transfer Reactions

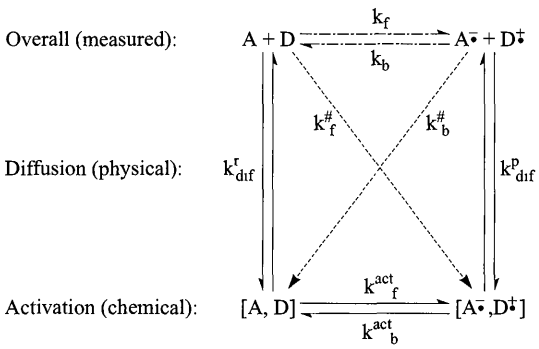
Owing to the aim and scope of the present chapter, it is impossible to discuss here all the subtleties and refinements of electron transfer theories. Yet our purpose is to give a general overview of the different concepts on which these theories are elaborated. As such, this text may constitute per se a presentation of the basic features essential to a thoughtful experimental use of outer sphere electron transfer mechanisms. On the other hand, we hope it may constitute an introduction to more specialized readings [42].

In the following, we tried to rely, for the sake of simplicity, on simple physicochemical pictures that often were not involved in the original works [41,43,44]. As a consequence, this text short-circuits some important but specialized theoretical aspects of the original theories.

1. Diffusion Limitation in Electron Transfer Reactions

A very common characteristic of electron transfer reactions is that they frequently involve activation energies lower than other chemical reactions that relate to group or atom transfers. As a consequence, the activated processes may be extremely fast compared with the physical process of bringing the two reactants close together (or separating the products) so that they can react. In such cases, the overall rate constant determined does not reflect activation parameters but rather transport properties. Note that this phenomenon is implicitly recognized in homogeneous chemistry. Indeed, the "diffusion limit" rate constant, of the order of $10^9 - 10^{10}\ M^{-1}\ s^{-1}$, corresponds to reactions that are limited by encounters of the reactants, whereas the limit related to produce separation is intuitively included within part of the notion invoked in "cage separation."

Thus, in a general situation, an electron transfer between a donor D and an acceptor A must be considered in terms of, at least, the three successive elementary steps outlined in Scheme 3. This representation may be even more segmented when, for example, different ion pairs are involved, such as [A^-, solvent, D^+] or [A^-, $(solvent)_n$, D^+]. Yet it is sufficient her to consider the simplest situation represented in Scheme 3 [45]. The formation or dissociation of cages in Scheme 3, each a physical process, is normally handled on physicochemical grounds. Yet following a notation by Debye their effects may be represented under the form of pseudo-rate constants: k^r_{dif} (reactant pair) and k^p_{dif} (product pair). Using this notation, it follows [46] that the overall k_f and backward rate constant k_b are given by Eqs. (48) and (49) as a function of the activation rate constants k_f^{act} and k_b^{act} relative to the pairs.



Scheme 3

$$\frac{1}{k_f} = \frac{e^{\Delta G^f_r/RT}}{k_f^{act}} + \frac{1}{k^r_{dif}} + \frac{e^{\Delta G^\circ/RT}}{k^p_{dif}} \tag{48}$$

$$\frac{1}{k_b} = \frac{e^{\Delta G^f_p/RT}}{k_b^{act}} + \frac{1}{k^p_{dif}} + \frac{e^{-\Delta G^\circ/RT}}{k^r_{dif}} \tag{49}$$

In Eqs. (48) and (49), $\Delta G^\circ = F(E^\circ_{D+/D} - E^\circ_{A/A-})$, while ΔG^r_f or ΔG^f_p represents the free energy necessary to form the pairs in Scheme 3 for the reactants and products, respectively. The diffusion rate constants are given by Eqs. (50) and (51) [45], where r is the distance between the pair centers and D_r or D_p the sum of the diffusion coefficients of the reactants or products, respectively.

$$k_{dif}^{r} = \frac{4\pi N_A D_r}{\int_r^{\infty} x^{-2} e^{W_r(x)/RT} dx} \tag{50}$$

$$k_{dif}^{p} = \frac{4\pi N_A D_p}{\int_r^{\infty} x^{-2} e^{W_p(x)/RT} dx} \tag{51}$$

Both pseudo-rate constants may then be evaluated from a suitable description of the work terms $W_r(x)$ and $W_p(x)$ necessary to bring the reactant centers or those of the products, respectively, from infinity to a distance x. When the work terms are negligible, straightforward integration of Eqs. (50) and (51) yields

$$k_{dif}^{r} = 4\pi N_A D_r r \quad \text{and} \quad k_{dif}^{p} = 4\pi N_A D_p r$$

which corresponds to the "diffusion limit rate constants" of the order of $10^9 - 10^{10}\ M^{-1}\ s^{-1}$ first proposed by Smoluchowsky [45b]. When the work terms are not negligible compared to RT (due to, e.g., specific interactions, electrostatic interactions between charged ions, or specific ion pairs), the diffusion limit rate constant may differ appreciably from these values, being larger when the work terms are negative (attractive pairs) or considerably smaller when the work terms are positive (repulsive pairs).

Because of the symmetry in Eqs. (48) and (49), we restrict the following discussion to the forward process. It is also noted that k_f and k_b fulfill the thermodynamic condition in Eq. (52):

$$k_f = k_b e^{\Delta G^{\circ}/RT} \tag{52}$$

$$k_f^{act} = k_b^{act} e^{-\Delta G^{\circ'}/RT} \tag{53}$$

Indeed, k_b^{act} and k_f^{act}, being true chemical rate constants, must obey Eq. (53), where $\Delta G^{\circ'}$ is the free energy change in the reaction between the pairs. When there is no other entropic contribution in the formation of the pairs besides those corresponding to the formation of rigid pairs, one has:

$$\Delta G_r^f - \Delta G_p^f \approx W_r - W_p \quad \text{and then} \quad \Delta G^{\circ'} = \Delta G^{\circ} - W_r + W_p$$

From Eq. (48) it is seen that the observed rate constant is always smaller than or equal to k_f^{dif}, defined by considering only the transport limitations in k_f expression, that is, by Eq. (54a).*

$$\frac{1}{k_f^{dif}} = \frac{1}{k_{dif}^{r}} + \frac{e^{\Delta G^{\circ}/RT}}{k_{dif}^{p}} \tag{54a}$$

When $\Delta G^{\circ} \ll RT\ln(k_{dif}^{p}/k_{dif}^{r})$, the first term in Eq. (54a) predominates, which means that in the corresponding range one obtains $k_f^{dif} \approx k_{dif}^{r}$. This corresponds to the traditional diffusion limit, that is, to the case of extremely exergonic reactions. Conversely, for highly endergonic reactions, Eq. (54a) yields $k_f^{dif} \approx k_{dif}^{p}\ e^{-\Delta G^{\circ}/RT}$. In the latter case it might be

*Note that, similarly, a transport limit

$$k_b^{dif} = k_f^{dif} e^{\Delta G^{\circ}/RT} \tag{54b}$$

is defined for the backward electron transfer. Based on Scheme 3 and Eqs. (48) and (49), k_b^{dif} is given as in Eq. (54b).

surprising that a diffusion control may be observed, yet this apparent paradox corresponds simply to the fulfillment of the thermodynamic conditions in Eqs. (52) and (54b), the highly exergonic backward reaction being diffusion controlled.

Thus under any circumstances the overall observed rate constant k_f cannot exceed the limit of k_f^{dif} given in Eq. (54a). This limit is represented in the form of a log k_f^{dif} versus ΔG° plot in Fig. 4. It must be noticed that since no special considerations have been given to the intrinsic nature of the overall reaction up to this point, these results are valid for any kind of bimolecular chemical reaction. Yet for reactions involving group or atom transfers, $W_r(r)$ and $W_p(r)$ may reach high values (precursor complexes) compared with electron transfer reactions [47]. As a result, the values of k_{dif}^r or k_{dif}^p may be considerably smaller than the usual figures observed in the $10^9 - 10^{10}\,M^{-1}\,s^{-1}$ range for electron transfers.

Activation control of the reaction is observed when $k_f \ll k_f^{dif}$, the latter being given in Eq. (54a). Indeed, formation of the precursor or successor complexes is then considerably faster than the activation process, which therefore limits the overall reaction. Thus is ensues from Eqs. (48) and (49) that $k_f \approx k_f^{\#}$, and $k_b \approx k_b^{\#}$,

$$k_f^{\#} = k_f^{act} e^{-\Delta G_r^f/RT} \quad \text{and} \quad k_b^{\#} = k_b^{act} e^{-\Delta G_p^f/RT} \tag{55}$$

where the rate constants $k_f^{\#}$ and $k_b^{\#}$, defined in Eq. (55), correspond to the usual definition of activation rate constants. Indeed, they refer to the activated process, the initial states being the dissociated A, D or $A^{\cdot-}$, $D^{\cdot+}$ pairs, respectively (compare Scheme 3). Owing to this formulation, Eqs. (48) and (49) are usually rewritten under their equivalent forms in Eqs. (56),

$$\frac{1}{k_f} = \frac{1}{k_f^{\#}} + \frac{1}{k_f^{dif}} \qquad \frac{1}{k_b} = \frac{1}{k_b^{\#}} + \frac{1}{k_b^{dif}} \tag{56a}$$

$$\frac{k_f}{k_b} = e^{\Delta G^\circ/RT} \tag{56b}$$

where $k_f^{\#}$, $k_b^{\#}$, k_f^{dif} are defined in Eqs. (55) and (54a,b). Yet when using such elegant but compact formulations, it is important to recall that k_f^{dif} and k_b^{dif} are not the usual diffusion

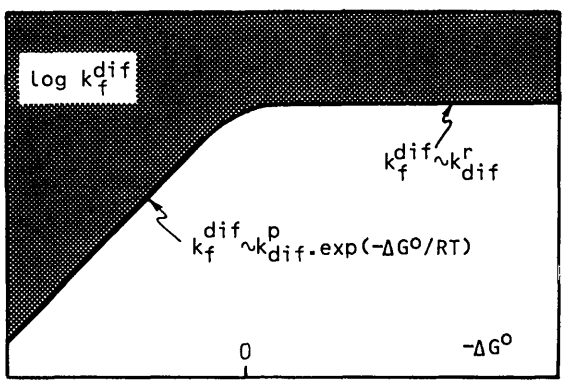


Figure 4. Variations in k_f^{dif}, as given in Eq. (54), with the driving force. The shaded area corresponds to the zone where an activation control is not achievable, the overall kinetics being under diffusion control.

limit rate constants defined in Eqs. (50) and (51) but may be considerably smaller for endergonic reactions [compare Fig. 4 and Eqs. (54)].

In the following we focus the presentation on the activation contributions, that is, on $k_f^{\#}$ or k_f^{act}, to the overall rate constant k_f. First we discuss the nature of an electron transfer reaction. Later, models for the evaluation of the activation energy $\Delta G_f^{\#}$ are presented.

2. Basic Features of Electron Transfer in Solution

The fundamental role of the surrounding medium in an electron transfer reaction was early recognized by Libby [48]. Indeed, because of the large number of molecular collisions in solution, molecules are thermalized, in contrast to what is observed in gas phase (EI,Ip, and so on). Thus radiative electron transfers (that is, analogous to photochemical excitation; see Sec. II.C.4) do not take place in condensed phases. In other words, an electron cannot be transferred between two systems in which its energy is different, as shown schematically in Fig. 5. In the following, a "system" designates a couple of molecules exchanging an electron, that is, A and D, or $A^{\cdot-}$ and $D^{\cdot+}$, together with the surrounding solvent. Thus the "initial system" corresponds to the reactants and the surrounding medium, in any out-of-equilibrium nuclear configuration, which may greatly differ from its equilibrium state, denoted [A, D] in scheme 3. Similarly, the "final system" is associated with the products. Because of the intrinsic difference in mass between the nuclei and the transferred electron, the Franck-Condon principle applies. In other words, nuclear motions (10^{-12} s) are frozen vis-à-vis those of the electron (10^{-15} s). Thus for any nuclear configuration of the initial (or final) system, a potential energy, termed the energy of the initial (or final) system, is associated with the electron, which probes the field of the nuclei (and other electrons). Because the electron is bound to be located in either D or A, the initial and final systems are potential energy minima as a function of the electron coordinate, as shown schematically in Fig. 5. In the physical process of being transferred the electron must then tunnel through a potential barrier corresponding to the virtual states in which the electron would be between A and D. The height of this barrier is inversely related to the degree of overlapping of the A and D orbitals effecting the electron transfer. It greatly influences Pe, the probability that the electron tunnels during the time interval in which the initial and final systems have identical energies (compare Fig. 5b). This time interval, a function of nuclear motions, is nearly independent of the acceptor and the donor, so that Pe depends mainly on the height of the barrier. As soon as the energy stabilization V_i arising from overlapping orbitals is larger than approximately 1 kcal/mol, Pe is close to unity and the electron transfer is termed adiabatic. In the converse situation, the electron transfer is called nonadiabatic and Pe is considerably smaller than unity (Sec. II.C.4).

From this presentation it is seen that the overall probability P of electron transfer is approximated by $P = Pn \cdot Pe$, where Pn is the probability that the nuclei achieve a configuration so that the electron energy is identical for the initial and final systems (Fig. 5b). In usual kinetic terms, this means that the rate constant k_f^{act} is given by $k_f^{act} = \kappa(k_f^{act})_{ad}$, where κ is the "transmission coefficient" ($\kappa = 1$ for an adiabatic electron transfer; $\kappa \ll 1$ for nondiabatic transfers) and $(k_f^{act})_{ad}$ is the rate constant observed for an adiabatic electron transfer. The latter then depends only on nuclear motions that affect the potential energy of the electron. In usual chemical terms, $(k_f^{act})_{ad}$ is directly related to the height of the activation barrier, that is, to the energetic separation between the state where the electron may tunnel and that corresponding to the initial system at equilibrium (compare Fig. 5b), denoted [A, D] in Scheme 3.

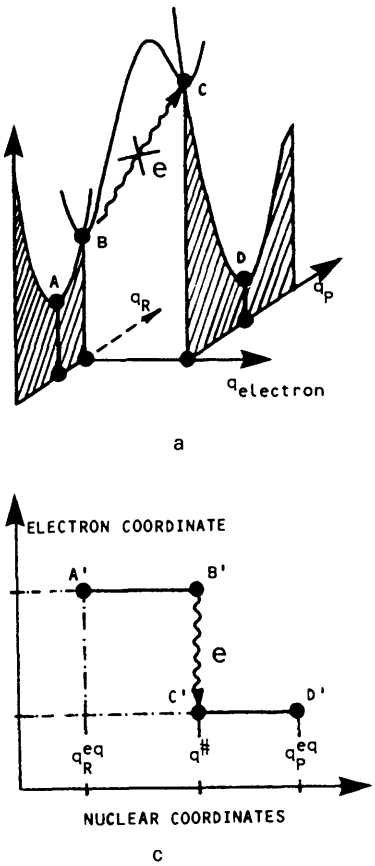


Figure 5. Schematic variation in the electron potential energy as a function of the nuclear coordinates (q_R and q_P for the reactant and product systems, respectively) and of the electron coordinate. (a) Forbidden electron transfer; (b) allowed electron transfer; (c) projection of the "system trajectory" on the electron coordinate-nuclear coordinates plane. q_R^{eq} and q_P^{eq} are the values of the nuclear coordinate at the equilibrium for the reactant or product systems, respectively, and $q^{\#}$ that at the transition state. Solid lines, variations of the nuclear coordinates; (⇝) electron tunneling.

$$k_f^{act} = \kappa \frac{kT}{h} e^{-\Delta E_f^{act}/RT} \tag{57}$$

From absolute rate theory [49], k_f^{act} is then given by Eq. (57), where ΔE_f^{act} is the activation energy barrier expressed for molar quantities. From Eq. (55) it follows that

$$k_f^{\#} = \kappa \frac{kT}{h} e^{-\Delta G_r^f/RT} e^{-\Delta E_f^{act}/RT}$$

Note that the same presentation applies to $k_b^{\#}$ and thus

$$k_b^{\#} = \kappa \frac{kT}{h} e^{-\Delta G_p^f/RT} e^{-\Delta E_b^{act}/RT}$$

It is usually more convenient to introduce explicitly the internal energy (W_r and W_p, respectively) and the entropic components of the free energies ΔG_r^f and ΔG_p^f. When the

formation of pairs involves no specific interaction, their entropy of formation is identical to that of a rigid rotator (ΔS_{rot}), which yields

$$\Delta G_r^f = W_r - T\Delta S_{rot} \quad \text{and} \quad \Delta G_p^f = W_p - T\Delta S_{rot}$$

and thus

$$k_f^{\#} = \kappa\left(\frac{kT}{h} e^{\Delta S_{rot}/R} e^{-W_r/RT} e^{-\Delta E_f^{act}/RT}\right)$$

and

$$k_b^{\#} = \kappa\left(\frac{kT}{h} e^{\Delta S_{rot}/R} e^{-W_p/RT} e^{-\Delta E_b^{act}/RT}\right)$$

From classic statistical thermodynamics [50] the product

$$(kT/h)e^{\Delta S_{rot}/RT}$$

is shown to be equal to the collision frequency Z [51], which is usually of the order $10^{11}\ M^{-1}\ s^{-1}$*:

$$Z = 10^{-3} N_A \left[\frac{8\pi RT(m_A + m_D)}{m_A m_D}\right]^{1/2} r^2$$

One then finally obtains [43,44]

$$k_f^{\#} = \kappa Z e^{-W_r/RT} e^{-\Delta E_f^{act}/RT} \tag{58}$$

and

$$k_b^{\#} = \kappa Z e^{-W_p/RT} e^{-\Delta E_b^{act}/RT} \tag{59}$$

with $k_f^{\#} = k_b^{\#}\, e^{\Delta G^{o'}/RT}$ because $\Delta G^{o'} = \Delta G^{o} - W_r + W_p \approx \Delta E_f^{act} - \Delta E_b^{act}$.

An absolute expression for κ is nearly impossible to derive in a general case owing to its close dependence on the orbital system of a specific A and D couple [52]. Thus general theories consider only adiabatic electron transfers, that is, those corresponding to $\kappa = 1$. In practice, owing to the very small (less than 1 kcal/mol) interaction required, this is not a limitation for most electron transfers in organic chemistry.

The theoretical predictions of $k_f^{\#}$ then amount to evaluating the magnitude of ΔE_f^{act} in Eq. (58). Various models have been proposed for this determination, and most of them rely on harmonic approximations for the variations of energy of the initial or final systems with nuclear deformation. The basis of the harmonic assumption is that, for outer sphere electron transfers, (1) only small perturbations in bond length or bond angle are involved and (2) a large number of nuclear coordinates participate in the activation process. Owing to these two considerations it is understood that although the accumulated energies may be important (from several kilocalories per mole to a few tens of kilocalories per mole), each of the nuclear coordinates may remain close to its equilibrium value, where harmonic descriptions of the corresponding energy variations are accurate. Note in this context that since for inner sphere electron transfers (Sec. II.A.2 and Table 1) bonds are broken or

*In this expression m_A and m_D are the molar masses of A and D, and r, the distance between the molecule centers in the precursor or successor complexes, is expressed in angstroms, Z being in $M^{-1}\ s^{-1}$.

created in the activation process, the harmonic assumption fails. Indeed, in such electron transfers the activation energy is concentrated within one given bond, which needs more detailed description of the potential energy reaction coordinate surfaces [54]. Similarly, the geometric requirements for κ to be unity are certainly more important than for outer sphere electron transfers, owing to the extreme localization of the orbitals concerned in the electron exchange. Thus in the following we limit out presentation to the harmonic model approximation.

Let us denote by q_i the i^{th} nuclear coordinate ($i = 1, N$), q_i^{in} and q_i^{fin}, its equilibrium values in the initial and final systems, respectively, and Ω_i, the corresponding reduced force constant (i.e., $\Omega_i = 2\Omega_i^{in}\Omega_i^{fin}/(\Omega_i^{in} + \Omega_i^{fin})$, where Ω_i^{in} and Ω_i^{fin} are the force constants in the initial and final systems, respectively [43]). With these notations the energy of the initial and final systems are given in Eqs. (60) and (61):

$$E^{in} = E_{eq}^{in} + \tfrac{1}{2}\sum \Omega_i(q_i - q_i^{in})^2 \tag{60}$$

$$E^{fin} = E_{eq}^{fin} + \tfrac{1}{2}\sum \Omega_i(q_i - q_i^{fin})^2 \tag{61}$$

where E_{eq}^{in} and E_{eq}^{fin} are the respective equilibrium, values, such as

$$E_{eq}^{fin} - E_{eq}^{in} = \Delta G^{o'} = \Delta G^{o} - W_r + W_p \tag{62}$$

The energy $E^{\#}$ of the transition state must be such as $E^{\#} = E^{in} = E^{fin}$. Then by substraction of Eqs. (60) and (61) and denoting by $q^{\#}{}_i$ the value of q_i at the transition state, one obtains

$$0 = \Delta G^{o'} - \tfrac{1}{2}\sum \Omega_i[(q_i^{\#} - q_i^{in})^2 - (q_i^{\#} - q_i^{fin})^2] \tag{63}$$

Equation (63) describes a hypersurface of $N - 1$ dimensions, which correspond to all the possible transition states (compare Fig. 6 when $N = 2$). Yet the transition state through which the system reacts is that of lower energy. This is obtained by derivation of Eq. (63) versus $q_i^{\#}$. From the resulting equation and Eq. (63), one shows readily by the Lagrange factor method that ΔE_f^{act} is given in Eq. (64):

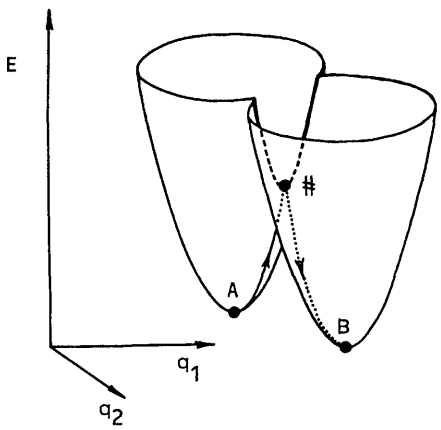


Figure 6. Schematic representation of the reaction pathway (···), for two nuclear coordinates ($N = 2$). The dashed line represents the location of all possible transition states.

$$\Delta E_f^{act} = E^{\#} - E_{eq}^{in} = \frac{\lambda}{4}\left(1 + \frac{\Delta G^{o'}}{\lambda}\right)^2 \tag{64}$$

where

$$\lambda = \tfrac{1}{2}\sum \Omega_i (q_i^{fin} - q_i^{in})^2 \tag{65}$$

is the *reorganization energy of the system*. Because λ is a sum, one may separate the terms relative to bond length or bond angle variations in the A and D molecules (i = 1, M) from those relative to the surrounding medium (i = M + 1, N). Thus λ is usually written as the sum of two contributions:

$$\lambda = \lambda_1 + \lambda_o \tag{66}$$

with

$$\lambda_1 = \tfrac{1}{2}\sum \Omega_1 (q_i^{fin} - q_i^{in})^2 \qquad \text{for i} = 1,\ \text{M} \tag{67}$$

being the *inner shell reorganization energy* and

$$\lambda_o = \tfrac{1}{2}\sum \Omega_i (q_i^{fin} - q_i^{in})^2 \qquad \text{for i} = \text{M} + 1,\ \text{N} \tag{68}$$

the *outer shell reorganization energy*. Note, however, that these terms must not be confused with the inner sphere or outer sphere nature of an electron transfer (Sec. II.A.2 and Table 1).

λ_1 may be evaluated from x-ray and infrared (IR) data or from theoretical calculations. However, for organic outer sphere electron transfers, this contribution is usually much smaller than λ_o. In our opinion one of the greatest merits of the Marcus [43] and Levich-Dogonadze [44] theories is that they allow rather correct predictions of λ_o through simple equations. Thus for most outer sphere electron transfers, reasonably accurate values of the rate constants can be predicted.

3. Role of the Solvent: The Outer Shell Reorganization Energy

Owing to the usually small energetic interactions between a solvent molecule and the solutes, random fluctuations of the medium surrounding the reactants or the products constantly take place.* Figure 7 gives a schematic representation of such solvent

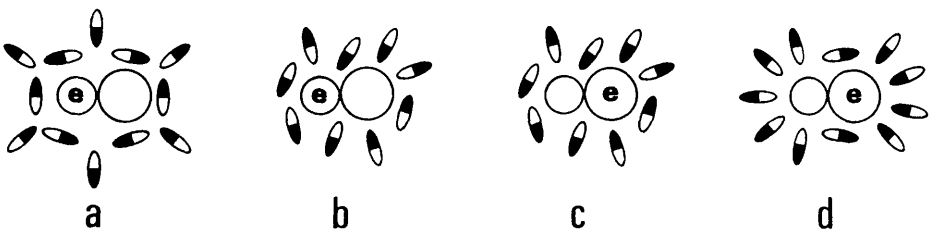


Figure 7. Schematic representation of the solvent fluctuations inducing the electron transfer. (a, d) Equilibrium states for the reactants and products, respectively. (b, c) Out-of-equilibrium states for the reactants and products at the transition state.

*Note that the tightly bound solvent molecules are then considered as belonging to the inner shell subsystem and their contributions to the activation energy are then included in λ_1.

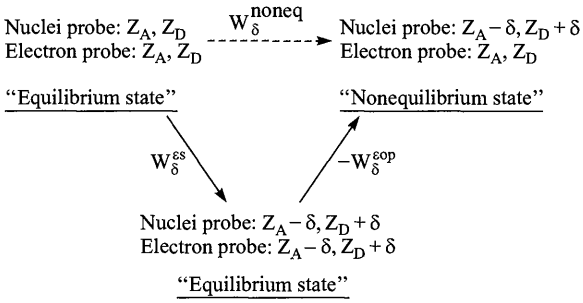
fluctuations. During these fluctuations, the solvent nuclei have out-of-equilibrium positions, which then induce nonequilibrium values for the electrostatic field probed by the electron to be transferred. Yet the electrons of the solvent instantly adjust to the local field. This then results in equilibrium values for the electronic components of the electrostatic field probed by the electron exchanged. This dichotomy between the nuclei (vibrational-orientational-translational) and the electronic polarizations arises because of large differences in motion frequencies (10^{-12} s for atoms and 10^{-15} s for electrons).

To determine the resulting energetic variations, the solvent is treated as a dielectric continuum surrounding the reactants or the products. Since we need to consider only virtual charges, the reactant pair (or the product one) are represented by a pair of two metallized spheres† of initial charges $Z_A = 0$ and $Z_D = 0$ (i.e., before the exchange of one electron) for the reactants, or $Z_A - 1$ and $Z_D + 1$ for the products (i.e., after the exchange of one electron). Electron transfer is supposed to proceed through virtual states in which only a fractional electron change δ has been transferred, corresponding to virtual charges $Z_A - \delta$ and $Z_D + \delta$ for the reactant or product pairs. The metallized spheres radii (respectively a_A and a_D in each pair) are supposed constant during the electron transfer and their centers are separated by a constant distance r.

Within this model the energy associated with a nonequilibrium polarization state is determined by considering [57]: (1) for the solvent nuclei the polarization corresponds to an equilibrium state in which a virtual fractional charge δe has been transferred, whereas (2) the solvent electronic polarization still corresponds to the real charges. In practice, for the initial system, for example, this is equivalent to determining the variation in the overall electrostatic energy, that is, that associated with the static dielectric constant ε_s of the solvent when the reactant charges vary from (Z_A, Z_D) to $(Z_A - \delta, Z_D + \delta)$, and to correcting it from the electronic contribution, which is associated with ε_{op}, the optical dielectric constant of the solvent ($\varepsilon_{op} = n_{op}^2$; n_{op} being the refractive index of the solvent). From the corresponding energetic cycle represented in Scheme 4, it is easily deduced that the free energy required to produce an appropriate nonequilibrium polarization is $W_\delta^{noneq} = W_\delta^{\varepsilon s} - W_\delta^{\varepsilon op}$ and can be evaluated from simple electrostatics, as in the Born solvation model [27]. Thus both $W_\delta^{\varepsilon s}$ and $W_\delta^{\varepsilon op}$ are obtained, using ε_s or ε_{op}, respectively, by the sum of the three electrostatic contributions: (1) charge of the A sphere from Z_A to $Z_A - \delta$, (2) charge of the D sphere from Z_D to $Z_D + \delta$, and (3) variation of the electrostatic interaction between the two metallized spheres A and D at distance r. Thus one obtains

$$W_\delta^{\varepsilon s} \text{ or } W_\delta^{\varepsilon op} = -\left[\frac{N_A(\delta e)^2}{8\pi\varepsilon}\right]\left(\frac{1}{a_A} + \frac{1}{a_D} - \frac{2}{r}\right)$$

†Note that more sophisticated models have been proposed to take into account the nonspherical nature of reactant and products, the eventual distribution of charges on different centers within the molecule [55], the eventual coupling between the inner shell and solvent fluctuation modes, and other factors [56]. Yet the simplest model described here is sufficient for our purposes, since it includes most of the essential features of electron transfer reactions.



Scheme 4

where $\varepsilon = \varepsilon_s$ or ε_{op} and e is the charge of the electron. It is thus seen that for a given δ the outer shell component of the energy of the out-of-equilibrium state of the initial system is given by Eq. (69):

$$(E^{in})_o = (E_{eq}^{in})_o - \left(\frac{N_A e^2}{8\pi}\right)\left(\frac{1}{\varepsilon_s} - \frac{1}{\varepsilon_{op}}\right)\left(\frac{1}{a_A} + \frac{1}{a_D} - \frac{2}{r}\right)\delta^2 \tag{69}$$

A similar expression would be obtained along the same lines for the final system, yet with δ replaced by $1 - \delta$. Comparison of Eqs. (69) and (60) shows that the outer shell (solvent) contributions are equivalent to a single harmonic oscillator of force constant Ω_0, given in Eq. (70),

$$\Omega_o = -\left[\frac{N_A e^2}{4\pi}\left(\frac{1}{\varepsilon_s} - \frac{1}{\varepsilon_{op}}\right)\right]\left(\frac{1}{a_A} + \frac{1}{a_D} - \frac{2}{r}\right) \tag{70}$$

where the virtual charge transferred δ represents the elongation. It then results from Eq. (68) that

$$\lambda_o = \tfrac{1}{2}\Omega_o(\delta^{fin} - \delta^{in})^2 = \tfrac{1}{2}\Omega_o \tag{71}$$

since $\delta^{in} = 0$ and $\delta^{fin} = 1$ for one electron transferred. The outer shall reorganization energy λ_o is thus finally obtained under the formulation [57] in Eq. (72):

$$\lambda_o = \left[\frac{N_A e^2}{8\pi}\left(\frac{1}{\varepsilon_{op}} - \frac{1}{\varepsilon_s}\right)\right]\left(\frac{1}{a_A} + \frac{1}{a_D} - \frac{2}{r}\right) \tag{72}$$

The latter equation, involving easily acessible data, allows predictions of λ_o for most situations of interest. Note that because of the involvement of a squared term in Eq. (71), the reorganization energy for a simultaneous transfer of n electrons is n^2 times larger than that for a single electron transfer since $\delta^{fin} - \delta^{in} = n$ for n electrons transferred.

4. Physical Meaning of the Reorganization Energy and of Energy Diagrams

From the preceding discussion it is understood that although the real phenomenon of electron transfer affects a large number of nuclear coordinates, the overall effect is akin to what would be observed for a single generalized coordinate q. This is particularly true for the external medium contribution as established earlier. For simplification of the following discussion, let us assume that only one coordinate q is involved, which varies from q^{in} at the initial system equilibrium to q^{fin} at the final system equilibrium. Let us then introduce

the normalized coordinate $x = (q - q^{in})/(q^{fin} - q^{in})$. It is seen from Eq. (60) or Eqs. (61) and (65) that E^{in} and E^{fin} are given as a function of x by

$$E^{in} = E^{in}_{eq} + \lambda x^2 \tag{73}$$

$$E^{fin} = E^{fin}_{eq} + \lambda(1 - x)^2 \tag{74}$$

with $x = 0$ corresponding to the initial system equilibrium point whereas $x = 1$ corresponds to the final system equilibrium point. Note that the following harmonic model can be adapted to encompass a larger variety of nonharmonic situations that are amenable to harmonic ones simply by using a suitable change of space variable. For example, a simple logarithmic change of variable $y = -(\ln x)/\beta$, i.e., $x = \exp(-\beta y)$, transforms any associative/dissociative Morse potential curve, which represents an energy well in the real space y, into a parabola that represents the same well in the transformed space x. Thus, Eqs. (73) and (74) apply in the transformed space, although the real energy well is strongly nonharmonic. Through this smart procedure, dissociative electron transfers can be treated within the same framework as harmonic ones. For a recent discussion and review of these features, see Ref. 57d. Figure 8a represents the resulting variations in the two energies with x. It is seen from this figure that, if the electron transfer were to occur radiatively from the initial system equilibrium point, as in the gas phase (e.g., in I_p determinations), then the final system curve would be reached at the point $x = 0$, that is, from Eq. (74), at $E = E^{fin}_{eq} + \lambda$. The system would then relax to its equilibrium, that is, $x = 1$ and $E = E^{fin}_{eq}$, thus radiating an energy λ during its reorganization.

A second common interpretation of the reorganization energy is related to the activation process rather than to a comparison between the gas and the condensed phases. The activation barrier for the forward reaction is given by equating E^{in} and E^{fin} in Eqs. (73) and (74). Thus it follows that $x^{\#}$, the normalized coordinate at the transition state, is given by resolution of

$$E^{\#} = E^{in}_{eq} + \lambda(x^{\#})^2 = E^{fin}_{eq} + \lambda(1 - x^{\#})^2$$

which easily yields Eq. (75) when taking into account that $\Delta G^{o'} = E^{fin}_{eq} - E^{in_{eq}}$.

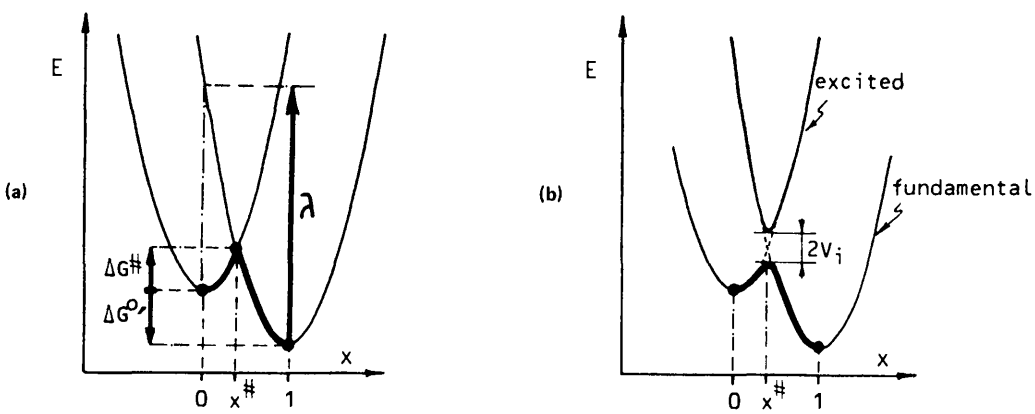


Figure 8. Potential energy-normalized reaction coordinate diagrams, without (a) or with (b) interaction between the initial and final subsystems (see text).

$$x^{\#} = \tfrac{1}{2}\left(\frac{\Delta G^{o'}}{\lambda} + 1\right) \tag{75}$$

$$\Delta E_f^{act} = E^{\#} - E_{eq}^{in} = \lambda(x^{\#})^2 = \frac{\lambda}{4}\left(1 + \frac{\Delta G^{o'}}{\lambda}\right)^2 \tag{76}$$

Introduction of this value into Eq. (73) gives the activation energy in Eq. (76) for the forward reaction.* Thus it is seen from the latter equation that $\lambda/4$ is equal to the "intrinsic activation barrier" $\Delta G_o^{\#}$, that is, to the activation energy that would be obtained for $\Delta G^{o'} = 0$. Thus if a series of electron transfers with virtually identical λ is considered, determination of the activation barrier for $\Delta G^{o'} = 0$ gives direct access to the experimental value of λ. Proponents of this second interpretation then prefer to reformulate Eqs. (64) or (76) under the equivalent form

$$\Delta E_f^{act} = \Delta G_o^{\#}\left(1 + \frac{\Delta G^{o'}}{4\Delta G_o^{\#}}\right)^2 \tag{77}$$

To conclude, we discuss more deeply the energetic diagrams like that presented in Fig. 8a. As noted previously, the A and D orbitals must interact in order that the electron may be transferred. This simply means that an electronic coupling is observed between the initial system and the final system. This results in mixing of the two systems, which amounts to separating the potential energy curves in Fig. 8a into a lower (or fundamental) state and an upper (or excited) state, as represented in Fig. 8b. Because the potential energies of the electron tend to be identical for the initial and final systems when the transition state is approached, the degree of mixing in this region is higher than near the bottom of each potential well. Thus the maximal effect is reached at the transition state, where a splitting of magnitude $2V_i$ is observed [58].

In practice, as soon as $2V_i > RT$, that is, $V_i > 0.25$ kcal/mol at room temperature, when the system crosses the transition point it remains on the lower curve and then reaches the final system equilibrium. This corresponds to a probability of 1 for electron transfer each time the system crosses the barrier (provided its momentum is in the right direction); that is, $\kappa = 1$.

When $2V_i \simeq RT$, when reaching the transition point the system may "jump" onto the upper curve. If so, when it goes backward it "falls" onto the lower curve, with a large probability (because of the direction of its momentum) of advancing toward the initial potential well. In such a case the electron has not been transferred and then $\kappa < 1$.

When $2V_i \ll RT$, this phenomenon occurs almost every time the system crosses the transition point, which means that $\kappa \approx 0$ and no electron transfer occurs.

From these considerations it is understood that Eqs. (64), (76), and (77), derived without considering electronic coupling, give activation energies overestimated by a term V_i and should normally be corrected. However, as noted for κ, V_i is predictable with difficulty from simple considerations and is usually not included in the activation energy.

*Note that Eq. (76) is identical to Eq. (64).

5. Energies and Free Energies in Electron Transfer Theories

In the preceding description of electron transfer theories, energies were used rather than free energies. For a reaction in liquid phase ΔE is nearly identical with ΔH, so that the results obtained earlier are valid as soon as entropic variations are negligible,* and thus $\Delta E \approx \Delta H \approx \Delta G$. In practice the distinction between ΔG and ΔE is forgotten. Since outer sphere electron transfers involve small bond lengths or angle variations, this is acceptable for inner shell components of activation free energies. Concerning outer shell components, the approximation is considered not drastic and is equivalent [59] to those made for solvation models (Born) or according to the Debye-Hückel theory [1a,c]. Thus, within these approximations and that previously discussed dealing with V_i, it is considered that the activation rate constant of outer sphere electron transfers is given by [from Eq. (58)]

$$k_f^{\#} = \kappa Z e^{\Delta G_f^{\#}/RT} \tag{78}$$

with

$$\Delta G_f^{\#} = W_r + \frac{\lambda}{4}\left(1 + \frac{\Delta G^{o'}}{\lambda}\right)^2 \tag{79}$$

where $\Delta G^{o'}$ is the free energy change between the precursor and successor complexes:

$$\Delta G^{o'} = F(E^{o}_{D^+/D} - E^{o}_{A/A^-}) - W_r + W_p \tag{80}$$

and λ is given in Eqs. (66), (67), and (72).

6. Quadratic Free Energy Relationships (QFER)

When one considers a series of related electron transfers, that is, involving acceptors (and donors) of reasonably close chemical electronic structures and radii, the reorganization energy λ should remain constant for the series. Thus it is seen from Eq. (79) that the activation energy varies as a quadratic function of the driving force, in contrast to the usual observation of linear free energy relationships in organic chemistry. As a result, the Brönsted coefficient β varies linearly with the driving force, with a value of 0.5 at $\Delta G^{o} = 0$. Indeed, from Eq. (78) and a derivation of Eq. (79), one obtains

$$\beta = -RT\left(\frac{\partial \ln k_f^{\#}}{\partial \Delta G^{o}}\right) = \tfrac{1}{2} + \frac{\Delta G^{o'}}{2\lambda} \tag{81}$$

When $|\Delta G^{o'}| < \lambda$, the predictions of such an equation are in agreement with the deductions of the Hammond postulate. Indeed, for exergonic reactions, β tends to zero when $\Delta G^{o'} \longrightarrow -\lambda$, which corresponds to an activationless reaction. Conversely, for endergonic reactions, β tends to unity when $\Delta G^{o'} \longrightarrow \lambda$, which features a barrierless reaction.

However, when $|\Delta G^{o'}| > \lambda$, β reaches negative values in the exergonic domain and is greater than unity in the endergonic case, according to Eq. (81). To recall these facts, the region such as $|\Delta G^{o'}| > \lambda$ is usually called the abnormal or inverted region, the second

*Note that for the transition state, the entropy corresponding to the formation of pairs is included in the models through the free energies of formation of the precursor or successor complexes (Secs. II.C.1 and II.C.2).

term referring to the unusual decrease in rate constant with larger exergonicity of the reaction. In actual practice there is a large debate about the experimental existence of this inverted region. Moreover, more elaborate models have been proposed involving the possible participation of excited vibronic states, which show that for most organic electron transfers one should observe a normal behavior, that is [60],

$$\Delta G^{\#} \approx W_r, \text{ or } \beta = 0 \text{ for } \quad \Delta G^{o'} < -\lambda \tag{82}$$

$$\Delta G^{\#} \approx W_r, +\Delta G^{o'}, \text{ or } \beta = 1 \text{ for } \quad \Delta G^{o'} > \lambda \tag{83}$$

although $\Delta G^{\#}$, given in Eq. (79), remains valid for $|\Delta G^{o'}| > \lambda$.

Similarly other models, such as the Marcus-Levine-Agmon [61] model, have been developed that predict the nonexistence of the inverted region. The latter model leads to the $\Delta G^{\#}$ variations with $\Delta G^{o'}$ and λ in Eq. (84):

$$\Delta G^{\#} = \Delta G^{o'} + \frac{\lambda}{4 \ln 2} \ln(1 + e^{-\Delta G^{o'} \cdot 4 \ln 2/\lambda}) \tag{84}$$

Particularly interesting is that Eq. (84) respects the limits in Eqs. (82) and (83). For intermediate values of the driving force, the calculated activation barrier from Eq. (84) is very close to that obtained in the classic harmonic model developed in this section [Eq. (79)]. Thus from an experimental point of view, distinction between the two models is rather difficult or impossible [36a], although totally different mathematical expressions for $\Delta G^{\#}$ variations with $\Delta G^{o'}$ and λ are obtained.

To conclude, we discuss the experimental use of Eq. (81). Indeed, in experimental practice one has access to overall rate constants k_f or k_b in Scheme 3 and Eqs. (56). Thus the experimental Brönsted coefficient β_{exp} is determined as in Eq. (85):

$$\beta_{exp} = -RT\left(\frac{\partial \ln k_f}{\partial \Delta G^{o}}\right) \tag{85}$$

The latter becomes identical to that in Eq. (81) only when $k_f \approx k_f^{\#}$, that is, when $k_f^{\#} \ll k_f^{dif}$ in Eq. (54a). However, when diffusion of the reactants or products becomes the rate-determining factor, $k_f \approx k_f^{dif}$, as discussed earlier. Owing to the discreteness of homogeneous experimental data, the shift from an activation control to a diffusion control of the reaction is usually difficult to appreciate, particularly in the endergonic region. The perversity of the problem is even larger when one realizes that application of Eq. (85) to a diffusion-controlled reaction yields $\beta_{exp} = 0$ for exergonic situations and $\beta_{exp} = 1$ for endergonic, owing to the two components in the overall pseudo-rate constant k_f^{dif} in Eq. (54a). The difficulty is greater as the reorganization energy λ decreases, as evidenced by Fig. 9. This caveat [36] is conveniently represented in Fig. 10, which summarizes the various conclusions reached here in the form of a plot of $\Delta G^{o'}$ versus λ. Indeed, it is seen from this diagram that according to the location of a given system, the physical meaning of experimental activation energies obtained by strict application of Eq. (86) [deduced from Eq. (78), assuming $\kappa = 1$] may greatly differ [36a].

$$\Delta G_{exp}^{\#} = -RT \ln \frac{k_f}{Z} \tag{86}$$

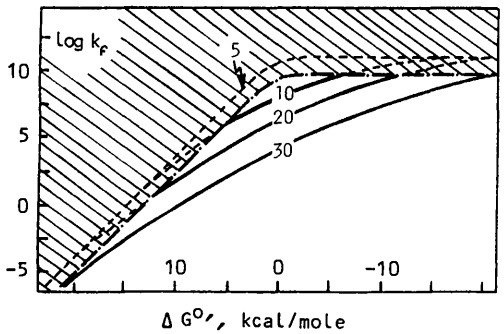


Figure 9. Variations in the observed rate constant k_f as a function of the driving force for various values of the reorganization energy (numbers on the curves in kcal/mol). The solid curves correspond to an activation control. The hatched zone corresponds to a diffusion control (compare Fig. 4).

7. Cross-Relationships: Evaluation of Rate Constants from Isotopic Rate Constants

An interesting consequence of the additive formulation in Eqs. (66) and (67) of the reorganization energy λ^{AD} for an A/D electron transfer is that it may be broken in three components: λ_o^{AD}, the outer shell reorganization, and λ_i^A and λ_i^D, which involve the inner shell contributions related specifically to bond length and bond angle variations in the acceptor (and the donor) center:

$$\lambda^{AD} = \lambda_o^{AD} + \lambda_i^A + \lambda_i^D \tag{87}$$

On the other hand, for the isotopic electron transfer, that is,

$$A^* + A^{\cdot -} \rightleftharpoons A^{*\cdot -} + A \quad (\text{or} \quad D^* + D^{\cdot +} \rightleftharpoons D^{*\cdot +} + D)$$

the inner shell component for the reorganization energy becomes

$$\lambda_i^{AA} = 2\lambda_i^A$$

since two A centers are involved; similarly, $\lambda_i^{DD} = 2\lambda_i^D$ for the isotopic electron transfer relative to the donor. Thus it follows that Eq. (87) may be rewritten under the form in Eq. (88):

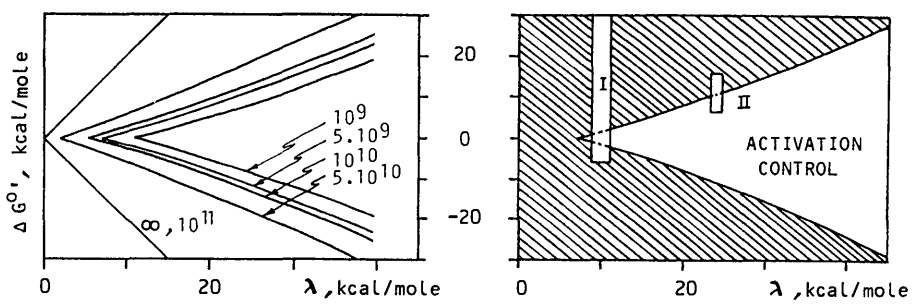


Figure 10. Relationship between the driving force and the reorganization energy for the reaction to be under activation control or diffusion control (hatched zone). The boundaries between the two zones are given for various values of $k_i^{dif} = k_p^{dif}$. The boxes correspond to the location of the experimental systems in Fig. 11 (I) or 12 (II).

$$\lambda^{AD} = \lambda_o^{AD} + \tfrac{1}{2}(\lambda_i^{AA} + \lambda_i^{DD}) \tag{88}$$

Formally λ_o^{AD} cannot be split into two (A and D) components because of the presence of $r \approx a_A + a_D$ in Eq. (72), which acts as a coupling term. Yet a tedious but elementary algebraic transformation allows Eq. (72) to be rewritten as

$$\lambda_o^{AD} = \tfrac{1}{2}(\lambda_o^{AA} + \lambda_o^{DD})\left[1 + \frac{(a_A - a_D)^2}{(a_A + a_D)^2}\right] \tag{89}$$

In Eq. (89), λ_o^{AA} and λ_o^{DD} are the outer shell reorganization energies for the respective isotopic electron transfers, defined similarly as λ_o^{AD} in Eq. (72). Thus as soon as the equivalent radii for the acceptor and the donor do not differ by a factor larger than 2, one gets within about 10% precision:

$$\lambda_o^{AD} = \tfrac{1}{2}(\lambda_o^{AA} + \lambda_o^{DD})$$

Introduction of this latter result into Eq. (88) allows one to formulate λ^{AD} as the sum of two components relative to the individual isotopic reactions in Eq. (90):

$$\lambda^{AD} = \tfrac{1}{2}[(\lambda_o^{AA} + \lambda_i^{AA}) + (\lambda_o^{DD} + \lambda_i^{DD})] = \tfrac{1}{2}(\lambda^{AA} + \lambda^{DD}) \tag{90}$$

The operative interest of such a cross-relationship is extreme, since when associated with Eqs. (78) through (80) it allows an a priori estimation of the rate constant of any outer sphere electron transfer reaction provided the corresponding standard reduction potentials and isotopic rate constants are known. Yet a caveat in this approach is the necessity that $\kappa = 1$ for all reactions, that is, that there is always sufficient overlap between the orbitals [62].

8. Experimental Illustrations

The purpose of this section is not to present a compendium or a discussion of the numerous experimental illustrations of the validity of electron transfer theories, but rather to select two typical examples that illustrate the main features of these theories in organic chemistry [63].

a. Validity of QFER over a Wide Domain of Free Energies. The main difficulty in discussing the dependence of rate constants with driving force over a wide domain stems from the fact that, to be significant, the series must involve electron transfers with nearly constant reorganization energies. However, it is easily understood that the two requirements (ΔG° over several tens of kilocalories per mole but λ invariant) are difficult to satisfy simultaneously.

Such a series, which extends over nearly 70 kcal/mol in ΔG°, has been presented by Rehm and Weller [64]. The series corresponds to electron transfer between an excited acceptor and a donor acting as a quencher or between an excited donor and an acceptor quencher. Thus rate constants, ranging from 10^6 to $2 \times 10^{10}\,M^{-1}\,s^{-1}$, have been determined for more than 60 different donor-acceptor systems in acetonitrile. Examination of the corresponding results, presented in Fig. 11, clearly shows that three domains may be defined: (1) $\Delta G^\circ < -10$ kcal/mol, where k_f is independent of the driving force, that is, where $\beta_{exp} = 0$; (2) -10 kcal/mol $< \Delta G^\circ < 10$ kcal/mol, where β_{exp} varies from zero to unity; (3) $\Delta G^\circ > 10$ kcal/mol, where $\beta = 1$. These data, corrected for diffusion components, correspond to an activation control of the electron transfer reactions. They qualitatively agree with the predictions of Eqs. (78) and (79) for $|\Delta G^\circ| < 10$ kcal/mol but show that Eq. (79) is not valid outside this range, Eqs. (82) and (83) being more adequate. As

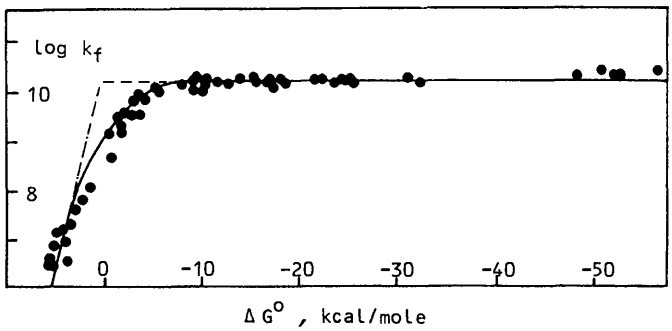


Figure 11. Linear energy relationship over an extended domain of driving force. (Experimental data from Ref. 64.)

such they have been considered a convincing experimental argument for the nonexistence of the inverted region [65]. Yet, owing to the large scatter of the data, a precise determination of the validity of Eq. (79) in the intermediate ($|\Delta G^\circ| < 10$ kcal/mol) free energy range is impossible.

b. Validity of the QFER for Low-Endergonicities or Exergonicities. In order to test the experimental validity of the quadratic relationship between $\Delta G^{\#}$ and ΔG°, a rather small free energy domain needs to be investigated. As a consequence, even small variations in λ result in too large a scatter of the data for significant quantitative conclusions to be drawn (compare the data in Fig. 11 for $|\Delta G^\circ| < 10$ kcal/mol). Thus a series of very closely related redox couples must be investigated.* A series meeting these requirements is given by the endergonic oxidation in acetronitrile of methylbenzenes by tris-(5X-phenantroline)-iron(III), X = H, Cl, NO_2, already discussed [36a,c]. Indeed, for such a series the inner shell contributions are minimal owing to the close identity of the iron(II/III) complexes [66] and the small distortions of the arene cation radical vis-à-vis the neutral (for $C_6H_6^+$ the inner shell reorganization energy from a nuclear configuration corresponding to benzene involves a Jahn-Teller distortion [67] and has been evaluated to approximately 3 kcal/mol by Salem [67c]). Thus the outer shell reorganization energy predicted according to Eq. (72) is (λ_o in kcal/mol: a_{Ar}, a_{Fe}, and $r = a_{Ar} + a_{Fe}$ in Å)

$$\lambda_o = 1.67 \times 10^2 \left(\frac{1}{\varepsilon_{op}} - \frac{1}{\varepsilon_s}\right)\left(\frac{1}{a_{Ar}} + \frac{1}{a_{Fe}} - \frac{2}{r}\right)$$

that is, $\lambda_o \approx 21$ kcal/mol for $a_{Ar} \approx 3.5$ Å, $a_{Fe} \approx 7$ Å [68], and $\varepsilon_s = 37.5$ and $\varepsilon_{op} = n_{op}^2 = (1.34)^2$ for acetonitrile. The resulting predicted value of the global reorganization energy is then 24 kcal/mol for each couple in the series.

Figure 12a indicates how the measured rate constant k_f for the endergonic electron transfer oxidation of methylbenzene by $(phen)_3$-iron(III) complexes varies with the driving force. It is seen from these data that, provided that $\Delta G^{\circ'} < 10$ kcal/mol, a very good fit is obtained with the rate constant predicted from Eqs. (78) through (80) on the basis of an activation control of the overall reaction when using $\kappa = 1$, $Z = 10^{11}\,M^{-1}\,s^{-1}$, and

*Note that the corresponding condition is more easily satisfied for electron transfer at electrodes, owing to the easy variation of the driving force, by adjustment of the electrode potential without modification of the redox couple.

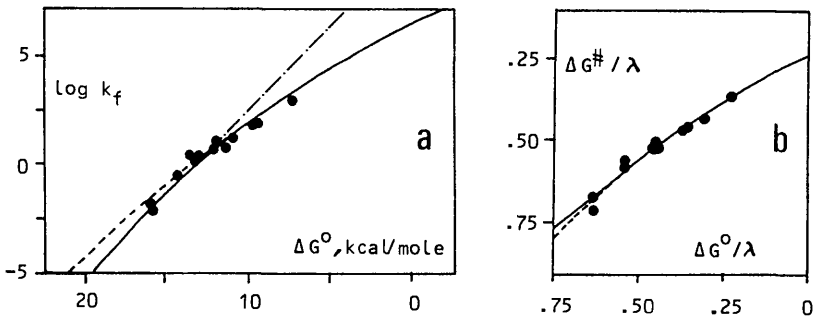


Figure 12. Quadratic free energy relationship in the low endergonic region for the oxidation of methylbenzenes by $Fe(phen)_3^{3+}$. (a) Experimental variation of the observed rate constant compared with the theoretical variations (solid curve): (- - -) activation or (·····) diffusion controls. (b) Experimental relationship between the activation free energy and the driving force compared with the theoretical variations for $\lambda = 27$ kcal/mol in the solid curve: (- - -) polynomial regression in Eq. (92) [36a,c]. (Data from Ref. 36.)

$\lambda = 24$ kcal/mol, determined earlier. However, for larger positive values of $\Delta G^{o'}$, the diffusion processes contribute significantly to the experimental rate constant. Yet the activation rate constant $k_f^{\#}$ may be extracted from the experimental k_f data through the use of Eq. (56a). The real activation free energy $\Delta G_f^{\#}$ is then derived through Eq. (78) and plotted as a function of $\Delta G^{o'} = \Delta G^o + W_p$ in Fig. 12b. Quadratic regression analysis of these data allowed their fit by a second-order polynomial expression in Eq. (91) [36a,c] (represented as the dashed line in Fig. 12b):

$$\Delta G_f^{\#} = 6.7 + 0.50\Delta G^{o'} + 8.7 \times 10^{-3}(\Delta G^{o'})^2 \tag{91}$$

which is in good agreement with the predicted variations in Eq. (79) for $= 27$ kcal/mol. Indeed, development of Eq. (79) with $\lambda = 27$ kcal/mol yields

$$\Delta G_f^{\#} = 6.7 + 0.50\Delta G^{o'} + 9.3 \times 10^{-3}(\Delta G^{o'})^2$$

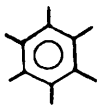
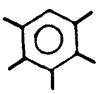
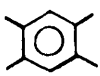
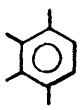
Another way to appreciate the correctness of Eq. (79) in the prediction of the experimental barrier consists in the evaluation of λ for each individual couple as presented in Table 3. Indeed, from Eq. (79), λ is obtained through the solution of the second-order equation

$$\lambda^2 + 2(\Delta G^{o'} - 2\Delta G_f^{\#})\lambda + (\Delta G^{o'})^2 = 0 \tag{92}$$

$$\Delta G_f^{\#} = RT \ln \frac{Z}{k_f^{\#}} \tag{93}$$

where $\Delta G^{o'}$ and the experimental activation free energy $\Delta G_f^{\#}$ from Eq. (93) are known. Thus a value of 27.0 kcal/mol (standard deviation 3.3 kcal/mol, 11 data) is obtained for the average reorganization energy, which is in very close agreement with that predicted (24 kcal/mol).

Table 3. Experimental Evaluation of the Reorganization Energy λ for the Oxidation of Methylbenzenes by Tris-(5X-phenantroline)-Iron(III) Complexes

Methylbenzene	X	$\Delta G^{o\prime a}$	$\Delta G_f^{\#a}$	λ^a	$\lambda_{average}{}^{a,b}$
	H	11.2	13.4	26.4	
	Cl	8.86	12.6	30.1	28.2 (1.8)
	NO_2	6.55	10.7	28.2	
	H	14.2	15.6	26.4	
	Cl	11.9	13.9	26.4	26.3 (0.4)
	NO_2	9.55	12.4	27.1	
	H	16.0	16.8	24.9	
	Cl	13.7	13.4	—[c]	25.1 (0.2)
	NO_2	11.4	13.3	25.2	
	H	15.8	18.0	32.8	
	Cl	13.5	14.0	19.8	27.3 (6.7)
	NO_2	11.2	14.0	29.3	

[a]In kcal/mol.
[b]Average value for a given arene, standard deviation indicated in parentheses. For all couples $\lambda_{av} = 27.0$ (3.3) kcal/mol.
[c]Not determinable since $\Delta G' > \Delta G^{o\prime}$
Source: Data from Ref. 36a.

III. FUNDAMENTAL ASPECTS OF ELECTRODE PHENOMENA

A. Monitoring a Half-Reaction: The Electrochemical Cell

1. Monitoring a Half-Reaction

In homogeneous chemistry an electron transfer reaction involves two reactants, an acceptor A and a donor D. Thus, formally, an electron transfer reaction consists of the superimposition of two elementary chemical acts: the reduction of the acceptor and the oxidation of the donor. Yet as discussed in the first part of this chapter, since more attention is given to one of these elemental reactions, the overall reaction is termed a reduction when the acceptor is the compound of interest or an oxidation when chemical transformation of the donor is favored.

In electrochemistry the same phenomenon (essentially related to charge conservation) occurs, yet the reduction of the acceptor A occurs at one electrode (the cathode in electrolytic cells) and the oxidation of the donor D at the other (anode). Thus the kinetics* of the overall cell reaction depends on both half-reactions, in a similar way as the kinetics of a homogeneous electron transfer depends on the acceptor and the donor. However,

*That is, the current flowing through the cell, since it corresponds to the number of electrons consumed at each electrode per unit of time.

because the two half-reactions occur at different locations, it is technologically possible to break the coupling between the two electrodes. This is done via two different approaches, based on the same principle, that take advantage of the potential distribution in an electrochemical cell, shown in Fig. 13a. From this schematic representation it is seen that the potential difference Φ between the two electrodes is the sum of three components: two of them, Φ_{cat} and Φ_{an}, are related to each electrode, and the third, Ri, arises because of the ohmic drop due to the current flow through the resistive solution. The potential variation observed at each electrode is localized within an extremely thin layer (< 100 Å) of solution adjacent to the solution (Sec. III.A.4), which means that the overall cell behaves like an electrical circuit composed in part of two capacitors and a resistance as sketched in Fig. 13b. However, such a simple circuit is not sufficient since it does not allow constant current to flow through the cell because of the capacitors. In practice, two additional impedances, Z_{cat} and Z_{an}[†] must be added in parallel with each capacitor, which correspond to the electrochemical reactions taking place at the electrodes. The latter are necessarily in parallel with the capacitors, as shown in Fig. 13c, since they use the potential difference between the electrode and the local solution as their driving force and act as derivations allowing the current to flow. Thus it is easily understood that when a given potential difference is imposed between the two electrodes, the three individual potential drops Φ_{cat}, Φ_{an}, and Ri must adjust in order that the currents flowing through each impedance and through the solution are equal; this results in coupling the processes occurring at each electrode and in the solution.

Thus to individualize one of the electrodes it is necessary to control, that is, to measure or to impose, its individual potential difference versus the solution (Φ_{cat} or Φ_{an}). This is done via the introduction of a third electrode, the reference electrode Ref, placed in the solution near the electrode of interest (hereafter named the working electrode W, the other electrode being called the auxiliary electrode A). Because of its characteristics (Sec. III.C.3), the reference electrode imposes a potential difference $\Phi_{Ref} \approx E^{\circ}_{Ref}$ vis-à-vis the point of the solution where it is located. Φ_{Ref} may include various components related to the redox half-reaction or junction potentials, for example, but is independent of the current flowing through the reference electrode. Such a three-electrode system, sketched in Fig. 13d, formally allows the physical individualization of the working electrode. Indeed, one may, impose an arbitrary potential difference $\Phi_W - \Phi_A$, for example, between the working and auxiliary electrode, measure the resulting $\Phi_W - \Phi_{Ref}$ potential difference, and compare it to the desired value E to be imposed. If $\Phi_W - \Phi_{Ref}$ is too small, $\Phi_W - \Phi_A$ is increased; if $\Phi_W - \Phi_{Ref}$ is too large, $\Phi_W - \Phi_A$ is decreased. Thus $\Phi_W - \Phi_{Ref}$ is progressively adjusted to the selected value E (note then that $\Phi_{Ref} - \Phi_A$ is also imposed as a result of the procedure, but its exact value is a priori of no interest). Then the current i flowing through the cell may be measured and related to the potential E. Repetition of the whole procedure allows the current-potential characteristic, that is, the (i, E) relationship, of the half-reaction taking place at the working electrode to be determined. Yet, although possible, if the whole procedure were performed manually, it would take several hours to record precisely an (i, E) characteristic. Thus pertinent electronic apparatus, called potentiostats [69], have been designed to perform the whole procedure within microseconds or less [70]. Besides their convenience, potentiostats allow the recording of transient electrochemical kinetics, which would not have been possible manually.

[†] Z_{cat} and Z_{an} are called faradaic impedances because of their origin.

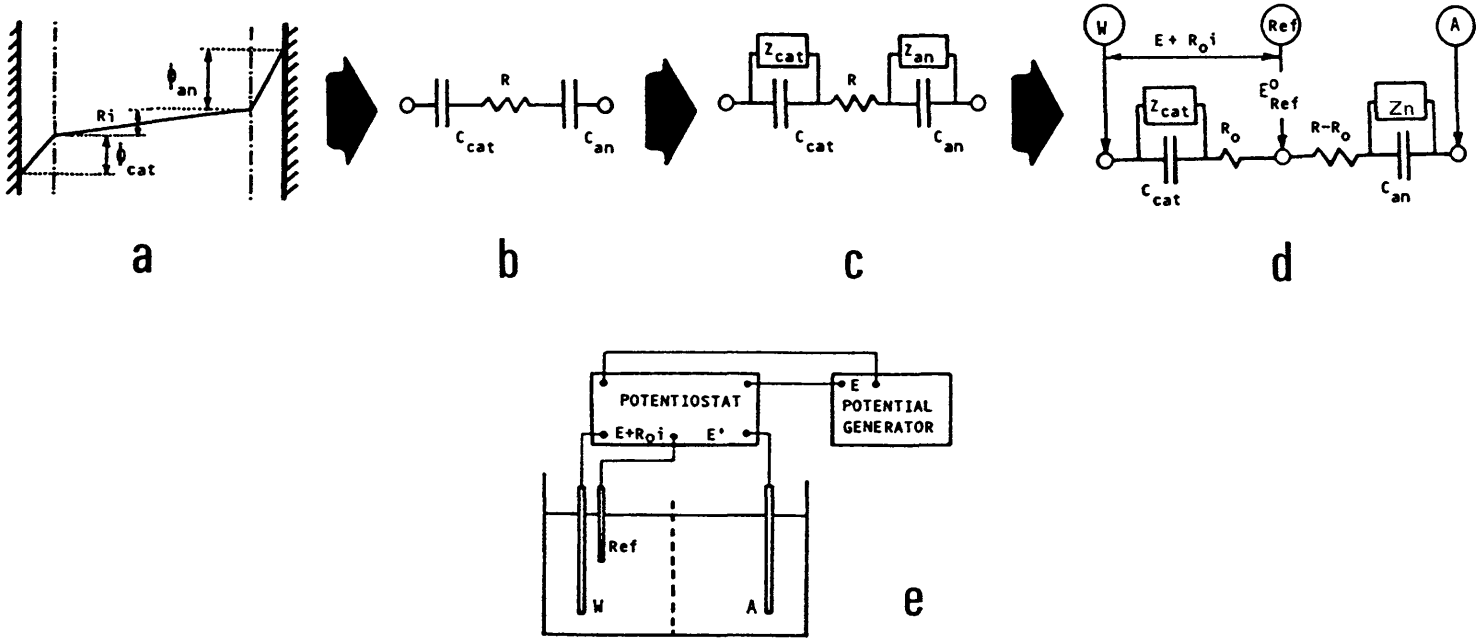


Figure 13. Representation of the potential variations in the electrochemical cell and associated electronic schemes (a–d). ($\Phi = \Phi_{cat} + Ri + \Phi_{an}$; see text). W, working electrode; Ref, reference electrode; A, auxiliary electrode. (e) Schematic description of the electrochemical cell with a potentiostat.

The second approach, although used first in electrochemistry, derives from that corresponding to three electrodes and potentiostat. It consists of using a reference electrode as the auxiliary electrode. This is indeed possible, provided the size of the reference electrode is sufficiently large for the current density flowing through it to be infinitely small, although the current may be large. The potential difference between the reference-auxiliary electrode (called a counterelectrode in a two-electrode device) and the solution in its near proximity is thus constant (Sec. III.C.3). The potential difference Φ_W associated with the working electrode is then given by

$$\Phi_W = \Phi - \Phi_{CE} - Ri \tag{94}$$

which shows that, provided that $\Phi \gg Ri$, Φ_W is measured (or imposed) within a constant term Φ_{CE} when the overall potential difference Φ is measured (or imposed). This second approach has been discarded vis-à-vis the three-electrode potentiostat approach because in organic electrochemistry the resistance of solutions is usually large so that the ohmic drop term Ri is not negligible under the usual conditions.* Thus the relationship between Φ_W and Φ depends on the current flowing through the cell. Note that a similar problem is also involved for the three-electrode approach, since the working and reference electrodes are separated physically by part of the solution, which introduces an ohmic drop component in the potential difference between the working electrode and the reference electrode. Yet this effect is usually smaller because the resistance R_0 involved is smaller and is eventually corrected via additional electronic circuitry in the potentiostat [69].†

2. The Electrochemical Cell

From this presentation it is seen that electrochemical data that pertain to a single half-reaction taking place at the working electrode can be experimentally obtained. In our opinion this is one of the greatest advantages of electrochemistry, although not really identified and recognized in other fields of chemistry. Indeed, whatever the homogeneous chemical technique used, the chemistry associated with a donor-acceptor couple necessarily depends on both members.

Another important advantage, less apparent in this presentation, is that because of the involvement of an external electrical driving force, electrochemistry allows overall endergonic reactions to be performed at a considerable rate. Indeed, let us consider the a priori endergonic electron transfer reaction in Eq. (95):

$$A + D \rightleftharpoons A^{-} + D^{+} \tag{95}$$

Thus under electrochemical conditions, A can be reduced and D oxidized provided that sufficient cathodic and anodic potentials are applied. Yet upon preparative-scale electrolysis, A^{-} and D^{+} recombine to A and D, except if they react chemically:

---

*However, it regains interest with the development of ultramicroelectrodes. Indeed, because of their micrometer (or smaller) sizes, the currents are of the order of nanoamperes. Thus even with R of several kilo-ohms, the ohmic drop term is totally negligible.

†In the latter case, the current is measured and a $R_0 i$ term is reinjected via a feedback loop so that the potentiostat actually imposes the potential difference $E + R_0 i$ between the working electrode and the reference electrode; this results in "cancelling" the ohmic drop (Fig. 13e).

Cathode: $A + e \rightleftharpoons A^{\cdot -} \longrightarrow \cdots$

Anode: $D - e \rightleftharpoons D^{\cdot +} \longrightarrow \cdots$

Thus in the absence of chemical reaction or when undesired reactions between the follow-up product(s) may arise, it is necessary to avoid the unwanted reaction. Taking advantage of the different physical locations of the two electrodes, this is done by separating the solution into two parts (catholyte and anolyte, respectively) using a glass frit or a membrane so that the electrical connection (via ionic transport; see Sec. IV.A.2) is not interrupted [71].

3. Resistive Effects and Ohmic Drop: The Supporting Electrolyte-Solvent System

In the preceding part of this section we focused our attention on the electrodes, where the real electrochemical events occur. Yet as already explained, the current exchanged at the electrodes must flow through the cell, that is, through the solution between the working and counter or auxiliary electrodes. For this reason the solution must be conducting; otherwise no current flows, even when the electrode processes are extremely easy. Indeed, if the resistance of the solution is R and i the current flowing through the cell, Ohm's law indicates that the potential "lost" for conducting purposes is Ri.* In practice, ohmic drop can be overcome by increasing the potential difference between the working and auxiliary electrodes by the amount required. Yet this is not an acceptable solution because of the electrical power required and the thermal energy dissipation. Indeed, Ri is associated with an electrical power Ri^2 that is dissipated thermally in the solution and needs to be supplied by the potentiostat or the external power supply connected to the cell. To roughly quantify these effects, let us consider a laboratory electrolysis cell in which $i = 1\,A$ is required. Let us assume that $R = 100\,\Omega$, a common figure for most organic solutions. Thus $Ri = 100\,V$ and $Ri^2 = 0.1\,kW$. For an average thermal capacitance of 1 cal/K per ml and a cell of 100 ml, for example, this amounts to a temperature increase in the cell of approximately 0.25°C/s when it does not exchange energy with the external atmosphere. Thus in an actual experiment the cell must be cooled so that its temperature is maintained within reasonable limits. In other words, this means that an additional 0.1 kW power must be lost to cool the cell.

At the laboratory scale these energetic losses are easily controlled; thus the main problem, relates to the potentiostat, or potential supply, power limitation, since most of the usual equipment affords between 70 and 100 W of usable electrical power. At the industrial scale, since the current intensities are considerably larger, serious problems arise from lost energy and temperature control of the cell.

To conclude this introductory section concerning ohmic drop effects, let us consider the case of transient electrochemical techniques. In this case the currents are of the order of few milliamperes or less, and thus all these effects should cancel. Unfortunately, this is not the case because of the size of the working electrodes. Indeed, these are often of millimetric dimensions, which amounts to a considerable narrowing of the field lines near the tip of the working electrode.† As a result the resistance increases, and most of

*Ri is usually said to be the "ohmic drop" to recall that this potential is not used for purely electrochemical purposes.

†The auxiliary electrode is usually of considerably larger dimensions (1 to several cm^2). Thus the equivalent conductor should be thought of as a cone rather than as a cylinder as for preparative cells.

it is concentrated near the very tip of the working electrode, even when a Luggin-Haber capillary probe is used for the reference [72]. Resistances of several kilo-ohms are frequently involved, which introduces important difficulties for an exact control of the potential of the working electrode [compare Eq. (94)]. Obviously, when one does not care about such control, this should not be perceived as a limitation, and rather resistive solutions may be used. Note also in this respect that when the working electrode is a disk of radius r_0, the resistance R varies as $1/r_0$ provided the auxiliary electrode is of considerably larger dimensions. On the other hand, the current flowing through the electrode is proportional to its surface area (Sec. III.B), provided the electrode is not under diffusional steady state. Thus the ohmic drop is proportional to r_0 and decreases when the latter decreases. This explains one of the advantages of ultramicroelectrodes, at which ohmic drop effects naturally cancel since r_0 is of the order of a few micrometers [73].

This discussion and presentation of ohmic drop problems should lead to the conclusion that, with maybe an exception for ultramicroelectrodes, the resistivity of electrochemical solutions must be decreased as much as possible.

In solutions, the current is necessarily carried by dissociated ionic species. Theories of this phenomenon are well developed and presented in most introductory electrochemistry textbooks. Yet it is sufficient for our purpose here to recall that the resistance is then inversely proportional to the concentration of the dissociated electrolyte (Sec. IV.A.2) for the usual case of a 1:1 electrolyte (e.g., $NBu_4^+BF_4^-$ and $NE_4^+BF_4^-$). Thus a normal means to decrease ohmic drop is to add an inert* electrolyte in large concentration. Yet as mentioned earlier, only the dissociated ions participate in the current transport since electrically neutral ion pairs play no role. Thus it is important that most of the supporting electrolyte be dissociated. Such a condition, together with the large concentrations required (approximately 0.1 M), implies that a rather dissociating solvent is used. This is the reason that, in organic electrochemistry, the preference is for solvents with rather large dielectric constants ($\varepsilon_s > 10$) and supporting electrolytes with rather large ions (e.g., $NBu_4^+BF_4^-$). Considering these conditions and that the solvent should be able to dissolve organic molecules explains why most electrochemical experiments involve a narrow class of solvents, such as acetonitrile ($\varepsilon_s = 37.5$), dimethylformamide (40), dimethyl sulfoxide (46.7), and propylene carbonate (36.7) [71].

4. The Electrode/Solution Interfacial Region

To simplify the following discussion, we restrict it to the case of a cathode. Obviously, however, the results and phenomena directly apply to anodes, cations being replaced by anions, and vice versa.

Experimentally it was early recognized that an electrode/solution interphase behaves as a capacitor† [74]. This is because the negatively charged surface of the cathode generates a very strong electrical field that tends to attract positive ions from the solution, as sketched in Fig. 14a. The positive layer thus formed exerts, on the solution side, an electrical field of opposite direction that attracts negative ions from the solution.

*"Inert" means that the electrolyte is not involved in the electrochemical transformation occurring at the electrodes. The electrolyte is usually also called the supporting electrolyte after its function of "supporting" the current flow through the cell.

†Note that this property is used in electronics in the so-called electrochemical capacitors, which are no more than electrochemical cells without faradaic reactions.

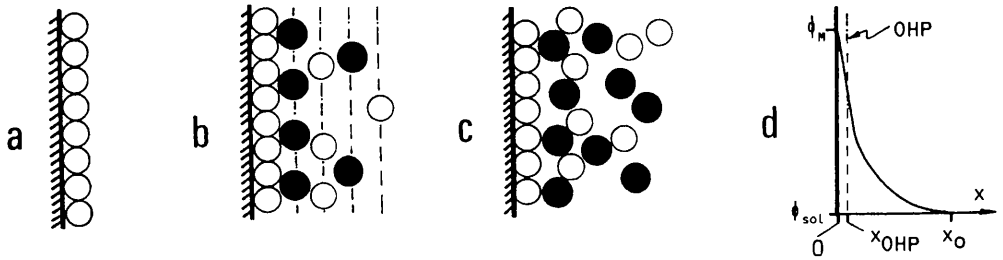


Figure 14. Schematic representation of the electrode-solution interfacial region. (a) Helmholtz model; (b) structured layer model; (c) thermally disorganized layers; and (d) resulting potential variations with distance of the electrode; Φ_M, electrode potential; Φ_{sol}, solution potential; OHP, outer Helmholtz plane (few Å); x_o, extremity of the diffuse layer (few tens of Å); $x < x_{OHP}$, compact layer; $x_{OHP} < x < x_o$, diffuse layer.

However, since this latter field is partly compensated by that resulting from the negative charges in the electrode, the charge density of the anionic layer is smaller than that of the cationic one. Repetition of this phenomenon results in alternating layers of positive and negative charges, with a charge density in each layer, however, decreasing with the electrode distance, as pictured in Fig. 14b. Because of the decreased in electrical field with distance, the successive layers are less and less bound. Then, owing to thermal agitation, these layers cannot be as rigid as might be deduced from the preceding presentation and interpenetrate each other except for the first, which is tightly bound to the electrode [75]. This phenomenon is indicated by the corresponding names *compact layer* for the first layer and *diffuse layer* for the remaining part; both of them constitute the double layer and act as two capacitors in series. The capacitance (usually 20–50 $\mu F/cm^2$) and dimensions (a few angstroms for the compact layer and a few tens of angstroms for the diffuse layer) may be evaluated via the Gouy-Chapman-Stern theory [76], which is developed in most electrochemical textbooks. The main conclusions of this model, which are in general agreement with experimental observations, are the following: (1) because of the compact layer, a large potential drop arises within a few angstroms of the electrode surface (compare Fig. 14d); thus most of the potential difference between the electrode and the solution is lost at the end of the compact layer (i.e., at the outer Helmholtz plane, OHP); (2) the potential difference between the OHP and the solution results in an electrical field considerably lower than that between the electrode and the OHP, which nearly exponentially decays with distance; (3) beyond several tens of angstroms from the electrode the potential is identical to that in the bulk of the solution, except for eventual ohmic drop effects, as discussed earlier (compare Fig. 13a); (4) as a result of the third conclusion, beyond a few tens of angstroms the electrode exerts no electrostatic attraction or repulsion on any ionic species, which explains why an anion may be reduced or a cation oxidized at electrodes.

B. General Overview of an Electrode Reaction

When thinking of any electrochemical reaction, it is important to remember that the very act of electron transfer takes place at a surface, whereas the material to be reduced or oxidized is dispersed in a volumetric phase. Thus mass transfer from the bulk of the solution (or to the bulk solution, for the products) plays a central role in electrochemical processes. As such the physical processes of mass transfer (diffusion, migration, and

convection; see Sec. IV.A.1) have received considerable attention in the electrochemical literature and are discussed separately in a later section of this chapter. For our purpose here, it is sufficient to know that mass transfer results in the creation of concentration profiles as a function of the distance from the electrode, as illustrated in Fig. 15. For most of the usual electrochemical situations these profiles extend over a few to a few tens of micrometers from the electrode surface. Beyond this region, called the diffusion layer, where mass transfer processes are effective, the solution is homogeneous (except for convective effects as in "homogeneous chemistry").

Thus a simple electrode reaction involves successively the following three steps: (1) mass transfer of the reactant from the bulk solution to the electrode; (2) electron transfer at the electrode surface; and (3) mass transfer of the product of the reaction from the electrode surface to the bulk solution. These three elementary steps may be perturbed by earlier or later chemical steps and by adsorption or desorption phenomena at the electrode surface. Each of these processes may become the rate-determining step or may interfere significantly in the overall kinetics. At first glance the situation then seems much more complicated than in homogeneous chemistry. Yet this is only an illusion because most of these steps have their exact counterparts in homogeneous chemistry. Mass transfer corresponds to the diffusion control of a chemical reaction as described. Earlier or later chemical steps are involved in most homogeneous electron transfer reactions. Adsorption and desorption are analogous to the formation of stable precursor or successor complexes. Electron transfer to or from an adsorbed species is very reminiscent of inner sphere reductions or oxidations. These analogies are not fortuitous; indeed, an electrode may be viewed as a gigantic molecule whose reducing or oxidizing power is adjustable at will.

C. Kinetics of Heterogeneous Electron Transfers

1. Mechanism and Theory of Outer Sphere Electron Transfers at Electrodes

In the following we consider an outer sphere electron transfer reaction involving the exchange of n electrons ($n > 0$ for reduction; $n < 0$ for an oxidation) in Eq. (96), taking place at an electrode whose potential is E.*

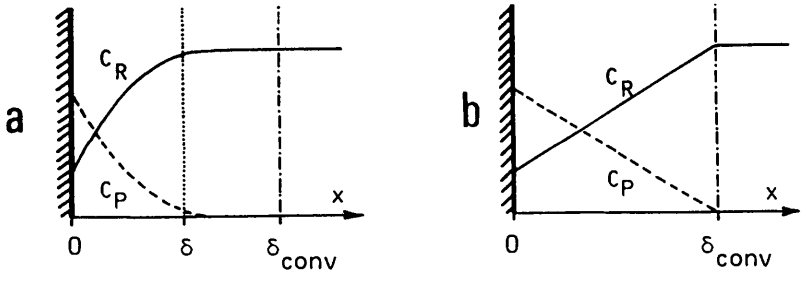


Figure 15. Concentration profiles for the reactant and the product as a function of the electrode distance x in (a) transient or (b) steady-state electrochemical techniques: δ and δ_{conv}, diffusion layer and stagnant layer thicknesses.

*From the discussion in Sec. III.A.1), $E = \Phi_W - \Phi_{Ref}$. Yet when E° is given vis-à-vis the same reference, the contribution of the reference cancels in the difference $E - E^\circ$. Thus in the following E is considered the electrode potential vis-à-vis that of the solution.

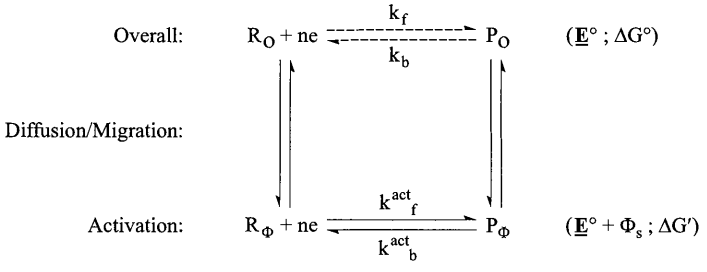
$$R + ne \rightleftharpoons P \qquad (E^\circ) \tag{96}$$

The electrode is supposed to have no particular interaction with R or P. Its surface area is hereafter designated by A.

Because in electrochemical reactions electron transfers occur near the electrode/solution interface, that is, at a two-dimensional surface, it is more suitable to refer to the number of moles converted per unit of time and unit of electrode surface area, dN_R/dt and dN_p/dt, rather than using concentrations as in homogeneous kinetics. Since there is no stable interaction with the electrode, $dN_R/dt = -dN_p/dt$. On the other hand, each mole of the reactant R electrolyzed corresponds to a charge nF transferred that affords the charge consumed per unit of time, that is, the current:

$$i = -nFA\frac{dN_R}{dt} = nFA\frac{dN_P}{dt} \tag{97}$$

Since the definition of E° in Eq. (96) refers to standard conditions, that is, conditions in which no external electrical field applies on the reactant or the product, it is more convenient to consider the act of electron transfer as a succession of three individual steps as outlined in Scheme 5, which is reminiscent of that in Scheme 3 established for the homogeneous analogous situation (Sec. II.C.1). In Scheme 5, R_0 or P_0 relates to R or P in the closest plane to the electrode where no electrical potential applies, that is, at the "end" of the diffuse layer,† denoted x_o in Fig. 14d. R_Φ and P_Φ relates to R and P at the site of electron transfer x_Φ, usually considered close to or slightly within the OHP, where an electrical potential Φ_s (i.e., the electrical potential at the electron transfer site) applies.



Scheme 5

Let $(R)_0$ and $(P)_0$ be the activities of R and P at x_o and $(R)_\Phi$ and $(P)_\Phi$ those at $x = x_\Phi$ (the electron activity is not considered because it is implicitly included in the potentials). For all the electron transfer reactions investigated up to now, the rates of the diffusion-migration steps in Scheme 5 do not limit the overall process. Although this may be of importance for the prediction of the maximal rate of electron transfer at an electrode, we do not consider the possible kinetic limitation by either of these physical processes (compare the diffusion control of an homogeneous electron transfer discussed earlier). Thus, within this restriction, the existence of the diffusion-migration processes involves only thermodynamic contributions. Thus the overall rate constants in Scheme 5, defined in Eq. (98),

†Note that this limit must not be confused with that of the diffusion layer/bulk solution interface, owing to the extreme differences in size: some tens of angstroms for the double layer and some tens of micrometers for the diffusion layer.

$$\frac{i}{nFA} = \frac{-dN_R}{dt} = \frac{dN_P}{dt} = k_f(R)_0 - k_b(P)_0 \tag{98}$$

are related to the true activation constants via the relationship in Eqs. (99) and (100) where ΔG_Φ^R and ΔG_Φ^P, are the respective free energy changes for R and P between the end of the diffuse layer and the electron transfer site.

$$k_f = k_f^{act} e^{-\Delta G_\Phi^R/RT} \tag{99}$$

$$k_b = k_b^{act} e^{-\Delta G_\Phi^P/RT} \tag{100}$$

Note that because of their definitions in Eq. (98), the heterogeneous rate constants are expressed in units of length per units of time (usually in $cm\,s^{-1}$ in the electrochemical literature). As for the homogeneous case, it is more convenient to separate the terms arising from electrical potential from those, ΔS_{pair}, of entropic nature, due to the formation of a pair electrode/molecule. Thus $\Delta G_\Phi^R = Z_R F\Phi_s - T\Delta S_{pair}$ and $\Delta G_\Phi^P = Z_p F\Phi_s - T\Delta S_{pair}$, where Z_R and Z_P are the respective ionic charges of R and P (note that $Z_P = Z_R - n$ because of the charge balance). On the other hand, k_f^{act} and k_b^{act} are obtained from the absolute rate constant theory as

$$k_f^{act} = \frac{kT}{h} e^{-\Delta G_f^{act}/RT}$$

$$k_b^{act} = \frac{kT}{h} e^{-\Delta G_b^{act}/RT}$$

This allows one finally to write the experimentally observed rate constants as in Eqs. (101) and (102):

$$k_f = Z_{el} e^{-Z_R F\Phi/RT} e^{-\Delta G_f^{act}/RT} \tag{101}$$

$$k_b = Z_{el} e^{-Z_P F\Phi/RT} e^{-\Delta G_b^{act}/RT} \tag{102}$$

where $Z_{el} = (kT/h)e^{\Delta S_{Pair}/R}$ is shown from classic statistic thermodynamics to be related to the collision frequency of a molecule on a wall [50], that is,

$$Z_{el} = \left(\frac{RT}{2\pi m}\right)^{1/2} \tag{103}$$

in which m is the molar mass of R or P. For most organic molecules, Z_{el} is of the order of approximately $2 \times 10^3\,cm\,s^{-1}$. Note, however, that no transmission coefficient [compare the κ terms in the homogeneous analog rate constants in Eqs. (58) and (59)] is included in Eqs. (101) and (102). Indeed, the orbital variety at an electrode surface is sufficiently wide for convenient overlap to occur with most organic molecules prone to outer sphere electron transfer, so that the adiabatic requirement is generally fulfilled. Moreover, Hale [77] estimated that electron transfers at an electrode are adabatic as soon as the electron transfer site is within 15 Å of the electrode surface, for most organic molecules.

Thus, determination of the rate constants in Eq. (101) or (102) requires only that of ΔG_f^{act}, since $\Delta G_f^{act} = \Delta G_f^{act} - \Delta G^{o'}$, $\Delta G^{o'}$ being the free energy of the electron transfer between R_Φ and P_Φ (compare Scheme 5):

$$\Delta G^{o'} = \Delta G^o - Z_R F\Phi_s + Z_P F\Phi_s = nF(E - E^o) - nF\Phi_s$$

that is,

$$\Delta G^{o'} = nF(E - E^o - \Phi_s) \tag{104}$$

The forward activation free energy is determined along the same lines as presented for homogeneous electron transfer since both problems are strictly equivalent [43,44,78,79]. Thus, ΔG_f^{act} is given as a function of the local driving force [$\Delta G^{o'}$ in Eq. (104)] and of the associated reorganization energy λ^{el} by the expression in Eq. (105), which derives from Eq. (64).

$$\Delta G_f^{act} = \frac{\lambda^{el}}{4}\left(1 + \frac{\Delta G^{o'}}{\lambda^{el}}\right)^2 \tag{105}$$

Again λ^{el} involves two contributions, of inner shell λ_i^{el} and outer shell λ_o^{el} nature, but these are contributions that relate only to the R/P couple since the electrode is not affected by the electron transfer. λ_i^{el} may be evaluated from bond length and bond angle variations, as is its homogeneous analog in Eq. (67).

For the evaluation of λ_o^{el}, the same model as in the homogeneous case is used, yet the electrode is replaced by the electrical image of reactant for the initial system (or that of the product for the final system) through the electrode, which acts as a electrostatic mirror. However, since these images are imaginary, only the real contributions are considered for the final evaluation of λ_o^{el}, given in Eq. (106).

$$\lambda_o^{el} = N_A \frac{e^2}{8\pi}\left(\frac{1}{\varepsilon_{op}} - \frac{1}{\varepsilon_s}\right)\left(\frac{1}{a_R} - \frac{1}{r_\Phi}\right)n^2 \tag{106}$$

In Eq. (106), a_R is the equivalent radius of R (or P) and r_Φ is the distance between the centers of the R (or P) molecule and its electrical image when R (or P) is at the electron transfer site. In practice, Marcus approximates r_Φ by $2a_R$, assuming that the molecule is in contact with the electrode surface when at the electron transfer site. Thus it follows that λ_o^{el} is given in Eq. (107) [43a,b]:

$$(\lambda_o^{el})_{Marcus} = N_A \frac{e^2}{8\pi}\left(\frac{1}{\varepsilon_{op}} - \frac{1}{\varepsilon_s}\right)\frac{1}{2a_R}n^2 \tag{107}$$

Hush [78c] disagrees with the formulation in Eq. (106), considering that the solvent polarization does not affect the potential in the double layer, the compact layer acting as an electrostatic Faraday cage. Thus the incidental solvent fluctuations energetically affect only R or P, without consideration of their images [note that this amounts to considering r_Φ as infinite in Eq. (106)]. Thus Hush proposed the expression in Eq. (108) for the outer shell reorganization energy:

$$(\lambda_o^{el})_{Hush} = N_A \frac{e^2}{8\pi}\left(\frac{1}{\varepsilon_{op}} - \frac{1}{\varepsilon_s}\right)\frac{1}{a_R}n^2 \tag{108}$$

Interestingly, the Marcus heterogeneous reorganization energy $(\lambda_o^{el})_{Marcus}$ in Eq. (107) is exactly half that, λ_o^{RR}, of the homogeneous isotopic electron transfer:

$$R^* + P \rightleftharpoons P^* + R$$

whereas that proposed by Hush is identical to λ_o^{RR}. Based on this analogy, an elegant series of experiments by Kojima and Bard [80] led to the conclusion that Hush's reorganization energy is more adequate [81].

Introduction of $\lambda^{el} = \lambda_o^{el} + \lambda_i^{el}$ in Eq. (105), when taking into account Eqs. (104), (101), (102), and (98), allows the expression of the current to be predicted as in Eq. (109), where k(E) is the apparent rate constant for an electrode potential E. k(E) is given in Eq. (110) under a formulation modeled on that of the empirical Volmer and Butler law [82], where the transfer coefficient α is given in Eq. (111).

$$i = nFAk(E)[(R)_0 - (P)_0 e^{nF[E-E^\circ]/RT}] \tag{109}$$

$$k(E) = k_t^0 e^{(\alpha n - Z_R)F\Phi_s/RT} e^{-\alpha nF(E-E^\circ)/RT} \tag{110}$$

$$\alpha = \tfrac{1}{2} + \frac{F(E - E^\circ - \Phi_s)}{4\lambda^{el}} \tag{111}$$

The true standard heterogeneous rate constant k_t^0 is expressed in Eq. (112) as a function of λ^{el}. Yet note that usually the intrinsic standard heterogeneous rate constant k^0 in Eq. (113) is defined and used rather than k_t^0.

$$k_t^0 = Z_{el} e^{-\lambda^{el}/4RT} \tag{112}$$

$$k^0 = k_t^0 e^{(\alpha n - Z_R)F\Phi_s/RT} \tag{113}$$

Provided the exponential term in Eq. (113), called the Frumkin correction, is invariant with E, that is, when Φ_s does not depend on the electrode potential, both are constant and characterize the R/P electron transfer independently of the electrode potential. Otherwise k_t^0 is preferred. In the following we nevertheless use k^0 for simplicity in the formulations.

2. The Transfer Coefficient α

The formulation in Eq. (110) shows that the apparent heterogeneous rate constant k(E) depends on the potential. This dependence has been observed experimentally since the earliest times of electrode kinetics and is at the origin of the so-called Tafel plots [83]. Indeed, when the potential E is sufficiently different from E°, for example $nF(E - E^\circ) \ll 0$, the term relative to $(P)_0$ in Eq. (109) vanishes and the current is given by Eq. (114).

$$i = nFAk(E)(R)_0 = nFAk^0 e^{-\alpha nF(E-E^\circ)/RT}(R)_0 \tag{114}$$

When $(R)_0$ is maintained constant, then a plot of the logarithm of the current versus the potential yields a straight line of slope $\alpha nF/RT$, provided that α is constant. Thus such observations led Butler and Volmer, two pioneers in this area, to propose an empirical law [82], named after them, in the form of Eq. (109), with α an adjustable constant parameter. α is called the transfer coefficient after the following observation: when the driving force, that is, $-nF(E - E^\circ)$ in Eq. (114), is increased, only a fraction α of the additional energy is used to increase the apparent rate constant. Thus, α is the fraction of the driving force transferred for kinetic purposes and plays a role identical to that of the Brönsted coefficient in organic chemistry (Sec. II.C.6).

From Eq. (111) it is seen that, provided that λ^{el} is large enough, α remains constant with the potential and is close to 0.5. This is generally in agreement with observations dealing with reactions with low values of k_t^0 [compare the λ^{el} term in Eq. (112)]. However, for organic molecules with small inner shell contributions and rather large radii, $\lambda^{el}(\approx \lambda_o^{el})$ is not expected to be extremely large, and therefore variations of α with the potential should be observed. This is indeed the case in practice [84], as illustrated by the curvature

of the logarithmic plot of k(E) with the potential in Fig. 16 for the reduction of 2-methyl-2-nitropropane, in DMF at the HMDE [84].

$$(CH_3)_3C - NO_2 + e \rightleftharpoons (CH_3)_3C - NO_2^- \tag{115}$$

Moreover, the plot of the corresponding $\alpha(E)$ variations in Fig. 16b shows that α depends linearly on the potential with a slope ($0.249\,V^{-1}$), in close agreement with that predicted ($0.210\,V^{-1}$) from the Marcus reorganization energy (29 kcal/mol) determined from Eq. (107).

3. Reversible and Irreversible Electron Transfers: Their Role in the Meaning of Oxidation or Reduction Potentials

From the current expression in Eq. (109), it is seen that when k^0 is extremely large, the bracketed term on the far right must tend to zero in order that the current remain finite. Thus in these conditions,*

$$(R)_{x=0} \approx (P)_{x=0} e^{nF(E-E^\circ)/RT}$$

which may be written under the form of the classic Nernst law in Eq. (116). Thus, provided the heterogeneous rate constant is large ($> 0.1\,cm\,s^{-1}$), the electron transfer is controlled entirely by thermodynamics and the relative activities of the oxidant and the reductant at the electrode surface obey the Nernst law in Eq. (116). The electron transfer is thus termed *reversible* or *nernstian*.

$$E = E^\circ + \frac{RT}{nF} \ln \frac{(R^0)_{x=0}}{(P)_{x=0}} \tag{116}$$

In other words, when $(R^0)_{x=0}$ and $(P)_{x=0}$ are kept constant, because of a large excess of material at the electrode surface, for example, the electrode potential is given in Eq.

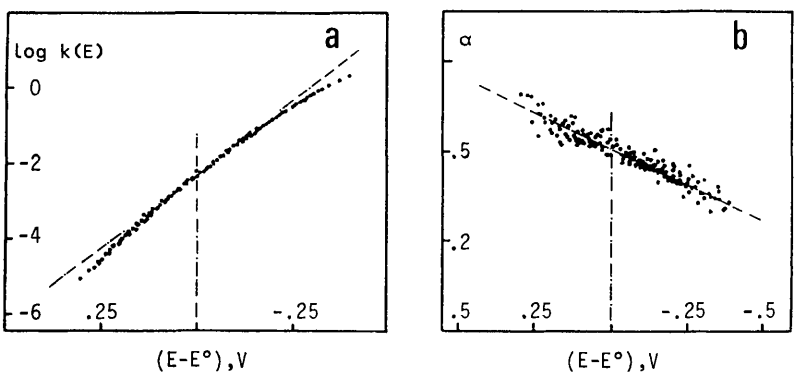


Figure 16. Variations in the apparent heterogeneous rate constant k(E) in Eq. (110) with the electrode potential for the reduction of $(CH_3)_3C - NO_2$ in DMF at the hanging mercury drop. A dashed line with slope 0.5 is positioned at $E = E^\circ$ to emphasize the curvature. (b) Resulting variations in the transfer coefficient α in Eq. (111). (Experimental data from Ref. 84b.)

*Hereafter, $(R)_0$ and $(P)_0$ are considered the activities at the "electrode surface" and denoted $(R)_{x=0}$ and $(P)_{x=0}$ to recall this definition, x being the distance from the electrode.

(116) independently of the current flow. Such an electrode is then suitable for use as a reference electrode (large k^0, large surface area A, and excess of material).

Conversely, when k^0 is extremely small, the current flow is negligible in the potential range around E°. Thus, in order that a measurable current may flow, the value of $E - E^\circ$ must be significantly increased [compare k(E) in Eq. (110)]. For example, in order that a cathodic current ($n > 0$) be observed, E must be considerably more negative than E°. Thus, in Eq. (109), $e^{nF(E-E^\circ)/RT} \longrightarrow 0$ in the potential range where the wave is observed, and Eq. (109) can be rewritten as in Eq. (117):

$$i = nFAk^0 e^{-\alpha nF(E-E^\circ)/RT}(R)_{x=0} \tag{117}$$

Similarly, the observation of an anodic current requires that E is considerably positive to E°. Then in the potential range where an anodic current is observed, $e^{nF(E-E^\circ)/RT} \longrightarrow \infty$, and Eq. (109) becomes

$$i = -nFAk^0 e^{(1-\alpha)nF(E-E^\circ)/RT}(P)_{x=0} \tag{118}$$

In these situations the current flow is entirely controlled by the kinetics of the heterogeneous electron transfer, which is then said to be *slow* or *irreversible*. The current-potential characteristic of the redox couple under study then reflects thermodynamic (E°) and kinetic (k^0) properties. Indeed, the driving force $E - E^\circ$ is used to overcome not only thermodynamic but also kinetic limitations.

In this presentation we discussed the reversible or irreversible nature of the electron transfer on an absolute basis. Yet in practice the notion of "measurable" current flow is obviously related to a given scale. In electrochemistry the usual scale referred to is based on the mass transfer rate. Thus for a given mass transfer rate, a given current density is expected to flow through the electrode. This limit is defined by the current density that would be observed if the electron transfer under investigation is nernstian. Within this context it is easily understood that any electron transfer is nernstian at very low mass transfer rates. Similarly, it should become slow or irreversible for large mass transfer rates, because then the current scale is made very high. In practice, the largest mass transfer rates currently achievable with standard equipment are such that if $k^0 > 0.1\ \text{cm s}^{-1}$ the electron transfer may be considered "intrinsically" nernstian.

A second point not considered in the discussion is related to the possible involvement of chemical reactions. For the sake of simplicity, let us restrict the presentation to the most common situation in which the product P formed upon electron transfer is consumed by a fast chemical step, as outlined in Scheme 6.

$$R + ne \underset{k_b}{\overset{k_f}{\rightleftharpoons}} P \longrightarrow \cdots$$

Scheme 6

It is easily seen from this simple representation that as soon as the rate of the chemical removal of P is larger than that of the back electron transfer, the rate-determining step of the overall process is the forward electron transfer. Thus, independently of the intrinsic value of k^0, the Butler-Volmer law in Eq. (109) simplifies to that in Eq. (117), because $(P)_{x=0}$ is made negligible. As a result, the R/P electron transfer presents all the kinetic characteristics of a slow electron transfer [85]. However, since this behavior is not related to the intrinsic value of k^0, the current-potential curve may be observed in the close vicinity of E° or even positive to E° for a reduction (negative to E° for an oxidation) [81]

D. Adsorption Phenomena

Many solutes or follow-up products of electrochemical reactions may have a large tendency to adsorb on electrode surfaces [86]. This may be related to long-range electrostatic interactions, such as those discussed in the presentation of the double layer; there is then no specificity of the ions attached, particularly as concerns their chemical properties. In such cases the phenomenon is said to be *nonspecific* and is akin to nonspecific salt effects or ion pairing in organic chemistry. On the other hand, because of particular chemical affinities between the electrode surface and a substrate, *specific adsorption* occurs, which involves generally strong interactions and may result in the creation of organic layers at the electrode surface. Analogies of the latter are given by complexation reactions or specific salt effects (e.g., Li^+ with an enolate ion or Bu^-Li^+ solutions) in organic chemistry or chemisorption and physisorption in heterogeneous catalysis.

Both classes are distinct because of the nature of the electrode-adsorbed species interactions. Yet from a phenomenological point of view, a better classification seems to be that based on the possible electroactivity or conductive properties of the adsorbed material.

When adsorbed, electroinactive species usually give rise to partial or total blocking of the electrode surface, which may then not be able to effect electron transfers to other electroactive molecules. Thus depending on the nature of the electrode coverage, various phenomena may be observed, ranging from an apparent decrease in the electrode surface (large and separated islands of adsorbed species) to an apparent decrease in the electron transfer rate but with the appearance of unchanged electrode surface area (micrometric islands at micrometric distances from each other) [87]. Related also to this class is the "natural" blocking of electrodes by oxide layers or functional groups at carbon electrodes [88].

Conducting (via electrons or via permeation of electroactive species) adsorbed species usually introduce small disturbances in electrochemical behavior compared with the former class. Yet obviously the diffuse layer is extremely affected vis-à-vis the bare electrode. Thus the rate constants k^0 may be modified to a high degree* because of large changes in the Frumkin correction. Such effects may easily explain, at least on a qualitative basis, the well-known dependence of k^0 on the size of the supporting electrolyte cation (reductions) or anion (oxidations), as well as on ionic additives [89].

The third class involves electroactive adsorbed species, yet it also encompasses the case in which, although originally inactive, the species is activated or modified in the adsorption process to give rise to the formation of electroactive adsorbed molecules. Obviously, all these effects discussed for the two previous classes are observed for this class, but additional effects are observed for the adsorbed species itself. Indeed, adsorption modifies (1) the concentration of the species at the electrode surface vis-à-vis that predicted from its bulk concentration, and (2) the energetics of the electron transfer reaction. The latter point arises because of additional thermodynamic contributions to be considered in the R_0/R_Φ or P_0/P_Φ equilibria in Scheme 5 and also from changes in the reorganization energies. The former point leads to a variety of behaviors, since it is obviously a function of the kinetics of adsorption-desorption phenomena. A third additional effect of electroactive adsorbed species arises from their possible ability to act as electron transfer med-

*Note that for $n = 1$, an increase by 0.2 V in Φ_s results in the multiplication of k^0 by approximately 50 when $\alpha = 0.5$, and by approximately 350 when $\alpha = 0.75$, as determined from Eq. (113).

iators for other species that are reduced or oxidized with more difficulty. This special class (the term "electrode modification" is then more adequate), is at present a very active area of research.

E. Coupled Chemical Reactions

1. Electrochemical Versus Homogeneous Chemical Reactivities

In the preceding sections of this chapter, much attention was devoted to the essential act of electron transfer. Yet although being, for fundamental or analytic purposes, the subject of a large body of the electrochemical literature, pure electron transfer reactions generally are of less interest in terms of preparative electrochemistry. In the opinion of this author, electron transfer at an electrode must be considered as a particular class of activation of molecules to enhance their chemical reactivity. As such, electrode kinetics must be understood (as for other methods of chemical activation) in order to control and eventually direct the overall process to the selected target (compare Chapter 3).

From the preceding discussion, it should appear that electrochemistry affords a very facile and precise way to generate highly energetic intermediates via control of the electrode potential. Note in this respect that one electron exchanged over a potential difference of 1 V amounts to injecting 1 eV in a molecule, that is, approximately 23 kcal/mol. Owing to the possibility of performing electrochemisry over potential differences of several volts, it is easily seen that the method may involve energies comparable to those of most chemical bonds and largely beyond most activation energies. Thus highly energetic intermediates may be generated under mild and precisely controlled conditions. Another useful aspect of electrochemical generation of chemical intermediates is related to the current flow through the cell. Indeed, the current is a direct measure of the production rate of the intermediate. It ensures that the production rate, an important parameter in product selectivity, is easily controlled and adjusted.

At this point, two questions must be addressed: Are these intermediates identical to those obtained under usual chemical conditions? Do they react under conditions matching those of homogeneous experiments?

The answer to the first question is obviously positive. Indeed, since the substrates are generally neutral, the primary electron transfer affords paramagnetic intermediates (anion or cation radicals) that may undergo selected cascades of reactions to afford most of the well-identified intermediates of organic chemistry: radicals, carbocations, carbanions, carbenes, and so on. Neutral radicals may also be generated by reduction or oxidation of stable cations or anions, respectively. It is thus seen that all the basic intermediates of organic chemistry may be electrochemically generated, provided an electroactive precursor exists. Yet this is not always a serious limitation, since the intermediates sought may be eventually formed indirectly, that is, through an electroactive proreagent, as discussed elsewhere in this book (Chapter 29).

The second question is more difficult to answer. Indeed, since the electrical perturbation extends only over a few angstroms from the electrode surface, the medium in which the electrogenerated intermediates react is identical to the bulk of the solution, which favors a positive answer. On the other hand, they react under essentially nonisotropic conditions because of the existence of concentration profiles, that is, of concentration changes with distance of the electrode (see Fig. 15). Yet this is a situation identical to that encountered when heterogeneous reagents or polyphasic conditions are used in usual "homogeneous" chemistry. A more serious difference is related to the nature of the media

often used under electrochemical conditions. As explained in the section devoted to ohmic drop effects, electrochemical solutions must generally be rather conducting, a requirement met by using solvents with rather high dielectric constants (see Chapter 5). Thus although solvents, such as liquid ammonia, or media with smaller dieletric constants, such as methylene chloride, THF, DME, or even arenes and alkanes, can be used [90,91], the preference of most organic electrochemists is for convenience or by tradition, to such solvents as acetonitrile and dimethylformamide. The latter are prone to intervene in the reaction paths of the electrogenerated intermediates via their nucleophilic or acidobasic properties, for example, as well as via hydrogen atom transfers to radicals [92]. The same is true for the so-called inert electrolytes, frequently quaternary ammonium salts, known for their acidic (Hofman reaction) abilities, as well as for being relatively good hydrogen atom donors. Thus the usual electrochemical media may induce reaction paths that are quite different from those observed with identical intermediates under conventional organic conditions. We want to emphasize, however, that this is not to be viewed as a limitation of the method. Indeed, these induced reaction paths may be used with great profit, as in organic chemistry when methanol is used as the solvent to incorporate methoxy groups. Several examples of this strategy are given in various places in this book. On the other hand, as mentioned earlier, a large variety of solvent-electrolyte systems may be used in electrochemistry [71,90], although the general body of reported data pertains to a limited class of media.

2. Chemical Reversibility and Irreversibility: Their Role in the Meaning of Oxidation or Reduction Potentials

When considering a simple electron transfer reaction at an electrode, as in Eq. (119), one can conceive easily that there are, a priori, four limiting situations in which chemical reactivity may affect the electrochemical measurements: R may be consumed or produced and P may be consumed or produced.

$$R + ne \rightleftharpoons P\ (E^\circ) \tag{119}$$

In practice all four possibilities may be combined, which leads to a large variety of electrochemical mechanisms. Thus our purpose in this section cannot be quantitative if we wish to keep some generality. We want, however, to describe qualitatively the role and the effect of chemical reactions on the overall electrode kinetics. Thus for the sake of simplicity, we discuss the case of simple EC (electrochemical-chemical steps; see Sec. III.E.3) sequence, in Eqs. (120) and (121) as a typical example:

$$R + ne \rightleftharpoons P\ (E^\circ, k^0, \alpha) \tag{120}$$

$$P \longrightarrow \cdots \quad (k) \tag{121}$$

The chemical step in Eq. (121) is homogeneous and thus intervenes while P, which is formed at the electrode, is transported to the bulk of the solution via the mass transfer mechanisms discussed earlier. From this simple consideration, it is easily understood that an important factor is the relative magnitude of the rate constant of the chemical reaction vis-à-vis that of mass transfer, as outlined in Scheme 7.

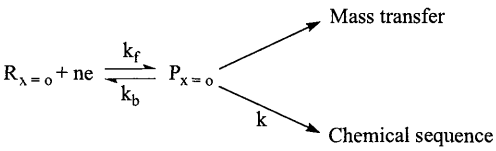
Obviously, when the mass transfer rate is much larger than that of the chemical steps, the transfer of P from the electrode surface to the bulk solution is not affected by the presence of kinetics. Thus the electrochemical behavior of the EC sequence in Eqs. (120) and (121) is identical to that of a simple electron transfer mechanism. The R/P electron

transfer is then said to be chemically reversible* but may be nernstian or slow, according to the magnitude of k^0 in Eq. (120).

In the converse situation, three limiting cases may be observed. In the first case the electron transfer is intrinsically slow. The RDS of the overall process is then the forward electron transfer, and the redox system is said to be slow and chemically irreversible. The electrochemical wave is then observed at potentials sufficiently different from E° for $n(E - E^\circ) \ll 0$ (Sec. III.C.3). The two other situations are encountered when k^0 is large enough for the electron transfer to be nernstian in the absence of the follow-up chemical step.

When, although vis-à-vis the mass transfer rate, the chemical reaction is slow compared with the backward electron transfer, the reduction or oxidation in Eq. (120) remains at equilibrium. The electrode potential is then given by the Nernst law in Eq. (122):

$$E = E^\circ + \frac{RT}{nF} \ln \frac{(R)_{x=0}}{(P)_{x=0}} \tag{122}$$



Scheme 7

Yet because of the chemical reaction, the activity of P at the electrode surface is considerably decreased. From Eq. (122) it is seen that the electrode potential is then positive (for a reduction; negative for an oxidation) to that observed for the same current density, but in the absence of the follow-up reaction. As a result the current-potential characteristic is observed in a potential range positive to E° for a reduction and negative to E° for an oxidation. The system is then said to be nernstian and chemically irreversible.

In the last situation the rate of back electron transfer, although intrinsically fast, is slower than that of the chemical step. Thus as in the first situation, the RDS is the forward electron transfer, and the redox system is said to be slow and chemically irreversible. Yet since k^0 is large, the electrochemical wave is observed before E° [81,85].

From this description it is seen that, depending on the exact degree of competition between the four rates in Scheme 7, the electrochemical wave is observed in potential ranges that may be positive or negative to E°, as summarized in Table 4. Without a quantitative treatment of the pertinent electrochemical data, it is almost impossible to decide the position of E° vis-à-vis the potential location E_w, where the wave is observed. This is an important caveat to remember when using potential data, such as peak potentials or half-wave potentials, instead of E° values. The experimental difficulty is even more severe in practice. Indeed, when one considers a series of related chemicals, there are great chances that E°, k^0, and k vary uniformly with respect to each other because they relate intimately to the orbital energy and characteristics of the acquired (LUMO) or lost

*To avoid possible confusion with the "reversible" or "irreversible" nature of the electron transfer step per se, we suggest that reversibility or irreversibility be reserved to the chemical part and the electron transfer be designated by "nernstian" or "slow," respectively. In the following we use this terminology.

Table 4 Nature and Location[a] of the Electrochemical Wave Observed for an EC Sequence[b] as a Function of the Mass Transfer Rate

k versus mass transfer rate	k^0 versus mass transfer rate	
	Small	Large
Small	Slow reversible,[c] $n(E_w - E^\circ) < 0$	Nernstian, reversible,[c] $E_w \approx E^\circ$
Large	Slow, irreversible,[c] $n(E_w - E^\circ) < 0$	Nernstian or slow irreversible,[c] $n(E_w - E^\circ) > 0$

[a] E_w, any characteristic potential of the wave: $E_{1/2}$, E_p, $E_{p/2}$, $\cdots$; E°, standard reduction potential of the electron transfer step, involving an exchange of n electrons ($n > 0$ for a reduction; $n < 0$ for an oxidation). [b] k^0, intrinsic standard heterogeneous rate constant; k, rate constant of the homogeneous follow-up chemical reaction. [c] Chemically reversible or irreversible (see footnote page 55).

(HOMO) electron [16,29]. Thus, the potential E_w at which the electrochemical wave is observed may correlate with E°, since it depends on the three figures. Such a case is presented in Fig. 17 for the series of akylbenzenes [29] already mentioned in this chapter, in which the peak potentials of the chemically irreversible voltammograms (at $0.1\,V\,s^{-1}$) correlate with E° with a slope close to unity.

To conclude this section we discuss the special case of follow-up equilibria, that is, when the chemical step in Eq. (121) is reversible [93].

$$R + ne \rightleftharpoons P \rightleftharpoons Z \quad (E^\circ,\ k(E);\ k_f,\ k_b)$$

Obviously, when $K = k_f/k_b \ll 1$, the equilibrium lies toward P and does not affect the R/P electron transfer. In the converse situation, and when k_f and k_b are larger than the mass transfer rate, a rapid equilibrium displaced toward Z establishes, and $(P)_{x=0} \approx (Z)_{x=0}/K$. Introduction of this relation in the current rate law [Eq. (109)] then yields Eq. (123), which is identical in its formulation to a Butler-Volmer law but for a

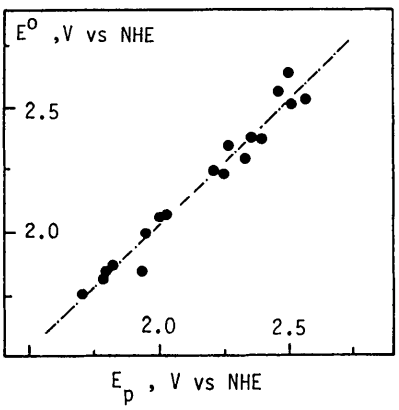


Figure 17. Correlation between E° and anodic peak potentials E_p of the chemically irreversible cyclic voltammograms at $v = 0.1\,V\,s^{-1}$ for an extended series of alkylbenzenes. (Data from Ref. 29.)

hypothetical electron transfer $R + ne \rightleftharpoons Z$, whose formal potential is $E^{o'} = E^o + (RT/nF)\ln K$, as evidenced by the formulation in Eq. (124).

$$i = nFAk(E)[(R)_{x=0} - (Z)_{x=0}e^{nF(E-E^o)/RT}/K] \tag{123}$$

$$i = nFAk(E)[(R)_{x=0} - (Z)_{x=0}e^{nF(E-E^{o'})/RT}] \tag{124}$$

This constitutes the basis of the operational significance of formal potentials introduced in Sec. II.B.5. Yet the formal analogy between Eqs. (109) and (124) should not mask the fact that k(E), that is, α, k_t^0, or k^0 in Eq. (124), remains related to the real electron transfer $R + ne \rightleftharpoons P$, that is, to E^o, not to $E^{o'}$, [compare Eqs. (110) through (113)].

3. Classification of Coupled Chemical Reactions

From this discussion, it is seen that the electrochemical behavior of a given electron transfer reaction may be extremely perturbed by the intervention of coupled chemical steps. The resulting modifications obviously depend on the exact nature of the chemical sequence associated with the electron transfer step. It is thus convenient to classify the different possible reaction schemes that may arise. Yet as in organic chemistry, for the basic mechanisms (e.g., S_N1, S_N2, E_1, and E_2) such a classification is viewed as a general frame to which real mechanisms are referred. Indeed, the latter may often be more subtle (compare, e.g., S_{Ni} or E_{1cb} vis-à-vis the mechanisms mentioned earlier) or involve cooperative or competitive combinations of the elementary schemes presented later. A second similarity with the organic basic schemes is that there is no unity in the denominations of the various sequences of electron transfers and chemical steps. Indeed, each school or laboratory has proposed its own nomenclature, which has received a different audience and may have evolved with time. In the following we use as much as possible the most frequent designations, and when not possible we refer to the nomenclature used in Savéant's group, owing to its large contributions to this area [94].

The following classification is based upon the fact that electrochemical behavior depends on the location of the electron transfer step in the overall sequence. Also, electron transfer steps are considered to involve the exchange of a single electron, that is, $n = \pm 1$ ($n = 1$ for a reduction and $n = -1$ for an oxidation), a normal situation in organic electrochemistry. Indeed, although overall stoichiometries involving the net exchange of many electrons are frequently observed, the energetic and activation requirements for a direct polyelectron transfer are too high for any to exist concurrently with a rapid succession of single-electron transfer steps.

Within this frame, the most frequently encountered situations are the following.*

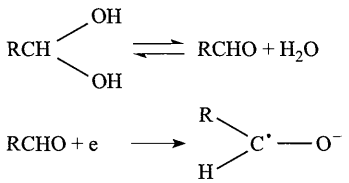
Preceding Chemical Reaction: CE Mechanism.

$$Z \rightleftharpoons A \left(k_f, k_b, K = \frac{k_f}{k_b}\right) \quad (C)$$

$$A + ne \rightleftharpoons B\ (E^o) \quad (E)$$

*E is a heterogeneous electron transfer; C, a chemical step; also, A, B, and so on, designate the electroactive molecules or their reaction products, whereas Y, Z, and so on, relate to coreactants or nonelectroactive species.

The electroactive species A is generated by a reaction, generally an equilibrium displaced toward Z, that precedes the electron transfer step. Z is the reactant introduced in the cell or the predominant form of the reactant in the reaction medium. These reaction schemes were introduced to rationalize the various electrochemical phenomena observed during the reduction of certain aldehydes in aqueous solutions. Indeed, in water, formaldehyde, π-electron-poor heterocyclic aldehydes, and a few aldehydes with strongly electron-attracting groups exist as their nonreducible hydrated form in rapid equilibrium with the reducible carbonyl:

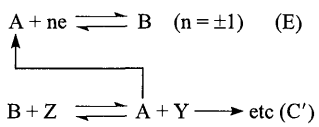


When the rate of the $Z \rightleftharpoons A$ interconversion is slow vis-à-vis the rate of mass transfer,* it acts as the RDS for the overall sequence. The currents observed are then abnormally low for the mass transfer rate and reactant concentration considered and are said to be kinetic currents.

Conversely, when both rates are fast, the preceding chemical reaction acts as a rapid pre-equilibrium, and $(A) = K(Z)$. The electrochemical data are then formally identical to that of the virtual $Z + ne \rightleftharpoons B$ electron transfer, with a formal potential

$$E^{o'} = E^{o} - \frac{RT}{nF} \ln \frac{K}{K+1}$$

Redox Catalysis or Mediated Electron Transfer: EC′ Mechanism.



In this sequence, the A/B couple acts as an electron transfer mediator, which allows the reduction or the oxidation of the electroinactive (at the A/B wave potential) Z species. The electroactive species A is regenerated via the homogeneous electron transfer step C′, which results in a considerable enhancement of the current observed for the A/B wave as soon as the C′ step is rapid.

Various subclassifications exist according to the exact nature of the chemical step, which may eventually be a succession of elementary steps with formation of intermediate products. As explained earlier for the displacement of endergonic electron transfer steps, the C′ step occurs because it is continuously pulled to the right by the further chemical reaction of the Y species. Note that Chapter 28 is devoted to this class of mechanisms.

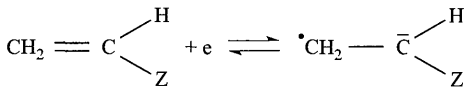
Consecutive Reaction: EC Mechanism.

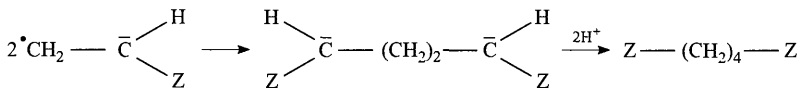
$$A + ne \rightleftharpoons B \qquad (n = \pm 1) \quad (E)$$

$$B \longrightarrow C \qquad (C')$$

*In the following, "rapid," "fast," and "slow" always refer to the rate of mass transfer.

This sequence is one of the most ubiquituous in organic or organometallic chemistry and has already been discussed in preceding parts of this section. The chemical step may involve reactions (or a succession of chemical reactions) of high-order molecularities, not only first-order reactions as suggested by the notation. Classic examples are given by activated olefin electrohydrodimerization mechanisms:





a. Multielectron Reactions: ECE and Related Mechanisms. As explained earlier, a direct exchange of many electrons at the same redox center appears to be extremely difficult because of energetic and activation requirements. From the formulation in Eq. (106), it is indeed noted that the exchange of 2e involves a reorganization energy λ_o^{el} four times larger than that for a single-electron exchange at the same center. For this reason and because of the free energy relationship in Eq. (105), a two-electron step without formation of an intermediate should correspond to a slower process than the corresponding EE sequence in Eq. (125):

$$A + 2e \rightleftharpoons A^{-} + e \rightleftharpoons A^{2-} \qquad (125)$$

On the other hand, in the second step of this sequence, the electron is transferred to a molecule with an additional negative charge compared with A. Thus at least a coulombic repulsion term must be overcome, which implies that the second electron transfer is necessarily performed at a more negative potential than the first (by at least 0.250 V for an equivalent radius of 2 Å for the redox centers, and for example, $\varepsilon \approx 37.5$ for acetonitrile as the solvent). As a result, the overall EE sequence should not be observed at the potential of the A reduction but should occur in two separate waves.

However, there are two ways in which this conclusion may be invalid, and both need the relay of a chemical reaction.

The first possibility is that the reorganization energy associated with the first electron transfer is considerably larger than that of the second. Such a difference is obviously not related to the outer shell components, which are necessarily close, as evidenced by Eq. (106). Thus the origin for the differences must be sought in the inner shell reorganization energy, which implies that a profound molecular reorganization must be involved during the first electron transfer. Examples of this situation are given by the numerous cases in which two redox centers are electronically coupled in the same molecule, as in $O_2N - (CH_2)_n - NO_2$. Similarly, for inner sphere electron transfers, the molecular moiety bearing the negative charge may be lost, leaving a neutral and easily reducible species. This is so in the reduction of alkyl halides to alkanes:

$$RX + e \longrightarrow R^{\cdot} + X \qquad (E_1)$$

$$R^{\cdot} + e \longrightarrow R^{-} \qquad (E_2)$$

$$R^{-} + H^{+} \longrightarrow RH \qquad (C)$$

in which the first electron transfer is induced by the carbon-halogen bond cleavage and affords an easily reducible neutral radical [95].

However, for most organic electroactive molecules, such large reorganization energies cannot be invoked, owing to the extended delocalization of the orbitals participating in electron transfers. Yet the interposition of a chemical step between the two electron transfers results in the same effect, as soon as the chemical reaction gives rise to a species more easily reducible (or oxidizable, in oxidations) than the starting reactant.

$$A + ne \rightleftharpoons B \quad (E_1^\circ) \qquad (E)$$

$$B \longrightarrow C \qquad (C)$$

$$C + ne \rightleftharpoons D \quad (E_2^\circ; n(E_2^\circ - E_1^\circ) > 0) \quad (E)$$

The intermediate formed is then reduced (or oxidized) at the electrode or in the solution owing to the large exergonicity of the resulting reaction:

$$B + C \longrightarrow A + D \quad (\Delta G^\circ = -nF(E_2^\circ - E_1^\circ) \ll 0) \quad (DISP)$$

In the former case (second electron transfer at the electrode), the overall sequence is termed ECE; it is designated a "DISP" (rather than an ECDisp) mechanism in the second case because the homogeneous electron transfer step is close to being a disproportionation reaction. Indeed, the latter involves an electron transfer between two chemically related molecules with the same oxidation numbers. In practice the distinction between the two mechanisms is nearly impossible on experimental grounds [96] because their rate-determining step, the B⟶C reaction is identical.

A typical example of this sequence is given by the reduction of aromatic halides:

$$ArX + e \rightleftharpoons ArX^{\cdot -}$$

$$ArX^{\cdot -} \longrightarrow Ar^{\cdot} + X^-$$

$$Ar^{\cdot} + e \longrightarrow Ar^- \quad \text{and/or} \quad Ar^{\cdot} + ArX^{\cdot -} \longrightarrow Ar^- + ArX$$

$$Ar^- + H^+ \longrightarrow ArH$$

As in the EC electrochemical sequence, a large variety of mechanisms belong to the general ECE-DISP frame and differ according to the exact molecularity of the interposed chemical step, which may also be a succession of elementary steps. Similarly, cascades of ECECE... sequences are possible, as in the classic reduction of nitro derivatives to hydroxylamines, which involves four electrons and four protons [97]:

$$Ar - NO_2 + 4e + 4ROH \longrightarrow Ar - NH - OH + 4RO^- + H_2O \qquad (126)$$

b. Zero-Electron Reactions: Electron Transfer Catalysis of Chemical Reactions. In the preceding ECE sequence, both electron transfers are of the same kind, that is, both reductions or oxidations, and thus their combination gives an increase in the absolute value of the number of electrons exchanged. Yet when the second electron transfer is of a nature opposite to the first, the overall number of electrons consumed is zero. Thus the sequence amounts to an electron transfer catalysis of a nonredox chemical reaction [98], as outlined in the following sequence:

$$A + ne \rightleftharpoons B \qquad (E)$$

$$B \longrightarrow C \qquad (C)$$

$$C - ne \longrightarrow D \quad \text{and/or} \quad C + A \longrightarrow D + B \qquad (E)$$

Naturally, such mechanisms are observed only when the overall $A \longrightarrow D$ reaction is exergonic but is considerably slower than that occurring at the level of the reduced or oxidized states B and C. Although rather recent in the electrochemical literature, these processes have been shown to be general and to encompass a large variety of chemical reactions. Among the most documented in the $S_{RN}1$ reaction, which amounts to an aromatic nucleophilic substitution. Although initially postulated by Bunnett [99a], the confirmation and the subtleties of its mechanism have been established on electrochemical grounds [100]:

$$ArX + e \longrightarrow ArX^{\cdot -}$$

$$ArX^{\cdot -} \longrightarrow Ar^{\cdot} + X^{-}$$

$$Ar^{\cdot} + Nu^{-} \longrightarrow ArNu^{\cdot -}$$

$$ArNu^{\cdot -} - e \longrightarrow ArNu \quad \text{and/or} \quad ArNu^{\cdot -} + ArX \longrightarrow ArNu + ArX^{\cdot -}$$

Overall:

$$ArX + Nu^{-} \longrightarrow ArNu + X^{-}$$

4. Electrochemical Reaction Mechanisms and the Principle of Microscopic Reversibility

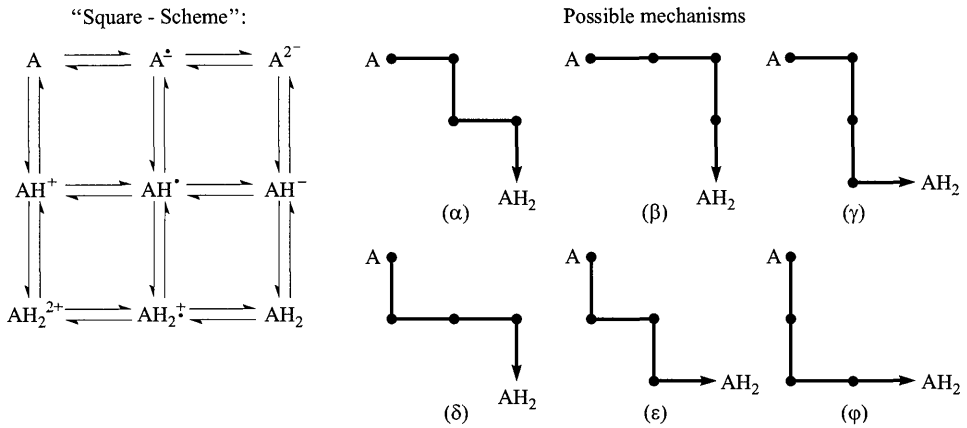
As understood from the large variety of possible reaction sequences outlined in the preceding section, a large number of reaction paths may be invoked a priori to explain the same overall electrochemical transformation. Yet owing to the great capabilities of electrochemical techniques for the identification of reaction mechanisms, the problem of their distinction frequently arises. For example, let us consider the very common two-electron two-proton electrochemical sequence in Eq. (127):

$$A + 2e + 2H^{+} \rightleftharpoons AH_2 \qquad (127)$$

The latter is involved, for example, in the reduction of aromatics to their dihydro derivatives, of quinones to hydroquinones, carbonyls to alcohols. A priori, there are six plausible different possibilities of transferring two electrons and two protons, depending on the exact order of the steps. These six paths involve the participation of seven different intermediates: $A^{\cdot -}$, A^{2-}, $AH^{\cdot -}$, $AH^{\cdot}$, AH^{+}, AH_2^{2+}, and $AH_2^{\cdot +}$. It is thus seen that the discussion of the possible mechanism(s) may rapidly become an overwhelming task, particularly when more steps are involved, as in the $4e + 4H^{+}$ sequence in Eq. (126). Thus in order to discuss the exact route followed, a convenient representation of the different possible schemes is highly desirable. Such a representation of all possible paths is given by "square-schemes" diagrams [101], such as that shown in Scheme 8 for the A/AH_2 reduction. The horizontal

transformations correspond to electron exchanges, whereas the vertical transformations involve a proton transfer.

Based on chemical grounds, several routes may be ruled out in Scheme 8. For example, starting from an aromatic hydrocarbon A, routes δ, ε, and φ, may be excluded, except in a superacidic medium. This is also certainly true for the γ route, which involves a difficult protonation of $AH^{\cdot}$ to AH_2^{+}. Thus only two routes, α and β, appear chemically reasonable under the usual electrochemical conditions. In practice, both may be followed, path α prevailing under weakly acidic media and low cathodic potentials, and path β predominating in less acidic conditions and at more negative values of the potential. Note, however, that additional complications, not considered in Scheme 8, involve the possible role of homogeneous electron exchanges. Thus $AH^{\cdot}$ may be reduced at the electrode but also by the strong reductant $A^{-\cdot}$.



Scheme 8

The reverse transformation may also be considered, as in the oxidation of aromatic dihydro derivatives to their parent hydrocarbon. Then one starts from AH_2, and routes α, β, and δ must be eliminated, except in very basic media. This is also certainly true for route γ, since the anion radicals $A^{-\cdot}$ usually have a marked basic character. Thus, under the usual electrochemical conditions, only routes ε and φ must be retained. Path ε predominates at less positive potentials and weakly basic conditions, whereas path φ should be observed at more positive potentials.

Consider now a given $Ar \rightleftharpoons ArH_2$ reaction under rather neutral conditions. It is inferred from the preceding discussion that route α is followed for the reduction, whereas the oxidation goes through path ε. At first glance, such a result seems to have to be rejected since it contradicts the principle of microreversibility, which claims that both reactions should follow the same mechanism.

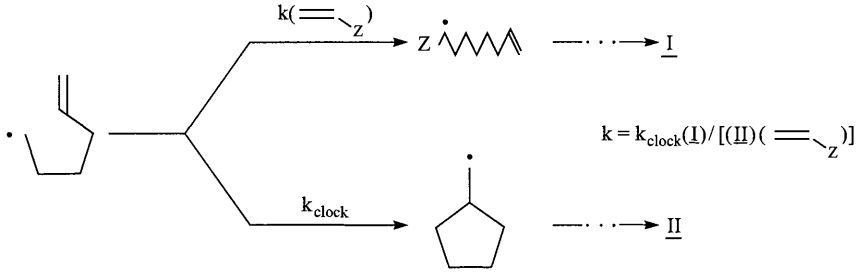
However, both transformations do not occur at the same electrode potentials: the reduction $Ar \longrightarrow ArH_2$ needs rather negative values, whereas the oxidation $ArH_2 \longrightarrow Ar$ is performed at rather positive values. Thus the two reactions occur under driving forces of opposite direction, with an energetic difference of approximately 100–130 kcal/mol. Thus, invoking the principle of microreversibility under such conditions is no more reasonable than invoking it when comparing the Birch reduction to the oxidation of aromatic dihydro derivatives by a strong oxidant.

IV. MASS TRANSFER IN ELECTROCHEMISTRY

A. Fundamental Aspects of Mass Transfer Processes

As mentioned in the preceding sections, mass transfer plays a crucial role in electrochemistry. The ubiquity of this phenomenon evidently arises because the electrons are exchanged at a two-dimensional surface boundary but the reactants and products are dispersed in a three-dimensional solution. Thus in the absence of mass transfer, only a small layer (of a few molecular radii thicknesses) would exchange electrons with each electrode, as is the case, for example, when the electroactive material is adsorbed at the electrode (Sec. III.D). As such, mass transfer is essential in controlling the success and rate of any preparative electrochemical reaction.

Another important feature of mass transfer processes is related to the very physical nature of the phenomenon. As such it is easily quantifiable and predictable. Thus the rate of mass transfer to and from an electrode may be determined a priori for a given electrochemical system. As a result this rate may be used as natural built-in clock by which the rate of other electrochemical processes may be measured. Such a property was apparent in our earlier discussions related to electrode kinetics (electron transfer and coupled chemical reactions). Basically it proceeds from the same idea as that frequently used in organic chemistry for relative rate constant determinations, when opposing a chemical reaction of known (or taken as the reference in a series of experiments) rate constant against a chemical reaction whose rate constant (or relative rate constant) is to be determined. Many such examples exist in the organic literature, among which are the famous "radical-clocks":



However, because of the intrinsic specifity of such chemical clocks, they cannot have a general use outside a given class of chemistry. Thus a better analogy with the electrochemical approach involving mass transfer rates would be that in which a reaction rate constant is matched to the diffusion limit rate constant that represents the physical process of bringing two reactants to distances such that they can interact chemically (Sec. II.C.1). Obviously such methods are not developed in homogeneous chemistry, principally because most chemical reactions, with maybe a few exceptions, among which are electron transfer or radical reactions, proceed with rates considerably slower than that of the diffusion limit. Another limitation to the development of such an approach is also related to the fact that diffusion limit is a rate of mass transfer (analogous to that involved in electrochemical experiments) but relates to mass transfer over atomic distances and is thus not prone to be adjusted at will.

In this respect, electrochemical mass transfer is particularly convenient. As mentioned earlier, its physical nature and its necessary involvement in any electrochemical experiment confer on it one of the characteristics of the internal clock just described. On the other hand, that it is active in the vicinity of a macroscopic object, the electrode, allows

its precise control. In practice, mass transfer rates at electrodes are continuously adjustable from equivalent times of a few seconds to a few tenths of microseconds [102]. When this is coupled to the use of a diffusion limit in the nanosecond or less time scale, it explains why electrochemical transient techniques allow kinetic information to be obtained and rate constants determined for reactions whose lifetimes range from seconds to tens of picoseconds [103].

1. The Physical Processes of Mass Transfer: Fick's First Law

There are three physical processes involved in the transport of molecules in considered media: convection, migration, and diffusion.

Convection may be the most intuitive and is present in all areas of chemistry; it corresponds to forced displacements of small volumic parts of the solution. The molecule is then carried within the fluid elements in which it is dissolved. The flux of particles J_{conv} through an elementary surface, that is, the number of moles of particles crossing a surface of area unity per unit of time, is then simply expressed as in Eq. (128),

$$J_{conv} = Cv(x) \tag{128}$$

where v(x) is the velocity of the fluid normal to the surface and C the concentration of the particle in the fluid element. It then follows that the mass transfer contribution is independent of the particle but is only a function of the local hydrodynamics (natural or thermal convection, forced convection, eddies, and so on). A large amount of work has already been devoted to quantifying the hydrodynamics of a solution [104]. Yet for our purposes here it is sufficient to recall two conclusions that apply in most electrochemical situations. (1) Because of shocks and interpenetration of the fluid elements in motion, concentrations are nearly identical at any point of a solution far from any wall. (2) Near any wall or solid surface, solid-liquid frictions and bouncing phenomena result in the creation of an immobile solution layer in which no convective effects occur.* Obviously the thickness δ_{conv} of this layer depends on the fluid velocity in the vicinity of the wall. Yet the resulting variation is small: thermal agitation and average vibrations result in $\delta_{conv} \approx 30$–$50\ \mu m$, whereas magnetic stirring at maximum agitation results in $\delta_{conv} \approx 10$–$20\ \mu m$.

From an electrochemical point of view it is easily inferred that the solution in a cell near an electrode is separable into two parts: a stagnant layer adjacent to the electrode in which no convective motions occur, and the remainder of the solution, which is homogeneous (bulk solution). Yet this is not a particularity of electrochemical methods since the same phenomena occur at any solid/liquid interface, as when metal particles (reductions by Zn or Na, for example) or any heterogeneous reagent is used in organic homogeneous chemistry, as well as in phase-transfer catalysis or related methods.

The other two contributions to mass transfer arise from forces on the molecule considered. When the molecule or particle is charged and an external electrical field is applied, electrostatic forces are effective and a positive molecule "descends" the electrical potential gradient, that is, goes in the direction of lower potentials, whereas a negative ion

*Note that the separation of the solution into two parts near a wall, that is, the immobile layer and the agitated homogeneous solution, is really simplistic since there is a continuous variation in the fluid velocity from the wall to the bulk [105]. Yet this dichotomous approximation is sufficient for most purposes and allows great simplifications in physicomathematical treatments of the transport problem.

"climbs" the potential gradient. Because of frequent shocks and bounding against solvent molecules, the molecule reaches a limiting velocity proportional to the potential gradient times its charge z, the proportionality coefficient γ depending on the molecules shape and size, as well as on the viscosity of the medium. This phenomenon, designated migration, then corresponds to a flux J_{migr} given in Eq. (129),

$$J_{migr} = -\gamma zF\frac{\partial \Phi}{\partial x}C \tag{129}$$

where x is the coordinate normal to the elementary surface crossed, $\partial\Phi/\partial x$ the electrical potential gradient along the x axis, and C the local molecule concentration. Φ can have an external origin as in electrophoresis or can be the result of local changes in the distribution of other charges. In the presence of a sufficient excess of supporting electrolyte, the latter contribution is shown to be extremely small [106].

The third contribution is called diffusion, but a better name, although not used, would be "spreading." Indeed, it corresponds to the natural tendency of nonrigid objects to spread so that the object's constituents are levelled. This is well known in any field of chemistry and particularly disturbing in chromatography, since it is responsible for the enlarging of peaks with retention times. The physical origin of this phenomenon is easily understood when considering the chemical potential μ of a solute (for simplicity, concentrations and activities are assumed equal) given in Eq. (130), where μ^0 is the standard value. Thus when C is not uniformly distributed along the x axis, one obtains the chemical potential gradient in Eq. (131).

$$\mu = \mu^0 + RT\ln C \tag{130}$$

$$\frac{\partial \mu}{\partial x} = RT\frac{\partial \ln C}{\partial x} = \frac{RT}{C}\frac{\partial C}{\partial x} \tag{131}$$

This potential gradient corresponds to a force that acts on the molecule, as in an electrical potential gradient. Again this gives the molecule a limiting velocity oriented in the direction opposite to the gradient, that is, toward the lesser values of μ, and proportional to the force $-\partial\mu/\partial x$. Because of the same collisions and bouncing effects as in the migration case, the proportionality coefficient is γ, identical to that in Eq. (120). Thus the diffusion flux J_{dif} is given in Eq. (132a):

$$J_{dif} = -\gamma\frac{\partial \mu}{\partial x}C = -\gamma RT\frac{\partial C}{\partial x} \tag{132a}$$

In practice one prefers to reformulate Eqs. (129) and (132a) by introducing the diffusion coefficient $D = \gamma RT$ of the molecule in the medium considered; that is,

$$J_{dif} = -D\frac{\partial C}{\partial x} \tag{132b}$$

which is commonly designated as Fick's first law.

In the most general situation, all three mass transfer modes cooperate algebraically; thus the number of moles crossing a surface of unit area per unit of time is given in Eq. (133), which constitutes an extension of the Fick's first law.

$$J(x) = J_{conv} + J_{migr} + J_{dif} = Cv(x) - CD\frac{zF}{RT}\frac{\partial \Phi}{\partial x} - D\frac{\partial C}{\partial x} \tag{133}$$

2. Relationships Between the Electrochemical Current and Mass Transfers

On the basis of the dichotomous representation of the solution near the electrode surface, Eq. (133) simplifies in the two domains. Within the stagnant layer and in the presence of an excess of supporting electrolyte, the two first terms are negligible and one obtains Eq. (134). Conversely, when $x > \delta_{conv}$, the solution is macroscopically homogeneous; the diffusional contribution then vanishes, and the flux is given in Eq. (135).

$$0 < x < \delta_{conv}: \quad J(x) = -D\frac{\partial C}{\partial x} \tag{134}$$

$$x > \delta_{conv}: \quad J(x) = C\left(v(x) - D\frac{zF}{RT}\frac{\partial \Phi}{\partial x}\right) \tag{135}$$

Equation (135) allows one to discuss more specifically the problem of ohmic drop. Indeed, the current density at any point in the bulk solution is given by addition of the fluxes of all ionic species times their charge:

$$\frac{i}{FA} = -\sum z_j J_j(x) = -v(x)\sum z_j C_j + \frac{F}{RT}\frac{\partial \Phi}{\partial x}\sum z_j^2 C_j D_j$$

Because of electroneutrality, the first summation term on the right-hand side of this equation vanishes, which yields Eq. (136):

$$d\Phi = i\frac{RT}{\sum(z_j^2 F^2 C_j D_j)}\frac{dx}{A} \tag{136}$$

The latter gives the potential drop $d\Phi$ associated with the current i through a space element of cross section A and thickness dx. By comparison with Ohm's law and definition of the resistivity it is seen that the resistivity ρ of the solution is given by Eq. (137). The ensuing resistance R_Ω for a solution of cross section A and length ℓ is obtained in Eq. (138).

$$\rho = \frac{1}{\sum[(z_j F)^2 C_j (D_j/RT]} \tag{137}$$

$$R_\Omega = \frac{\rho \ell}{A} \tag{138}$$

Such an expression justifies a posteriori the previous discussion of the ohmic drop effect in electrochemical cells (Sec. III.A.3). Indeed, for a given resistance of the solution in Eq. (138), the ohmic drop across the cell is expressed as in Eq. (139):

$$\Phi_\Omega = R_\Omega i \tag{139}$$

Thus the larger the concentration of dissociated ions, the smaller the ohmic drop. This in turn depends on the nature and affinity of the solvent/supporting electrolyte system, as discussed earlier and in Chapter 5.

Let us now discuss more precisely the relationship between current and mass transfer at the electrode surface. From Eq. (134) it is seen that the flux of electroactive species is given, in the absence of migration, by Eq. (140), at the electrode surface ($x = 0$).

$$J_{x=0} = -D\left(\frac{\partial C}{\partial x}\right)_{x=0} \tag{140}$$

$$i = -nFAJ_{x=0} = nFAD\left(\frac{\partial C}{\partial x}\right)_{x=0} \tag{141}$$

When there is no accumulation of material at the electrode surface, this flux corresponds to an exchange of n electrons per molecule, that is, to a current given in Eq. (141).* Thus for the electrochemical reaction in Eq. (142), the reactant flux is associated with an identical, but opposite sign, product flux; that is,

$$R + ne \rightleftharpoons P$$

$$i = nFAD_R\left(\frac{\partial[R]}{\partial x}\right)_{x=0} = -nFAD_P\left(\frac{\partial[P]}{\partial x}\right)_{x=0} \tag{142}$$

Both fluxes must also correspond to the rate of electron exchange at the electrode surface. Since this latter has already been shown to be given by the Butler-Volmer rate law in Eq. (109), the current must fulfill simultaneously the set of the three Eqs. (143) through (145).

$$i = nFAk^0 e^{-\alpha nF[E-E^\circ]/RT}([R]_{x=0} - [P]_{x=0}e^{nF(E-E^\circ)/RT}) \tag{143}$$

$$i = nFAD_R\left(\frac{\partial[R]}{\partial x}\right)_{x=0} \tag{144}$$

$$i = -nFAD_P\left(\frac{\partial[P]}{\partial x}\right)_{x=0} \tag{145}$$

Comparison of Eqs. (143) and (144) for example, allows us to discuss more quantitatively the relationship between mass transfer rate and reversibility or irreversibility of an electron transfer step (see Table 4). Indeed, by equalizing both equations, one readily obtains Eq. (146) for $E = E^\circ$.

$$1 - \frac{[P]_{x=0}}{[R]_{x=0}} = \frac{D_R(\partial[R]/\partial x)_{x=0}}{k^0[R]_{x=0}} \tag{146}$$

From this simple equation it is seen that when k^0 is much larger than the flux at the electrode, the right-hand side tends to be zero, and thus $[P]_{x=0} \approx [R]_{x=0}$, which corresponds to the fulfillment of a Nernst equation at the electrode surface for $E = E^\circ$. Conversely, when k^0 is much smaller than the demanded flux, one obtains $[P]_{x=0} > [R]_{x=0}$ or $[P]_{x=0} < [R]_{x=0}$, according to the flux sign. Thus to obtain $[P]_{x=0} \approx [R]_{x=0}$, one must impose an electrode potential E, such as

$$(1 - e^{nF[E-E^\circ]/RT})e^{-\alpha nF(E-E^\circ)/RT} = \frac{D_R(\partial[R]/\partial x)_{x=0}}{k^0[R]_{x=0}} \tag{147}$$

that is, such that $n(E - E^\circ) \ll 0$, which is highly cathodic with respect to E^o for a reduction and highly anodic versus E° for an oxidation.

*Note that a minus sign is used so that cathodic currents ($n > 0$) are positive and anodic currents ($n < 0$) are negative according to polarographic conventions.

3. The Microscopic Origin of the Diffusion Coefficient: Mass Transfer Rates and Diffusion Layer Thickness

Before concluding this section devoted to Fick's first law, we discuss the microscopic origin of the ubiquituous diffusion coefficient D [compare Eqs. (133) through (137), (140) through (142), and (144) through (147)]. In the preceding presentation, D was introduced as $D = \gamma RT$, where γ is the proportionality constant between the velocity of the molecule and the forces acting on it, based on semimacroscopic considerations.

In the absence of any applied force, a molecule is nevertheless moving because of thermal agitation. Yet owing to frequent collisions with the surrounding molecules, free motions occur only over atomic distances. The overall molecular movement then resembles a random succession of linear segments of approximately identical length ℓ, and duration τ. Over a time period $t = m\tau$, the average square displacement $\bar{\Delta}^2$ is determined via statistical equations to be $\bar{\Delta}^2 = m\ell^2 = (\ell^2/\tau)t$ [107]. Let us now suppose that a force is applied to the particle arising, for example, from a concentration gradient along the x axis. Consider a plane perpendicular to the x axis at $x = 0$, as shown in Fig. 18a. During a time of t seconds, a "random-walking" molecule covers a mean distance $L = (\bar{\Delta}^2)^{1/2}$. Thus those molecules from the negative axis region that may cross the plane at $x = 0$ during the time duration t originate from a volume element, adjacent to the plane, of thickness L. Let $C(-L/2)$ be the average concentration of molecules within this element. Similarly, those that may also cross the plane but originate from the positive axis pertain to an identical volume element of thickness L in which the average concentration is $C(+L/2)$. Since movements in a positive or negative direction are equally probable, one half the molecules contained in each of these elements of solution cross the plane. Thus a unit surface area of the plane at $x = 0$ is crossed by $\frac{1}{2}LC(-L/2)$ molecules moving toward positive values of x and $\frac{1}{2}LC(L/2)$ molecules moving toward negative values. The flux of molecules, that is, the balanced number of molecules that have crossed the unit surface area of the plane at $x = 0$ per unit of time and are lost (algebraically) from the layer on the negative axis side, is then

$$J_{x=0} = \frac{\frac{1}{2}LC(-L/2) - \frac{1}{2}LC(L/2)}{t}$$

Noting that $[C(L/2) - C(-L/2)]/L$ is the concentration gradient at $x = 0$, which is $(dC/dx)_{x=0}$, this equation is rewritten as

$$J_{x=0} = -\frac{L^2}{2t}\left(\frac{dC}{dx}\right)_{x=0}$$

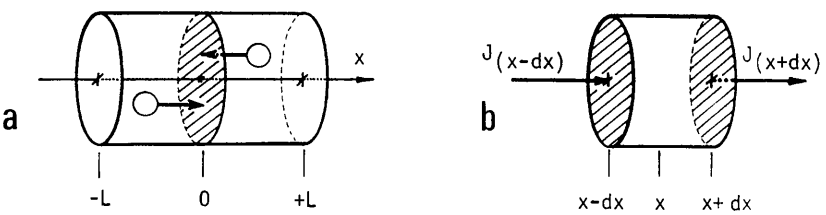


Figure 18. Symbolic representations of (a) the mass fluxes through an unit area surface, and (b) the "entering and outgoing" mass fluxes in an elementary volume of solution of unit area cross section (see text).

which, owing to the definition of L, yields finally

$$J_{x=0} = -\frac{\ell^2}{2\tau}\left(\frac{dC}{dx}\right)_{x=0}$$

and thus

$$D = \frac{\ell^2}{2\tau} \tag{148}$$

Comparison of this equation with Eq. (132b) or (134) allows the microscopic formulation of the diffusion coefficient D in Eq. (148), where ℓ is the average free motion length and τ the average time duration between two collisions. Besides its intrinsic value, such a result allows one to estimate how far a molecule has moved over an average period of time t. Indeed, from the expressions of L and D, one readily obtains Eq. (149):

$$L = (2Dt)^{1/2} \tag{149}$$

This equation provides a very convenient means to estimate, for example, the average distance covered by a molecule during a time interval t. In other words, a molecule generated at time zero at an electrode reaches a distance of approximately $\delta = (2Dt)^{1/2}$ after a time t has elapsed, provided its movements are controlled only by diffusion. For this reason, δ is usually called the diffusion layer thickness. This figure has an extreme importance in discussing the nature of mass transfer at an electrode. Indeed, it is easily understood that when $\delta < \delta_{conv}$, the concentrations of the species generated or consumed at an electrode have their bulk values before reaching a solution region in which convection is involved. This corresponds to the shortest times of electrochemical experiments, since taking into account Eq. (149), the preceding inequality yields $t < t_{max} = \delta_{conv}^2/2D$. All the mass transfer processes at the electrode are then governed by diffusion (and possibly, at low excesses of supporting electrolyte, by migration). Conversely, when $t > t_{max}$, only an extremely small part of the molecular trajectories is controlled by diffusion, convection being the main means of mass transfer. As is elaborated in the following, this simple notion is extremely important in discriminating transient electrochemical techniques ($t \leq t_{max}$) from steady-state techniques ($t > t_{max}$), that is, diffusion-controlled from convection-controlled mass transfer.

A second important property of Eq. (149) is that it provides an estimate of the rate, in terms of a characteristic time θ, associated with mass transfer. Indeed, this is the time θ needed for a molecule to reach the electrode, that is, to cover the space interval in which the molecular concentration differs from that in the bulk. In transient methods this time is identical to that elapsed since the beginning of the experiment, provided that it is lower than $t_{max} = \delta_{conv}^2/2D$. For steady-state methods, the length to be covered is δ_{conv}, and thus from Eq. (149) it follows that $\theta = \delta_{conv}^2/2D$. The rate of mass transfer can be defined as $1/\theta$, since it is obviously equivalent to a first-order process (see Chapter 3 for a demonstration of this point). Yet in light of the previous discussion, it is preferable to think in terms of a characteristic time θ associated with a given electrochemical method rather than in terms of mass transfer rate, although this intuitive latter notion was extremely worthwhile up to this point.*

*Note also that all the preceding discussions immediately transpose when comparing the half-life times $t_{1/2}$ associated with chemical reactions to θ. In our opinion this is more satisfactory since it avoids the necessity of defining a rate constant associated with mass transfer processes, which are essentially of a physical, not a chemical, nature.

4. Electrochemical Homogeneous Kinetics: Fick's Second Law

Fick's second law is based upon mass conservation at any point in time and space. To formulate this point more precisely, let us consider that the spatial distribution of the concentration C of the species of interest depends on a single direction x[†]. Consider now a cylindrical space element of length 2 dx and cross-sectional area A, centered at x, and let us designate C(x, t) the average concentration at time t within this element, as shown in Fig. 18b.

During a time interval dt, an algebraic flux J[x − dx, t] enters the volume element through its boundary at x − dx.[*] Similarly, an algebraic flux J[x + dx, t] leaves the element through the boundary at x + dx. During the same time interval, K_p dt moles of the species have been produced, and K_c dt have been consumed via chemical reactions within the volume element. Thus the number of moles of the species varied by dN, in Eq. (150), during the time duration dt.

$$dN = J(x - dx,\ t)A\,dt - J(x + dx,\ t)A\,dt + K_p\,dt - K_c\,dt \tag{150}$$

Dividing the dN expression by the volume of element, 2A dx, gives the concentration variation; that is,

$$\frac{\partial C}{\partial t} = -\frac{J[x - dx, t] - J[x + dx, t]}{2dx} + \frac{K_p}{2A\,dx} - \frac{K_c}{2A\,dx}$$

The first term on the right-hand side is the derivative of the flux vis-à-vis x, whereas $K_p/2A$ dx and $K_c/2A$ dx relate to the concentration variations from chemical origin, denoted $(\partial C/\partial t)_{chem}$.

$$\frac{\partial C}{\partial t} = -\frac{\partial J}{\partial x} + \left(\frac{\partial C}{\partial t}\right)_{chem} \tag{151}$$

Then Eq. (151) simply relates the overall time dependence of the concentration to the algebraically additive mass transfer and chemical components. In this respect it is important to point out that the chemical term is identical to that obtained under homogeneous conditions for the same chemical sequence. Thus Eq. (151) constitutes a generalization of the usual kinetic rate laws to conditions in which concentrations are not homogeneous. Although developed here in the context of electrochemical techniques, it is valid in any kind of chemical situation in which concentrations are not uniform, as nearly any heterogeneous reactant or phase-transfer boundaries.

Under electrochemical conditions, that is, near an electrode surface, two limiting formulations are obtained for Eq. (151). For distances from the electrode larger than δ_{conv}, the solution is macroscopically homogeneous. Thus $\partial J/\partial x = 0$, and Eq. (151) simplifies to the usual kinetic rate law in Eq. (152).

$$x > \delta_{conv}: \quad \frac{\partial C}{\partial t} = \left(\frac{\partial C}{\partial t}\right)_{chem} \tag{152}$$

[†]Note that, as for Fick's first law, all the demonstrations easily adapt to a three-dimensional space. Yet since for most electrochemical methods the linear space approximation, that is, depending only on the normal distance from the electrode, is adequate, we restrict ourselves to this simpler case in this presentation.

[*]Note that the terms "enter" and "leave" are used because fluxes are oriented with respect to the x axis. Thus J > 0 through a surface corresponds to a flux oriented toward positive x values, and the converse is also true.

$$0 < x < \delta_{conv}: \quad \frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} + \left(\frac{\partial C}{\partial t}\right)_{chem} \tag{153}$$

Conversely, within the stagnant layer and in the presence of a sufficient excess of supporting electrolyte, the flux is given in Eq. (134). Introduction of this latter figure in Eq. (151) yields finally Eq. (153), which is also commonly designated as Fick's second law for diffusion-reaction.

In the derivation of Eq. (152), we neglected the quantity of the species produced or consumed at the electrode. In practice this is true for microscale electrochemical experiments but is necessarily inexact for macroscale or exhaustive electrolysis. To derive the general equation, let us consider the total equation for the bulk solution. The chemical contribution is given in Eq. (152). On the other hand, a flux of the species at the convection layer limit δ_{conv} must be considered. This flux corresponds to an algebraic number dN_{elec} of moles of the species produced, given in Eq. (154),

$$dN_{elec} = (J(x = \delta_{conv}-, t))A\, dt \tag{154}$$

where A is the electrode surface area.* Dividing both members of Eq. (154) by the volume V of the bulk solution allows the reformulation of Eq. (154) as

$$\left(\frac{\partial C}{\partial t}\right)_{elec} = -\frac{DA}{V}\left(\frac{\partial C}{\partial x}\right)_{x=\delta_{conv}-} \tag{155}$$

Thus the overall concentration rate law in the solution is finally expressed as in Eq. (156) in a general case.

$$x > \delta_{conv}: \quad \frac{\partial C}{\partial t} = -\frac{DA}{V}\left(\frac{\partial C}{\partial t}\right)_{x=\delta_{conv}-} + \left(\frac{\partial C}{\partial t}\right)_{chem} \tag{156}$$

The absolute value of the first term on the right-hand side of Eq. (156) is at maximum equal to $(DA/V)C^0/\delta_{conv}$, where C^0 is the bulk concentration of the electroactive reactant (Sec. IV.B). The electrode consumption or production is then equivalent to pseudo-first-order kinetics whose apparent rate constant is at maximum equal to

$$k_{elec} = \frac{DA}{V\delta_{conv}} \tag{157}$$

To evaluate k_{elec}, let us consider the following average figures: $D = 10^{-5}\,cm^2\,s^{-1}$, $\delta_{conv} = 10\,\mu m = 10^{-3}$ cm, and cell volume = $100\,cm^3$. Then $k_{elec} = 10^{-4}$ A, when expressed in s^{-1} and A is expressed in cm^2. For microscale electrochemical experiments, A is of the order of few square millimeters, that is, a few hundredths of a square centimeter; thus $k_{elec} \approx 10^{-6}\,s^{-1}$. This means that several hours of continuous electrolysis are needed to significantly perturb (> 1%) the bulk solution. This is the reason why this term is neglected in practice, Eq. (152) being used instead of the more rigorous Eq. (156). Obviously, when preparative-scale electrolysis is considered, one wants to increase k_{elec} in Eq. (157), that is, use large A/V ratios and small δ_{conv} by increasing the electrode surface area and convection within the cell.

Owing to the organization of this book, preparative-scale electrolysis is discussed separately in Chapter 3. Thus in the following we assume that Eq. (152) represents the

*The minus superscript in $\delta_{conv}-$ means that the flux is that within the diffusion layer, that is, the limit of J(x), when x tends to δ_{conv}, from lower values.

dependence on time of the bulk solution concentration. In other words, the electrochemical behavior, in the absence of migrational contributions, is given by a set of equations analogous to that in Eq. (158), with boundary conditions at $x = 0$, depending on the electrode potential and kinetics [compare Eqs. (143) through (145)] and at $x = \delta_{conv}$, $C = C^b$, where the bulk concentration C^b is given as a function of time by Eq. (159)*:

$$0 < x < \delta_{conv}: \quad \frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} + \left(\frac{\partial C}{\partial t}\right)_{chem} \tag{158}$$

$$x > \delta_{conv}: \quad C = C^b \quad \text{such as} \quad \frac{dC^b}{dt} = \left(\frac{dC^b}{dt}\right)_{chem} \tag{159}$$

5. Dimensionless Formulation of Electrochemical Equations

The dimensionless analysis of equations is an analytic mathematical technique of frequent use in engineering. Indeed, this technique allows one to "concentrate" all the a priori independent parameters resulting in an identical effect into a single dimensionless parameter. To illustrate the principle and operational interest of the method, let us consider a general second-order homogeneous reaction, such as that in Eq. (160), the reactant concentration being C^0 at the beginning ($t = 0$) of the experiment:

$$2R \longrightarrow P \quad (k) \tag{160}$$

Strict application of homogeneous chemical kinetics readily yields the rate law in Eq. (161), which governs the reactant concentration, as a function of time. Integration of this rate law gives the classic expression in Eq. (162) for an experiment of duration θ. Yet Eq. (162) may be rewritten under the equivalent form in Eq. (163).

$$\frac{d[R]}{dt} = -2k[R]^2 \tag{161}$$

$$\frac{1}{[R]} = \frac{1}{C^0} + 2k\theta \tag{162}$$

$$\frac{[R]}{C^0} = \frac{1}{1 + 2kC^0\theta} \tag{163}$$

In many respects, the formulation in Eq. (163) is more interesting than that in Eq. (162). Indeed, its left-hand side gives the instantaneous fraction of the reactant not converted to the product at any time θ. Chemically this is usually more significant than the actual concentration. Its right-hand side shown that this fraction depends on a single factor (or parameter) $2kC^0\theta$, which includes the effect of the a priori three independent factors: an intrinsic factor k and two experimental parameters C^0 and θ. Just at a glance it shows that doubling the concentration, for example, results in the same effect as keeping the

*Note that when a figure C depends on several independent variables x and t, its variations vis-à-vis one of these variables are given by its partial derivative $\partial C/\partial x$ with respect to the variable. When C depends on a single variable, the usual derivation is used: dC/dx. The intrinsic difference between the two kinds of derivations is indicated by the symbolic use of ∂ or d in the derivative notations.

same concentration and doubling the duration of the experiment, or increasing the temperature, so that k is doubled.

In this example the dimensionless reactant fraction $r = [R]/C^0$ and dimensionless rate parameter $\lambda = 2kC^0\theta$ were introduced by reformulating the integrated rate law in Eq. (162). However, this could have been done directly on the rate law in Eq. (161) by introducing a dimensionless time $\tau = t/\theta$ (i.e., the elapsed fraction of the overall experiment duration θ) and the reactant fraction r defined earlier. Then Eq. (161) reformulates as in Eq. (164a) and is associated with the initial condition in Eq. (164b). Integration of Eq. (164a), owing to the initial condition, yields readily Eq. (165), which is identical to Eq. (163).

$$\tau > 0: \quad \frac{dr}{r^2} = -\lambda \, d\tau \tag{164a}$$

$$\tau = 0: \quad r = 1 \tag{164b}$$

$$\tau = 1: \quad r = \frac{1}{1+\lambda} \tag{165}$$

The interest of this second approach, that is, dimensionless analysis of the rate law itself, becomes obvious for cases in which the integration of the rate law is not achievable analytically and must be performed numerically. Indeed, the set of Eqs. (164) shows that the variable of interest, $r = [R]/C^0$, depends only on $\lambda = 2kC^0\theta$. Thus numerical integration must be performed only for a selected number of λ values to obtain a single curve giving r as a function of λ, that is, a function of all factors k, C^0, and θ affecting the conversion yield. If one says that 10 different values of λ, for example, are needed to determine the curve with the required accuracy, the process needs 10 calculations. Yet without dimensionless analysis the same information with the same accuracy would be contained in at least 100 curves, that is [R] as a function of θ, for 10 selected values of C^0 and for each 10 values of k, which would need 1000 calculations. Besides the intrinsic interest of having all the information contained in a single curve rather than in a hundred, the method is essentially time saving. For example, consider that a numerical integration requires 5 min; the whole dimensionless curve needs about 1 h calculation time, whereas the normal or direct method requires at least 100 h!

a. Application to Electrochemical Systems. As explained in the previous parts of this section, two figures tightly control electrochemical kinetics: a spatial one δ, the thickness of the diffusion layer, and a temporal one θ, the time elapsed since the beginning of the electrochemical perturbation. Thus in most situations these figures constitute adequate and suitable references for the definitions of the dimensionless space $y = x/\delta$ and time $\tau = t/\theta$. Similarly, in most electrochemical kinetic experiments, the bulk concentration C^0 of the starting material remains constant (see, however, Chapter 3 for preparative electrochemistry). It follows that $s = [S]/C^0$ constitutes a meaningful dimensionless concentration for any species S whose real concentration is [S]. Another obvious dimensionless parameter concerns the potential figures. Indeed, in nearly all electrochemical circumstances, the electrode potential per se is not important but influences the electrochemical behavior through its difference from E° times nF/RT. [Compare, e.g., the Nernst equation or the Volmer-Butler rate law in Eq. (143)]. Thus definition of the dimensionless potentials as $\xi = (nF/RT)(E^\circ - E)$ appears suitable. y, τ, s, and ξ constitute the master dimensionless parameters from which the definition of all others ensues, as is shown in the following.

Let us consider first the electrode boundary conditions in Eq. (144) or (145). Introduction of $r = [R]/C^0$ and $y = x/\delta$ in Eq. (144), for example, directly affords Eq. (166):

$$i = \frac{nFADC^0}{\delta}\left(\frac{\partial r}{\partial y}\right)_0 \tag{166}$$

where the subscript 0 is used to indicate "at $y = 0$," which shows that a convenient dimensionless definition for the current is $\psi = i/(nFADC^0/\delta)$, which yields Eq. (167):

$$\psi = \left(\frac{\partial r}{\partial y}\right)_0 \tag{167}$$

$$\psi = \frac{k^0\delta}{D}e^{\alpha\xi}(r_0 - p_0e^{-\xi}) \tag{168}$$

$$\psi = \Lambda e^{\alpha\xi}(r_0 - p_0e^{-\xi}) \tag{169}$$

Introduction of r, $p = [P]/C^0$, $\xi = nF/RT(E^0 - E)$, and ψ in the Volmer-Butler rate law [Eq. (143)] readily yields Eq. (168). The latter shows that a convenient dimensionless rate of electron transfer is $\Lambda = k^0\delta/D$, since it compares the intrinsic value of the rate constant to that of the mass transfer process. Thus Eq. (168) reformulates as Eq. (169). Let us now examine the time- and space-dependent partial derivative equation of the kind demonstrated by Eq. (158), which describes variations in the concentration profiles in the stagnant layer adjacent to the electrode. For any species S, introducing τ, y, and s leads to reformulation of Eq. (158) as in Eq. (170):

$$0 < y < \frac{\delta_{conv}}{\delta}: \quad \frac{C^0}{\theta}\frac{\partial s}{\partial \tau} = \frac{DC^0}{\delta^2}\frac{\partial^2 s}{\partial y^2} + \left(\frac{\partial [S]}{\partial t}\right)_{chem} \tag{170}$$

To proceed further it is necessary to define the nature of the chemical production or consumption terms in $(\partial[S]/\partial\tau)_{chem}$. For that, let us consider the general term K_j in Eq. (171).

$$\left(\frac{\partial [S]}{\partial t}\right)_{chem} = \sum K_j \quad \text{with} \quad K_j = \pm k_j[S]^{\alpha j}\prod[Z_l]^{\beta l} \tag{171}$$

$$K_j = \pm\lambda_j[s^{\alpha j}\prod z_l^{\beta l}]\frac{C^0D}{\delta^2} = \tilde{\lambda}_j\frac{C^0D}{\delta^2} \tag{172}$$

where the + or − sign corresponds to an S production or consumption, respectively. Thus K_j reformulates as in Eq. (172), where the dimensionless rate constant λ_j is defined* as

*Note that an alternative formulation, when the $[Z_l]$ concentrations in Eq. (171) are kept constant, consists of including their contribution into the rate constant, which amounts to defining a pseudo-rate constant $k_j^{ap} = k_j\prod[Z_l]^{\beta l}$. Thus Eq. (171) is rewritten as

$$K_j = \pm k_j^{ap}[S]^{\alpha j}$$

which results in the definition of $\lambda_j = k_j^{ap}(\delta^2/D)(C^0)^{\alpha j - 1}$. Obviously, any intermediate attitude is possible as a function of the particular experiment dealt with.

$\lambda_j = k_j(\delta^2/D)(C^0)^{\alpha j-1+\Sigma\beta 1}$. Introduction of these expressions in Eq. (170) yields, after multiplication of both members by δ^2/DC^0,

$$0 < y < \frac{\delta_{conv}}{\delta}: \quad \frac{\delta^2}{D\theta}\frac{\partial s}{\partial \tau} = \frac{\partial^2 s}{\partial y^2} + \sum \tilde{\lambda}_j \tag{173}$$

The formulation in Eq. (173) shows that the dimensionless parameter $\delta^2/D\theta$ plays a crucial role in the time dependence of the S concentration profile. This parameter compares the diffusion layer thickness δ to $(D\theta)^{1/2}$. On the other hand, we have discussed the dependence of δ on the duration of the experiment. Thus from Eq. (149), $\delta \approx (D\theta)^{1/2}$, provided that $\delta \ll \delta_{conv}$, that is, that $\theta \ll \delta_{conv}^2/D$. Then the diffusion layer extends within a small fraction of the stagnant layer and Eq. (173) reformulates as in Eq. (174),

$$0 < y < \frac{\delta_{conv}}{(D\theta)^{1/2}} \approx \infty: \quad \frac{\partial s}{\partial \tau} = \frac{\partial^2 s}{\partial y^2} + \sum \tilde{\lambda}_j \tag{174}$$

which shows that the concentration profile of S depends on the space as well as on the time. For this reason the corresponding electrochemical methods are said to be transient. Note also that since $\theta = \delta^2/D$ under these conditions, the dimensionless rate constant is then $\lambda_j = k_j\theta(C^0)^{\alpha j-1+\Sigma\beta 1}$ or $\lambda_j = k_j^{ap}\theta(C^0)^{\alpha j-1}$.

Conversely, when $\theta \gg \delta_{conv}^2/D$, the diffusion layer would extend well beyond the stagnant layer, which is physically impossible. Thus one has $\delta = \delta_{conv}$, and $\delta^2/D\theta \approx 0$. On the other hand, $\partial s/\partial \tau$ cannot assume infinite values, except maybe at temporal discontinuities related to the exact electrochemical perturbation considered. Thus, with the exception of these discontinuities, the left-hand side member of Eq. (173) tends to zero. Thus, Eq. (173) reformulates as in Eq. (175),

$$0 < y < 1: \quad 0 = \frac{\partial^2 s}{\partial y^2} + \sum \tilde{\lambda}_j \tag{175}$$

which shows that a steady-state concentration profile is observed. For this reason the corresponding electrochemical methods are said to be steady-state methods. Note that the expression of the dimensionless rate constants reformulates as

$$\lambda_j = k_j \frac{\delta_{conv}^2}{D}(C^0)^{\alpha j-1+\Sigma\beta 1} \quad \text{or} \quad \lambda_j = k_j^{ap}\frac{\delta_{conv}^2}{D}(C^0)^{\alpha j-1}$$

It is thus seen that dimensionless analysis of electrochemical equations allows a very straightforward classification of the electrochemical methods into two limiting classes. Transient methods (including linear sweep voltammetry, cyclic voltammetry, chronoamperometries, and chronocoulometries; see Sec. IV.C and Chapter 2) correspond to the shortest perturbation times (usually less than 10 s) and the widest convection layers (usually = 20–50 μm, as imposed by natural convection and vibrations). On the other hand, steady-state methods (e.g., polarography and rotating disk electrodes; see Sec. IV.B and Chapter 2) need δ_{conv} to be as small as possible (usually = 5–10 μm, as imposed by forced convection) and the experiment to be of long enough duration.

The preceding presentation encompassed the widest class of electrochemical methods. As such, the reference figures used in the definition of the dimensionless parameters used were not specifically related to a particular method. Yet when a specific electrochemcal method is considered, other equivalent definitions may be used for greater convenience. For example, in cyclic voltammetry, θ is frequently defined as the time elapsed, $\theta = \Delta E/v$, between two waves separated by a potential difference ΔE at a scan rate v (in $V\,s^{-1}$). Yet in

linear sweep voltammetry, θ is usually defined as $\theta = RT/nFv$, that is, approximately the time needed to describe the rising branch of a nernstian voltammogram (see Chapter 2). Table 5 presents the most widely used dimensionless formulations.

B. Steady-State Electrochemical Methods: Half-Wave Potential $E_{1/2}$

1. Pure Electron Transfer Mechanisms

In the following we consider a simple electron transfer mechanism in order to discuss quantitatively the variations in the potential location of the steady-state voltammogram of the system according to the kinetics of the heterogeneous electron transfer. In the derivation of the kinetics we consider that the solution contains only the reactant at concentration C^0 before the electrochemical experiment. Let E°, k^0, and α be the standard reduction potential, the standard heterogeneous rate constant, and the transfer coefficient of the electron transfer in Eq. (176).

$$R + ne \rightleftharpoons P \quad (E^\circ, k^0, \alpha) \tag{176}$$

For most organic electroactive molecules, the variations in shape and solvation upon electron transfer are minimal, owing to the usually large delocalization. It follows that the diffusion coefficients relative to R and P are generally very close to their average value D, which is then used to introduce a simplification in the following derivations.

From the general equation (175), the concentration profiles of R and P are solutions of the following differential equations in dimensionless variables (see Table 5):

Table 5 Dimensionless Variables for Electrochemical Kinetics

Variable		Variable	
Real	Dimensionless	Real	Dimensionless
Time t[a]	$\tau = \dfrac{t}{\theta}$	Rate constants k:	
Distance x[b]	$y = \dfrac{x}{\delta}$	First order	$\lambda = \dfrac{k\delta^2}{D}$
		Second order	$\lambda = k\dfrac{C^0\delta^2}{D}$
Concentration or activity [S]	$s = \dfrac{[S]}{C^0}$	ρth order	$\lambda = k(C^0)^{(\rho-1)}\dfrac{\delta^2}{D}$
Potential E[c]	$\xi = \dfrac{nF}{RT}(E^\circ - E)$	Heterogeneous k^0	$\Lambda = \dfrac{k^0\delta}{D}$
Current i[b]	$\psi = i\dfrac{\delta}{nFADC^0}$	Equilibrium constant[d] K	$\kappa = \dfrac{K}{(C^0)^m}$

[a]Cyclic voltammetry: $\theta = RT/nFv$; v, scan rate. Staircase methods: θ = duration of the forward pulse.
[b]Steady-state methods: $\delta = \delta_{conv}$. Transient methods, $\delta = (D\theta)^{1/2}$.
[c]E°, standard reduction potential; n, number of electrons exchanged; $n > 0$ for reductions, $n < 0$ for oxidations.
[d]The dimensions of K are considered $mol^m \cdot l^{-m}$.

$$\left.\begin{aligned}\frac{d^2r}{dy^2} &= 0 \\ \frac{d^2p}{dy^2} &= 0\end{aligned}\right\} \quad 0 < y < 1 \tag{177, 178}$$

These equations are associated with the boundary conditions

$$\left.\begin{aligned}\psi &= \left(\frac{dr}{dy}\right)_0 = -\left(\frac{dp}{dy}\right)_0 \\ \psi &= \Lambda e^{\alpha\xi}(r_0 - p_0 e^{-\xi})\end{aligned}\right\} \quad \text{electrode } (y=0) \tag{179, 180}$$

$$\left.\begin{aligned}r &= 1 \\ p &= 0\end{aligned}\right\} \quad \text{convection layer boundary } (y=1) \tag{181, 182}$$

Integration of Eqs. (177) and (178), when taking Eq. (179) into account, readily yields

$$r = r_0 + \psi y \quad \text{and} \quad p = p_0 - \psi y$$

Introduction of conditions (181) and (182) into these linear concentration profiles gives the relationships between r_0, p_0, and ψ in Eq. (183). Incorporation of these latter figures into Eq. (180) and reorganization of the latter as a function of the dimensionless current ψ yields the equation of the dimensionless voltammogram in Eq. (184).

$$r_0 = 1 - \psi \quad \text{and} \quad p_0 = \psi \tag{183}$$

$$\psi = \frac{1}{1 + e^{-\xi} + (1/\Lambda)e^{-\alpha\xi}} \tag{184}$$

The latter shows that the current reaches two limiting values for $\xi \longrightarrow -\infty$ [i.e., for $n(E - E^\circ) \ll 0$] and $\xi \longrightarrow +\infty$ [i.e., for $n(E - E^\circ) \gg 0$]. Indeed, from Eq. (184) it ensues easily that $\psi \longrightarrow 0$ for $\xi \longrightarrow -\infty$ and $\psi \longrightarrow 1$ for $\xi \longrightarrow +\infty$, which shows that no current is observed when the potential is much less cathodic than E° (for a reduction; $n > 0$) or anodic than E° (for an oxidation; $n < 0$). Conversely, at sufficient cathodic ($n > 0$) or anodic ($n < 0$) values of the electrode potential, the current tends to a plateau value ($\psi \longrightarrow 1$) given in Eq. (185):

$$i^{lim} = \frac{nFADC^0}{\delta_{conv}} \tag{185}$$

Of interest is the proportionality of i^{lim} to the bulk concentration of the reactant. Indeed, Eq. (185) demonstrates that the electrochemical current can be used to monitor the bulk concentration of any chemical species, provided the latter is electroactive. This is the basis of a large variety of chemical or biochemical sensors, as well as that of electrochemical detectors in high-performance liquid chromotography (HPLC). From Eq. (183) it is seen that the observance of the current plateau corresponds to the fact that the reactant concentration has been completely depleted ($r^0 = 0$) at the electrode, so that increasing ξ results in no further change in the concentration profiles and therefore of the current. Similarly, the limit at $\psi = 0$ corresponds to $p_0 = 0$; thus decreasing the dimensionless potential results in no further change. The observation of the two limits thus corresponds to the fact that the concentrations of R and P at the electrode are limited by 0 and C^0. This is independent of the electrode kinetics, which explains that the limiting current i^{lim} does

not depend on the kinetics of the electron exchange. However, the location of the voltammogram depends on the rate of electron transfer.

When $\Lambda \gg 1$, that is, when $k^0 \gg D/\delta$,* the second term in the denominator in Eq. (184) vanishes and the voltammogram equation simplifies to Eq. (186),

$$\frac{i}{i^{lim}} = \psi = \frac{1}{1 + e^{-\xi}} \tag{186}$$

which is independent of the electron transfer rate. Moreover, introduction of r_0 and p_0, as given by Eq. (183), into Eq. (186) shows that

$$r_0 = p_0 e^{-\xi} \tag{187}$$

that is, in real variables,

$$E = E^\circ + \frac{RT}{nF} \ln \frac{[R]_{x=0}}{[P]_{x=0}}$$

which demonstrates that the electrode potential obeys the Nernst equation. Thus the electron transfer is sufficiently fast to be controlled thermodynamically. It is then said to be fast or nernstian. At $E = E^\circ$, $[R]_{x=0} = [P]_{x=0}$, that is, from Eq. (183), $i/i^{lim} = 0.5$. Thus E° may be determined as the potential for which $i/i^{lim} = 0.5$. This potential, the half-wave potential $E_{1/2}$, thus bears an important thermodynamic significance since it allows the determination of E°. Indeed, most E° values determined for organic redox couples have been measured through this or related techniques. Yet it must be emphasized that $E_{1/2}$ involves contributions other than E°. In a real situation, the activity and diffusion coefficients of R and P may differ, which yields [108]

$$E_{1/2} = E^\circ + \frac{RT}{nF} \ln \left[\frac{f_R}{f_P} \left(\frac{D_P}{D_R} \right)^{1/2} \right]$$

However, most of the time, the corrective term to E° is unfortunately unknown and beyond the error associated with potential measurements on an absolute (NHE) scale, mainly because of junction potential and reference electrode potential drifts. Thus in actual experiments $E_{1/2}$ and E° (or $E^{\circ\prime}$) are generally considered identical [94].

Let us now consider the converse situation, that in which $\Lambda \ll 1$ (i.e., $k^0 \ll D/\delta$). Then Eq. (184) simplifies to Eq. (188):

$$\psi = \frac{i}{i^{lim}} = \frac{1}{1 + (1/\Lambda)e^{-\alpha\xi}} \tag{188}$$

The half-wave potential, that is $E_{1/2}$ at which $i/i^{lim} = 0.5$, is then such that

$$E_{1/2} = E^\circ + \frac{RT}{\alpha nF} \ln \Lambda = E^\circ + \frac{RT}{\alpha nF} \ln \frac{k^0 \delta}{D} \tag{189}$$

Since $k^0\delta \ll 1$, the logarithmic term in Eq. (189) is negative and $n(E_{1/2} - E^\circ) \ll 0$. The wave is thus located in a potential range well cathodic of E° for a reduction process ($n > 0$) or anocid of E° for an oxidation process. The $E_{1/2}$ represents both thermodynamic (E°) and kinetic contributions ($\ln k^0\delta/D$) and must not be used as a substitute for E°.

*In practice, $D \approx 5 \times 10^{-6}$ cm^2 s^{-1} and $\delta \approx 5\,\mu m = 5 \times 10^{-4}$ cm are average values: thus the inequality is satisfied for $k^0 \gg 0.01$ cm s^{-1}.

Figure 19a presents the variations in the steady-state voltammograms for the R/P redox system as a function of $\Lambda = k^0\delta/D$ for α constant and equal to 0.5. The variations in $E_{1/2}$ with the same parameter $k^0\delta/D$ are presented in Fig. 19b for selected constant values of α. Therefore, in an actual experiment, variations in $E_{1/2}$ with δ (note that k^0 and D are intrinsic figures for a given couple R/P and a given medium) are indicative of kinetic complications and should warn against the use of $E_{1/2}$ as an estimate of E°.

2. Mechanism Involving a Follow-Up Reaction: EC Mechanisms

Let us first consider the case in which the initial electron transfer in Eq. (190) is sufficiently rapid to be nernstian (i.e., $\Lambda = k^0\delta/D \gg 1$) but is followed by an irreversible, pseudo-first-order, chemical reaction (that is, k may include the concentration of other reagent, when constant).

$$R + ne \rightleftharpoons P \quad (E^\circ, k^0, \alpha) \tag{190}$$

$$P \longrightarrow \cdots \quad (k) \tag{191}$$

The dimensionless equations governing the R and P concentration profiles are obtained from table 5, as in Eqs. (192) and (193).

$$\left.\begin{aligned} \frac{d^2r}{dy^2} &= 0 \qquad (192)\\ \frac{d^2p}{dy^2} &= \lambda p \qquad (193) \end{aligned}\right\} 0 < y < 1$$

For an nernstian heterogeneous electron transfer, the boundary conditions at the electrode formulate as in Eqs. (194) and (195):

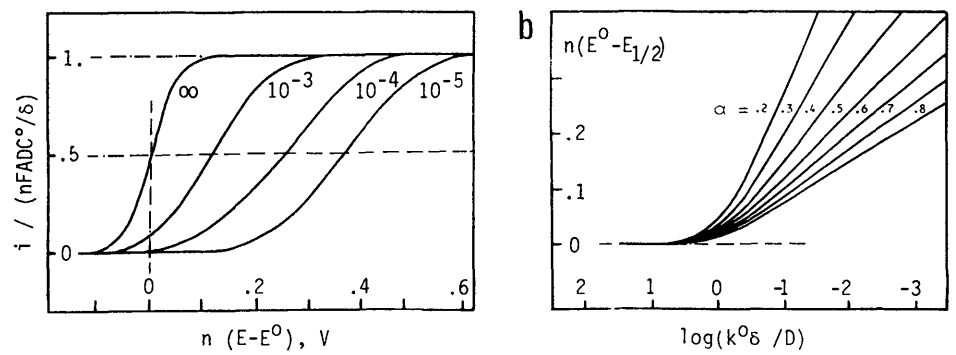


Figure 19. (a) Steady-state voltammograms of a simple redox system as a function of its intrinsic heterogeneous rate constant (number on the curves: k^0 in cm s^{-1}) for $\delta^2/D = 0.1$ s. (b) Variations in the half-wave potential $E_{1/2}$ as a function of the dimensionless rate constant $\Lambda = k^0\delta/D$ for different values of the transfer coefficient α.

$$\left.\begin{aligned} \psi &= \left(\frac{dr}{dy}\right)_0 = -\left(\frac{dp}{dy}\right)_0 \\ r_0 &= p_0 e^{-\xi} \end{aligned}\right\} y = 0 \qquad \begin{matrix}(194)\\(195)\end{matrix}$$

[Compare Eq. (187).] For a bulk solution containing only R, the boundary condition at the extremity of the convection layer is then

$$y = 1: \quad r = 1, \quad p = 0 \tag{196}$$

Integration of Eq. (192), taking into account Eqs. (194) and (196), yields Eq. (197):

$$r = r_0 + \psi y, \quad \text{with} \quad r_0 = 1 - \psi \tag{197}$$

From this simple equation, it is seen that, as for the preceding situations, the voltammogram has two limiting values. When $r_0 \approx 1$, $\psi \approx 0$, which corresponds to large negative values of ξ according to Eq. (195). Conversely, $\psi \approx 1$ when $r_0 \approx 0$, which is observed for large positive values of ξ as seen from Eq. (195). Thus the overall qualitative shape of the steady-state voltammogram remains identical to that observed in the absence of a chemical follow-up reaction. Yet they differ considerably on a quantitative basis, as shown by the following analysis.

Integration of Eq. (193) yields the dimensionless concentration profile of P in Eq. (198),

$$p = Ae^{(\lambda^{1/2}y)} + Be^{(-\lambda^{1/2}y)} \tag{198}$$

where A and B are two constants. These constants are determined according to the boundary conditions (194) and (196). Indeed, Eq. (194) yields by derivation (and setting $y = 0$) of Eq. (198):

$$\psi = -\lambda^{1/2}A + \lambda^{1/2}B \tag{199}$$

$$0 = Ae^{(\lambda^{1/2})} + Be^{(-\lambda^{1/2})} \tag{200}$$

whereas Eq. (196) affords Eq. (200) by setting $y = 1$ in Eq. (198). The system of two linear equations (199) and (200) with two unknowns (A and B) allows A and B to be determined as a function of ψ and λ. Thus,

$$A = \frac{\psi/\lambda^{1/2}}{1 + e^{(2\lambda^{1/2})}} \quad \text{and} \quad B = -Ae^{(2\lambda^{1/2})}$$

$$p_0 = A + B = \frac{\psi \tanh \lambda^{1/2}}{\lambda^{1/2}} \tag{201}$$

Determination of $p_0 = A + B$ from Eq. (198) is thus readily obtained as in Eq. (201). Incorporation of this latter value, as well as $r_0 = 1 - \psi$ from Eq. (197), into the Nernst equation (195), gives access to the equation of the steady-state voltammogram in Eq. (202).

$$\frac{i}{i^{lim}} = \psi = \frac{1}{1 + e^{(-\xi^*)}} \tag{202}$$

$$\xi^* = \xi + \tfrac{1}{2}\ln\lambda - \ln\tanh\lambda^{1/2} \tag{203}$$

Eq. (202) is identical with that obtained for a nernstian system [compare Eq. (186)] but one in which the potential axis has been translated by a constant term (for a constant value of $\lambda = k\delta^2/D$), as evidenced by Eq. (203). Its half-wave potential then corresponds to $\xi^* = 0$ instead of $\xi = 0$. From Eq. (203) and the definition of ξ in Table 5, one obtains the expression in Eq. (204). Since one always has $\lambda^{1/2} > \tanh \lambda^{1/2}$, the corrective term to E° in Eq. (204) always has the sign of n. Thus the wave is observed in a potential range E_w such that $n(E_w - E^\circ) > 0$, that is, anodic to E° for a reduction ($n > 0$) and cathodic to E° for an oxidation ($n < 0$).

$$E_{1/2} = E^\circ + \frac{RT}{2nF} \ln \lambda - \frac{RT}{nF} \ln \tanh \lambda^{1/2} \tag{204}$$

When $\lambda \longrightarrow 0$ i.e., $k \ll D/\delta^2$, one obtains $E_{1/2} \approx E^\circ$, since then $\tanh \lambda^{1/2} \approx \lambda^{1/2}$, resulting in a negligible corrective term in Eq. (204). This means that the chemical reaction in Eq. (191) is too slow vis-à-vis the mass transfer rate to significantly affect the voltammogram. The system is then said to be nernstian and chemically reversible. Conversely, when $k \gg D/\delta^2$, that is, when the chemical reaction is faster than the mass transfer at the electrode, $\lambda \longrightarrow \infty$. Then, because $\tanh \lambda^{1/2} \longrightarrow 1$ for $\lambda^{1/2} \longrightarrow \infty$, Eq. (204) simplifies to Eq. (205):

$$E_{1/2} = E^\circ + \frac{RT}{2nF} \ln \frac{k\delta^2}{D} \tag{205}$$

From the latter, it is seen that for $n = 1$ and room temperature, for example, $E_{1/2}$ shifts anodically by approximately 30 mV per unit of $\log k\delta^2/D$. As for the slow electron transfer case, $E_{1/2}$ is therefore not an acceptable substitute for E° since it incorporates kinetic contributions that then arise from the follow-up chemical reaction.

The variations in $E_{1/2}$ with $\lambda = k\delta^2/D$ result from the fact that when λ increases, the P concentration at the electrode surface decreases, as is apparent in Eq. (201)* and Fig. 20.

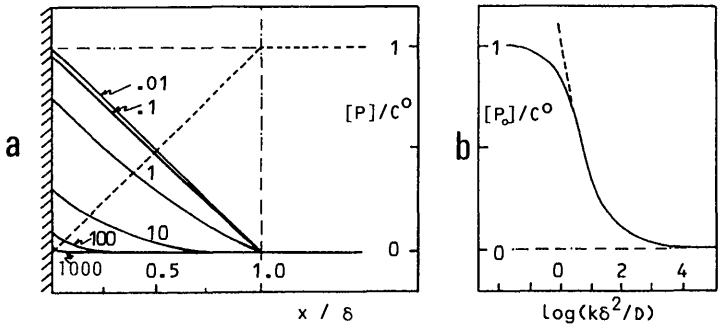


Figure 20. Steady-state electrochemical method. (a) Concentration profiles of the product obtained upon electron transfer in the EC sequence in Eqs. (190) to (191) as a function of the dimensionless chemical rate constant $k\delta^2/D$ (numbers on the solid curves). The reactant concentration is shown for comparison as the dashed line. (b) Variations in the product electrode concentration as a function of $k\delta^2/D$. The dashed curve corresponds to the approximation in Eq. (206).

*Indeed from this equation, when $\lambda > 7$, one obtains $p_0 \approx \psi/\lambda^{1/2}$ with an accuracy better than 1%.

Thus at any driving force imposed by the value of ξ, one obtains from Eq. (195) for large λ values:

$$r_0 = \frac{\psi}{\lambda^{1/2}} e^{(-\xi)} = \frac{\psi}{(k\delta^2/D)^{1/2}} e^{(-\xi)} \tag{206}$$

which shows that the reactant concentration is considerably less than that, $r_0 = \psi e^{(-\xi)}$, obtained at the same potential in the absence of a fast follow-up chemical step. Thus the heterogeneous electron transfer is continuously displaced by P removal in a way similar to that already observed for the corresponding homogeneous situation in Eqs. (207) and (208). Yet in the latter case, as elaborated in a previous section [Sec. II.B, Eqs. (45) and (47)], the follow-up chemical step affects the overall kinetics by a factor involving k with a unity exponent, whereas an exponent of one-half is involved in the heterogeneous equivalent case:

$$M + ne \rightleftharpoons N$$

$$N + R \rightleftharpoons M + P \quad (K) \tag{207}$$

$$P \longrightarrow \cdots \tag{208}$$

[Compare the half-factor in Eq. (205) or the half-exponent in Eq. (206.] This effect, which arises from the heterogeneous nature of the electrochemical process (i.e., a surface reaction vis-á-vis a volume reaction in homogeneous phases), is the basis of the efficiency of redox catalysis or mediated electron transfer (see Sec. III.E.3 and also Chapter 28 mainly devoted to this topic). Thus for a given redox system, as in the sequence in Eqs. (190) and (191), the use of a redox mediator M in Eq. (207) allows the reduction of R to be performed at potentials less cathodic than $E_{1/2}$ in Eq. (205) (or the R oxidation at potentials less anodic than $E_{1/2}$) for the same electrochemical setup (i.e., an identical mass transfer rate).

3. Chemical Kinetics from Half-Wave Potentials: Determination of Rate Constants and Reaction Orders

The preceding two examples were presented to illustrate the simplicity of electrochemical analysis under steady-state conditions. Indeed, the kinetic derivations are very similar to those encountered in the homogeneous chemical situation, except for the replacement of the usual derivative dC/dt by a second-order derivative vis-à-vis the space variable d^2C/dy^2 as apparent in Eq. (193), for example. The existence of a second-order differentiation introduces unusual dependencies on reaction orders when compared with those observed in homogeneous kinetics. Thus if one considers the rate constant k in the chemical reaction (191) to be a pseudo-first-order rate constant, that is, $k = k_0[Z]$, where Z is a coreagent, the concentration of which is maintained constant, a dependency on $[Z]^{1/2}$ is observed [because of the involvement of k with a power of one-half in Eq. (198)] for electrochemical experiments rather than the dependency on [Z] that would be observed under homogeneous experiments. Let us consider a general case in which the product formed upon electron transfer reacts via a chemical reaction of the ρ^{th} order in P, and involving other coreagents A, B, ..., in excess, as featured in the reaction sequence (209) and (210):

$$R + ne \rightleftharpoons P \quad (E^\circ) \tag{209}$$

$$\rho P + \alpha A + \beta B + \cdots \longrightarrow \cdots \quad (k_0) \tag{210}$$

One obtains the pseudo-rate constant $k = k_0[A]^{\alpha}[B]^{\beta}\ldots$ Thus dimensionless analysis affords the differential equation in Eq. (211), which describes the concentration profile of the P species when λ is given as in Eq. (212).

$$\frac{d^2p}{dy^2} = \rho\lambda p^{\rho} \tag{211}$$

$$\lambda = k(C^0)^{(\rho-1)}\frac{\delta^2}{D} \qquad k = k_0[A]^{\alpha}[B]^{\beta}\cdots \tag{212}$$

When λ is extremely large and the usual situation in which the bulk solution contains no P is considered, integration of Eq. (211) is performed as follows. Multiplication of both members by 2(dp/dy) dy yields Eq. (213):

$$2\frac{dp}{dy}\frac{d^2p}{dy^2}dy = 2\rho\lambda p^{\rho}\,dp \tag{213}$$

The left-hand term in Eq. (213) is the derivation of $(dp/dy)^2$ vis-à-vis y. The right-hand side is the derivation of $[2\rho\lambda/(\rho+1)]p^{(\rho+1)}$ versus p. Thus integration of Eq. (213) yields

$$\left(\frac{dp}{dy}\right)^2 = \frac{2\rho\lambda}{\rho+1}p^{(\rho+1)} + \text{cst} \tag{214}$$

The integration constant in Eq. (214) is determined by the condition $p_0 \approx 0$ when $y \approx 1$. When λ is large this is also equivalent to saying that $dp/dy \approx 0$ when $y \approx 1$, since P exists only in a thin layer (called the kinetic layer) adjacent to the electrode (compare, e.g., Fig. 20a). The integration constant in Eq. (214) is then zero, and one obtains at the electrode surface, for $y = 0$,

$$\psi^2 = \frac{2\rho\lambda}{\rho+1}p_0^{(\rho+1)} \quad \text{since} \quad \psi = -\left(\frac{dp}{dy}\right)_0 \tag{215}$$

On the other hand, since R is not involved in chemical reactions, one obtains as in Eq. (183), $r_0 = 1 - \psi$. Thus for the nernstian electron transfer in Eq. (209), one obtains Eq. (216) when taking Eq. (215) into account.

$$r_0 = p_0 e^{(-\xi)}$$

$$1 - \psi = \psi^{2/(\rho+1)}\left(\frac{\rho+1}{2\lambda\rho}\right)^{1/(\rho+1)} e^{(-\xi)} \tag{216}$$

λ being a constant term, it may be included in the exponential factor, which yields the final equation of the steady-state voltammogram in Eq. (217). From this equation it is seen that the current depends only on the apparent dimensionless potential ξ^* given in Eq. (218).

$$\psi + \psi^{2/(\rho+1)}e^{(-\xi^*)} = 1 \tag{217}$$

$$\begin{aligned}\xi^* &= \xi + \frac{1}{\rho+1}\ln\frac{2\lambda\rho}{\rho+1} \\ &= \frac{nF}{RT}(E^{\circ} - E) + \frac{1}{\rho+1}\ln\frac{2\lambda\rho}{\rho+1}\end{aligned} \tag{218}$$

From the equation $\psi = 1 - r_0$, the limiting plateau current corresponds to $\psi = 1$. Thus the half-wave potential $E_{1/2}$ is obtained by replacing ψ by 1/2 in Eq. (217), which yields

$$E_{1/2} = E^\circ + \frac{RT}{nF}\frac{1-\rho}{1+\rho}\ln 2 + \frac{RT/nF}{\rho+1}\ln\frac{2\rho}{\rho+1} + \left[\frac{RT}{nF}(\rho+1)\right]\ln\left\{k_0[A]^\alpha[B]^\beta\cdots(C^0)^{(\rho-1)}\frac{\delta^2}{D}\right\} \quad (219)$$

Because of the expression of the last term, it is seen that at room temperature, for example, where $RT/F \ln 10 \approx 60\,mV$, $E_{1/2}$ varies by $[60\alpha(\rho+1)/n]$, $[60\beta(\rho+1)/n]$, and $[60(\rho-1)(\rho+1)/n]\,mV$ per unit of log [A], log [B], and log C^0, respectively. These variations then allows an easy determination of the various reaction orders of any follow-up chemical reactions, provided the initial electron transfer is fast enough and the number n of electrons exchanged is known.

Another approach consist of varying a reactant concentration and modifying the mass transfer rate δ in order that $E^{1/2}$ remain constant. The term in braces in Eq. (219) must then be kept constant; this is achieved when δ is equal to $\delta_{1/2}$, as given in Eq. (220):

$$\delta_{1/2} = \text{constant}[A]^{\alpha/2}[B]^{\beta/2}\cdots(C^0)^{(\rho-1)/2}\left(\frac{k_0}{D}\right)^{1/2} \quad (220)$$

Expression (220) shows that the slope of log $\delta_{1/2}$ versus log [A] is $\alpha/2$. Similarly, $\beta/2$ and $(\rho-1)/2$ are the slopes observed for the variations with log [B] or log C^0, which is a convenient way to determine the reaction orders. Note that although developed here for $E_{1/2}$, this procedure may be used with any chosen potential E_ε such that i/i^{lim} has a fixed value ε. Similarly, variations in k_0/D with the temperature (i.e., activation energy determinations) can be obtained through this procedure, provided care is taken of the RT/F factors, which need to be corrected [compare Eq. (219)] (see, e.g., Chapter 2 for extensions of this method).

All these methods stem from the fact that for a given reaction sequence, such as that in Eqs. (209) and (210), which involve a single rate-determining step, all the kinetics and thus the shape and location of the voltammogram depends only on the dimensionless rate constant parameter λ in Eq. (212). As a result, any modification of the experimental conditions that keep λ constant does not modify the dimensionless voltammogram.* Thus quantitative information on the chemical mechanism [Eq. (210) may be a succession of chemical steps] is obtained without mathematical derivation, but only from dimensionless analysis (compare Chapter 2).

However, determination of the intrinsic rate constant k_0 or of the apparent ρ^{th} order rate constant k requires that the precise mathematical dependence of $E_{1/2}$, for example., on the dimensionless rate constant be determined as in Eq. (219). Indeed, the principle of all methods for determining k_0 or k consists of increasing the mass transfer rate (i.e., here decreasing δ) so that $k\delta^2/D \approx 0$ and thus $E_{1/2} \approx E^\circ$.

These methods constitute the frame on which any particular method can be elaborated. Yet in practice, the experimental difficulty is that with standard apparatus, δ^2/D cannot be varied over an extremely wide range. For example, with the rotating disk electrode (RDE), which is the most convenient steady-state method (with the exception of ultramicroelectrodes [109]), δ depends on the rotation frequency w of the electrode (see Chapter 2). Yet to maintain correct hydrodynamic conditions w cannot be varied, with

*Yet the variations associated with the temperature may result in additional effects because of the temperature involvement in Eq. (219).

standard apparatus, outside the range of 10 rotations per second (rps) to 1000 rps, which limits access to fast kinetics.

Transient electrochemical techniques [110] allow this range of investigation to be widely extended (from 1 s to approximately 10 ns). Indeed, the same method may be used in a time domain extending over approximately eight orders of magnitude. Besides this very important point, transient electrochemical techniques provide current-intensity and current-potential patterns that are easily recognizable, for example in cyclic voltammetry. Thus with minimal eye training, a large amount of qualitative or nearly quantitative data may be obtained just by inspection of a transient voltammogram. This is in many respects an important advantage for diagnosis of kinetics, analogous with that of IR, ultraviolet (UV), or nuclear magnetic resonance (NMR) spectroscopies for structural information. In our opinion this is one of the main reasons why transient electrochemical methods have progressively supplanted steady-state methods. Indeed, as illustrated by the preceding examples, steady-state voltammograms have generally sigmoidal shapes that are difficult to relate to a particular mechanism without quantitative analysis.

C. Transient Electrochemical Methods

1. Introduction: Time Hysteresis in Current Reversal Techniques

As explained earlier, in transient electrochemical methods an electrical perturbation (potential, current, charge, and so on) is imposed at the working electrode during a time period θ (usually less than 10 s) short enough for the diffusion layer $\delta \approx (2D\theta)^{1/2}$ to be smaller than the convection layer δ_{conv} imposed by natural convection. Thus the electrochemical response of the system investigated depends on the exact perturbation as well as on the elapsed time. This duality is apparent when one considers a double-pulse potentiostatic perturbation applied to the electrode as in the double-step chronoamperometric method.

$$R + ne \rightleftharpoons P \quad (E^\circ) \quad (n > 0) \tag{221}$$

Let us consider, for example, the simple nernstian reduction reaction in Eq. (221) and a solution containing initially only the reactant R. Before any electrochemical perturbation the electrode rest potential E_1 is made largely positive to E°. At time zero the potential is stepped to a value E_2, sufficiently negative to E°, so that the concentration of R is close to zero at the electrode surface. After a time θ, the electrode potential is stepped back to E_1, so that the concentration of P at the electrode surface becomes zero. When this potentiostatic perturbation, represented in Fig. 21a, is applied in a steady-state method, the R and P concentration profiles are linear and depend only on the electrode potential but not on time, as shown in Fig. 20a (for $k \approx 0$). Yet when the same perturbation is applied in transient methods, the concentration profiles are curved and time dependent, as evidenced in Fig. 21b. Thus it is seen from this figure that a step duration at E_1, much longer than the step duration θ at E_2, is needed for the initial concentration profiles to be restored. This hysterisis corresponds to the propagation of the diffusion perturbation within the solution, which then keeps a "memory" of the past perturbation. This information is stored via the structuring of the concentrations in the space near the electrode as a function of the elapsed time.

The current flowing through the electrode is proportional to the gradient of the R (or the P) concentration profile at the electrode surface. Thus the progressive smoothing of the

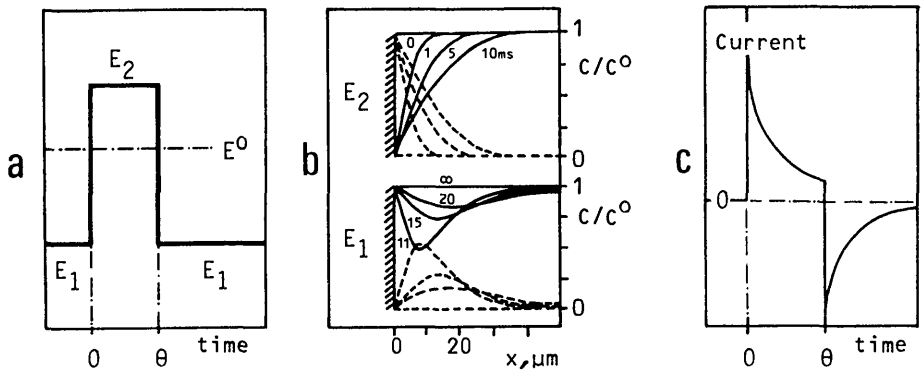


Figure 21. Transient potentiostatic electrochemical perturbation of a simple electron transfer reaction: (a) imposed potential; (b) resulting concentration profiles for the reactant (solid curves) or the product (dashed curves) for a step duration $\theta = 10$ ms at various times from the beginning of the pulse; (c) resulting variations in the current.

concentration profiles with the time elapsed after each discontinuity of the perturbation results in a constant decrease of the current with time, as represented in Fig. 21c.

Let us now assume that the produce P formed upon the electron transfer in Eq. (221) may react chemically with a half-life $t_{1/2}$. When $\theta \ll t_{1/2}$, almost no P has time to disappear during the time duration of the experiment. The P concentration profile then remains identical to that shown in Fig. 21b, and the current observed for $t > \theta$, which corresponds to P reoxidation, is identical to that in Fig. 21c. Conversely, when $\theta \gg t_{1/2}$, nearly all P molecules produced at the electrode are consumed and the P concentration profile is flat and close to zero, except in the close vicinity of the electrode. As a result almost no oxidation current is observed for $t > \theta$, that is, during the period in which the electrode potential is stepped positive to E° (see Fig. 21a). In the intermediate range, that is, when θ and $t_{1/2}$ are of similar orders of magnitude (generally $0.1t_{1/2} < \theta < 10t_{1/2}$), intermediate values of the oxidation current are observed as in Fig. 22. Determination of these variations allows the precise determination of the chemical follow-up sequence in which P is involved, as well as of the pertinent rate constants (see Chapter 2).

However, this large sensitivity for mechanistic analysis is earned at the expense of two important factors. First, owing to the large potential variations, the fine dependence of the system on the electrode potential around E° is not seen. Second, and maybe more important, the current versus time variations have no important visual characteristics. Indeed, as seen from Fig. 22, for example, all the curves are very similar and only their juxtaposition on the same figure allows their shapes to be compared.

For these two reasons cyclic voltammetry has progressively supplanted potentiostatic or galvanostatic methods in electrochemical kinetic investigations. A more complete description of this method is given in Chapter 2, yet for our purposes here we present the method briefly. It basically consists of applying a linear variation of the electrode potential E with time from a potential E_i, where the reactant R is not electroactive, to a potential E_f sufficient for the reactant concentration to be zero at the electrode surface. At E_f the potential is linearly scanned back to E_i, usually with an identical slope with respect to the time. The latter, v, is designated as the scan rate (in volts per second). Figure 23a presents such a potential-time dependence, together with

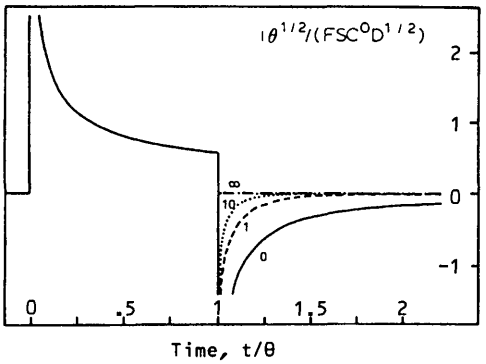


Figure 22. Variations in the current trace in a potentiostatic experiment for an EC sequence for different values of the dimensionless chemical rate constant $k\theta$ (numbers on the curves).

the corresponding i – E curve* (Fig. 23b) obtained for the reduction process in Eq. (221). Eye inspection of the cyclic voltammogram in Fig. 23b shows the presence of two current peaks, in contrast to the monotonous variations of the current in Fig. 21c. These peaks result from the existence of two opposite effects that successively control the magnitude of the current. For example, for the cathodic scan in Fig. 23, the gradual decrease in R concentration at the electrode surface, when the potential is made more and more cathodic, tends to increase the current by making the R concentration profile steeper. Yet the propagation of the perturbation into the solution, as shown in Fig. 21b, tends to flatten the concentration profile, which results in a progressive decay of the current. In practice it is easily understood that the large variations in the surface concentrations for potentials in the vicinity of E^{o} overwhelm the diffusion effect, the current then tending to rise. Yet when $[R]_{x=0}$ is close to zero, the potential variations affect the current magnitude less than the diffusion propagation in the solution, which explains why the current progressively decays. For the backward scan the same phenomenology applies to the product concentration $[P]_{x=0}$, which then results in the appearance of an inverted peak on the lower trace in Fig. 23b. When P reacts chemically, the magnitude of the reverse peak gradually decreases (Fig. 23c) because there is less and less P present in the solution. Again this allows determination of mechanisms and their pertinent rate constants, as explained for the double-step chronamperometric method. From this brief presentation it is seen that an important aspect of cyclic voltammetry is that the shapes of cyclic voltammograms are extremely indicative of the chemical processes occurring at the electrode or in the solution. As such it is an extremely useful tool for kinetic diagnosis. Yet the much more complicated shapes, when compared with those in Fig. 22, for example, makes quantitative information on the current difficult to obtain.

*Note that rather than presenting the current variations versus a time axis, a current versus potential plot is preferred. Thus in Fig. 23b, the upper trace corresponds to the forward cathodic scan, whereas the lower trace corresponds to the backward anodic scan.

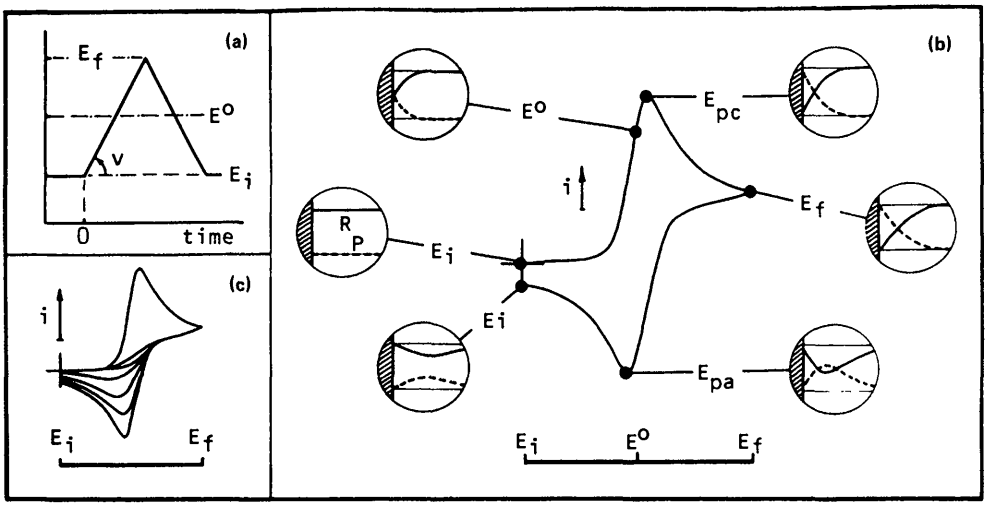


Figure 23. Cyclic voltammetry. (a) Imposed potential versus time variations. (b) Resulting transient current-potential curve for a simple electron transfer. The concentration profiles of the reactant R and product P are indicated at various characteristic potentials of the voltammogram. E_{pc} and E_{pa}, cathodic and anodic peak potentials. (c) Schematic change of the cyclic voltammogram as a function of the chemical stability of the product.

2. Transient Electrochemical Methods and Chemical Kinetics [110]

From the preceding presentation it is seen that the current variations with time or potential-time are intimately related to the concentration profiles of the species engaged in heterogeneous electron transfers at the electrode surface. Thus any kinetic or thermodynamic perturbation of these concentration profiles results in a variation of the current/time or current/potential-time transient characteristics as outlined in Fig. 22 or 23c. As was also apparent in the preceding discussion, as well as in several other places in this chapter, the degree to which these perturbations affect the concentration profiles is a function of their relative effect vis-à-vis the mass transfer rate. Dimensionless analysis again proves to be a very convenient way to appreciate this degree of interference through the dimensionless rate constants λ, equilibrium constants κ, or heterogeneous rate constants Λ in Table 5. Thus any experimental variation resulting in an overall constancy of these dimensionless parameters does not change the dimensionless ψ versus τ or ψ versus ξ curve, that is, the dimensionless voltammogram. This is a situation identical to that developed more extensively for the steady-state methods and is the basis of most electrochemical methods for the determination of reaction orders and rate constants.

Yet when applied to current reversal techniques, such as double-step chronamperometry of cyclic voltammetry, these methods require that an appreciable current be observed during the backward perturbation, that is, for $t > \theta$, in potentiostatic methods or after the potential scan inversion in cyclic voltammetry. This requires that the characteristic time θ of the method is adjusted to match the half-life $t_{1/2}$ of the electrogenerated intermediate. Today, owing to the recent development of ultramicroelectrodes, θ can be routinely varied from a few seconds to a few nanoseconds [102]. Yet with basic standard electrochemical equipment, θ is usually restricted from the second to the low millisecond range. Thus for experimental situations involving faster chemical reactions, current rever-

sal techniques are of little use. Yet, as is the case for steady-state methods, much kinetic information allowing mechanistic discriminations and reaction order determinations may be gathered from characteristic potential changes. Obviously, staircase methods, such as chronoamperometries, which are blind to these variations, are not convenient, but such methods as cyclic voltammetry or its descendants (Chapter 2) are extremely precise and adequate through peak potential or half-peak potential analysis.

Indeed, in cyclic voltammetry, peak potentials E_p play a role identical to that of half-wave potentials $E_{1/2}$ in steady-state methods. As for the later methods, peak potentials vary linearly with the logarithm of dimensionless kinetic parameters λ or Λ in Table 5, provided these latter have values sufficiently large when compared to unity [94]. These linear variations, which may be used for determination of reaction orders, stem from the same mathematical reasons as explained in the case of $E_{1/2}$. Yet the physical reason is quite different as evidenced by the case of the simple EC sequence in Eqs. (222) and (223):

$$R + ne \rightleftharpoons P \quad (E^\circ) \tag{222}$$

$$P \longrightarrow \cdots \quad (k) \tag{223}$$

From Eq. (174), the partial derivative equation describing the concentration profile of P is written in dimensionless terms (compare Table 5):

$$0 < y: \qquad \frac{\partial p}{\partial \tau} = \frac{\partial^2 p}{\partial y^2} - \lambda p \tag{224}$$

When $\lambda = k\theta \gg 1$, the kinetic term in Eq. (224) tends to be extremely large. On the other hand, $\partial p/\partial \tau$ cannot be infinite, for obvious physical reasons (except at possible discontinuities in the potential variations). Thus the diffusion term $\partial^2 p/\partial y^2$ must compensate* for the kinetic term in order that $\partial p/\partial \tau$ remain finite. In other words, a quasi-steady state is reached by mutual compensation of kinetics and diffusion. As a result, $\partial p/\partial \tau \ll \partial^2 p/\partial y^2$ and λp. Equation (224) thus becomes equivalent to Eq. (225), at least as concerns the derivation of the concentration profile of P.

$$0 < y: \quad 0 \approx \frac{\partial^2 p}{\partial y^2} - \lambda p \tag{225}$$

Comparison of Eq. (225) and Eq. (193) or (211) shows that the problem is identical to that presented for steady-state methods. Thus, the same mathematical derivations show that any characteristic potential figure (E_p or half-peak potential $E_{p/2}$, and so on) varies linearly with the logarithm of $\lambda = k\theta$. Indeed, one obtains by simple transposition in Eq. (219),

$$E_p = E^\circ + \left[\frac{RT}{nF(\rho + 1)}\right] \ln [k_0[A]^\alpha[B]^\beta \cdots (C^0)^{(\rho-1)}\theta] + \text{cst} \tag{226}$$

for the peak potential variations relative to the EC sequence in Eqs. (227) and (228).

$$R + ne \rightleftharpoons P \quad (E^\circ) \tag{227}$$

$$\rho P + \alpha A + \beta B + \cdots \longrightarrow \cdots \quad (k_0;\ k = k_0[A]^\alpha[B]^\beta \cdots) \tag{228}$$

*Note that this may be established on firm mathematical grounds, but it is beyond the scope of this presentation [94].

In Eq. (226), θ is usually defined as $\theta = RT/Fvn$, v being the scan rate, yet any dimensionless parameter, such as $\theta = \Delta E/v$, where ΔE is an adequate difference of potential, is equally convenient. Then, even when k_0 cannot be determined, its temperature variations, that is, $\Delta H^{\#}$, as well as the different reaction orders $\rho, \alpha, \beta, \ldots$, may be determined through the same experimental procedures already discussed for the analogous case of $E_{1/2}$ in steady-state methods.

Extension of these approaches to much more sophisticated kinetic situations, which involve, for example, two or three routes for a key intermediate, have been developed (Ref. 94 and references therein). Relative rate constants (or relations between rate constants) may then be obtained that allow, by reference to a known value, the absolute determination of all the series. For example, rate constants for the cleavage of aromatic halide anion radicals, corresponding to a half-life from about a second to a few picoseconds, have been determined using these procedures [103].

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2

Methods for Studies of Electrochemical Reactions

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I. INTRODUCTION

Electrochemical methods are widely used to gain information about the kinetics and mechanisms of chemical reactions associated with the electron transfer at an electrode. A unique feature of these methods is that the electrode serves both as the means of generating an intermediate, for instance a radical ion, and as the means to monitor its reactions to products.

This chapter is meant to serve both as a guide for the beginner and as an overview for the nonelectrochemist with a need to know the methods available. Approximately half of the chapter is concerned with various aspects of linear sweep and cyclic voltammetry in view of the importance and widespread use of these techniques. Some general aspects of the heterogeneous electron transfer process, and the chemical reactions associated with it, are introduced in this part. Electrochemical reactions in which the electroactive substrate is formed in a chemical reaction in solution prior to the electron transfer [1–5] and catalysis of chemical reactions by electron transfer [6] are not included in this chapter. The reader interested in the details of such reactions should consult the presentations referred to. The reader is encouraged also to consult Chapter 1, where a number of basic electrochemical concepts are discussed in detail.

In organic chemistry electrons are, as a rule, transferred one by one [7]. This is in contrast to inorganic electron transfer reactions, where two- and three-electron processes are common. However, in order to preserve the formalism generally used in electrochemistry, the number of electrons n is maintained in most formulas, although n equals one in practically all cases.

The general discussion of electrochemical reactions is, for the sake of consistency, restricted to cover reductions only. The transposition to oxidations should not present any problem, but the reader should be aware that the plus or minus sign in some equations has to be changed.

II. LINEAR SWEEP VOLTAMMETRY AND CYCLIC VOLTAMMETRY

Voltammetry in unstirred solution where the predominant mode of mass transport is limited to diffusion is one of the most useful techniques for the study of electrochemical reactions [1–5,8–11]. Most often, a triangular potential-time waveform with equal positive and negative slopes is used, and usually also the initial potential ($E_{initial}$) and final potential (E_{final}) are the same as illustrated in Fig. 1(a). This has given rise to the term cyclic voltammetry (CV). However, sometimes the voltage sweep is continued to include one or more additional E-t half-cycles or includes more complicated sawtooth-like waveforms to meet special needs.

An example of a current-potential curve, a so-called voltammogram, resulting from a simple triangular sweep is shown in Fig. 1(b). A characteristic feature is the presence of peaks, in this case two, identified by the peak potential E_p (see Chapter 1). The particular voltammogram shown in Fig. 1(b) results from a process in which a substrate during the forward sweep is reduced at $E_p = -1.57\,V$ to a product or intermediate, the oxidation of which is observed at $E_p = -1.22\,V$ during the backward sweep. In addition to E_p, a voltammogram is normally characterized by the peak current i_p and the half-peak width $E_p - E_{p/2}$, where $E_{p/2}$ is the half-peak potential, that is, the value of E at which $i = i_p/2$ [see Fig. 1(b)]. Analysis of how E_p, $E_p - E_{p/2}$, and i_p vary with, for instance, changes in the voltage sweep rate ν, and the bulk concentrations of substrate C_A^* and reagents C_x^* may

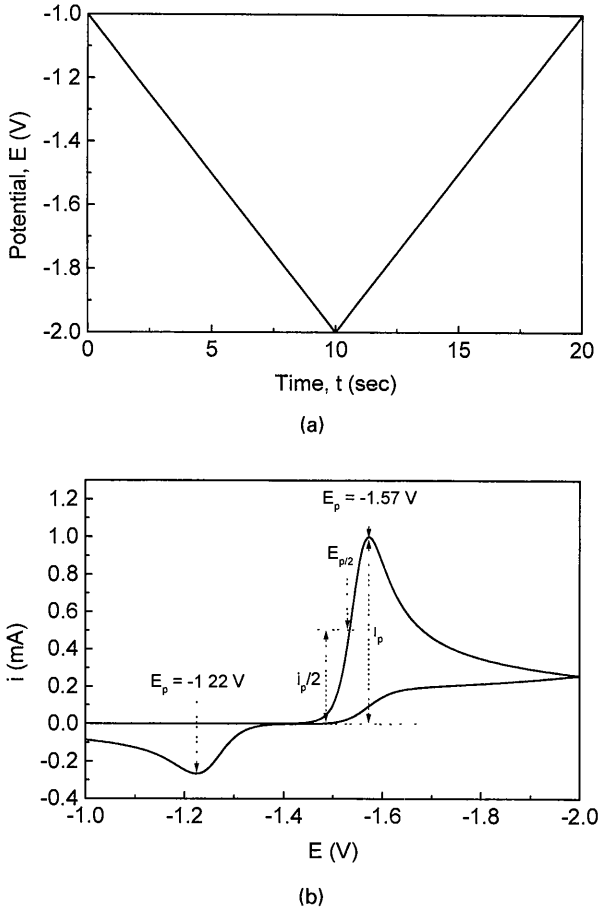


Figure 1. (a) Potential-time waveform for a triangular voltage sweep between -1 and -2 V at a sweep rate (ν) of 0.1 V s^{-1} and (b) a simulated (DigiSim) voltammogram for a substrate that is reduced at $E_p = -1.57$ V to a product or intermediate, the oxidation of which is observed at $E_p = -1.22$ V.

provide information about the thermodynamics and kinetics associated with the electrochemical reaction. This type of analysis is discussed in some detail in Secs. II.B and II.C. If only the voltammogram corresponding to the first half-cycle is used for data analysis, the technique is referred to as linear sweep voltammetry (LSV).

Significant theoretical contributions to this type of voltammetry were published in 1955 by Matsuda and Ayabe [12] and in 1964 by Nicholson and Shain [13]. The years to follow were a period of intense activity in the calculation of the electrode response for many different mechanisms. Most notable of the large volume of papers published are those of Nicholson and coworkers [14–17] and of the Savéant group [18–26]. Efforts initiated by Parker and coworkers [27–38] have been directed toward the development of LSV and CV as practical tools for quantitative studies of electrode processes. The application of digital simulation, originally described by Feldberg [39], has had a very strong impact in that the mathematical complexity of the calculations is greatly reduced and the approach is readily adopted for simple reaction schemes. The method has since

been further developed with the aim of including more complex reaction schemes, and to improve the precision and reduce the computer time [40–44]. User-friendly commercial software (DigiSim from BAS) is now available and has been used in this chapter for illustration purposes. In addition, simulation software is available directly from various authors. The interested reader may obtain the necessary information through the Internet.

A. The Experimental Setup

1. The Electrochemical Cell

An example of the instrumentation for LSV and CV is shown in Fig. 2. The cell is a simple and convenient design consisting of a 30-ml tube fitted with a B19/26 ground-glass joint. The electrode holder is made of Teflon and has holes for the three electrodes [1]. In addition, there is an inlet for an inert gas, usually nitrogen or argon, by which the voltammetry solution is purged before the measurements are made. This serves to remove dissolved oxygen, which, during the study of reduction processes, may itself be reduced or may react with intermediates such as radical anions produced at the cathode. Oxygen may react also with radical cations generated at the anode. Therefore, even for oxidations it is recommended that measurements are carried out in the absence of oxygen. The fixed arrangement of the electrodes is desirable to avoid changes in the geometry when an electrode is taken out of the electrolyte and then replaced.

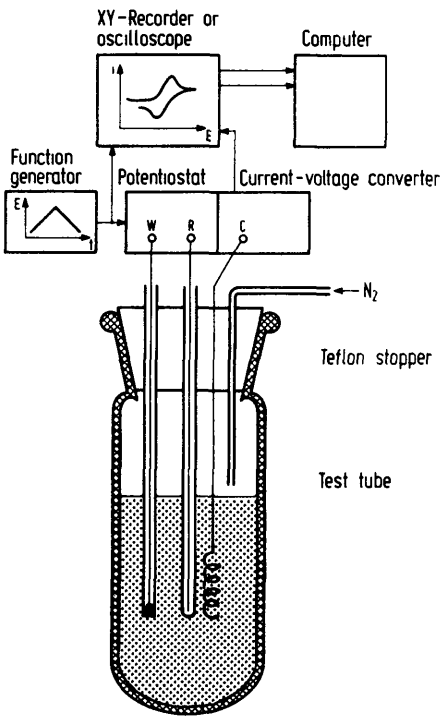


Figure 2. Experimental setup for linear sweep and cyclic voltammetry. W, working electrode; R, reference electrode; C, counterelectrode.

The working electrode usually is a circular disk made of platinum, gold, or glassy carbon, and which together with the electrical connection is inserted in a nonconducting material and polished to mirror quality. For reductions, mercury (film) electrodes are frequently used also owing to their microscopic smoothness and because of the large overpotential for hydrogen evolution characteristic for this electrode material. The latter makes possible the study of difficult-to-reduce substrates in water and other hydroxylic solvents. The oxidation of mercury at a low potential (0.3–0.4 V versus the saturated calomel electrode SCE) to mercury salts or organomercurials prevents the use of these electrodes for oxidations.

Reference electrodes are frequently commercial aqueous calomel electrodes or similar. However, the use of these types of electrodes may cause unnecessary complications, such as the need to separate the reference and working compartments of the cell in order to avoid exchange of dissolved species; or solvents if the electrochemical process is studied under nonaqueous conditions. In the latter case, it is often more convenient to use nonaqueous reference electrodes [45] containing a silver wire immersed in the same solvent-supporting electrolyte solution as that in the working compartment. A disadvantage of the latter type of reference electrode is that the potential usually cannot be accurately predicted. Thus, it is necessary to calibrate the electrode, for instance by recording the voltammogram of a standard redox couple, if the measured potentials are to be used in comparison with published values. A commonly used standard is the ferrocene/ferrocenium (Fc/Fc^+) redox couple [46].

The counterelectrode usually consists of a platinum wire or a small platinum foil.

Without any further refinement, the cell shown in Fig. 2 is suitable for measurements at voltage sweep rates from about 0.1 to 500 V s^{-1} using working electrodes with surface diameters ranging from about 2 to 0.1 mm (see also Sec. II.D).

2. The Solvent-Supporting Electrolyte System

For routine work, solvents and supporting electrolytes of the highest commercial quality may usually be used without further purification. It is, however, often necessary to have solvent-supporting electrolyte solutions that are essentially free of reactive impurities in order to study the voltammetric behavior of highly reactive intermediates. Elaborate vacuum line apparatus has been described for this purpose [47–51]. Sometimes it is more convenient instead to conduct the voltammetric experiments over neutral alumina [52]. The method is simply to add active neutral alumina directly to the voltammetric cell—for example, of the type shown in Fig. 2—and to mix vigorously for a few minutes before the measurements are made. The method is very effective in removing the electrophilic and nucleophilic impurities normally present in trace amounts even in the most carefully purified solvent-supporting electrolyte solutions. However, one should be aware that also the substrate may be adsorbed at alumina, and therefore this approach can in general be used only in qualitative work.

3. The Electronic Equipment

A discussion of the instrumental aspects of voltammetry and leading references to the original literature can be found in some of the monographs already cited in the introduction [1–4]. The essential units are the potentiostat, a triangular waveform generator, and a recording device. The latter is most conveniently a digital oscilloscope or a transient recorder. Commercial equipment with the units combined into one instrument controlled by a PC is available from a number of manufacturers. Also, homebuilt instrumentation

has found use in many cases, for instance, in studies in which so-called ultramicroelectrodes (discussed later) have been used.

B. Simple Electron Transfer Reactions

In this section we examine the relationship between current and potential in the case where the primary product of the electrode reaction is stable in solution, that is, there are no chemical reactions coupled to the electron transfer reaction.

An electron transfer reaction, Eq. (1), is characterized thermodynamically by the standard potential E°, that is, the value of E at which the activities of the oxidized form A and the reduced form B of the redox couple are the same. Thus, the second term in the Nernst equation, Eq. (2), cancels. Here, R is the molar gas constant ($8.314\,J\,K^{-1}\,mol^{-1}$), T is the temperature (K), n is the number of electrons, and F is Faraday's constant (96,485 C). Parentheses are used for activities, brackets for concentrations, and f_A and f_B are the activity coefficients. However, what may be measured directly is the formal potential $E^{\circ'}$ defined in Eq. (3). It follows that the relation between E° and $E^{\circ'}$ is given by Eq. (4). In this chapter we assume that activity coefficients are unity and therefore that $E^{\circ'} = E^\circ$

$$A + ne^- \underset{k_{s,b}}{\overset{k_{s,f}}{\rightleftharpoons}} B \qquad (E^\circ) \tag{1}$$

$$E = E^\circ + \frac{RT}{nF}\ln\frac{(A)}{(B)} = E^\circ + \frac{RT}{nF}\ln\frac{f_A[A]}{f_B[B]} \tag{2}$$

$$E = E^{\circ\prime} + \frac{RT}{nF}\ln\frac{[A]}{[B]} \tag{3}$$

$$E^{\circ\prime} = E^\circ + \frac{RT}{nF}\ln\frac{f_A}{f_B} \tag{4}$$

The kinetics of the electron transfer reaction, Eq. (1), are described by the heterogeneous electron transfer rate constants $k_{s,f}$ and $k_{s,b}$ ($cm\,s^{-1}$), where the subscript s indicates a surface process. The values of $k_{s,f}$ and $k_{s,b}$ depend exponentially on the potential E as seen in Eqs. (5) and (6), in which k° is the standard heterogeneous electron transfer rate constant and α is the electrochemical transfer coefficient [53] (see also Chapter 1). It is seen from Eqs. (5) and (6) that $k_{s,f} = k_{s,b} = k^\circ$ at $E = E^\circ$. The relation between $k_{s,f}$ and $k_{s,b}$ and the current i is given by the Butler-Volmer equation, Eq. (7), where A is the electrode area (cm^2), and $[A]_s$ and $[B]_s$ are the concentrations of A and B at the electrode surface.

$$k_{s,f} = k^\circ \exp[-\alpha nF(E - E^\circ)/(RT)] \tag{5}$$

$$k_{s,b} = k^\circ \exp[(1 - \alpha)nF(E - E^\circ)/(RT)] \tag{6}$$

$$\begin{aligned} i &= nFA(k_{s,f}[A]_s - k_{s,b}[B]_s) \\ &= nFAk^\circ\{[A]_s \exp[-\alpha nF(E - E^\circ)/(RT)] - [B]_s \exp[(1 - \alpha)nF(E - E^\circ)/(RT)]\} \end{aligned} \tag{7}$$

In electrochemistry, electron transfer reactions are classified as reversible, quasi-reversible, or irreversible, depending on the ability of the reaction to respond to changes in E. In voltammetry the relevant kinetic parameters are k°, α, and ν. The mutual influence of k° and ν is conveniently expressed through the magnitude of the dimensionless para-

meter Λ defined in Eq. (8) [12], where D_A and D_B are the diffusion coefficients for A and B, respectively. Usually these are assumed to be identical.

$$\Lambda = \frac{k^\circ \left(\frac{D_A}{D_B}\right)^{\alpha/2}}{\left(\frac{D_A \nu n F}{RT}\right)^{1/2}} = \frac{k^\circ}{\left(\frac{D \nu n F}{RT}\right)^{1/2}} \quad \text{for } D_A = D_B = D \tag{8}$$

1. Reversible Electron Transfer

A reversible electron transfer reaction is, strictly speaking, the limiting case where A and B are in thermodynamic equilibrium at the electrode surface, that is, the electron transfer reaction responds instantaneously to a change in E. Thus, the ratio between $[A]_s$ and $[B]_s$ depends only on $E - E^\circ$, the relationship being given by the rearranged Nernst equation, Eq. (9).

$$[A]_s/[B]_s = \exp[nF(E - E^\circ)/(RT)] \tag{9}$$

The equilibrium condition implies an infinitely large value of Λ, which may result from an infinitely large value of k° and/or an infinitely small value of ν. In practical work, an electron transfer process is called reversible if the deviations from this limiting case are so small that they cannot be detected experimentally. This happens typically when Λ is larger than approximately 12 (discussed later). It also follows from the preceding discussion that the shape and position of the voltammogram, defined for instance by the values of E_p, $E_p - E_{p/2}$, and i_p, are independent of the kinetic parameters k° and α.

A cyclic voltammogram for a reversible one-electron reduction is shown in Fig. 3.

Ideally, the part of voltammogram recorded during the forward sweep satisfies the following three criteria [12], where the values given in mV refer to T = 298 K:

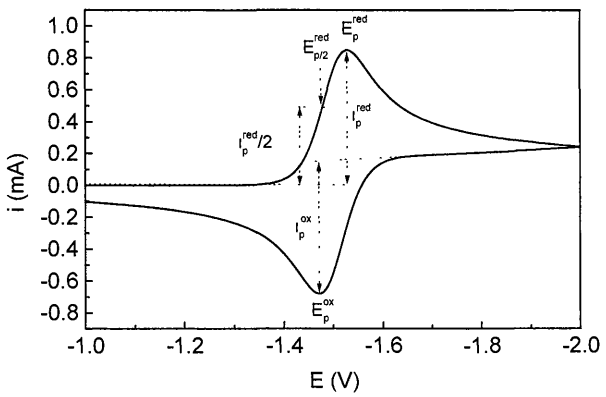


Figure 3. Simulated (DigiSim) cyclic voltammogram for a reversible one-electron reduction with $E^\circ = -1.5$ V. The other simulation parameters are $k^\circ = 10^4$ cm s^{-1}, $\alpha = 0.5$, T = 298.2 K, $C_A^* = 1$ mM, and A = 1 cm^2. These are the same for the other simulations included in this section unless otherwise stated. The simulations do not include effects caused by uncompensated solution resistance (see Sec. II.D.2) and double-layer charging (see Chapter 1).

1. The value of $E_p - E^\circ$ is given by Eq. (10) and is independent of ν. This is often expressed as in Eq. (11).

$$E_p - E^\circ = -1.11\frac{RT}{nF}V = -\frac{28.5}{n}\ mV \tag{10}$$

$$dE_p/d(\log \nu) = 0 \tag{11}$$

2. The value of $E_p - E_{p/2}$ is given by Eq. (12).

$$E_p - E_{p/2} = -2.20\frac{RT}{nF}\ V = -\frac{56.5}{n}\ mV \tag{12}$$

3. The value of i_p is given by Eq. (13). It is seen that i_p increases linearly with $\nu^{1/2}$

$$i_p = 0.4463nFAC_A^* D_A^{1/2}\nu^{1/2}\left(\frac{nF}{RT}\right)^{1/2} \tag{13}$$

If also the part of the voltammogram recorded during the backward sweep is included, we have:

4. The peak current ratio $-i_p^{ox}/i_p^{red}$ is unity and independent of ν. For a simple electron transfer process, measurements of the peak current ratio serve to control the assumption that B is indeed stable in the solution on the time scale of the experiment.
5. The peak separation, $\Delta E_p = E_p^{ox} - E_p^{red}$, is equal to approximately 57 mV, with the exact value depending on the potential E_{switch} at which the voltage sweep is reversed. Equation (14) refers to the limiting case $E^\circ - E_{switch} = \infty$, where ΔE_p for obvious reasons is twice the value of $E_p - E^\circ$.

$$\Delta E_p = E_p^{ox} - E_p^{red} = 2 \times 1.11\frac{RT}{nF}\ V = \frac{57.0}{n}\ mV \tag{14}$$

6. E° may be determined as the average of E_p^{ox} and E_p^{red}, Eq. (15), often referred to as the midpoint potential. Again, this equation is only strictly valid for $E^\circ - E_{switch} = \infty$, but the error at, for instance, $E^\circ - E_{switch} = 0.3$ V is negligible in most practical work.

$$E^\circ = (E_p^{ox} - E_p^{red})/2 \tag{15}$$

A difficulty arises in determining $-i_p^{ox}/i_p^{red}$ in that it is not obvious how the base line for i_p^{ox} should be determined. Indeed, experimental voltammograms are often less well behaved than the simulated one shown in Fig. 3. The most reliable procedure appears to be a graphical method [54], which, however, should be used with care [55].

It is often possible to observe a second electron transfer reaction, Eq. (16), within the potential window defined by the discharge of the solvent-supporting electrolyte solution.

$$B + ne^- \rightleftharpoons C \tag{16}$$

An example of a voltammogram for two consecutive one-electron reductions is shown in Fig. 4. When the two electron transfer reactions are as well separated as those shown in Fig. 4, the difference between the peak potentials for the first and the second electron transfer is to a good approximation equal to the difference in standard potentials $E_2^\circ - E_1^\circ$. When the two electron transfer reactions are closely spaced, the difference in standard potentials may be determined from the half-peak width of the overlapping waves [56].

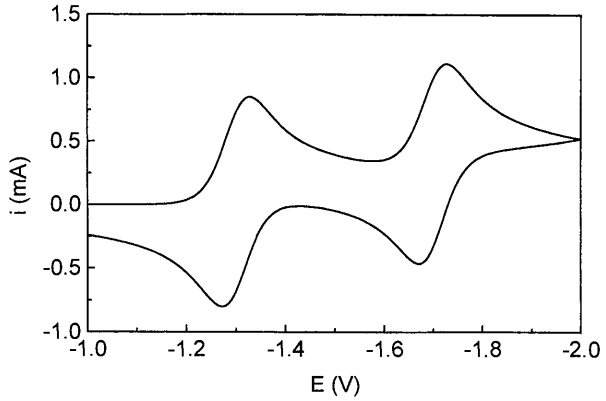


Figure 4. Simulated (DigiSim) cyclic voltammogram for two consecutive reversible one-electron reductions with $E_1^\circ = -1.3\,V$ and $E_2^\circ = -1.7\,V$. For other simulation parameters, see Fig. 3.

When $E_2^\circ - E_1^\circ$ is known, the equilibrium constant for disproportionation K_{dispr}, Eq. (17), may calculated from Eq. (18). Introduction of the E° values used in the simulation for Fig. 4, that is, $E_1^\circ = -1.3\,V$ and $E_2^\circ = -1.7\,V$, together with $n = 1$ results in $K_{dispr} = 1.7 \times 10^{-7}$. The value of K_{dispr} is dependent on solvent and is, as a rule, found to decrease with decreasing polarity of the solvent [52].

$$2B \rightleftharpoons A + C \qquad (K_{dispr}) \tag{17}$$

$$K_{dispr} = \exp[(E_2^\circ - E_1^\circ)nF/(RT)] \tag{18}$$

The formation of more highly charged species may be observed in special cases.

2. Quasi-Reversible Electron Transfer

In the general case, named quasi-reversible, the electron transfer reaction, Eq. (1), does not respond instantaneously to changes in E. In other words, $[A]_s$ and $[B]_s$ are determined not only by the value of $E - E^\circ$, but also, via Eqs. (5) and (6), by the magnitudes of k° and α.

Typical voltammograms for quasi-reversible electron transfers are shown in Fig. 5. In comparison with the voltammogram for the reversible case (Fig. 3), it is seen that the reduction peak has moved in the negative direction and the oxidation peak in the positive direction, resulting in a peak separation ΔE_p larger than $\sim 57\,mV$. It appears from Eqs. (5) and (6) that decreasing values of α cause $k_{s,f}$ to decrease and $k_{s,b}$ to increase and, as a consequence, E_p^{red} and E_p^{ox} both move in the negative direction (Fig. 5). Conversely, increasing values of α cause E_p^{red} and E_p^{ox} to move in the positive direction (Fig. 5). The overall result is that the effect of the magnitude of α on ΔE_p is small as long as α does not deviate too much from 0.5 [14,57]. In that case k° may conveniently be determined from values of ΔE_p recorded at different ν. It is important to notice, however, that the mere observation of ΔE_p larger than $\sim 57\,mV$ (at $T = 298\,K$) is not in itself a sufficient criterion for the classification of an electron transfer reaction as quasi-reversible. Many other factors, such as adsorption phenomena and insufficient electronic compensation of the voltage drop caused by the solution resistance (discussed later), may cause voltammograms to have peak separations larger than $\sim 57\,mV$.

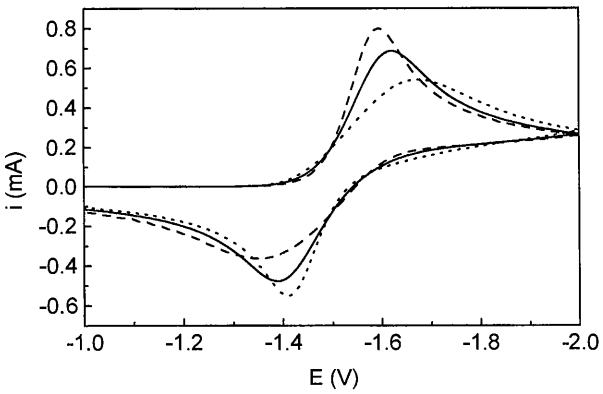


Figure 5. Simulated (DigiSim) cyclic voltammograms at $\nu = 1\,V\,s^{-1}$ for a quasi-reversible one-electron reduction with $E^\circ = -1.5\,V$, $k^\circ = 3 \times 10^{-3}\,cm\,s^{-1}$, and $\alpha = 0.3$ (dot), $\alpha = 0.5$ (solid), and $\alpha = 0.7$ (dash). For other simulation parameters, see Fig. 3.

The expressions for $E_p - E^\circ$, $E_p - E_{p/2}$ and i_p for the quasi-reversible case are given in Eqs. (19)–(21), where $\Xi(\Delta, \alpha)$, $\Delta(\Lambda, \alpha)$, and $K(\Lambda, \alpha)$ are nonlinear functions of Λ and α. These are available as graphical representations in the paper by Matsuda and Ayabe [12]. Alternatively, the reader may find expressions for $E_p - E^\circ$, $E_p - E_{p/2}$, and i_p in dimensionless notation in a paper by Savéant and coworkers [20].

$$E_p - E^\circ = -\Xi(\Lambda, \alpha)\frac{RT}{nF} \tag{19}$$

$$E_p - E_{p/2} = -\Delta(\Lambda, \alpha)\frac{RT}{nF} \tag{20}$$

$$i_p = 0.4463K(\Lambda, \alpha)nFAC_A^* D_A^{1/2} \nu^{1/2} \left(\frac{nF}{RT}\right)^{1/2} \tag{21}$$

3. Irreversible Electron Transfer

When Λ becomes progressively smaller, the shape of the voltammogram continues to change. Experimentally, a constant shape is reached when Λ is smaller than approximately 0.2 (discussed later). The value of E required to obtain an appreciable rate of reduction of A is now so much on the negative side of E° that the second term in Eq. (7) may be neglected. In other words, the electron transfer has become irreversible. By the same type of argument it is clear that the oxidation of B back to A during the backward sweep proceeds irreversibly as well.

Typical voltammograms for irreversible electron transfers are shown in Fig. 6. In comparison with the voltammograms for the quasi-reversible case (Fig. 5), it is seen that the reduction peak has moved even more in the negative direction and the oxidation peak even more in the positive direction, to the point that there is now a potential region between the two peaks in which essentially no current flows. The extension of this region depends on the magnitude of Λ. Also, the effect of α is more pronounced than for the quasi-reversible case.

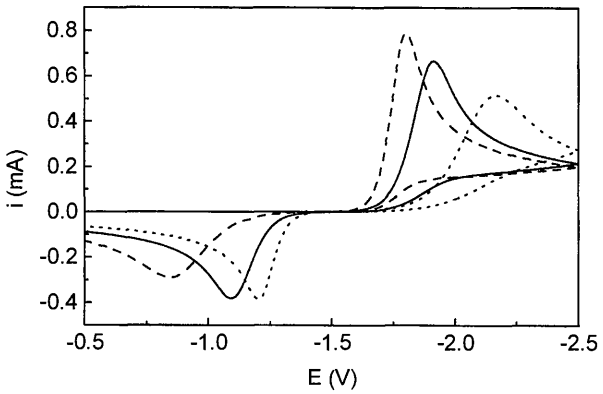


Figure 6. Simulated (DigiSim) cyclic voltammograms at $\nu = 1\,V\,s^{-1}$ for an irreversible one-electron reduction with $E^\circ = -1.5\,V$, $k^\circ = 10^{-5}\,cm\,s^{-1}$, and $\alpha = 0.3$ (dot), $\alpha = 0.5$ (solid), and $\alpha = 0.7$ (dash). For other simulation parameters, see Fig. 3.

Ideally, the voltammogram satisfies the following three criteria [12], where, as before, the values given in mV refer to T = 298 K:

1. The value of $E_p - E^\circ$ is given by Eq. (22) and depends on α, k°, D_A, and ν. It follows that E_p changes with ν as given in Eq. (23).

$$E_p - E^\circ = \left(-0.783 + \ln\frac{k^\circ}{D_A^{1/2}} - \tfrac{1}{2}\ln\frac{\alpha\nu nF}{RT}\right)\frac{RT}{\alpha nF} \tag{22}$$

$$\frac{dE_p}{d(\log\nu)} = -\frac{1}{2}\frac{RT}{\alpha nF}\ln 10 = -\frac{29.6}{\alpha n}\ \text{mV} \tag{23}$$

2. The value of $E_p - E_{p/2}$ is given by Eq. (24), which for $\alpha = 0.5$ results in $E_p - E_{p/2}$ equal to $-95.4\,mV$.

$$E_p - E_{p/2} = -1.857\frac{RT}{\alpha nF}\ V = -\frac{47.7}{\alpha n}\ \text{mV} \tag{24}$$

3. The value of i_p is given by Eq. (25). It is seen that i_p increases linearly with $\nu^{1/2}$. By comparison of Eqs. (13) and (25) it is seen that i_p for the irreversible case is $1.11\alpha^{1/2}$(0.78 for $\alpha = 0.5$) times i_p for the reversible case.

$$i_p = 0.4958nFAC_A^*D_A^{1/2}\nu^{1/2}\left(\frac{\alpha nF}{RT}\right)^{1/2} \tag{25}$$

4. Concluding Remarks and Examples

The borderlines between reversible, quasi-reversible, and irreversible behavior were originally defined by Matsuda and Ayabe [12] on the basis of mathematical reasoning. However, in practical work it is more convenient to define borderlines reflecting where deviations from the two limiting cases, reversible and irreversible, may be observed experi-

mentally. Using the rather conservative estimate (discussed later) that the error in peak potential measurements is typically ±2 mV, Savéant and coworkers [20] arrived at the borderlines given by Eqs. (26)–(28) for $\alpha = 0.5$. The handy expressions for k° refer to $n = 1$, $T = 298\,K$, and $D = 1 \times 10^{-5}\,cm^2\,s^{-1}$, and assumes that ν is measured in $V\,s^{-1}$.

Reversible: $$\Lambda \geq 11.5 \quad \text{or} \quad k^\circ \geq 0.23\nu^{1/2}\ cm\,s^{-1} \tag{26}$$

Quasi-reversible: $$11.5 \geq \Lambda \geq 0.2 \quad \text{or} \quad 0.23\nu^{1/2}\ cm\,s^{-1} \geq k^\circ \geq 0.004\nu^{1/2}\ cm\,s^{-1} \tag{27}$$

Irreversible: $$\Lambda < 0.2 \quad \text{or} \quad k^\circ < 0.004\nu^{1/2}\ cm\,s^{-1} \tag{28}$$

It follows from this discussion that an electron transfer reaction that appears reversible at one (low) sweep rate may change to a quasi-reversible or even irreversible process at higher sweep rates. This should be kept in mind since the application of LSV and CV in kinetics and mechanism studies, detailed in Sec. II.C, usually includes the recording of voltammograms at a number of different sweep rates, and the analysis of the data is usually based on the assumption that the electron transfer is reversible.

Radical ions and radicals are usually highly reactive and react further on the time scale of voltammetric experiments at low ν. Exceptions are many heterocyclic compounds and substrates carrying a substituent that is able to stabilize a negative or positive charge and/or an unpaired electron. Examples include the reduction of nitro compounds (Chapter 9), quinones (Chapter 10), and compounds such as viologens containing two reducible functional groups [58], or the oxidation of thianthrene (Chapter 17), tetrathiafulvalenes (Chapter 17), and a number of methoxy substituted aromatic hydrocarbons (Chapter 16). Numerous other examples may be found throughout this book. In many of the examples mentioned, it is possible to observe also the second electron transfer leading to the dianion or dication. In a special case, reversible or quasi-reversible electron transfers leading ultimately to the formation of an octaanion have been observed [59].

The determination of E° for the oxidation or reduction of a substrate provides a direct measure of the free energy of formation of the resulting intermediate, a radical ion or radical. Values of E° are important quantities in thermochemical calculations of, for instance, bond energies [60]. The temperature dependence of E°, which gives insight into ΔS for the electron transfer reaction, has been investigated in a number of cases, in particular for the reduction of aromatic nitro compounds [61]. Values of $-\Delta S_{273.2}$ are typically in the range 5–20 cal $K^{-1}\,mol^{-1}$.

Electron transfer reactions that are accompanied by large structural changes may give rise to the rather unusual observation that the second electron is easier to add or remove than the first, so-called potential inversion [62–64].

Examples of the application of CV for the study of the kinetics of the heterogeneous electron transfer reaction include the reduction of quinones [65,66] and nitroalkanes [66–68]. For radical anions, the effect of the nature of the counterion, that is, the cation of the supporting electrolyte, has been investigated [66,69], and the general trend is that the value of k° decreases when the length of the carbon chain in R_4N^+ increases (see also Sec. II.C.5 for other counterion effects). Attention should be paid also to the fact that k° is sometimes observed to depend on the electrode material and thus is not a true standard value. [70]. In

addition to CV, methods based on AC voltammetry are useful for studies of heterogeneous electron transfer kinetics [71].

C. Electron Transfer Reactions Followed by Chemical Reactions in Solution

Some of the most successful applications of LSV and CV are concerned with the study of the kinetics and mechanisms of the reactions of electrode generated intermediates and a large share of the electrochemical literature deals with this aspect of voltammetry [8,9,13–38,72]. The majority of electrochemical reactions include radical ions as the primary intermediates, and the reaction schemes describing the conversion of a substrate A to products are typically composed of one or two one-electron transfers and one or two chemical steps. The examples include cathodic hydrogenations, ($+2e^-$, $+2H^+$) (see Chapter 6) and hydrodimerizations ($+e^-$, $+H^+$) (see Chapter 21), and anodic additions ($-2e^-$, $+2Nu^-$) (see Chapter 24), dehydrodimerizations ($-e^-$, $-H^+$) (see Chapter 22), and substitutions ($-2e^-$, $+Nu^-$, $-H^+$) (see Chapter 24), where Nu^- is nucleophile)

The electrochemical literature abounds with symbols and abbreviations that are not always strictly logical. Therefore, a few comments about the abbreviations used in the following to designate basic electrode mechanisms are necessary. The notation is based on that due to Testa and Reinmuth [73] where the letter e indicates an electron transfer process and the letter c indicates a chemical reaction. It is helpful to distinguish between reversible (fast) and rate-determining (slow) steps by using lower-case letters for reversible and capital letters for rate determining steps. Since electron transfer reactions can take place either at an electrode (heterogeneous electron transfer) or in solution (homogeneous electron transfer), those taking place in solution are given the subscript h. The use of this and other abbreviations frequently met in the literature is illustrated next. The presentation is restricted to cover only chemical reactions that follow a reversible electron transfer. Reaction schemes including quasi-reversible electron transfer, or dissociative electron transfer reactions [74,75], for instance, observed for the reduction of alkyl halides (Scheme 1), are only mentioned briefly.

Dissociative electron transfer reaction

$$R{-}X + e^- \longrightarrow R\bullet + X^-$$

Scheme 1

1. Typical Irreversible Follow-Up Reactions

Examples of mechanisms resulting in first-order rate laws are summarized in Scheme 2, where the right-hand part of Eq. (ii) refers to the situation where the reaction of B is with a reagent X. In that case the kinetics are usually studied under pseudo first-order conditions, that is, at $C_X^*/C_A^* \gg 1$. Often the product C is more easily reduced than A [76], resulting in a second electron transfer. This may take place either at the electrode (iii) or in solution (iv) [77], resulting in an eCe or an eCe_h mechanism, with the latter sometimes being referred to as a DISP1 mechanism. The intermediate D finally reacts with, for example, the reagent X, to the product E. The observed rate laws (vi)–(viii) for all these cases are the same.

Mechanisms resulting in first-order rate laws:

$A + e^- \rightleftharpoons B$ (i)

$B \xrightarrow{k_{II}} C$ or $B + X \xrightarrow{k_{II}'} C$ (ii)

$C + e^- \longrightarrow D$ (iii)

$B + C \longrightarrow A + D$ (iv)

$D + X \longrightarrow E$ (v)

Mechanism abbreviation	Observed rate law	k_{obs} ($C_X^*/C_A^* >> 1$)	
(i)-(ii): eC	$-d[B]/dt = k_{obs}[B]$	k_{II} or $k_{II}'C_X^*$	(vi)
(i)-(ii)-(iii): eCe	$-d[B]/dt = k_{obs}[B]$	k_{II} or $k_{II}'C_X^*$	(vii)
(i)-(ii)-(iv): eCe_h	$-d[B]/dt = k_{obs}[B]$	$2k_{II}$ or $2k_{II}'C_X^*$	(viii)

Scheme 2

Another important set of reactions are the dimerizations, which are usually discussed within the frames of the two mechanisms shown in Scheme 3. If the formation of C results from the coupling of two radicals or radical ions (ii), the reaction is referred to as a radical–radical process (RR). Another route to C, the radical–substrate process (RS), includes the coupling between A and B (iii) resulting in the formation of an intermediate I that is further reduced to C by reaction with B (iv). The direct reduction of I to C at the electrode is usually without importance. Finally, the intermediate C reacts with a reagent X to the product D. These dimerization mechanisms belong to a more general scheme to be discussed in some detail later (Sec. II.C.5).

Mechanisms resulting in second-order or third-order rate laws:

$A + e^- \rightleftharpoons B$ (i)

$2\,B \xrightarrow{k_{II}} C$ (ii)

$A + B \xrightarrow{k_{III}} I$ (iii)

$B + I \longrightarrow A + C$ (iv)

$C + X \longrightarrow D$ (v)

Mechanism abbreviation	Observed rate law	k_{obs}	
(i)-(ii): eC(dim) or RR	$-d[B]/dt = k_{obs}[B]^2$	$2k_{II}$	(vi)
(i)-(iii)-(iv): RS	$-d[B]/dt = k_{obs}[A][B]$	$2k_{III}$	(vii)

Scheme 3

2. Kinetic Classification of Simple Irreversible Follow-Up Reactions

Let us now consider the voltammetric response for a reversible one-electron reduction followed by an irreversible chemical reaction, for instance, an eC mechanism with the rate constant k ($=k_{II}$ in Scheme 2). The voltammograms resulting from different values of k at $\nu = 1\,V\,s^{-1}$ are shown in Fig. 7.

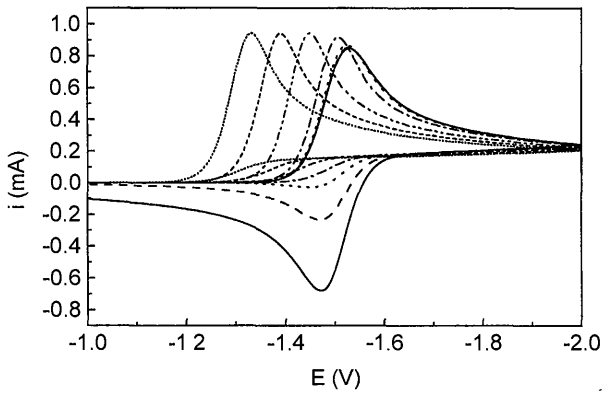


Figure 7. Simulated (DigiSim) cyclic voltammograms at $\nu = 1\,V\,s^{-1}$ for an eC mechanism with $E^\circ = -1.5\,V$ and $k = 2\,s^{-1}$ (dash), $10\,s^{-1}$ (dot), $10^2\,s^{-1}$ (dash-dot), $10^4\,s^{-1}$ (dash-dot-dot), $10^6\,s^{-1}$ (short dash), and $10^8\,s^{-1}$ (short dot), corresponding to $\lambda = 0.0513$, 0.257, 2.57, 2.57×10^2, 2.57×10^4, and 2.57×10^6, respectively. The solid line corresponds to the simple electron transfer reaction shown in Fig. 3, where also other simulation parameters are given.

Given the value of ν, it is seen that both the shape and the position of the voltammogram depend on the magnitude of k. On the other hand, given the value of k, it is intuitively understood that the effect of the chemical reaction will gradually diminish if the sweep rate is allowed to increase. In limit, the experiment time is so short that the chemical reaction does not have the time to manifest itself and, consequently, the voltammogram observed is just that for the electron transfer reaction, Eq. (1).

The effect of the relative magnitudes of k and ν on the position and shape of a voltammogram is conveniently discussed in terms of the dimensionless parameter λ, defined by Eq. (29) for a reaction following a first-order rate law and by Eq. (30) for a reaction following a second-order rate law [18–20].

$$\lambda = \frac{kRT}{\nu nF} \quad \text{(first-order rate law)} \tag{29}$$

$$\lambda = \frac{kC_A^* RT}{\nu nF} \quad \text{(second-order rate law)} \tag{30}$$

It is convenient also to classify the electrochemical reactions with regard to the nature of the response. Given the value of ν, it is seen from Eqs. (29)–(30) that increasing values of k correspond to increasing values of λ. Beginning with $\lambda = 0$, the effect of increasing values of λ is initially that the current associated with the oxidation of B during the backward sweep gradually disappears (see e.g., Fig. 7). The peak potential is, so far, only little affected. The region of λ values, from the point where the effect of the chemical reaction becomes experimentally detectable to the point where the current for the oxidation of B has totally disappeared, is given by Eq. (31) for the eC mechanism (first-order rate law) and by Eq. (32) for the RR dimerization (second-order rate law) [20]. Again, the handy expressions correspond to $n = 1$ and $T = 298\,K$. In this region the system is under mixed diffusion and kinetic control. Limits for λ relating to other mechanisms, including the eCe, eCe_h, and more complex reaction schemes, have been reported in the literature [18–20].

eC mechanism:

$$0.11 < \lambda < 1.89 \quad \text{or} \quad 4.3\nu\ s^{-1} < k < 73.5\nu\ s^{-1} \tag{31}$$

RR dimerization:

$$0.37 < \lambda < 1.35 \quad \text{or} \quad 14.5\nu\ s^{-1} < kC_A^* < 52.5\nu\ s^{-1} \tag{32}$$

At λ values higher than those given, for instance, by the upper limits in Eqs. (31)–(32) the shape of the voltammogram is essentially independent of λ and an increase in λ just results in displacement of the voltammogram in the positive direction. This is illustrated by the voltammograms corresponding to $k = 10^4$, 10^6 and $10^8\,s^{-1}$ in Fig. 7. A stationary state has now been established in solution by mutual compensation of the chemical reaction of B and the diffusion process, and the system is said to be under purely kinetic control.

3. Irreversible Follow-Up Reactions, Mixed Diffusion and Kinetic Control (CV and DCV)

As mentioned earlier, the characteristic features of processes in this category are that E_p is close to that for the no-reaction case, Eq.(1), and that the peak current ratio $-i_p^{ox}/i_p^{red}$ varies from approximately unity to zero. The observation of oxidation current for B during the backward sweep shows that the material conversion is low. By comparison of the voltammograms for the eC and the eCe_h mechanisms in Fig. 8, it is seen that the second electron transfer reaction in the eCe_h mechanism gives rise to only little additional current, illustrating that only a small fraction of B has been converted to C.

Although the value of E_p in this kinetic region is only slightly affected by the magnitude of λ, a careful investigation of the sweep rate dependence of E_p may, nevertheless, have diagnostic value, for instance, in the distinction between the RR and the RS dimerization mechanisms. This is illustrated by Fig. 9, which shows the theoretical curves, the so-called working curves, for $E_p - E^\circ$ for the two mechanisms together with experi-

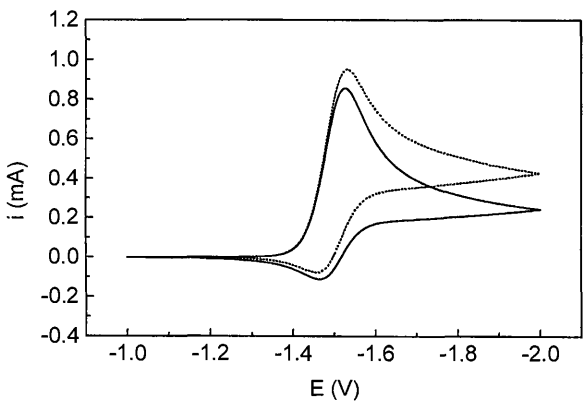


Figure 8. Simulated (DigiSim) cyclic voltammograms for the eC mechanism (solid) and the eCe_h mechanism (dot) at $\nu = 1\,V\,s^{-1}$ with $E^\circ = -1.5\,V$ and $k = 4\,s^{-1}$ ($\lambda = 0.103$). For other simulation parameters, see Fig. 3.

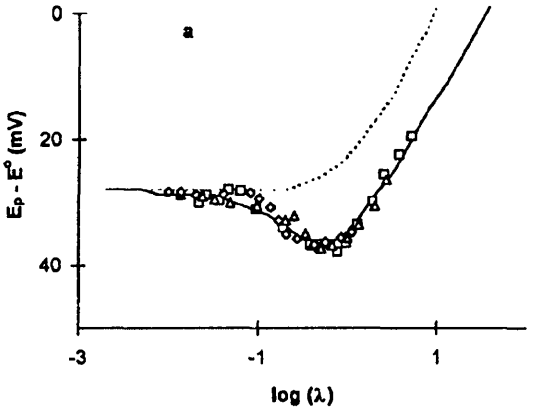


Figure 9. Working curves for RR (solid) and RS dimerization (dot) mechanisms showing the predicted variation of $E_p - E^\circ$ with $\log\lambda$ together with data obtained by LSV for the dimerization of the 7,12-diphenylbenzo[k]fluoranthene radical cation in benzene/MeCN (1/1); (◇) $C_A^* = 0.44\,mM$, (△) $C_A^* = 1.04\,mM$, and (□) $C_A^* = 2.00\,mM$. (From Ref. 78.)

mental data obtained for the dimerization of 7,12-diphenylbenzo[k]fluoranthene radical cation [78]. The data clearly indicate that the dimerization is of the RR type.

A common procedure for studying the kinetics of follow-up reactions by CV is to compare values of $-i_p^{ox}/i_p^{red}$ recorded at different sweep rates to the working curve for the proposed mechanism [13]. However, a problem with this approach is the difficulty already mentioned in evaluating the baseline for the backward sweep, and therefore CV suffers from some limitations when used in quantitative work. The development of derivative cyclic voltammetry (DCV) has changed this situation [9,38,79].

The application of the first derivative of the CV curve was investigated during the 1960s by Perone and coworkers [80,81], but due to difficulties in performing differentiation using analog electronic equipment the method was not recommended for the measurement of electrode potentials. It was later found that a commercially available selective amplifier (model 189 selective amplifier from Princeton Applied Research) could mimic an analog differentiator [29–32,36,82]. More accurate digital differentiation may be carried out by using fast Fourier transform methods [83].

The voltammogram shown in Fig. 3 is redrawn in Fig. 10(a), now showing the current i as a function of the time t. The problem of defining a baseline for the measurement of i_p^{ox} is illustrated by the two broken lines, a problem that becomes more serious as E_{switch} comes closer to E°. The differentiated curve, di/dt versus t, is shown in Fig. 10(b). The peaks labeled i'_f and i'_b, corresponding to the maximum steepness of the voltammogram during the forward and backward sweeps, respectively, reflect the CV peak heights. Both i'_f and i'_b are being measured relative to the zero line. Since the slope of the baseline for i_p^{ox}, that is, the extension of the reduction wave, is not far from zero where the measurement is made, it follows that the magnitude of i'_b is essentially baseline independent. Another advantage of recording the derivative signal is that the effect of the background current is strongly diminished.

The ratio $R'_I = -i'_b/i'_f$ plays the same role in DCV as the ratio $-i_p^{ox}/i_p^{red}$ in CV. It should be noticed, however, that $-i'_b/i'_f$, in contrast to $-i_p^{ox}/i_p^{red}$, does not approach zero for increasing values of λ, but a value close to 0.1. This is related to the fact that the

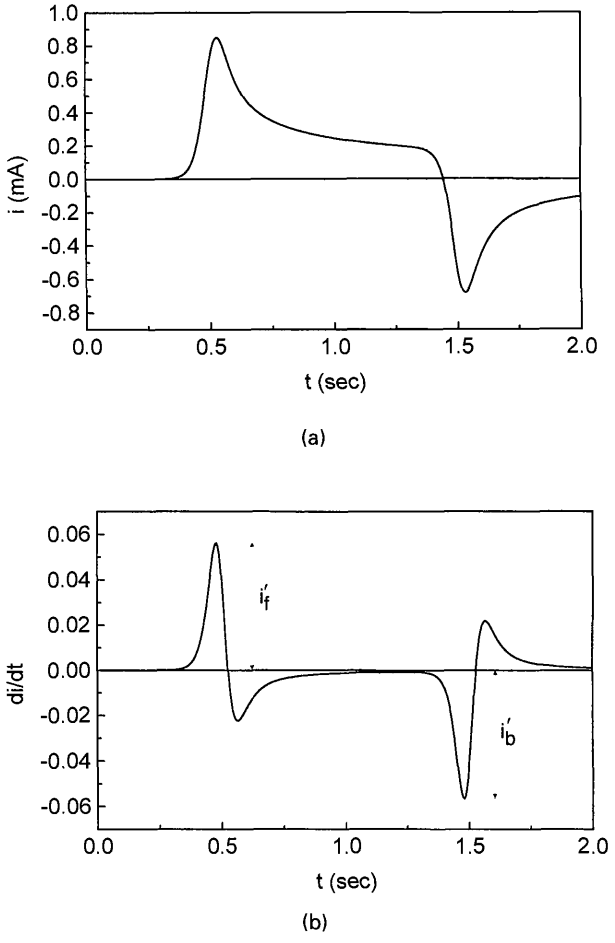


Figure 10. The cyclic voltammogram in Fig. 3 shown as (a) the current-time curve and (b) the differentiated current-time curve.

derivative curve during the backward sweep is not zero, even when the peak due to B has completely vanished.

The kinetic analysis of a follow-up reaction by DCV involves the recording of R'_I at different ν, and the rate constant k (or k_{obs}) is then obtained by fitting the working curve for the appropriate rate law, usually in the form of R'_I versus log λ, to these data. An example is shown in Fig. 11 where the working curve for the RR dimerization mechanism is fitted to the experimental data for the dimerization of (−)-bornyl cinnamate radical anions [84]. The rate constant is obtained by matching the two scales, which in the present case results in $k = 5.6 \times 10^2\ M^{-1}\ s^{-1}$.

The approach works equally well for reactions taking place after the second electron transfer, for instance, at the dication [85] or dianion [86] oxidation state.

The rate law necessary for making a mechanism suggestion is conveniently determined by DCV. The procedure, sometimes referred to as the reaction order approach, is based on measurements of the sweep rate necessary to maintain a certain constant conversion of B as a function of C^*_A, and C^*_X if relevant. Usually the sweep rate necessary to

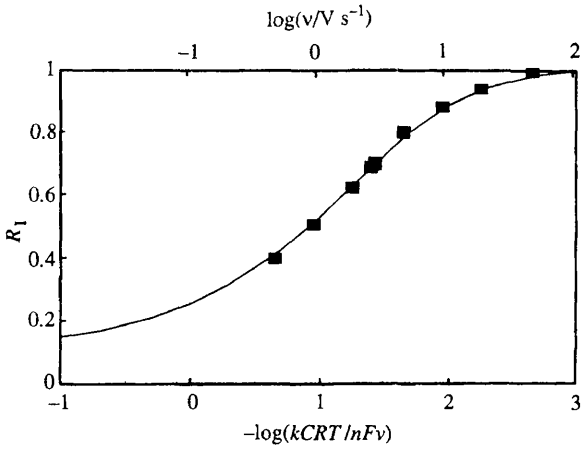


Figure 11. DCV working curve for the RR dimerization mechanism (bottom scale) together with experimental data obtained for the dimerization of (−)-bornyl cinnamate radical anion in DMF (top scale). (From Ref. 84.)

keep R_I' equal to 0.5 is used. This sweep rate is referred to as $\nu_{1/2}$ or $\nu_{0.5}$. The reciprocal value, $1/\nu_{1/2}$, is conceptually related to the half-life time $t_{1/2}$ in conventional kinetics. If the generalized rate law for the reaction to be investigated is written as Eq. (33), where k_{obs} is defined, for instance, as in Schemes 2 and 3, the relations between $\nu_{1/2}$ and the reaction orders are given by Eqs. (34) and (35), where $R_{A/B}$ is equal to a + b and R_X is equal to x. It is seen that R_A (= a) and R_B (= b) are not directly separable, a common feature of all reversal techniques, where A and B are in thermodynamic equilibrium at the electrode surface.

$$\text{Rate} = k_{obs}[A]^a[B]^b[X]^x \tag{33}$$

$$R_{A/B} = 1 + \frac{d(\log \nu_{1/2})}{d(\log C_A^*)} \tag{34}$$

$$R_x = \frac{d(\log \nu_{1/2})}{d(\log C_x^*)} \tag{35}$$

Usually, the data treatment includes that values of $\log \nu_{1/2}$ are plotted against $\log C_A^*$, or $\log C_X^*$, which, for a simple rate law such as Eq. (33), results in a straight line with the slope $R_{A/B} - 1$ or R_X. Data obtained for the protonation of the anthracene radical anion by phenol in dimethyl sulfoxide (DMSO) [87] are shown in Fig. 12 as an example. The slope of the regression line in this case is 1.06, indicating that the rate law is first order in the concentration of phenol.

Once the rate law is known, the value of k (or k_{obs}) may in principle be obtained directly from $\nu_{1/2}$ as illustrated by the relations given in Eq. (36) for the eC mechanism (first-order rate law) and Eq. (37) for the RR dimerization (second-order rate law), in both cases for $E^\circ - E_{switch} = 0.3$ V [88]. Relations for other mechanisms may be found in the literature [88].

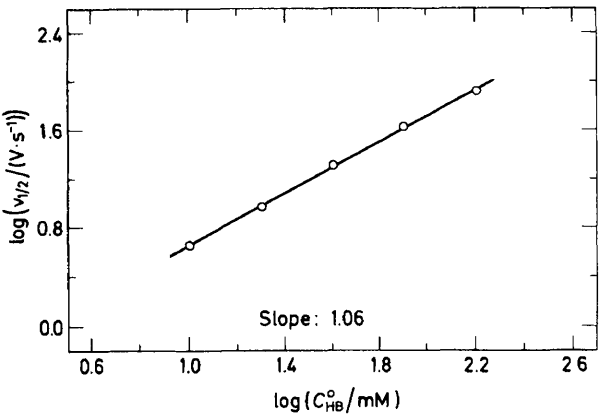


Figure 12. Data for $\log \nu_{1/2}$ as a function of $\log(C^{\circ}_{HB}/mM)$ obtained by DCV for the protonation of the anthracene radical anion by phenol (HB) in DMSO. (From Ref. 87.)

eC mechanism:

$$k = 0.078\frac{\nu_{1/2}nF}{RT}\ s^{-1} \tag{36}$$

RR dimerization:

$$k = 0.117\frac{\nu_{1/2}nF}{C^{*}_{A}RT}\ M^{-1}s^{-1} \tag{37}$$

However, in general it is recommended that the full working curve be used for determination of the rate constant in view of the larger number of data points included. This approach also offers the additional benefit that the validity of the mechanism hypothesis is tested by the goodness of the fit for each determination. This is particularly important in cases such as those where changes in the substrate substitution pattern or in the experimental conditions may result in a change in the mechanism or, for complex reaction schemes, in a change in the rate-determining step (see also Sec. II.C.5).

The kinetic window for CV and DCV may be derived from the limits for λ given for example in Eq. (31)–(32). Assuming that the applicable range of useful ν values is 0.1 to 500 $V\,s^{-1}$, the limits translates approximately to Eqs. (38) and (39).

eC mechanism:

$$0.4\,s^{-1} < k < 4 \times 10^{4}\,s^{-1} \tag{38}$$

RR dimerization:

$$1.5\,s^{-1} < kC^{*}_{A} < 3 \times 10^{4}\,s^{-1} \tag{39}$$

Typical examples of the application of DCV for kinetic and mechanistic studies include the cleavage of the carbon–halogen bond in the radical anions of aromatic halides [89], the protonation of radical anions [87,90–92], and the dimerization of radical ions [84].

4. Irreversible Follow-Up Reactions, Purely Kinetic Control (LSV)

The characteristic feature of the voltammogram in this region of λ values is the absence of a peak during the backward sweep, which for the same reason is not included in the data

analysis (LSV). The position of the voltammogram, as measured by E_p, is displaced in the positive direction relative to that for the no-reaction case, Eq. (1), and depends markedly on the value of λ. In contrast, the shape of the voltammogram, as measured by $E_p - E_{p/2}$, is nearly constant and independent of λ. However, $E_p - E_{p/2}$ depends on the mechanism, which is of diagnostic value (discussed later). It is appropriate to mention at this place that processes belonging to this category are often referred to as irreversible. This may be confusing, since the term *irreversible* in this case refers to the effect of an irreversible chemical reaction on the total process and not just to the electron transfer reaction. Common to the two types of irreversible processes is, however, the absence of an oxidation peak owing to B in the potential region where the reduction of A takes place.

The lack of an oxidation peak for B indicates a high material conversion, which can also be seen by comparison of the voltammograms for the eC and eCe_h mechanisms in Fig. 13. In contrast to the voltammograms in Fig. 8, it is seen that i_p for the eCe_h mechanism now is close to being twice that for the eC mechanism, illustrating that the conversion of B to C has proceeded almost to completion.

LSV is a powerful tool for the study of processes under purely kinetic control. Theoretical analyses of the response for various mechanisms have been carried out [13,15–26], and a series of papers [36,72,79,93] has been devoted to assimilating the theoretical results in a form useful to the experimentalist. For the general rate law, Eq. (33), the dependence of E_p on changes in $\log \nu$, $\log C_A^*$, and $\log C_X^*$, respectively, is linear with the slopes given by Eqs. (40)–(42), where a, b, and x are the reaction orders.

$$\frac{dE_p}{d(\log \nu)} = -\frac{1}{b+1}\frac{RT}{nF}\ln 10 \tag{40}$$

$$\frac{dE_p}{d(\log C_A^*)} = \frac{a+b-1}{b+1}\frac{RT}{nF}\ln 10 \tag{41}$$

$$\frac{dE_p}{d(\log C_X^*)} = \frac{x}{b+1}\frac{RT}{nF}\ln 10 \tag{42}$$

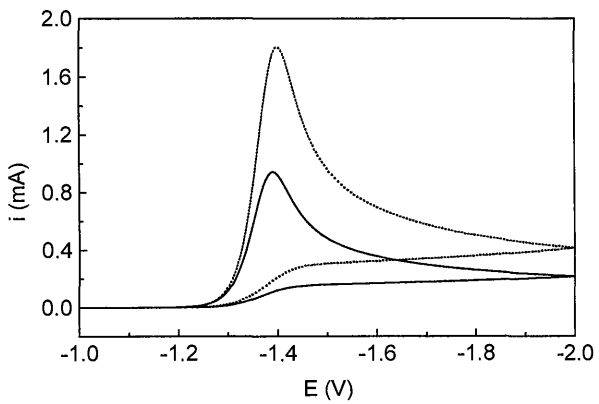


Figure 13. Simulated (DigiSim) cyclic voltammograms for the eC mechanism (solid) and the eCe_h mechanism (dot) at $\nu = 1\,V\,s^{-1}$ with $E^\circ = -1.5\,V$ and $k = 10^6\,s^{-1}$ ($\lambda = 2.57 \times 10^4$). For other simulation parameters, see Fig. 3.

Introduction of the reaction orders for, for instance, the eC mechanism under pseudo first-order conditions (a = 0, b = 1, and x = 1) results in $dE_p/d(\log \nu) = -29.6\,mV$, $dE_p/d(\log c_A^*) = 0\,mV$, and $dE_p/d(\log C_X^*) = 29.6\,mV$ at n = 1 and T = 298 K.

Important also is the shape of the voltammogram represented by the value of $E_p - E_{p/2}$. The limiting values for the eC and RR dimerization mechanisms are given in Eqs. (43)–(44), where, again, the values given in mV refer to T = 298 K. Values of $E_p - E_{p/2}$ for other mechanisms are available in the literature [18–20].

eC mechanism

$$E_p - E_{p/2} = -1.86\frac{RT}{nF}\ V = -\frac{47.8}{n}\ mV \tag{43}$$

RR dimerization:

$$E_p - E_{p/2} = -1.51\frac{RT}{nF}\ V = -\frac{38.8}{n}\ mV \tag{44}$$

When E° for the initial electron transfer reaction is known, the measurement of E_p gives access directly to the rate constant k. Examples of the relationship between $E_p - E^\circ$ and k are given by Eqs. (45) and (46) [20], where Eq. (46) refers to rate law (vi) in Scheme 3; that is, the stoichiometric coefficient 2 is not included in the rate constant.

eC mechanism:

$$E_p - E^\circ = \left(-0.738 + \tfrac{1}{2}\ln\frac{kRT}{\nu nF}\right) \times \left(\frac{RT}{nF}\right)\ V \tag{45}$$

RR dimerization:

$$E_p - E^\circ = \left(-0.902 + \tfrac{1}{3}\ln\frac{4kC_A^*RT}{3\nu nF}\right) \times \left(\frac{RT}{nF}\right)\ V \tag{46}$$

It is easily seen that the application of equations such as Eqs. (45) and (46) requires data for $E_p - E^\circ$ of high precision. For example, for the RR dimerization mechanism a change in k by a factor of 10 corresponds only to a change in E_p of 19.7 mV (at T = 298 K). Taking into account that both the precision and the accuracy of literature values for E° may not be better than ±10 mV, it is strongly recommended that the value of E° to be used is the result of a measurement made in conjunction with the E_p measurements. Since, by definition, the value of λ is rather large for Eqs. (45) and (46) to apply, it follows that large sweep rates are required to outrun the chemical reaction. This is conveniently achieved by using ultramicroelectrodes for the measurements [94,95] (see Sec. III). Reliable E° data may also be predicted from data obtained by nuclear magnetic resonance (NMR) spectroscopy [96].

Although LSV is experimentally easy to use, the technique should be used with care. The major concern is to make sure that the electron transfer reaction is reversible and that the process under investigation is indeed under purely kinetic control in the range of ν and concentrations employed. If increasing sweep rates bring the electron transfer into the quasi-reversible region (discussed later), the values of, for instance, $dE_p/d(\log \nu)$ will be larger than predicted for the reversible case [20,97], and if the follow-up reaction is brought into the region of mixed kinetic and diffusion control, $dE_p/\backslash d(\log \nu)$ will be smaller than predicted [20,98]. This may lead to a wrong mechanism assignment. However, in both cases the $E_p - E_{p/2}$ will be larger than predicted, and this therefore

serves as an excellent diagnostic tool for probing whether the reaction being studied does indeed confine to the purely kinetic conditions as defined earlier.

Another problem may arise in the study of processes of the type where B reacts with an added reagent X. In that case, the kinetic measurements are often carried out under pseudo first-order conditions—that is, at $C_X^*/C_A^* \gg 1$—and values of $dE_p/d(\log C_X^*)$ are obtained by carrying out a series of E_p measurements at increasing values of C_X^* . If now the ratio C_X^*/C_A^* at the lowest concentration of C_X^* is not sufficiently large, the consumption of X cannot be neglected and, accordingly, the rate of the chemical reaction is "too low." The problem gradually disappears with increasing values of C_X^* and the overall effect is that the increase in the reaction rate with increasing C_X^* becomes "too large" and, accordingly, the resulting value of $dE_p/d(\log C_X^*)$ becomes "too large" as well [98]. This may lead to the erroneous interpretation that the reaction order in X is larger than one.

Illustrations of the application of LSV for studies of reactions under purely kinetic conditions include the oxidation of 9-substituted fluorenide ions [99] and the reduction of 2,6-diphenylpyrylium ions [100], in both cases leading to the neutral radical, which dimerizes in an RR-type reaction, the oxidation of 1,4-dithiafulvenes into tetrathiafulvalenes [101], the oxidative ring opening of arylcyclopropanes [102], the reduction of fluoroalkoxyarenes in liquid ammonia [103], and the competition between protonation and dimerization during the reduction of cinnamic acid esters in MeOH [104].

5. Reversible Follow-Up Reactions

Let us now consider a reversible electron transfer reaction followed by a reversible chemical reaction. Typical examples, including the reaction of B with a reagent X (ii), here with p equivalents, and the reversible dimerization (iii), are shown in Scheme 4.

Mechanisms including reversible follow-up reactions

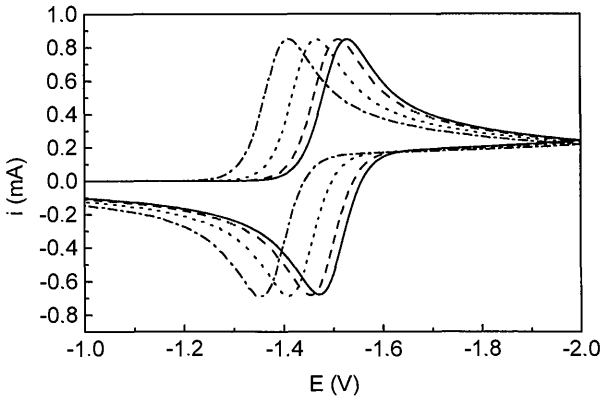
$$A + e^- \rightleftharpoons B \quad (E^\circ) \qquad \text{(i)}$$

$$B + pX \rightleftharpoons C \quad \left(K_{ii} = \frac{[C]}{[B][X]^p}\right) \qquad \text{(ii)}$$

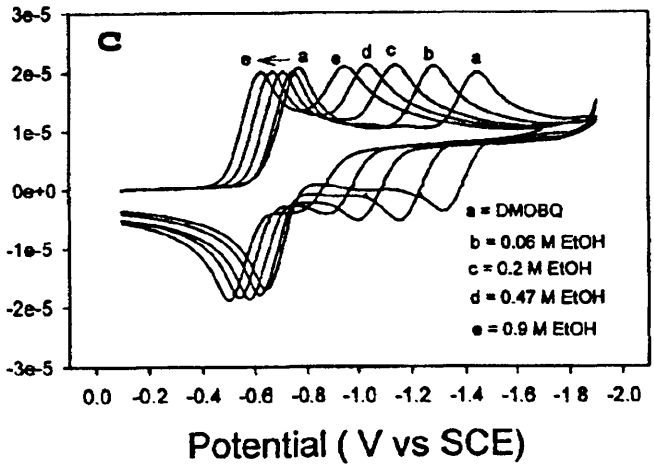
$$2B \rightleftharpoons C \quad \left(K_{iii} = \frac{[C]}{[B]^2}\right) \qquad \text{(iii)}$$

Scheme 4

If the chemical reaction responds instantaneously to changes in the concentration of B or C, it is adequately described by the magnitude of the equilibrium constant K, which means that the total system is reversible. For reaction (ii), the resulting voltammogram, shown in Fig. 14(a) for $p = 1$ and $C_X^*/C_A^* = 100$, has the same shape as that in Fig. 3, but is displaced on the voltage axis according to Eq. (47), where K corresponds to K_{ii} in Scheme 4. It is seen that E_p changes by 59.1 mV (at $T = 298$ K) in the positive direction for a 10-fold increase in K for $K \gg 1$. [See for example the voltammograms shown in Fig. 14(a) for $K = 100$ and 1000.] It follows from Eqs. (47) and (10) that the difference in peak potentials $\Delta(E_p$ for (i)–(ii) and (i) is given by Eq. (48) [105]. The relation between $E_p - E^\circ$ and K_{iii} for the dimerization reaction (iii) is more complex owing to the presence of the second-order term $[B]^2$ in the expression for K_{iii}. The reader is referred to the original literature [106] for details.



(a)



(b)

Figure 14. (a) Simulated (DigiSim) cyclic voltammograms for a reversible one-electron reduction followed by a reversible chemical reaction (Scheme 4) with $E^\circ = -1.5\,V$, $C_A^* = 1\,mM$, $C_X^* = 100\,mM$, and $K = 10$ (dash), 100 (dot), and 1000 (dash-dot). The solid line corresponds to the simple electron transfer reaction shown in Fig. 3, where other simulation parameters are also given. (b) Experimental cyclic voltammograms for the reduction of 2,5-dimethoxy-1,4-benzoquinone (DMOBQ) in benzonitrile containing Bu_4NPF_6 (0.1 M) and different concentrations of ethanol. (From Ref. 108.)

$$E_p - E^\circ = -1.11\frac{RT}{nF} + \frac{RT}{nF}\ln[1 + K(C_X^*)^p] \tag{47}$$

$$\Delta E_p = \frac{RT}{nF}\ln[1 + K(C_X^*)^p] \tag{48}$$

Reversible reactions of the type (ii) in Scheme 4 are typically observed for radical anions with X being a cation (formation of ion pairs) [107] or a hydroxylic compound such as water or an alcohol (formation of hydrogen-bond complexes) [107,108]. An example of

the latter is shown in Fig. 14(b), where also the (larger) effect on the second redox couple is shown. Usually, the product $K(C_X^*)^p$ is much larger than unity and consequently a plot of E_p versus $\log C_X^*$ should yield a straight line from the slope of which the stoichiometric number p may be obtained. Deviations from the linear dependence of E_p on $\log C_X^*$ are observed in some cases at high concentrations of X, which may be attributed to the formation of higher associates. Attention should also be brought to a series of papers in which reduction processes including reversible proton transfer reactions (Scheme 5) are thoroughly discussed [109].

$$A + ne^- + mH^+ \rightleftharpoons B$$

Scheme 5

Reversible dimerizations are observed less frequently, since often the reactions are not fast enough to be treated as thermodynamic equilibria. Examples are the dimerization of the radical cations of thianthrenes [110] and thiophene derivatives [111].

Let us now reexamine the dimerization mechanisms shown in Scheme 3 in a little more detail. The rate-determining steps, (ii) and (iii), in that scheme are both formulated as being irreversible. This, however, is not meant to imply that the dimerization of B, or the coupling of A and B, are irreversible processes by nature. In fact, the only well-documented example of an inherently irreversible reaction of this type is (ii) when B is a neutral free radical. More often, for instance when B is a radical ion, the chemical reactions (ii) and (iii) in which the intermediates C and I are produced, are reversible and the observed irreversibility is a kinetic phenomenon caused by the further reactions of C and I. Thus, a more natural starting point for the discussion would be the general situation in which both the forward and the backward reactions are considered for all steps except the last one. This is shown in Scheme 6.

Mechanisms including reversible dimerization:

$$A + e^- \rightleftharpoons B \qquad \text{(i)}$$

$$2B \underset{k_{-II}}{\overset{k_{II}}{\rightleftharpoons}} C \qquad (K_{II} = k_{II}/k_{-II}) \qquad \text{(ii)}$$

$$A + B \underset{k_{-III}}{\overset{k_{III}}{\rightleftharpoons}} I \qquad (K_{III} = k_{III}/k_{-III}) \qquad \text{(iii)}$$

$$B + I \underset{k_{-IV}}{\overset{k_{IV}}{\rightleftharpoons}} A + C \qquad (K_{IV} = k_{IV}/k_{-IV}) \qquad \text{(iv)}$$

$$C + X \xrightarrow{k_V} D \qquad \text{(v)}$$

Mechanism	Assumption	Observed rate law	k_{obs}	
RR	$k_V[X] >> k_{-II}$	$-d[B]/dt = k_{obs}[B]^2$	$2k_{II}$	(vi)
RR	$k_{-II} >> k_V[X]$	$-d[B]/dt = k_{obs}[B]^2[X]$	$2K_{II}k_V$	(vii)
RS	$k_{IV}[B] >> k_{-III}$	$-d[B]/dt = k_{obs}[A][B]$	$2k_{III}$	(viii)
RS	$k_{-III} >> k_{IV}[B]$	$-d[B]/dt = k_{obs}[A][B]^2$	$2K_{III}k_{IV}$	(ix)

Scheme 6

It is convenient first to examine briefly the RS dimerization mechanism. Usually, the intermediate I is more easy to reduce than A (or to oxidize, when B is a radical cation), which means that the equilibrium constant K_{iv} for the homogeneous electron transfer step (iv) is large. Also, the rate constant for this type of process is usually large. This allows for the application of the steady-state approximation for the intermediate I; that is, it is assumed that $d[I]/dt = 0$. The general rate law resulting for B degenerates to either of two limiting cases depending on the relative magnitudes of k_{-iii} and $k_{iv}[B]$. When $k_{iv}[B] \gg k_{-iii}$, the intermediate I reacts almost exclusively by reaction (iv) and forward reaction (iii) becomes rate-determining. The resulting rate law (viii) is the same as rate law (vii) in Scheme 3. On the other hand, when $k_{-iii} \gg k_{iv}[B]$, reaction (iii) behaves as a thermodynamic equilibrium prior to the rate-determining reaction (iv) resulting in rate law (ix). It is seen that under conditions where rate law (viii) applies, the reaction order $R_{A/B}$ is equal to 2, whereas rate law (ix) corresponds to $R_{A/B}$ equal to 3. Thus, ideally it would be possible to distinguish between the two limiting cases by a DCV reaction order analysis carried out as described earlier.

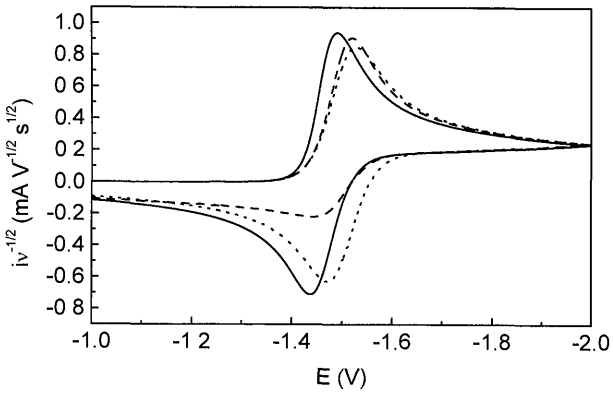
Next, let us examine the situation where the reversible RR dimerization (ii) results in a dimer C that is stable on the time scale of the voltammetric experiment. The voltammograms that ideally may be obtained in the different kinetic regimes are shown in Fig. 15(a). At low sweep rates (full line), reaction (ii) behaves like a thermodynamic equilibrium and the response observed is close to that shown in Fig. 14(a). At intermediate sweep rates the dissociation of C is too slow to allow for the observation of oxidation current for B, and at high sweep rates it is possible even to outrun forward reaction (ii) and the response is essentially that for a reversible electron transfer process.

For radical cations this situation is typically observed when deprotonation of the dimer dication is slow and for radical anions under conditions that are free from electrophiles, for example, acids, that otherwise would react with the dimer dianion. Most often, this type of process has been observed for radical anions derived from aromatic hydrocarbons carrying a substituent that is strongly electron withdrawing, most notably and well documented for 9-substituted anthracenes [112,113] (see also Chapter 21). Examples from the radical cation chemistry include the dimerization of the 1,5-dithiacyclooctane radical cations [114] and of the radical cations derived from a number of conjugated polyenes [115,116].

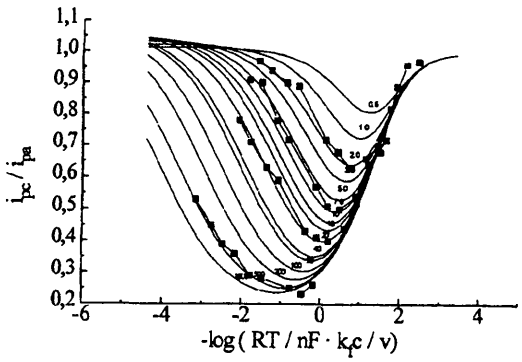
The kinetics (k_{ii} and k_{-iii}) and thermodynamics (K_{ii}) of such reactions are conveniently studied by CV or DCV. Working curves for CV are shown in Fig. 15(b) for different values of K_{ii} together with the experimental points obtained for the oxidation of conjugated polyenes, such as the all-*trans*-1,10-diphenyl-3,8-dimethyldecapentaene [115]. In going from right to left, corresponding to increasing values of λ, it is seen that the value of $-i_p^{red}/i_p^{ox}$ initially decreases until a minimum is reached. In this kinetic region the reaction is essentially controlled by the rate of the dimerization. The rising part of the working curve observed after the minimum illustrates the increasing kinetic importance of the dissociation of C to B. In the limit $\lambda = \infty$, corresponding to an infinitely large value of k_{ii} and/or an infinitely small value of ν, the chemical reaction responds as a thermodynamic equilibrium.

We now introduce the situation where the dimer C undergoes a subsequent chemical reaction (v). The corresponding working curves, in this case for DCV, are shown in Fig. 16 for two values of $K_{ii}C_A^*$ (1 and 10) and different values of $k_vC_X^*/k_{-ii}$ (shown in Fig. 16).

The detailed discussion [117] of the curves is beyond the scope of this chapter, but it is seen that the effect of increasing values of $k_vC_X^*/k_{-ii}$, as intuitively expected, is a gradual



(a)



(b)

Figure 15. (a) Simulated (DigiSim) cyclic voltammograms for a reversible one-electron reduction followed by a reversible RR dimerization reaction (Scheme 6) with $E^{\circ} = -1.5\,V$, $C_A^* = 1\,mM$, $K_{II} = 10^4\,M^{-1}$, $k_{II} = 10^6\,M^{-1}\,s^{-1}$, and $\nu = 0.1$ (solid), 30 (dash), and 10,000 (dot) $V\,s^{-1}$. For other simulation parameters, see Fig. 3. Note that units of $i\nu^{-1/2}$ are used at the y axis to facilitate the comparison of voltammograms obtained at different sweep rates. (b) Working curves for the reversible RR dimerization mechanism (solid line) and experimental values (■) of $-i_p^{red}/i_p^{ox}$ for the dimerization of the all-*trans*-1,10-diphenyl-3,8-dimethyldecapentaene radical cations and related compounds. The numbers on the curves refer to the value of $K_{II}C_A^*$ (see Scheme 6). (From Ref. 115.)

transition from the reversible case ($k_\nu C_X^*/k_{-i_{II}} = 0$, labeled "rev" in Fig. 16) to the totally irreversible case ($k_\nu C_X^*/k_{-II} = \infty$, labeled "irr" in Fig. 16). In other words, the reaction of C gradually changes from dissociation to irreversible conversion to D. The latter situation corresponds to the limiting case in which the dimerization is kinetically irreversible as described by rate law (vi) in Scheme 6 [= rate law (vi) in Scheme 3].

An important consequence of the different shapes of the working curves in Fig. 16 is that a reaction order analysis based on Eq. (34) may lead to a value of $R_{A/B}$ that is not related to rate law (33), and hence cannot easily be used for mechanism assignment. An example serves to illustrate this point. Let it be assumed that the reaction

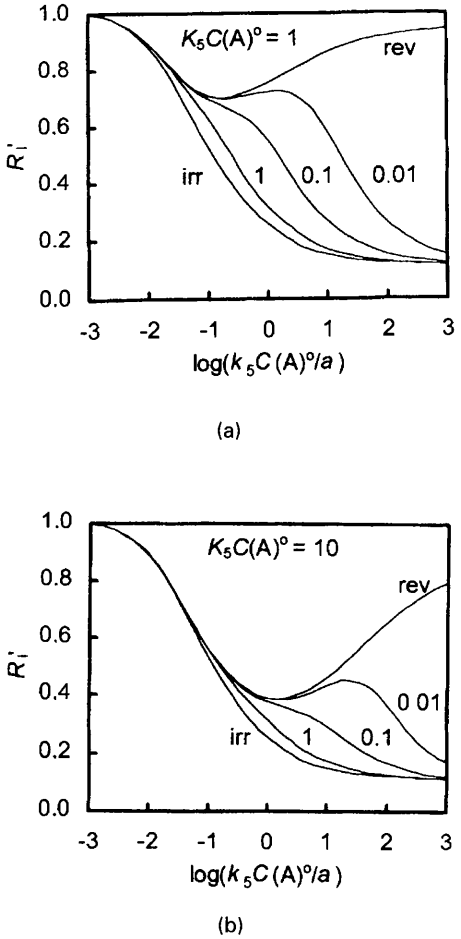


Figure 16. DCV working curves for a reversible dimerization followed by an irreversible reaction for (a) $K_{ii}C_A^* = 1$ and (b) $K_{ii}C_A^* = 10$ [$K_{ii}C_A^* = K_5C(A)^\circ$ in the figures]. The labels "1," "0.1," and "0.01" at the working curves refer to the values of $k_vC_X^*/k_{-ii}$. The rate constant k_5 in the figure corresponds to k_{ii} in Scheme 6 and the constant a is equal to $\nu nF/(RT)$. (From Ref. 117.)

being studied is described by $K_{ii}C_A^* = 1$ and $k_vC_X^*/k_{-ii} = 0.1$ corresponding to the working curve labeled "0.1" in Fig. 16(a). It is seen that $R_I' = 0.5$ in this case requires that $\log[k_{ii}C_A^*RT/(\nu nF)]$ equal to approximately 0.2. If now the concentration of substrate is increased by a factor of 10, the appropriate working curve is the one labeled "0.1" in Fig. 16(b) and it is seen that $R_I' = 0.5$ now requires that $\log[k_{ii}C_A^*RT/(\nu nF)]$ is equal to approximately −0.8. The two-point value of $d(\log \nu_{1/2})/d(\log C_A^*)$ calculated from these data is 2.0, which gives $R_{A/B}$ equal to 3.0 using Eq. (34). This would seem to be in good agreement with rate law (ix) for the RS mechanism with the electron transfer (iv) being rate-determining, but not with the RR mechanism with irreversible dimerization (ii), for which $R_{A/B}$ is equal to 2. The major origin of the problem is of course that $R_I' = 0.5$ at the low substrate concentration [Fig. 16(a)] corresponds to the part of the working curve that is essentially defined by rate law (vii), whereas $R_I' = 0.5$

at the high concentration [Fig. 16(b)] corresponds to the part essentially defined by rate law (vi). The same type of analysis carried out for $k_v C_X^*/k_{-ii} = 0.01$ and 1 results in $R_{A/B} = 4.1$, and 2.2 respectively. It is seen that $R_{A/B}$ increases with decreasing values of $k_v C_X^*/k_{-ii}$ and that therefore that virtually any value larger than 2 may result when the analysis is based on Eq. (34). Problems of this kind may be difficult to detect experimentally. For example, for the reaction following the working curves "0.1" it is seen that the shape of the working curve at the low concentration [Fig. 16(a)] is similar to that for "irr" as long as R_I' is lower than 0.7, and at the high concentration [Fig. 16(b)] the same is true as long as R_I' is higher than 0.4. Thus, if the data for R_I' recorded during a preliminary DCV investigation were all between 0.4 and 0.7, the results would seem to indicate that the kinetics would be adequately described by a simple rate law such as that in Eq. (33). The only solution to problems of this kind is to record the full working curves in all cases and to supply the data obtained by DCV (or DPSCA, see Sec. IV.A) with data from LSV. An example of the latter approach is the study of the dimerization of the radical cations derived from a series of 2,5-diaryl-1,4-dithiins [118].

6. Irreversible Follow-Up Reactions, the Prepeak Method

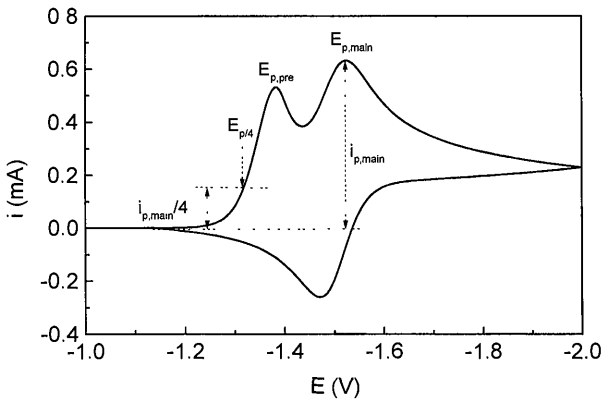
Reactions between B and X may conveniently be studied also under conditions where $C_X^*/C_A^* < 1$. In that case the reagent X is consumed during the early parts of the voltammetric wave giving rise to a prepeak (at $E_{p,pre}$) in front of the main peak (at $E_{p,main}$) for the reduction of A, now in a solution that close to the electrode is essentially free from X [119]. An example of such a voltammogram is shown in Fig. 17(a). The rate constant may be obtained from the potential difference $E_{p,pre} - E_{p,main}$, which has been tabulated for a number of reaction mechanisms [119]. This method has been used extensively in kinetic studies of reactions between radical cations and nucleophiles [119–122].

Alternatively, the determination of k may be based on measurements of $E_{p/4} - E_{p,main}$, where the quarter-peak potential $E_{p/4}$ is the value of E at $i = i_{p,main}/4$ [123] [see Fig. 17(a)]. The advantage of this approach is that measurements can be made even in cases where the prepeak appears only as a shoulder on the main peak, and where $E_{p,pre}$ therefore cannot be determined. The working curve for the eCe_h mechanism is shown in Fig. 17(b) together with experimental data obtained for the protonation of the anthracene radical anion by benzoic acid. The rate constant resulting from these data is $2.7 \times 10^6\ M^{-1}\ s^{-1}$[123].

The prepeak method may be used for reactions with second-order rate constants ranging from approximately $10^5\ M^{-1}\ s^{-1}$ to that for a diffusion-controlled reaction.

7. Irreversible Follow-Up Reactions, Redox Catalysis

Common to all the methods discussed earlier is that B is generated at the electrode surface, that is, by a direct electron exchange between the electrode and the substrate A. This approach is, however, sometimes hampered by the limitations imposed by the heterogeneous nature of the electron transfer reaction. For instance, studies of the kinetics of fast follow-up reactions may be difficult or even impossible owing to interference from the rate of the heterogeneous electron transfer process. In such cases, the kinetics of the follow-up reactions may be studied instead by an indirect method, generally known as redox catalysis [5,124–126]. Another application of redox



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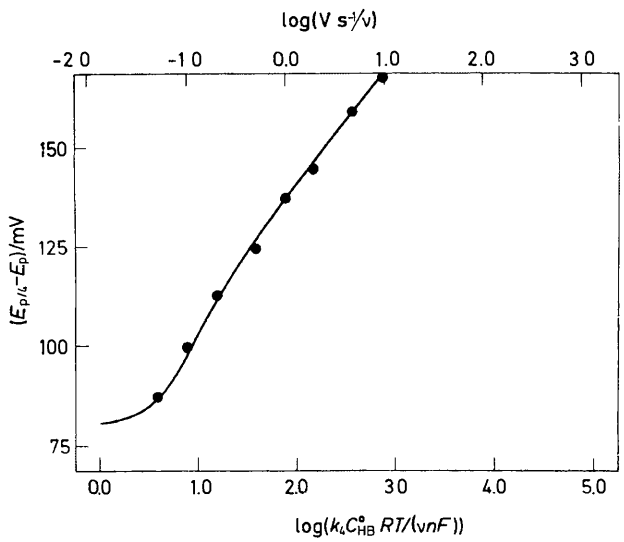


(b)

Figure 17. (a) Simulated (DigiSim) cyclic voltammogram at $\nu = 1\,V\,s^{-1}$ for an eC mechanism with $E^\circ = -1.5\,V$, $C^*_A = 1\,mM$, $C^*_X/C^*_A = 0.5$, and $k = 10^9\,M^{-1}\,s^{-1}$. For other simulation parameters, see Fig. 3. (b) Working curve for the quarter-peak width $E_{p/4} - E_{p,main}$ (bottom scale) together with experimental points (top scale) for the protonation of anthracene radical anion ($C^*_A = 2mM$) with benzoic acid ($C^*_{HB} = 1\,mM$) in DMSO (rate constant k_4). (From Ref. 123.)

catalysis is the study of dissociative electron transfer reactions (Scheme 1) [74,75,127,128].

The principle is illustrated in Scheme 7 for a reaction that in a direct process follows the eC mechanism.

Redox catalysis

$$A + e^- \rightleftharpoons B \qquad (E^\circ_{AB}) \qquad (i)$$

$$P + e^- \rightleftharpoons Q \qquad (E^\circ_{PQ}) \qquad (ii)$$

$$Q + A \underset{k_{-iii}}{\overset{k_{iii}}{\rightleftharpoons}} P + B \qquad (k_{iii}) \qquad (iii)$$

$$B \xrightarrow{k_{iv}} C \qquad (iv)$$

Scheme 7

The direct process includes the reduction of A to B (i) followed by the irreversible reaction of B to a product C (iv). If now a compound P, a so-called mediator, that is easier to reduce than A is added to the solution, the direct reduction of A is replaced by the reaction sequence (ii)–(iii). During the homogeneous electron transfer process (iii) the oxidized form P of the mediator is regenerated. In other words, the reduction of A to B is catalyzed by the redox couple P/Q. Cyclic voltammograms typical for the catalyzed process are shown in Fig. 18. The effect of increasing values of k_{iii} is shown in Fig. 18(a) and the effect of an increasing concentration ratio C^*_A/C^*_P is shown in Fig. 18(b).

The description of the kinetics is simplified considerably by the fact that often the three rate constants, k_{iii}, k_{-iii}, and k_{iv}, are all large, allowing for the application of the steady-state approximation for the concentration of B, that is, $-d[B]/dt = 0$ [124]. The system is conveniently discussed by introduction of three dimensionless parameters: (1) the kinetic parameter λ, Eq. (49); (2) the competition parameter σ, Eq. (50); and (3) the concentration excess factor γ, Eq. (51). In addition, it is convenient to introduce the catalytic efficiency CAT, Eq. (52), where $i_{p,cat}$ is the peak current during LSV observed for the catalytic system and $i_{p,rev}$ is the peak current observed for P in the absence of A [see Fig. 18(a)]. The product $i_{p,rev}\gamma$ then is the maximum possible catalytic current.

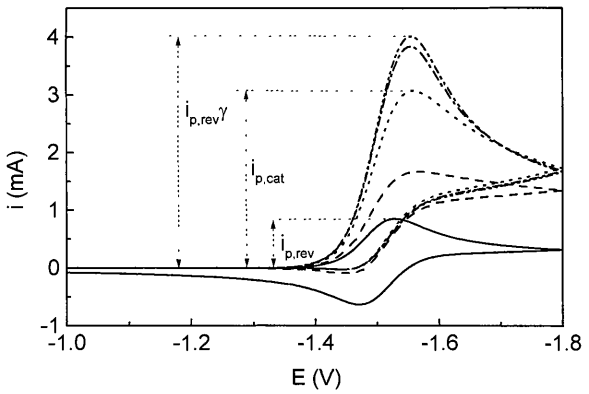
$$\lambda_{iii} = \frac{k_{iii} C^*_P RT}{\nu F} \tag{49}$$

$$\sigma = \frac{k_{iv}}{k_{-iii} C^*_P} \tag{50}$$

$$\gamma = \frac{C^*_A}{C^*_P} \tag{51}$$

$$CAT = \frac{i_{p,cat}}{i_{p,rev}\gamma} \tag{52}$$

Two limiting cases result depending on the magnitude of σ. For $\sigma \gg 1$ the kinetics are controlled by k_{iii}, that is, by the rate of the homogeneous electron transfer reaction, and for $\sigma \ll 1$ by $K_{iii}k_{iv}$, that is the case where the electron transfer reaction may be considered as a thermodynamic equilibrium prior to the reaction of B. The transition is shown by the voltammograms in Fig. 18(a) for σ varying between 5×10^2 (lower curve for $k_{iii} = 10^2$ $M^{-1}\,s^{-1}$) and 5×10^{-4} (upper curve for $k_{iii} = 10^8\,M^{-1}\,s^{-1}$). Under conditions where $\sigma \gg 1$ the value of k_{iii} may be obtained by fitting the appropriate working curve $CAT(\lambda_{iii}, \gamma)$ [124] to the experimental data. In this kinetic region the value of CAT is proportional to C^*_P. On



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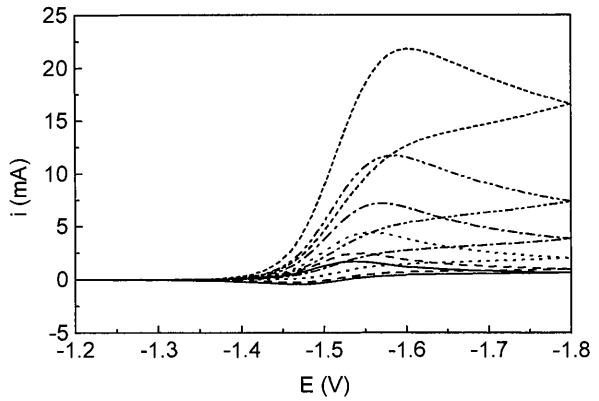


(b)

Figure 18. Simulated (DigiSim) cyclic voltammograms at $\nu = 1\,V\,s^{-1}$ for the catalytic reaction shown in Scheme 7 with $E^{\circ}_{PQ} = -1.5\,V$, $C^{*}_{P} = 1\,mM$, $K_{iii} = 5 \times 10^{-7}$, and (a) $k_{iv} = 10^{8}\,M^{-1}\,s^{-1}$, $C^{*}_{A}/C^{*}_{P} = 4$, and $k_{iii} = 0$ (solid), 10^{4} (dash), 10^{5} (dot), 10^{6} (dash-dot), and 10^{8} (dash-dot-dot) $M^{-1}\,s^{-1}$, and (b) $k_{iii} = 10^{6}\,M^{-1}\,s^{-1}$, $k_{iv} = 10^{8}\,M^{-1}\,s^{-1}$, and $C^{*}_{A}/C^{*}_{P} = 1$ (solid), 2 (dash), 5 (dot), 10 (dash-dot), 20 (dash-dot-dot), and 50 (short dash). For other simulation parameters, see Fig. 3. The magnitude of $i_{p,cat}$ is shown for $k_{iii} = 10^{5}\,M^{-1}\,s^{-1}$.

the other hand, for $\sigma \ll 1$, the value of $K_{iii}k_{iv}$ may be obtained by fitting the working curve for $CAT(\lambda_{iii}, \sigma, \gamma)$ [124]. In this region the value of CAT is independent of C^{*}_{p}. For the complete characterization of the system the value of k_{-iii} is needed. This may be obtained under condition where the system is under mixed control of reactions (iii) and (iv), again by fitting the appropriate working to the experimental data. Once K_{iii} is known, it is possible also to determine E°_{AB} from Eq. (53).

$$E^{\circ}_{AB} = E^{\circ}_{PQ} + \frac{RT}{nF} \ln K_{iii} \tag{53}$$

Numerous examples of the application of redox catalysis to studies of the kinetics of the cleavage of the carbon–halogen bond in the radical anions of aromatic halides have

been reported [125,129]. Other examples include the fragmentation of *tert*-butyl radicals from the radical cations of NADH model compounds [130], the reduction of CO_2 [131], and the cleavage of the carbon–nitrogen bond in the radical anions of 1,1-dinitroalkanes [132].

Another application of redox catalysis is the study of dissociative electron transfer reactions (Scheme 1). The resulting free radical R· may undergo either of two reactions, coupling with the mediator radical anion (iii) or reduction to R^- (iv) [128] (Scheme 8). The coupling reaction is usually considered as unwanted since the mediator is irreversibly consumed in this step. The reaction is, however, synthetically useful [128].

Redox catalysis, reduction of alkyl halides

$$A^{\cdot -} + R\text{–}X \rightleftharpoons A^{\cdot -} \quad (E^\circ_{A/A^{\cdot -}}) \qquad \text{(i)}$$

$$A^{\cdot -} + R\text{–}X \xrightarrow{k_{ii}} A + R^{\cdot} + X^- \qquad \text{(ii)}$$

$$A^{\cdot -} + R^{\cdot} \xrightarrow{k_{iii}} A - R^- \qquad \text{(iii)}$$

$$A^{\cdot -} + R^{\cdot} \xrightarrow{k_{iv}} A + R^- \qquad \text{(iv)}$$

Scheme 8

The competition between reaction (iii) and (iv) is usually described by the magnitude of the parameter q given by Eq. (54), which may be determined, for instance, by LSV [133,134].

$$q = \frac{k_{iv}}{k_{iii}} + k_{iv} \tag{54}$$

It is seen that $q = 0$ for a clean coupling reaction and that $q = 1$ for a clean electron transfer reaction. The value of k_{iii} is close to that for a diffusion-controlled process, whereas the value of k_{iv} increases when E°_{A/A^-} moves in the negative direction. Accordingly, a plot of q versus E°_{A/A^-} will give rise to an S-shaped curve from which the potential $E^q_{1/2}$ corresponding to $q = 0.5$ may be determined. Once the value of $E^q_{1/2}$ is known, the standard potential for the reduction of R· may be determined by application of the Marcus theory [128].

8. Chemical Reactions Following Quasi-Reversible or Irreversible Electron Transfer Reactions

Although processes of this kind are often met in practical work, the presentation of the theoretical data associated with these reactions is beyond the scope of this chapter. The reader is referred to the original literature for details [20,135]. When studied under purely kinetic conditions as defined earlier, processes belonging to this category are usually observed to result in values of $E_p - E_{p/2}$ larger than those given, for instance, in Eqs. (43)–(44). The analysis of the experimental data typically includes the simulation of working curves that take into account also the effect of k° and α. In spite of the fact that the description of the system now involves k° and α in addition to the usual kinetic parameters, it is often possible to gain information about all the parameters by a strategic variation of ν, C^*_A, and C^*_X. An illustrative example is the dimerization of 2,5-diaryl-1,4-dithiin radical cations [118].

9. General Remarks and Conclusions

The applications of LSV and CV to the study of chemical processes following an electron transfer reaction are so numerous that a review of the subject is clearly beyond the scope of this chapter. The examples were selected to demonstrate the application of the techniques in practical work. Although obvious, it should be emphasized that electrochemical reactions are not different from any other chemical reaction and, therefore, that the whole arsenal of methods of attack known from conventional kinetics may be used in the characterization of the process. This includes also temperature [85,120,136–138] and kinetic isotope effects [138,139].

D. Limiting Experimental Factors

The shape and position of the voltammogram depend not only on the kinetics and thermodynamics of the electrochemical reaction, but are affected also by the design of the voltammetry cell and the potentiostat. Closely related to this is the question of measurement precision.

1. The Cell and the Working Electrode

Two problems may arise at low ν. The first of these is related to the assumption that mass transport is caused by diffusion only. The time t after the voltage sweep has been initiated the approximate thickness of the diffusion layer δ at a planar electrode is given by Eq. (55).

$$\delta = 6\sqrt{D_A t} \tag{55}$$

When the δ becomes larger than a few tenths of a millimeter, natural convection begins to interfere and the assumption of diffusion as the only means of mass transport is no longer valid. For typical values of D_A ($10^{-5}\,cm^2\,s^{-1}$) this happens when t is of the order of 10 s, corresponding to $\nu = 0.2\,V\,s^{-1}$ for a CV sweep with $E_{initial} - E_{switch} = 1\,V$. At times larger than approximately 1 min, or ν approximately less than $0.025\,V\,s^{-1}$, the deviations from pure diffusion are so pronounced and unpredictable that the measured current cannot be related to a practical theoretical model. This influence of natural convection at low ν may be reduced by using a properly shielded working electrodes [140] (Fig. 19).

Another problem at low ν is the so-called edge effect observed when the thickness of the diffusion layer at an unshielded working electrode is comparable to its diameter [141,142]. At the edges the diffusion of material to and from the electrode is not limited to being linear as illustrated Fig. 20, and it is seen that the deviations becomes progressively larger when the diameter of the electrode becomes smaller until, in the limit, the transport may be described as hemispherical diffusion. This applies for the so-called ultramicroelectrodes (see Sec. III). By inspection of Fig. 20 it is easily understood that mass transport close to the edges is more effective than at the central part of a circular electrode and, accordingly, the current density (for example in units of $mA\,cm^{-2}$) increases when the diameter of the electrode decreases.

The effect of this change in the diffusion pattern on the voltammogram for a reversible electron transfer reaction, Eq. (1), is shown in Fig. 21. It is seen that the gradual change of the diffusion pattern has a profound influence not only on the magnitude of the current density, but also on the appearance of the voltammogram, which gradually changes to the S-shaped curve characteristic for hemispherical diffusion [142]. In the latter case the diffusion of material away from the electrode is so effective that reverse current

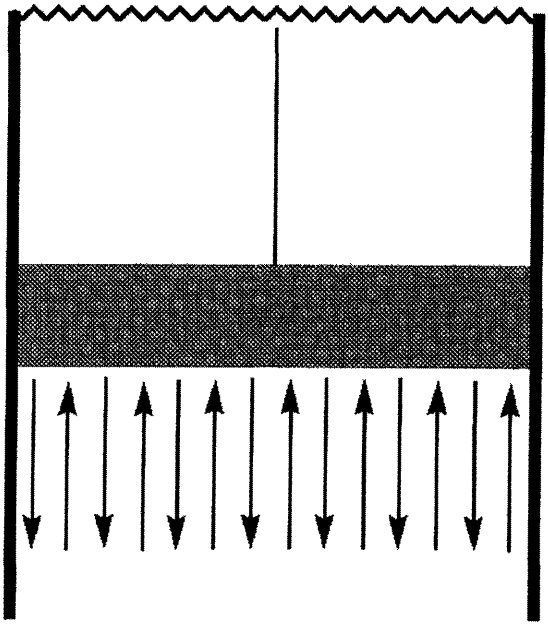


Figure 19. Schematic of a shielded working electrode. The arrows illustrate the diffusion pattern below the electrode.

for the reoxidation of B to A cannot be observed, even, as in this case, when B is perfectly stable in the solution.

At high v the relative positions of the three electrodes need to be optimized and the size of the working electrode needs to be reduced in order to minimize resistance and capacitance problems [143]. The quality of the potentiostat, usually reflected by the rise time, also becomes critical at high v. The two factors are actually not separable since the electrochemical cell is inherently a part of the total electronic circuit.

2. The Uncompensated Solution Resistance, R_u

The R_u problem in LSV and CV has received considerable attention [2,144–149]. The electrode potential during LSV for a sweep in the negative direction is described by Eq. (56), where i is the current flowing at the time t.

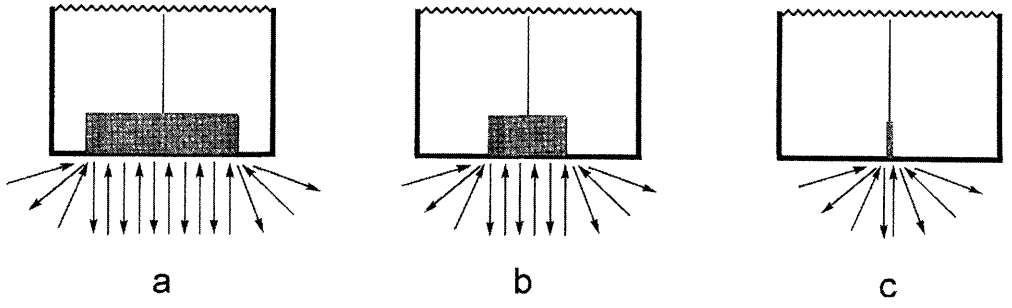


Figure 20. Schematic of the diffusion pattern below electrodes with decreasing diameters of the electrode surface.

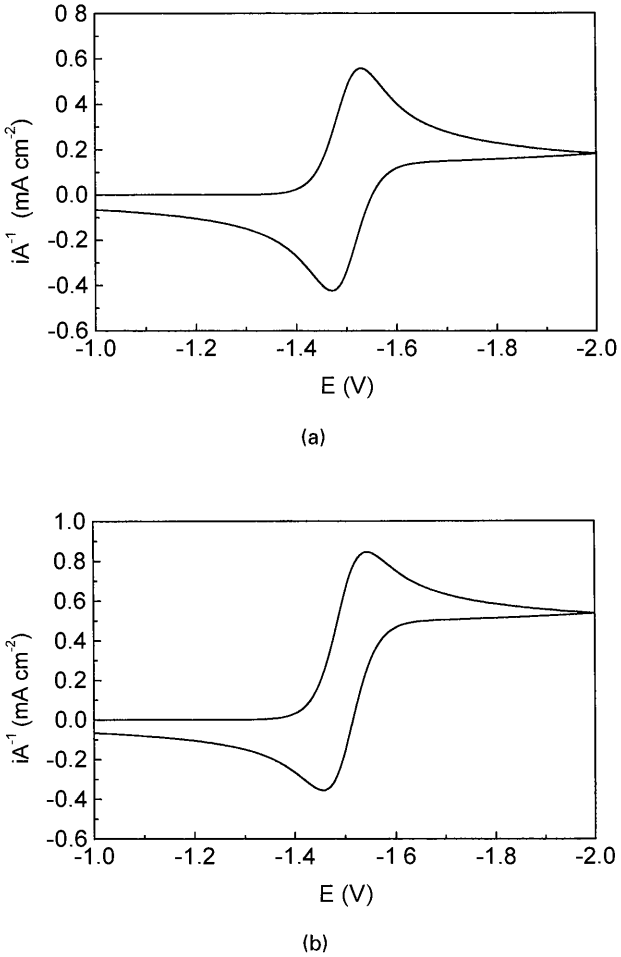
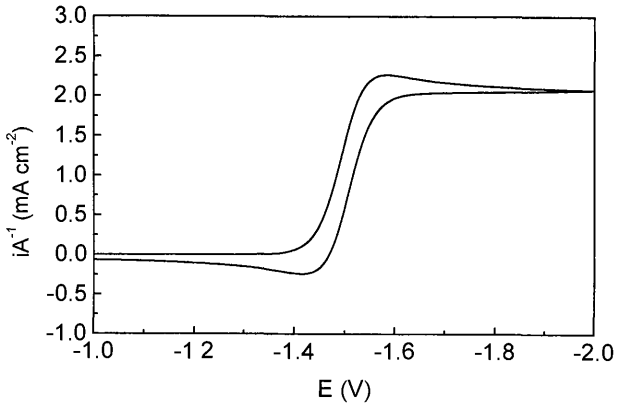


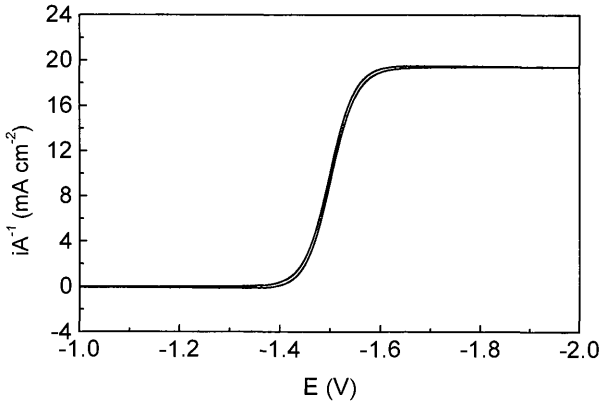
Figure 21. Simulated (DigiSim) cyclic voltammograms for a reversible one-electron reduction with $E^{\circ} = -1.5\,V$ at electrodes with (a) $r = 0.7\,mm$, (b) $r = 0.05\,mm$, (c) $r = 0.01\,mm$, and (d) $r = 0.001\,mm$. Note that the y axis displays the current density (in mA cm^{-2}) in order to facilitate the comparison of voltammograms obtained at different surface radii. For other simulation parameters, see Fig. 3.

$$E_{measured} = E_{initial} - \nu t + iR_u \tag{56}$$

This equation suggests that the real electrode potential E_{real} can be determined only under conditions where the last term vanishes. Thus, the problem is to correct $E_{measured}$ for the contribution of iR_u. This is normally accomplished by a positive feedback circuit incorporated in the potentiostat, which adds a fraction of the current follower output to the voltage provided by the function generator. If the feedback resistance R_f is exactly equal to R_u, the iR_u term in Eq. (56) is compensated for and $E_{measured}$ is equal to E_{real}. The problem then is the selection of the value of R_f. Although this can be accomplished by direct measurement of R_u and other procedures [2,144], a simpler procedure is desirable for the level of sophistication of most electrochemical studies. Such a simple and convenient method is to adjust the feedback circuit until



(c)



(d)

Figure 21. (Continued)

the output of the current follower goes into oscillation and then to back off slightly [149]. This method is quite effective for electrodes with diameters less than 2 mm as long as v is not larger than about $100\,V\,s^{-1}$

3. The Importance of Precision in Potential Measurements

The precision of E_p required for comparison with literature values is of the order of ± 5 mV. This can easily be accomplished by using XY recorders with scale expansion or commercial computer software.

In other cases, including LSV analysis (see Sec. II.C.4) and studies of the effect of small structural changes such as deuterium isotope effects, the required precision is ± 0.5–1 mV or better. This can easily be appreciated by considering that the theoretical values of, for instance, $dE_p/d(\log v)$ in LSV, Eq. (40), differ by only 10 mV for first- and second-order follow-up reactions. Similarly, it has been found that 2,7-d_2-pyrene is only 1.5 ± 0.2 mV more difficult to reduce than pyrene itself [150]. Such a high precision

requires highly stable reference electrodes and advanced data treatment, including averaging of measurements, baseline corrections, and sophisticated peak fitting routines.

Another approach involves the application of derivative linear sweep voltammetry or DCV [Fig. 10(b)]. These techniques allow a precision of the order of $\pm 0.2\,mV$ to be realized during peak potential measurements [29–31,36]. The feature giving the high precision is that the peak potential is measured at the point where the steeply descending first derivative crosses zero.

E. Computer-Based Methods for Analysis of Voltammetric Data

Most electrochemical studies carried out today make use of online computers for control of experiments and for data acquisition and analysis, including the techniques described earlier. Examples of the application of computer evaluation of experimental results include, for instance, pattern recognition [151] and the recording of current-time profiles of the form $\Delta(\ln i)/\Delta(\ln t)$ versus t for mechanistic classification [152] as well as nonlinear regression techniques [153–155]. Efforts have also been made to use knowledge-based systems for the elucidation of reaction mechanisms [156].

The advances in computer technology have, in more general terms, stimulated the development of techniques that use more than just a few data points, such as E_p, $E_{p/2}$, and i_p, along the voltammetric wave. This would at first glance seem to be an advantage. However, it should be kept in mind that the problems originating from, for instance, background currents and improper adjustments of the electronic equipment remain, and it requires some skill to incorporate parameters, for instance, for the uncompensated electrical solution resistance (discussed earlier) and the double-layer capacity (see Chapter 1) in the data treatment. The opinion of the author of this chapter is that trends in the kinetic data and their origin are often easier to locate when a more classical approach to the data analysis is taken, but admittedly, this opinion may just reflect a lack of experience. It should be mentioned here also that the commercial software package DigiSim offers the possibility to fit simulated voltammograms directly to experimental ones.

Most of the more advanced techniques have only rarely been used outside the laboratories where they have been developed, and for that reason it is not easy to give recommendations. Examples include normalized sweep voltammetry [34,35,157,158], linear current-potential analysis [33], and the so-called global analysis and related techniques [159–161]. However, one such technique, convolution potential sweep voltammetry, has gained some popularity, and is introduced briefly here.

1. Semi-Integration and Convolution Techniques

The essential feature of these methods is that semi-integration [162–167] or calculation of the convolution integrals, Eq. (57) [147,168–174], results in the transformation of the voltammogram into what has been called a neopolarogram. Experimentally, the convolution integral may be evaluated by using the Riemann-Liouville algorithm, Eq. (58). (See also Ref. 1.) The resulting curve is given by Eq. (59), where I_l is defined in Eq. (60).

$$I(t) = \frac{1}{\pi^{1/2}} \int_0^t \frac{i(u)}{(t-u)^{1/2}}\, du \tag{57}$$

$$I(t) = \left(\frac{\Delta}{\pi}\right)^{1/2} \sum_{j=1}^{t/\Delta} \left[i(j\Delta) + i(j\Delta - \Delta) \right] \left[\left(\frac{t}{\Delta} - j + 1\right)^{1/2} - \left(\frac{t}{\Delta} - j\right)^{1/2} \right] \tag{58}$$

$$E = E_{1/2} + \frac{RT}{nF} \ln \frac{I_l - I(t)}{I(t)} \tag{59}$$

$$I_l = nFAD_A^{1/2} C_A^* \tag{60}$$

Logarithmic analyses can be carried out on the neopolarogram in much the same way as with classical polarography (see Sec. V). Examples that illustrate the application of the convolution technique include reversible dimerization of radical cations [114], the study of dissociative electron transfer reactions [175,176], and investigations of the possible potential dependence of the transfer coefficient α [174,177].

III. ULTRAMICROELECTRODES AND SCANNING ELECTROCHEMICAL MICROSCOPY

A. Ultramicroelectrodes

The definition of ultramicroelectrodes is somewhat arbitrary and with reference to the common disk geometry is currently meant to describe electrodes with diameters of about 10 μm or less [125,143,178]. The electrochemical response at ultramicroelectrodes can be classified into two categories depending on the value of ν.

At low ν, the transport to and from an ultramicroelectrode is best described as hemispherical diffusion, which results in a faradaic current that greatly exceeds that expected for linear diffusion [142,179] (see Sec. II.D.1. and Fig. 21). An important feature of the voltammogram shown in Fig. 21(d) is the absence of a peak. Instead, the current reaches a plateau indicating that a steady-state has been obtained. The steady-state current for an ultramicroelectrode inserted in a large insulating shaft [Fig. 20(c)] is given by Eq. (61), where r is the radius of the electrode surface [180]. The effective transport resulting from hemispherical diffusion also results in an electrode system that is relatively insensitive to natural convection.

$$i = 4nFrD_A C_A^* \tag{61}$$

The second category of electrode response for an ultramicroelectrode occurs at high ν. Under these conditions, linear diffusion is operative and the response does not differ from that of conventional electrodes with surface diameters in the 0.1 to 2 mm range. However, the effects of double-layer charging (see Chapter 1) and solution resistance are considerably reduced owing to the small size of the electrode. The transition from low to high ν is shown in Fig. 22 for an electrode with $r = 1\,\mu m$ at $\nu = 0.03$, 10, 500, and 100,000 $V\,s^{-1}$, respectively.

Although the use of ultramicroelectrodes is not restricted to any specific measurement technique [125,143,178,181], only applications in the context of cyclic voltammetry at high sweep rates are considered here (see also Sec. IV). For the studies of reaction kinetics using ultramicroelectrodes under steady-state conditions the reader is referred to the original literature [182].

1. Determination of $E^{o\prime}$ for the A/B Redox Couple When B Is Highly Reactive

The perspective in using very high voltage sweep rates during CV has been demonstrated by several authors [125,143,183–187]. Historically, it is of interest to notice that Perone in 1966 already used sweep rates up to 50,000 $V\,s^{-1}$ [183] in studies of the electron transfer

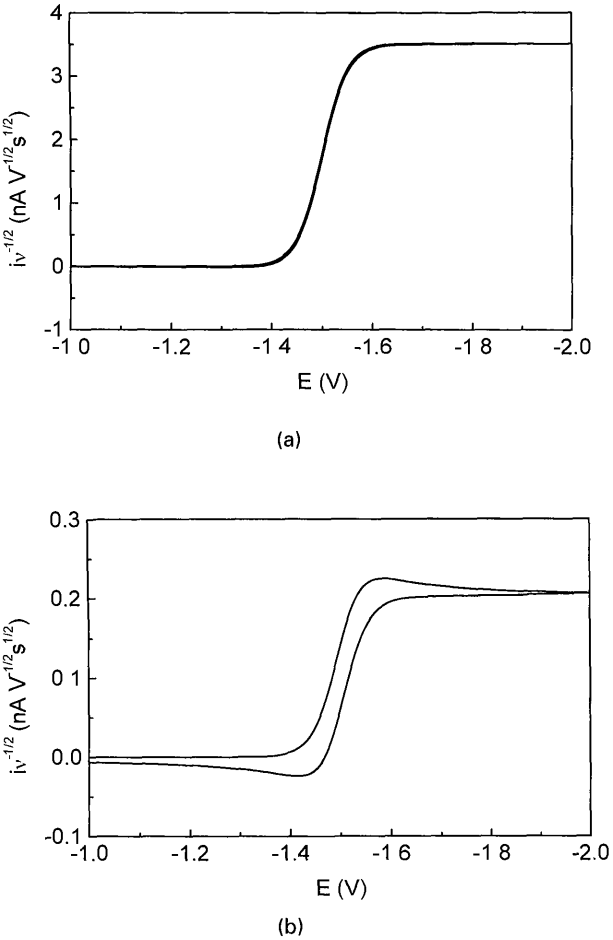


Figure 22. Simulated (DigiSim) cyclic voltammograms for a reversible one-electron reduction with $E^\circ = -1.5\,V$ at an electrode with $r = 1\mu m$ and (a) $\nu = 0.03$, (b) $\nu = 10$, (c) $\nu = 500$, and (d) $\nu = 100{,}000\,V\,s^{-1}$. For other simulation parameters, see Fig. 3. Note that units of $i\nu^{-1/2}$ are used at the y axis to facilitate the comparison of voltammograms obtained at different sweep rates.

rates for inorganic redox couples, and the $1{,}000{,}000\,V\,s^{-1}$ mark was passed in 1988 [186,187]. Cyclic voltammograms for the reduction of anthracene in MeCN at sweep rates up to $100{,}000\,V\,s^{-1}$ [185] are illustrated in Fig. 23. It is seen that the contribution from the double-layer charging current increases relative to the contribution from the faradaic current with increasing sweep rate. This is because the double-layer charging current is directly proportional to the sweep rate, whereas the faradaic current only increases with the square root of the sweep rate [Eq. (13)]. Subtraction of a background curve obtained in the absence of the substrate may eliminate the problem [188].

An obvious application of high sweep rates is the determination of E° values for A/B couples where B undergoes a chemical reaction so fast that it cannot to be outrun by the sweep rates applicable to conventional electrodes [94,100,189]. Once E° is known, the rate constant may be determined from LSV relations of the type already given, as in Eqs. (45)–(46).

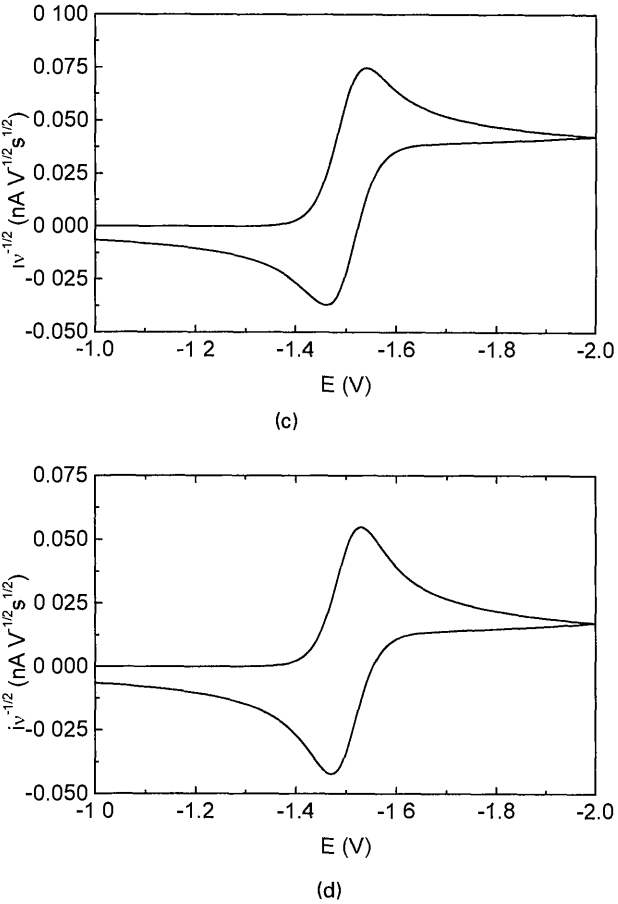


Figure 22. (Continued)

2. Determination of Heterogeneous Electron Transfer Rate Constant

It follows from the discussion of electron transfer reactions in Sec. II.B that a reversible process when studied by CV inevitably passes into the quasi-reversible regime at some value of ν when ν is allowed to increase. For $k^\circ = 3\,cm\,s^{-1}$, a value typical for many aromatic hydrocarbons, for example [71], it is seen from Eq. (27) that this happens at approximately $\nu = 170\,V\,s^{-1}$. Thus, studies of electron transfer rates in this region require voltage sweep rates in the range of 200–1000 $V\,s^{-1}$. Ultramicroelectrodes are superb for this purpose, as demonstrated, for example, in a study of the oxidation of ferrocene [190]. Peak potential separations recorded at sweep rates between 500 and 3000 $V\,s^{-1}$ at an electrode with a surface diameter of 10 μm over a range of substrate concentrations resulted in k° equal to 1.10, 1.13, and 1.13 $cm\,s^{-1}$. A more recent example is the oxidation of selenanthrene and related compounds [191].

3. Kinetics of Rapid Follow-Up Reactions

Ultramicroelectrodes are excellent tools also for the study of the kinetics of fast follow-up reactions, provided that the high sweep rates needed do not bring the electron transfer process into the quasi-reversible region. Thus, a reaction that during a study with con-

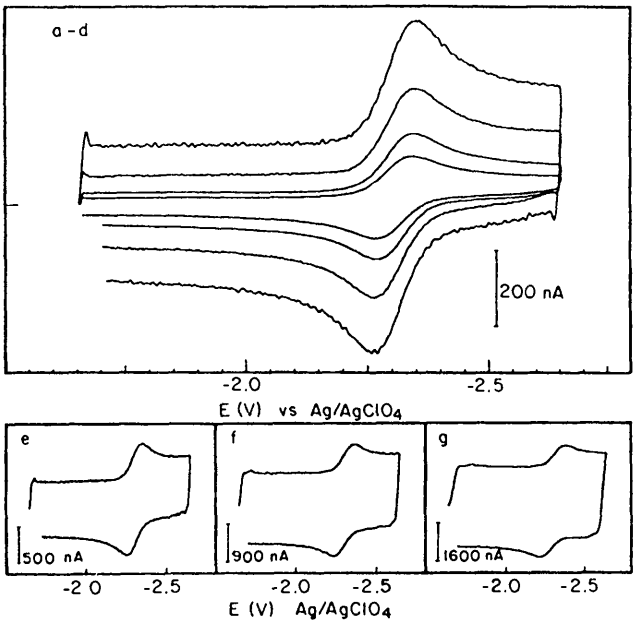


Figure 23. Cyclic voltammograms for the reduction of anthracene (2.22 mM) in MeCN containing Et_4NClO_4 (0.6 M) at a gold electrode with r = 6.5 μm and (a) $\nu = 1000$, (b) $\nu = 2000$, (c) $\nu = 5000$, (d) $\nu = 10{,}000$, (e) $\nu = 20{,}000$, (f) $\nu = 50{,}000$, and (g) $\nu = 100{,}000\ V\,s^{-1}$. (From Ref. 185.)

ventional electrodes is under purely kinetic conditions may at high sweep rates be studied under mixed diffusion and kinetic control using the approach described in Sec. II.C.3.

An early example of this approach is the study of the interconversion of the "A" and "B" form of bianthrone [192]. The stable isomer at ambient temperature is the yellow "A" form, which is equilibrated with the green "B" form as the temperature is increased. Reduction of "A" produces "A^-" which rapidly undergoes a conformation change to the "B"-like radical anion. The formal potentials for the two forms differ by about 230 mV for the isomers of 1,1′-dimethylbianthrone in dimethylformamide (DMF) at 361 K. The rate constant for the conversion of "B" to "A" could be determined to be equal to $500\ s^{-1}$ under these conditions by comparing experimental cyclic voltammograms obtained at 200, 500, 1000, and $5000\ V\,s^{-1}$, using 5-μm Pt disk electrodes, to theoretical voltammograms obtained by digital simulation. Other examples include studies of the cleavage of the carbon-halogen bond in the radical anions of aromatic halides [187,193] and the RR dimerizations of the *N,N*-dimethylaniline radical cation [194] and diphenylamine radical cation [195].

B. The Application of Scanning Electrochemical Microscopy for Studies of Reaction Kinetics

Scanning electrochemical microscopy (SECM) [196] is a member of the growing family of scanning probe techniques. In SECM the tip serves as an ultramicroelectrode at which, for instance, a radical ion may be generated at very short distances from the counterelectrode under steady-state conditions. The use of SECM for the study of the kinetics of chemical reactions following the electron transfer at an electrode [196] involves the SECM in the so-

called feedback mode [197], where the counterelectrode serves to collect the primary electrode intermediate generated at the ultramicroelectrode (Fig. 24). At sufficiently small distances between the ultramicroelectrode tip and the counterelectrode, the time of diffusion from the tip to the counterelectrode is of the same order as the lifetime of the intermediate, which makes possible the detection of the intermediate at the counterelectrode. The upper limit for first-order rate constants is close to $10^5 s^{-1}$ and for second-order rate constants 10^8–$10^9\ M^{-1}\ s^{-1}$ [198]. The relationship between the distance and the kinetics of the follow-up reaction is expressed by the dimensionless parameter K, [Eqs. (62)–(63)], where k is the rate constant of the chemical reaction, r is the radius of the tip, and d is the distance between the tip and the counterelectrode:

$$K = \frac{kd^3}{rD_A} \quad \text{(first-order rate law)} \tag{62}$$

$$K = \frac{kC_A^* d^3}{rD_A} \quad \text{(second-order rate law)} \tag{63}$$

At very short distances, depending on the rate of the chemical reaction, essentially all B generated at the tip is detected by the counterelectrode. When the distance gradually is made larger, an increasing fraction of B reacts to products until, in the limit, no B is detected at the counterelectrode. By plotting the ratio between the current at the counterelectrode i_c and the tip current i_t, $-i_c/i_t$, as a function of the distance, information about the kinetics of the follow-up reaction can be obtained by fitting the data to the appropriate working curve $-i_c/i_t$ versus $\log K$ (Fig. 25). Thus, the parameter $-i_c/i_t$ plays a role equivalent to that, for instance, of the collection efficiency in rotating ring-disk electrode voltammetry (Sec. VI). The distance between the tip and the counterelectrode is determined by a calibration procedure including the recording of $-i_c/i_t$ for a reversible redox couple for which B is stable and fitting the data to a working curve [200].

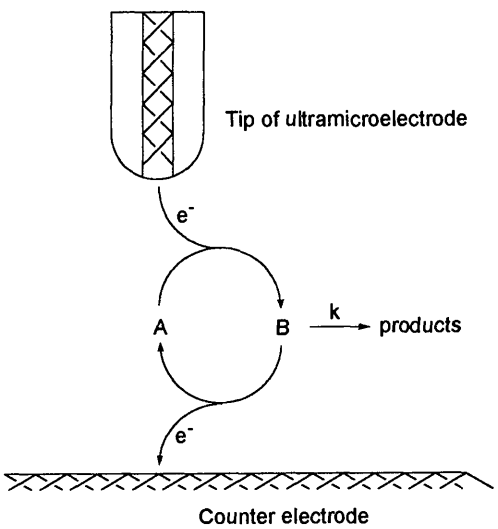


Figure 24. The principle of the application of scanning electrochemical microscopy for studies of reaction kinetics.

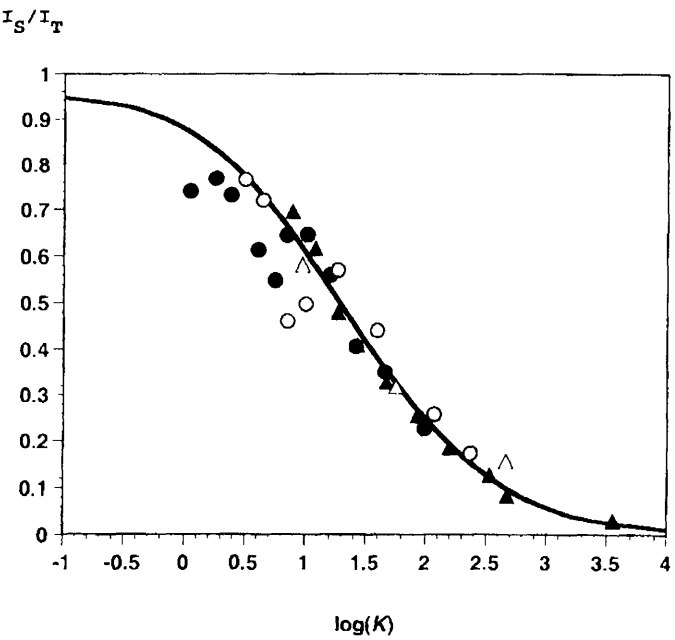


Figure 25. SECM working curve for the RR dimerization mechanism together with experimental points obtained for the oxidation of *trans*-anethole. The ratio I_s/I_t at the figure corresponds to $-i_c/i_t$ in the text and K is defined in Eq. (63). (From Ref. 199).

An advantage of SECM is that it is a steady-state technique that does not require the measurements of transient currents. The technique also offers the same advantage as, for instance, double potential-step chronoamperometry (Sec. IV.A) in that the potential of the tip electrode can be made sufficiently negative that the heterogeneous electron transfer proceeds at the diffusion-controlled rate.

An example of the application is the oxidation of *trans*-anethole [*trans*-1-(4-methoxyphenyl)propene], the radical cation of which by LSV was found to undergo rapid RR dimerization (through C-2). The rate constant measured by SECM is as high as $4 \times 10^8\ M^{-1}\ s^{-1}$ [199]. The fit of the experimental data to the working curve is shown in Fig. 25. The SECM technique has also been used to determine the rate constant for the dimerization of the radical anions of acrylonitrile, the prototype example of electrohydrodimerization (Chapter 21). The value of k was found to be $6 \times 10^7\ M^{-1}\ s^{-1}$ [201].

IV. POTENTIAL-STEP AND CURRENT-STEP METHODS

A. Chronoamperometry and Double Potential-Step Chronoamperometry

When the potential of a planar electrode is suddenly shifted from a value at which no current flows to a value where the electron transfer, Eq. (1), proceeds at the diffusion-controlled rate, the current-time behavior is given by Eq. (64), where i_c is the double layer charging current [1,2].

$$i = \frac{nFAC_A^* D_A^{1/2}}{(\pi t)^{1/2}} + i_c \tag{64}$$

When conventional electrodes with diameters between 0.1 and 2 mm are used, the latter quantity has usually decayed to zero after 0.5 ms or less and may be neglected in experiments lasting 1 ms or more. This decay time is reduced to the microsecond time regime when ultramicroelectrodes are used [94,125,202]. According to Eq. (64), which for $i_c = 0$ is known as the Cottrell equation, the current approaches zero when the time approaches infinity. However, undisturbed linear diffusion can be maintained only over rather short time intervals unless special precautions are taken (see Sec. II.D.1), and the measurements of current-time curves, called chronoamperometry (CA), are often complicated by additional modes of transport. Therefore, the use of properly shielded electrodes [140] should be considered in chronoamperometric experiments exceeding approximately 1 s. The mathematical formalism for chronoamperometry has been developed also for the application of ultramicroelectrodes [203].

The application of CA for monitoring the progress of chemical reactions following the heterogeneous electron transfer is limited by the nature of the process. As it appears from Eq. (64), the only parameter that may be affected by a follow-up reaction is n. Thus, important mechanisms such as the eC (Scheme 2) and eC(dim) (Scheme 3) cannot be characterized by this type of experiment. However, it has been demonstrated that if the potential is shifted to values insufficient for diffusion-controlled electron transfer, rate constants, for instance for the eC mechanism, may be determined [204]. Working curves have been calculated relating the apparent number of electrons exchanged n_{app}/n, given by Eq. (65), to the dimensionless parameter log(kt), where k is the first-order or pseudo first-order rate constant for the chemical step.

$$\frac{n_{app}}{n} = \frac{it^{1/2}_{actual}}{it^{1/2}_{diff.control}} \tag{65}$$

An example of the application of the technique is a study of the kinetics of the benzidine rearrangement, which follows the reduction of azobenzene in acidic aqueous ethanol [205]. The approach has been further developed and extended to encompass the automatic recording of three-dimensional i-E-t curves [206]. However, experiments of this kind may be hard to perform with high precision because of difficulties in the accurate control of the potential in the region close to E°.

If, during the chemical step, a product is formed that undergoes further electron transfer at the applied potential, as for example in the eCe and eCe_h-type mechanisms (Scheme 2), or if the electroactive substrate is regenerated in a catalytic process (Scheme 7), the value of n_{app}/n depends on k even under conditions in which the heterogeneous electron transfer is diffusion controlled [68,133]. It is easily understood that n_{app}/n approaches unity when k decreases toward zero, and a higher value, depending on the mechanism, when k increases.

The competition between heterogeneous electron transfer (eCe) and electron transfer in solution (eCe_h) in the second e step (Scheme 2) and the possibility of distinguishing between these two pathways have been analyzed in detail [207,208]. It was concluded that the eCe_h pathway dominates over the eCe pathway unless the measurement time is kept below approximately 10^{-7} s. The application of chronoamperometry to determine the rate constants in more complicated reaction schemes, such as, for example, the eCeCe-type mechanism, has been addressed as well [209].

An important extension of CA, double potential-step chronoamperometry (DPSCA), involves a second potential step to a potential at which B is converted back to A at the diffusion-controlled rate [1,2,210,211]. The potential-time program and the

current-time curve are illustrated in Fig. 26. The current is measured twice, the first time at $t = t_f$ (i_f) and the second time usually at $t = 2t_f$ (i_b). For a simple electron transfer reaction, the ratio $-i_b/i_f$ is independent of t_f and has the value 0.2928. However, if a chemical reaction is associated with the electron transfer reaction, the ratio $-i_b/i_f$ depends on t_f. Working curves based on analytical solutions of the diffusion-kinetics equations have been presented for simple mechanisms [212]. More generally, the working curves may be calculated by digital simulation and are usually presented as the normalized current ratio $R_I = -i_b/(i_f \cdot 0.2928)$ as a function of $\log(kt_f)$ (first-order rate law) or $\log(kC_A^* t_f)$ (second-order rate law) (Fig. 27). The value of k (or k_{obs}) may be determined by fitting the working curve to the experimental data as demonstrated in Fig. 27 for the protonation of anthracene radical anion by phenol.

Alternatively, the rate constant may also be determined directly from the measured value of $t_{1/2}$, that is the value of t required to obtain $R_I = 0.5$, [Eqs. (66) and (67)], in a fashion analogous to that described for DCV [see Eqs. (36) and (37)].

eC mechanism:

$$k_{obs} = \frac{0.406}{t_{1/2}} \ s^{-1} \tag{66}$$

RR dimerization:

$$k_{obs} = \frac{0.830}{t_{1/2} C_A^*} \ M^{-1} s^{-1} \tag{67}$$

The approximate kinetic window of DPSCA at electrodes with a diameter in the 0.1–2 mm range is given by Eq. (68), where k is a first-order or pseudo first-order rate constant:

$$0.3 \ s^{-1} < k < 300 \ s^{-1} \tag{68}$$

With the application of ultramicroelectrodes the upper limit can be extended considerably [202].

Double potential-step chronoamperometry offers two attractive features, at least. First, since the method includes potential steps to E values at which the heterogeneous

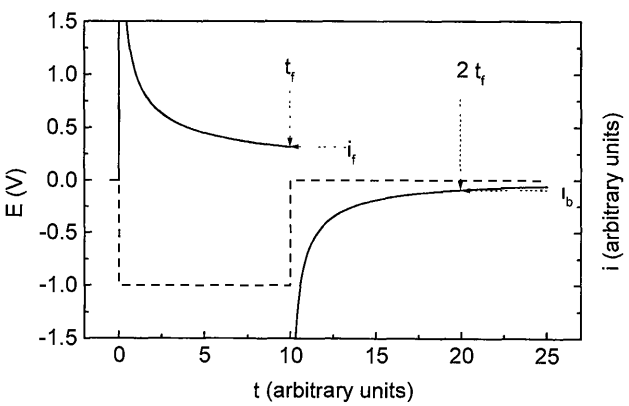


Figure 26. Double potential-step chronoamperometry; potential-time program for a potential-step from 0 to −1 V (dotted line and left-hand scale) and current-time curve (solid line and right-hand scale).

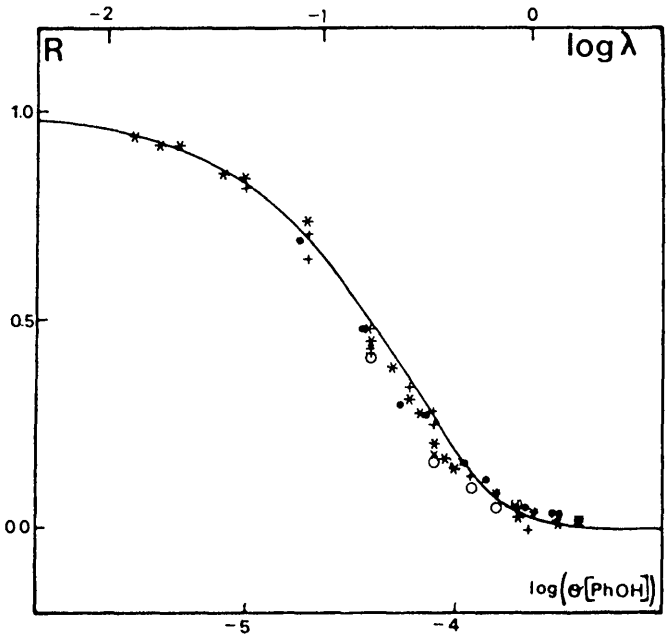


Figure 27. Double potential-step chronoamperometry working curve (top scale) for the eCe_h mechanism (solid line) and experimental data (bottom scale) for the protonation of the anthracene radical anion by phenol in DMF (0.1 M Bu_4NBF_4). $C_A^* = 1$ mM and $C_{PhOH}^*/mM = 9.95(+)$, 18.2 (·), 40.0 (○), 78.8 (×), 100 (□), and 200 (*). R in the figure corresponds to R_I in this chapter and $\lambda = kt_f C_{PhOH}^*$. (From Ref. 213.)

electron transfer is diffusion controlled, experiments may be performed with the iR compensation circuit of the potentiostat switched off. Second, the perturbation of the reaction layer is very small, which means that even a small excess of reagent relative to substrate ensures pseudo first-order conditions [90]. A disadvantage is that DPSCA is a "blind" technique, and current caused by, for example, long-lived intermediates may erroneously be attributed to regeneration of substrate. In such cases, it may be advantageous to use triple potential-step chronoamperometry [214], in which the current flowing after the third potential step reflects whether starting material has indeed been formed after the second step. In general, potential-step techniques should only be used together with a potential-sweep technique, such as CV.

Examples illustrating the application of DPSCA include the cleavage of the carbon–halogen bond in radical anions derived from aromatic compounds [215], the protonation of radical anions derived from aromatic hydrocarbons [90,213,216], the dimerization of radical anions [112,113,217], radical cations [218], and neutral radicals [219], and the conversion of the "B form" to the "A form" for 10,10′-dimethyl-9,9′-biacridylidene [220].

B. Chronocoulometry and Double Potential-Step Chronocoulometry

A method analogous to CA is chronocoulometry, by which the charge Q instead of the current is monitored as a function of time [1,2,221]. The method has found less widespread use than chronoamperometry in organic electrochemistry, but offers certain advantages

when, for instance, an electroactive reactant is adsorbed at the electrode surface [221–225]. Integration of Eq. (64) with respect to time results in Eq. (69), which illustrates that a plot of Q versus $t^{1/2}$ results in a straight line with the intercept Q_c, that is, the charge flowing into the interfacial capacitance as a result of the potential step. This quantity contains information about the degree of substrate adsorption at the electrode surface.

$$Q = \frac{2nFAC_A^*(D_A t)^{1/2}}{\pi^{1/2}} + Q_c \tag{69}$$

The application of chronocoulometry for mechanism analysis and evaluation of kinetic parameters is similar to the application of CA and is often based on visual comparison of experimental data with working curves.

Double potential-step chronocoulometry [1,2,221] may be used similarly to DPSCA. The working curves now include the charge ratio $-Q_b/Q_f$, which takes the value 0.414 for a simple electron transfer reaction. The reductive cyclization of ethyl cinnamate (see Chapter 21) illustrates the use of the technique [226,227].

C. Chronopotentiometry and Current-Reversal Chronopotentiometry

Chronopotentiometry in its most simple form involves the measurement of the potential of the working electrode as a function of time after the onset of a constant current i [1,2]. Because of the decrease in concentration of A close to the electrode, the potential changes with time, and when the concentration is sufficiently small a rapid potential shift is observed to the value of another redox system or to the value for discharge of the solvent-supporting electrolyte solution (Fig. 28).

The time at which the this rapid potential shift is observed, called the transition time τ, can, for reversible electron transfer, be calculated from the Sand equation:

$$\tau^{1/2} = \frac{\pi^{1/2} nFAD_A^{1/2} C_A^*}{2i} \tag{70}$$

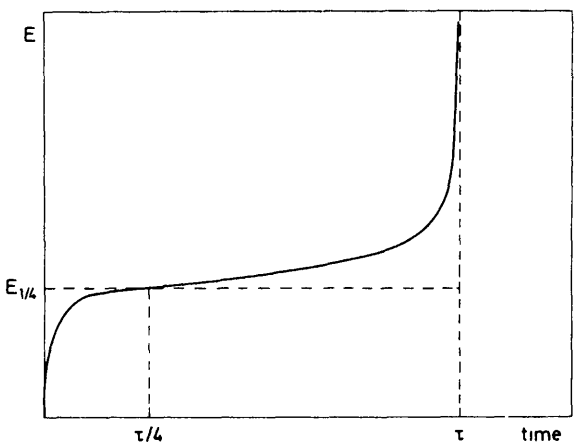


Figure 28. Chronopotentiometry; potential-time relationship after application of a constant current. $E_{1/4}$ is the potential acquired by the electrode at time $\tau/4$.

The complete chronopotentiometric wave is described by Eq. (71). If $t = \tau/4$, the third term cancels and Eq. (71) reduces to Eq. (72), which defines the quarter-wave potential $E_{1/4}$ and which is equal to E^o for $D_A = D_B$.

$$E = E^o + \frac{RT}{2nF}\ln\frac{D_B}{D_A} + \frac{RT}{nF}\ln\frac{\tau^{1/2} - t^{1/2}}{t^{1/2}} \tag{71}$$

$$E_{1/4} = E^o + \frac{RT}{2nF}\ln\frac{D_B}{D_A} \tag{72}$$

Thus, the quarter-wave potential plays the same role in chronopotentiometry [228] as the half-wave potential $E_{1/2}$ in polarography (see Sec. V). The mathematical formalism for chronopotentiometry has been developed also for the application of ultramicroelectrodes [229].

Chronopotentiometry has found only little use in mechanistic organic electrochemistry. This is primarily due to experimental difficulties in the accurate evaluation of the transition time. A solution to this problem includes the application of a convolution procedure [230]. Another extension includes the application of exponential current-time functions and theoretical data for this method are now available for a number of mechanisms [231].

When applied to the analysis of kinetic data, chronopotentiometry is most often used in the current-reversal mode, in which the direction of the current is changed after some time t_f (Fig. 29). When only the direction, but not the magnitude, of the current is changed, the reverse transition time τ_r is given by Eq. (73) [232].

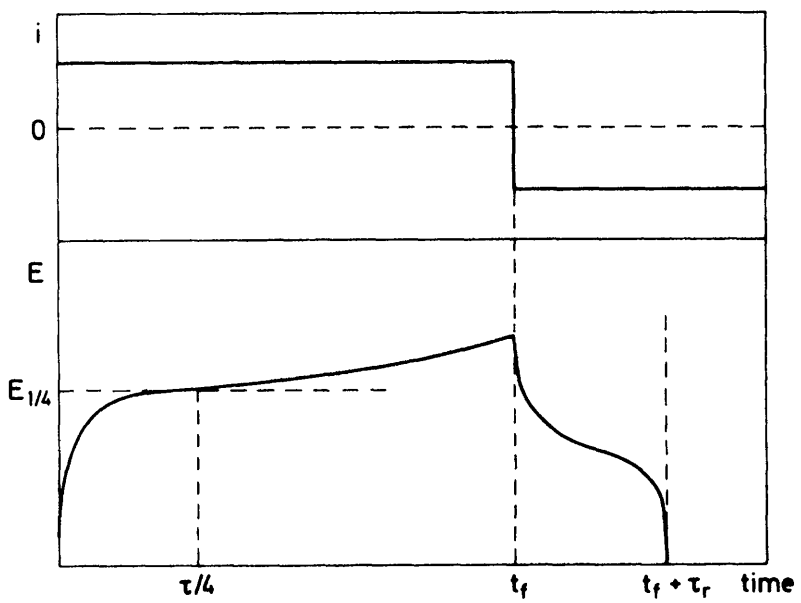


Figure 29. Current-reversal chronopotentiometry; current-time program and potential-time curve.

$$\tau_r = \frac{t_f}{3} \qquad t_f \leq \tau \tag{73}$$

Diagnostic criteria for a number of mechanisms have been summarized [233]. The analysis of experimental data is most conveniently carried out with the aid of a working curve (Fig. 30) relating the parameters t_f, τ_r, and the rate constant k (or k_{obs}).

An example of the application of chronopotentiometry is the oxidation of tropylidene [235,236] and thioxanthene [236].

V. POLAROGRAPHY

Polarography is the term used for voltammetry with the dropping mercury electrode (DME). The technique has been discussed extensively in several textbooks and reviews [1–4,237–242] to which the reader is referred for details concerning both theoretical problems and practical applications. The electrode (Fig. 31) was developed early in the century by Heyrovsky and was the dominating tool in electroanalytical chemistry for several decades. Because of the low oxidation potential of mercury (0.3–0.4 V versus SCE), the DME has been used almost exclusively for the study of reduction processes. Compared with mercury film electrodes, the DME offers the advantage that the electrode surface is continuously renewed. This property reduces undesirable surface effects caused by adsorption.

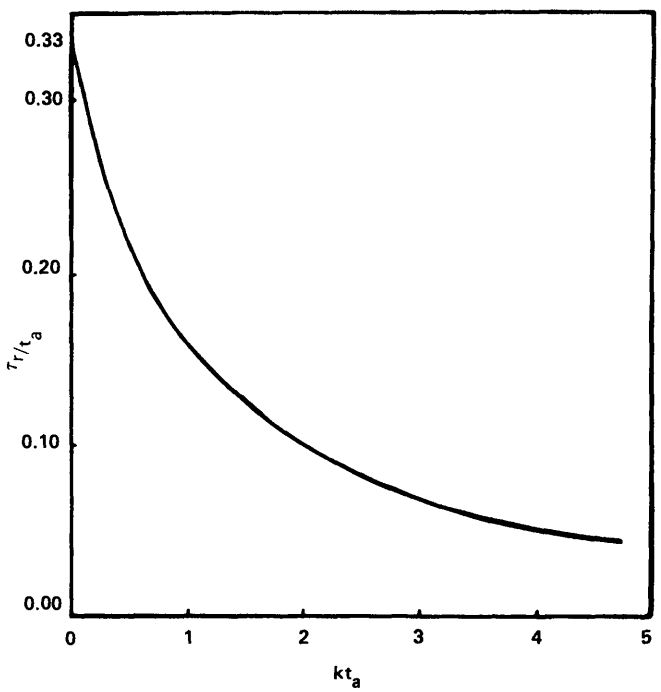


Figure 30. Current-reversal chronopotentiometry working curve for the catalytic eC mechanism. The parameter t_a on the figure corresponds to t_f in the text. (From Ref. 234.)

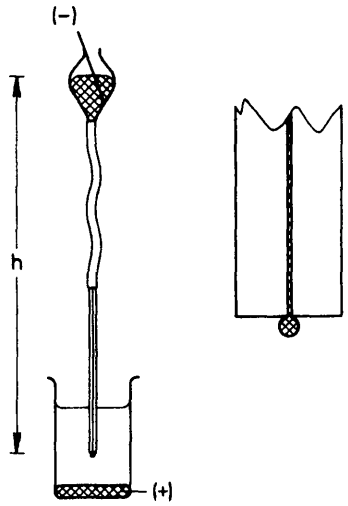


Figure 31. Schematic of a dropping mercury electrode.

A typical current-voltage curve, a so-called polarogram, obtained at the DME as the result of a slow (1–10 mV s^{-1}) linear potential sweep in the negative direction is shown in Fig. 32. The shape of the polarogram illustrates clearly the expansion of the electrode surface during the lifetime of the individual mercury drops. Two parameters are generally used to characterize the polarogram, the half-wave potential $E_{1/2}$ and the limiting current i_{lim}. For a simple electron transfer reaction the height of the current plateau, measured as the mean current during the drop lifetime $\bar{i}_d$, is given by the Ilkovic equation:

$$\bar{i}_d = 607\, n m^{2/3} t^{1/6} D_A^{1/2} C_A^* \tag{74}$$

The subscript d indicates that the surface concentration of substrate is dependent only on diffusion of material to the electrode; m is the mass (mg) of mercury flowing out of the capillary per second, and t is the drop lifetime (s). Polarographic current data are fre-

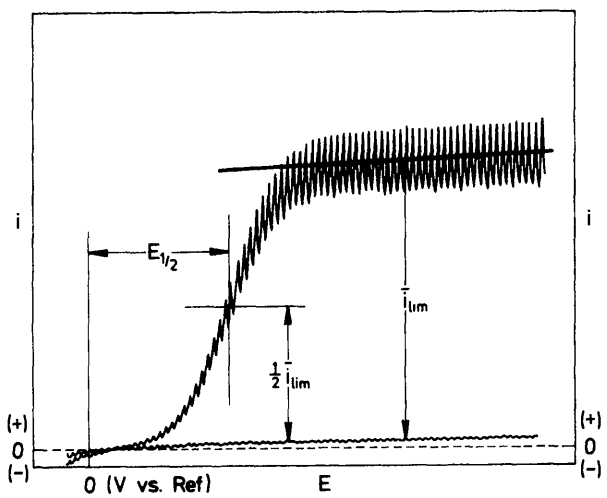


Figure 32. Polarogram obtained at the dropping mercury electrode.

quently normalized with respect to C_A^*, $m^{2/3}$, and $t^{1/6}$ to eliminate the parameters associated with a particular experiment. The current normalized as in Eq. (75) is called the diffusion current constant I.

$$I = \frac{\bar{i}_d}{C_A^* m^{2/3} t^{1/6}} = 607\, n D_A^{1/2} \tag{75}$$

If the electron transfer, Eq. (1), is reversible, the complete polarographic wave may be described by a modified Nernst equation [237,238]:

$$E = E^\circ + \frac{RT}{nF} \ln \frac{f_A D_B^{1/2}}{f_B D_A^{1/2}} + \frac{RT}{nF} \ln \frac{\bar{i}_d - \bar{i}}{\bar{i}} \tag{76}$$

If $\bar{i}_d = 0.5\bar{i}_d$, the third term in Eq. (76) cancels and the expression reduces to Eq. (77), which defines the half-wave potential $E_{1/2}$.

$$E = E_{1/2} = E^\circ + \frac{RT}{nF} \ln \frac{f_A D_B^{1/2}}{f_B D_A^{1/2}} \tag{77}$$

When $f_A = f_B$ and $D_A = D_B$, $E_{1/2}$ equals E°. It is seen also that $E_{1/2}$ is independent of the substrate concentration. Introduction of $E_{1/2}$ in Eq. (76) results in the more convenient Eq. (78), where the constant 0.0591 refers to T = 298 K.

$$E = E_{1/2} + \frac{RT}{nF} \ln \frac{\bar{i}_d - \bar{i}}{\bar{i}} = E_{1/2} + \frac{0.0591}{n} \log \frac{\bar{i}_d - \bar{i}}{\bar{i}} \tag{78}$$

The reversibility of the electron transfer reaction may be tested via this equation, which predicts that a plot of E versus $\log[(\bar{i}_d - \bar{i})/\bar{i}]$ results in a straight line with the slope 0.0591/n V (at T = 298 K) for a reversible redox system. Slopes smaller than 0.0591/n V are observed when the electrode process is quasi-reversible or irreversible. In the latter case, E and i are related through Eq. (79) [238,241].

$$E = \frac{RT}{\alpha nF} \ln \frac{1.349 k^\circ t^{1/2}}{D_A^{1/2}} + 0.9163 \frac{RT}{\alpha nF} \ln \frac{i_d - i}{i} \quad \text{for } i \geq i_d/10 \tag{79}$$

It should be noted that when Eq. (79) is used, it is the current at the end of the drop life rather than the mean current that should be measured. In analogy to the reversible case, the half-wave potential can be introduced, Eq. (80), resulting, finally, in Eq. (81).

$$E = E_{1/2} = \frac{RT}{\alpha nF} \ln \frac{1.349 k^\circ t^{1/2}}{D_A^{1/2}} \tag{80}$$

$$E = E_{1/2} + 0.9163 \frac{RT}{\alpha nF} \ln \frac{i_d - i}{i} = E_{1/2} + \frac{0.0542}{\alpha n} \log \frac{i_d - i}{i} \tag{81}$$

The transfer coefficient α may be obtained from a plot of E versus $\log[(i_d - i)/i]$ which should be linear with a slope of $0.0542/(\alpha n)$ V.

Both m and t in the Ilkovic equation [Eq. (74)] depend on the height of the mercury reservoir h, and since m is equal to c′h and t is equal to c″/h, where c′ and c″ are constants, we have the relationship between $\bar{i}_d$ and h given by Eq. (82). Thus the magnitude of a purely diffusion-controlled polarographic wave is proportional to the square root of the height of the mercury reservoir.

$$\bar{i}_d = 607n(c'h)^{2/3}\left(\frac{c''}{h}\right)^{1/6} D_A^{1/2}C_A^* = (\text{const})h^{1/2} \tag{82}$$

Polarography has been used to characterize the electrochemical reduction of numerous substrates under aqueous conditions [237–242]. Both $E_{1/2}$ and i_{lim} may be affected by the proton activity. The polarograms resulting from reduction of anthracene in solvent systems of increasing proton activity illustrate a general trend observed during this type of experiment (Fig. 33). Under essentially nonaqueous conditions, two reversible one-electron polarographic waves are observed corresponding to the successive formation of the radical anion and the dianion (Fig. 33, curve a). When the water content increases, the first wave grows at the expense of the second wave, with the sum of the two remaining almost constant, until finally at high proton activities the two waves have merged into one two-electron wave (Fig. 33, curve e). This behavior can be rationalized in terms of the eCe_h mechanism in Scheme 2 with X representing a water molecule. The increase in the height of the first wave is related to the increasing importance of the first proton transfer step (ii). In comparison with CV, curve a in Fig. 33 would correspond to Fig. 8, whereas curve e in Fig. 33 would correspond to Fig. 13.

In purely aqueous solution, the half-wave potential $E_{1/2}$ for the general reversible reaction shown in Scheme 5 is given by Eq. (83) (at T = 298 K).

$$E_{1/2} = E_{1/2}^{pH=0} - 0.0591\frac{m}{n}pH \tag{83}$$

Thus for two reaction schemes commonly met in organic electrochemistry, m = n = 1 and m = n = 2, a plot of $E_{1/2}$ versus pH should yield a straight line with the slope 59 mV/pH. Numerous examples of the variation of $E_{1/2}$ with changing pH have been reported [243–245].

Although polarography to some extent has lost some importance relative to new powerful techniques, the method deserves not to be forgotten [242]. Polarography is still in

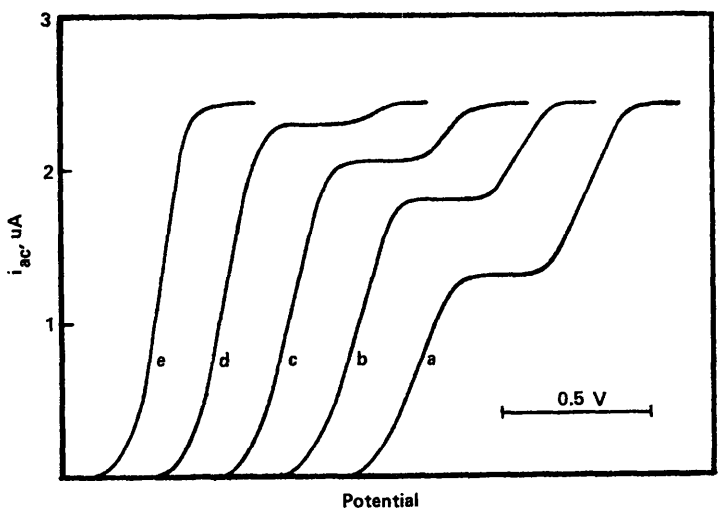


Figure 33. Effect of increasing proton activity, a through e, on the polarogram of anthracene. For the sake of clarity the five polarograms have been shifted horizontally. Note also that the oscillations caused by the growth and fall of the mercury drops are not shown. (From Ref. 76).

many cases a competitive method for the examination of, for example, electron transfer reactions preceded or followed by slow chemical steps or electrochemical reactions associated with adsorption phenomena.

VI. METHODS BASED ON FORCED CONVECTION

A. General Considerations

It is characteristic for the methods described so far that the measurements are carried out in a quiet solution and that the transport of material to and from the working electrode is assumed to be governed by diffusion only. It has been mentioned also that undisturbed diffusion cannot be maintained over longer periods of time unless the working electrode is properly shielded. Another way to suppress the effects caused by natural convection is to use a rotating disk electrode (RDE). Owing to the rotation of the electrode, a strong convective force is imposed on the solution (discussed later); and in comparison other forces that may influence the solution transport are small and can be neglected. Furthermore, the diffusion layer thickness for a rotating electrode is small compared to that of a stationary electrode, and taken together, these characteristics result in an experimental setup that is relatively insensitive to the nature of the surroundings. However, this advantage has to be paid for by the drawback that the RDE, when used in organic electrochemistry, often suffers from electrode fouling, presumably caused by the deposition of insulating films, a problem related to the high material conversion at the electrode surface.

Thorough discussions of the applications of rotating disk electrodes and the associated mathematics are found in several texts [1,246–249].

B. The Rotating Disk Electrode

The electrode tip of an RDE system may consist of a cylindrical piece of conducting material (usually Pt, Au, or glassy carbon), which together with a wire or a steel rod for electrical contact is sealed into an insulating shaft (Fig. 34). When the electrode is rotated, an adjacent thin layer of the solution dragged by the electrode surface acquires the tangential velocity of the electrode. Because of the centrifugal force, this is superimposed by a radial velocity, resulting in an overall flow pattern at the electrode surface, as illustrated in Fig. 35. The liquid thrown out horizontally is replaced through an upward vertical flow (Fig. 34).

The mathematical treatment on which the equations given in this section are based is valid only as long as the fluid flow is laminar. At very high rotation rates the flow becomes turbulent, and at very low rotation rates natural convection begins to play an unwanted role. The two extremes can be given in terms of the Reynolds number Re, which for the RDE is defined in Eq. (84), where r is the radius (cm) of the RDE, including the insulating shaft (!), ω is the angular rotation rate (rad s^{-1}), and ν_k is the kinematic viscosity coefficient ($cm^2\ s^{-1}$). Laminar flow can be maintained for Re values between 10 and 10^4, both values being approximate. For a typical commercial RDE these extremes limit the useful range of rotation rate to values roughly between 0.2 and 200 rev s^{-1}.

$$\mathrm{Re} = r^2 \omega \nu_k^{-1} \tag{84}$$

The tangential and radial velocities decrease with increasing distance from the electrode surface, and at some critical distance δ_0 it is sufficiently accurate to consider the

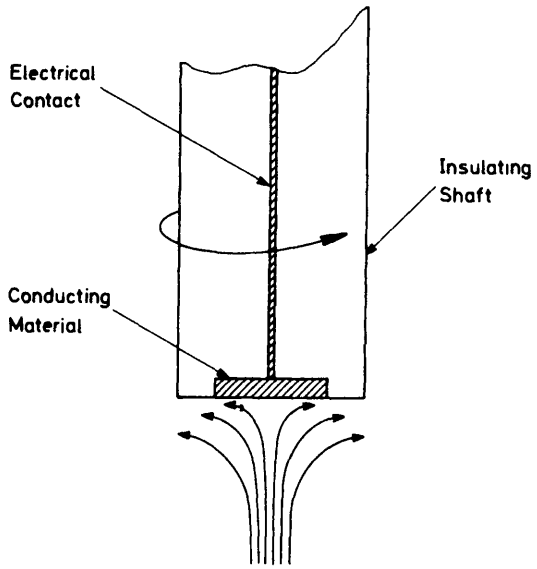


Figure 34. Schematic or a rotating disk electrode. The streamlines indicate the flow below the disk.

laminar upward motion as the only mode of transport. The liquid layer in which it is necessary to take into account both the tangential and the radial velocity is called the hydrodynamic boundary layer, and its thickness is given approximately by Eq. (85). Thus, the value of δ_o varies between 2.7 mm and 0.08 mm for rotation rates in the range 0.2 and 200 rev s^{-1} assuming the value 0.01 $cm^2\,s^{-1}$ for ν_k

$$\delta_o = 3\nu_k^{1/2}\omega^{-1/2} \tag{85}$$

When an electrochemical process takes place at the electrode surface, a concentration gradient develops near the surface, resulting in diffusion as an additional mode of mass transport. The liquid layer in which the transport by diffusion is comparable to the convectional motion is called the diffusion boundary layer, and its approximate thickness δ is given by Eq. (86), corresponding to approximately 5% of δ_o

$$\delta = 1.61 D_A^{1/3}\nu_k^{1/6}\omega^{-1/2} \tag{86}$$

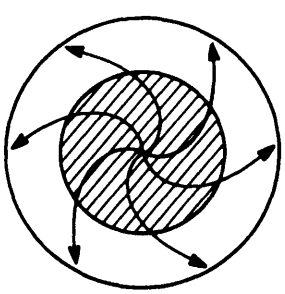


Figure 35. Streamlines at the electrode surface of a rotating disk electrode.

Both δ_0 and δ have the same value over the entire electrode surface, which has given rise to the description of the electrode as a uniformly accessible surface. The concepts of a hydrodynamic and a diffusion boundary layer have no theoretical significance as such but serve mainly to provide a suitable model for the hydrodynamic conditions related to the rotating electrode.

At constant rotation speed, the current-voltage curve (Fig. 36) for a simple reversible electron transfer reaction, Eq. (1), is similar to a polarographic wave and the half-wave potential $E_{1/2}$ for the current-voltage curve obtained by an RDE is defined in the same way as in polarography (Sec. V). The curve can be considered as consisting of three regions, a, b, and c, depending on the value of the applied potential compared to E°. For the general case where the process is under the mixed control of mass and electron transfer (region b in Fig. 36), the current is given by Eq. (87) [250,251].

$$i = \frac{nFAC_A^* D_A}{1.61 D_A^{1/3} \nu_k^{1/6} \omega^{-1/2} + \dfrac{D_A}{k_{s,f}}} = \frac{nFAC_A^* D_A}{\delta + \dfrac{D_A}{k_{s,f}}} \tag{87}$$

For a typical value of $\delta \approx 10^{-3}$ cm, the term $D_A/k_{s,f}$ can be neglected if $k_{s,f} > 10^{-1}\,\mathrm{cm\,s^{-1}}$. The current is now controlled solely by the mass transfer to the electrode (region c in Fig. 36) and the equation reduces to the so-called Levich equation, Eq. (88), which may be used together with the Cottrell equation, Eq. (64), in the experimental determination of δ [252].

$$i_{lim} = 0.62 nFAC_A^* D_A^{2/3} \nu_k^{-1/6} \omega^{1/2} = \frac{nFAC_A^* D_A}{\delta} \tag{88}$$

An important consequence of this equation is the prediction that i_{lim} varies linearly with $\omega^{1/2}$, a crucial test of the quality of the RDE. On the other hand, if $k_{s,f} < 10^{-4}\,\mathrm{cm\,s^{-1}}$, the term $D_A/k_{s,f}$ is large compared to δ, and for this situation, in which the current is controlled by the rate of the electrochemical process (region a in Fig. 36), Eq. (89) is valid.

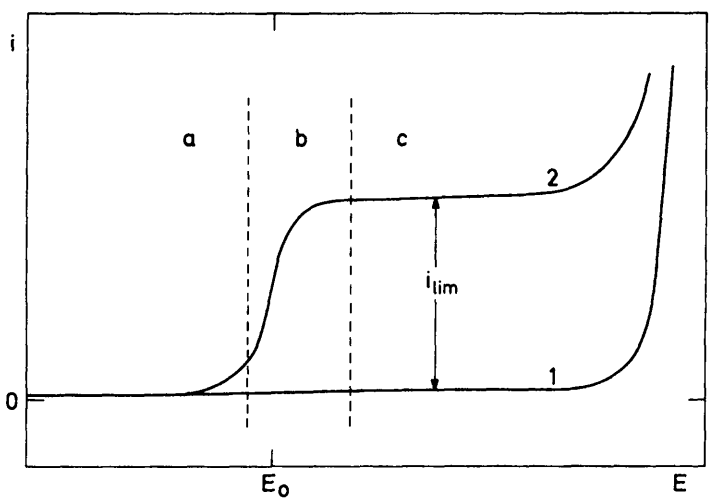


Figure 36. Current-voltage curves for a rotating disk electrode: (1) without and (2) with substrate added. The regions indicated are: a, control by electron transfer; b, mixed control by electron and mass transfer; c, control by mass transfer.

$$i = nFAC_A^* k_{s,f} \tag{89}$$

These relations have been discussed and experimentally tested [250]. Values of k° up to approximately $0.1\,cm\,s^{-1}$ may be measured using the RDE.

By inspection of Eqs. (87)–(89) it is seen that measurement of the rotating disk current may provide information concerning the value of n, C_A^*, D_A, ν_k, or $k_{s,f}$ if the remaining parameters are known. Accuracy in determination of n values depends mainly on how accurately the value of D_A for the compound in question is known. For the majority of organic compounds, diffusion coefficients in the common organic solvents have not been measured, but comparison with a suitable compound of similar structure for which both n and D are known can often solve the problem (assuming the same value of D for the two substrates). Since D_A appears only to the power of $\frac{2}{3}$ in Eq. (88), the resulting n value is only moderately dependent on variations in the D_A estimate. The measurement of diffusion coefficients by means of the RDE technique has been the subject of a number of papers [248,253] and need not be treated further at this place.

A major field of application of the RDE in organic electrochemistry is elucidation of the mechanistic details for reactions following the heterogeneous electron transfer. One way of using the RDE in kinetic work is based on the relationship between i_{lim} and ω. In the absence of kinetic complications, a plot of i_{lim} versus $\omega^{1/2}$ should be a straight line [Eq. (88)]. However, if the electron transfer reaction is followed by a chemical step, the linear dependence of i_{lim} on $\omega^{1/2}$ may change to a curved relationship. For the eCe mechanism (Scheme 2), the relationship between the apparent number of electrons, n_{app}, i_{lim}, and ω is given by Eq. (90) [254], where n and i_{lim}^1 are the number of electrons and the current observed for the first electron transfer step only, i.e., in the absence of the chemical reaction. Other mechanisms have been treated as well [248,255,256].

$$\frac{n_{app}}{n} = \frac{i_{lim}}{i_{lim}^1} = 2 - e^{(-0.834\nu_k^{1/3}k)/(D_A^{1/3}\omega)} \tag{90}$$

It is easily seen that for relatively fast chemical steps where $k \gg \omega$, the exponential term is close to zero and the current corresponds to the exchange of two electrons. On the other hand, if $k = 0$, the current will correspond to a one-electron process. Consequently, for intermediate values of k the apparent number of electrons varies between 1 and 2. Equation (90) predicts that n_{app} trends toward smaller values with increasing ω. The working curve showing the relationship between n_{app} and ω ($\omega^{1/2}$) can be calculated from Eq. (90) for any value of k provided that the remaining parameters are known. Working curves at different k values for the eCe_h mechanism (Scheme 2) are shown in Fig. 37.

The range of measurable first-order rate constants is given by Eq. (91).

$$0.1\,s^{-1} < k < 10^3\,s^{-1} \tag{91}$$

Typical studies, in which the RDE has been used, include the dimerization of the triphenylamine radical cation [257] and the cyclization of the tetraphenylethylene dication [258].

Another approach includes measurements of $E_{1/2}$ relative to that for the simple electron transfer reaction [259–261]. For instance, for the eCe_h mechanism, $\Delta E_{1/2}$ is given by Eq. (92) and it is seen that a plot of $\Delta E_{1/2}$ versus $\log \omega$ is predicted to be linear with the slope $-2.303RT/(2nF)$ ($= -29.5\,mV$ at $n = 1$ and $T = 298\,K$). The value of k can easily be determined from this plot.

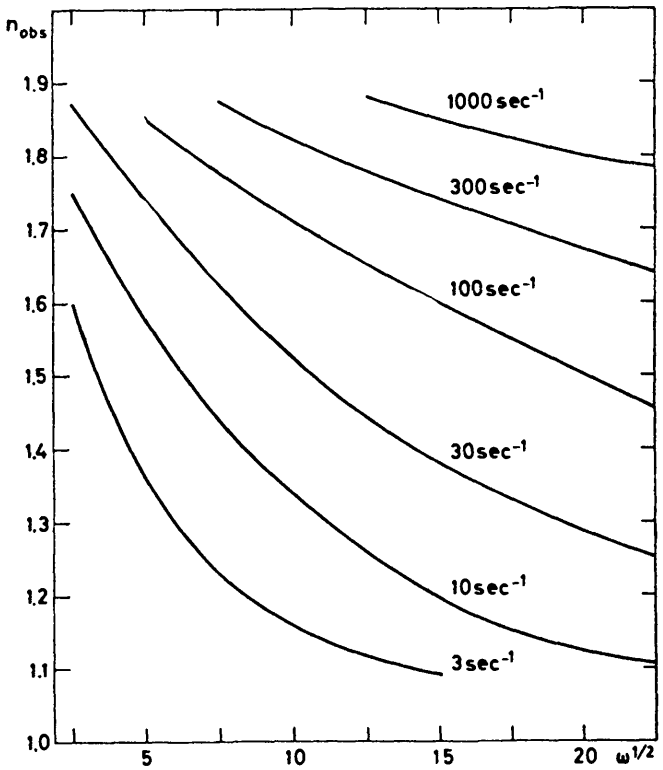


Figure 37. Rotating disk electrode working curves for the eCe_h mechanism at different values of the rate constant k for the chemical step.

$$\Delta E_{1/2} = -\frac{2.303RT}{nF}\log\left[\left(\frac{D_A}{\nu_k}\right)^{1/6}\frac{\sqrt{\omega}}{0.643\sqrt{k}}\right] + \log 2 \qquad (92)$$

An example is shown in Fig. 38 for the reduction of fluorescein in aqueous solution at pH 9.5–9.7 [259].

The applications of the RDE presented so far all relate to operation under steady-state conditions. However, it has been shown that the possibility of discriminating between closely related mechanisms, such as the eCe and the eCe_h, may be improved considerably by using a potential-step technique together with the RDE. The reader interested in the details is referred to the original literature [256,262,263].

C. The Rotating Ring-Disk Electrode

At the RDE the electrode products are thrown horizontally away from the electrode surface and thus escape further detection. A solution to the need for additional information in RDE experiments is the rotating ring-disk electrode (RRDE) [264]. The electrode consists of a conducting disk and a conducting ring in a concentric arrangement separated by insulating material (Fig. 39). By proper adjustment of the ring potential, initial electrode products or products from follow-up reactions may be monitored as a function of

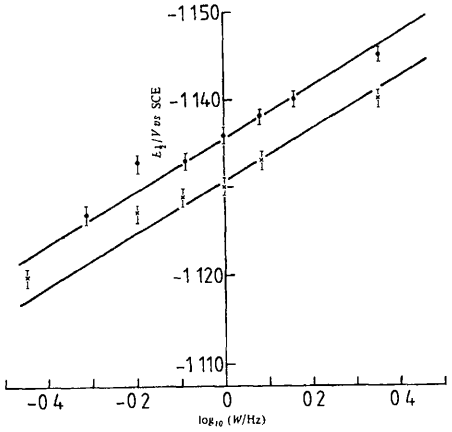


Figure 38. Variation of the half-wave potential for the reduction of fluorescin with the rotation speed for the current-voltage curves obtained at pH 9.68 (•) and 9.51 (×). (From Ref. 259.)

the angular rotation rate. The parameter most frequently used in RRDE experiments is the collection efficiency N, Eq. (93), which relates the ring current i_r to the disk current i_d.

$$N = \frac{i_r}{i_d} \tag{93}$$

These observables usually have opposite signs and should be measured at potentials where mass transport is rate-determining. The value of N is less than unity, even for a simple electron transfer reaction, because only a fraction of the molecules generated at the disk electrode reaches the ring owing to diffusion away from the electrode. The theoretical value of N depends on the geometry of the electrode system. Of special importance is the size of the gap between the two electrodes $r_2 - r_1$ (see Fig. 39). The value of N typically varies between 0.45 and 0.2 [265] and is independent of ω for a simple electron transfer reaction.

If the initial electrode product B undergoes a chemical reaction, the observed ring current, and therefore N, drops to a lower value. The fraction of the B molecules that escape detection at the ring depends on two factors, the rate of the chemical step and the time interval between the generation and detection of B, that is, on ω. Consequently, it can

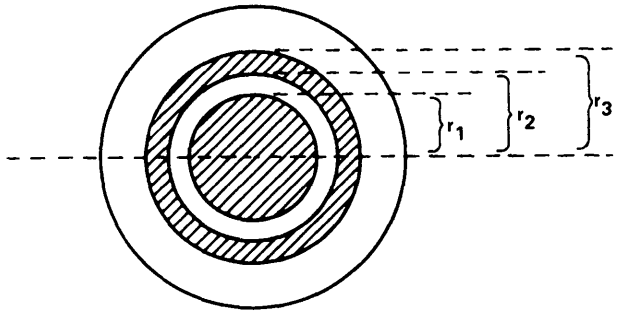


Figure 39. Schematic of a rotating ring-disk electrode.

be expected that for a given chemical reaction the value of N increases with increasing ω and in the limit approaches the value for the simple electron transfer reaction. Working curves for the determination of rate constants can be constructed by analogy to those already described for the RDE, this time relating N to ω or an expression containing this parameter. Because of the complexity of the mathematics associated with the calculation, digital simulation has been extensively used for this purpose [265–267]. Comparison of analytical and numerical solutions for a number of cases demonstrated satisfactory agreement between the two approaches [268]. If the mechanism is known, the rate constant can be obtained from the appropriate working curve, which for the RRDE usually relates the collection efficiency to one of the two parameters given in Eqs. (94) and (95) [265].

$$XKT = (0.51)^{-2/3} k\omega^{-1} \nu_k^{1/3} D_A^{-1/3} \quad \text{(first-order rate law)} \tag{94}$$

$$XKTC = (0.51)^{-2/3} kC_A^* \omega^{-1} \nu_k^{1/3} D_A^{-1/3} \quad \text{(second-order rate law)} \tag{95}$$

However, for a specific case it may be more convenient to use a set of working curves, similar to those shown for the RDE, that relates N to $\omega^{1/2}$ (Fig. 40).

Application of the RRDE as a diagnostic tool to explore the mechanism of an unknown reaction pathway relies, as most methods do, on the differences between the different working curves. For the RDE the working curves for different mechanisms in many cases do not deviate sufficiently to allow a distinction between two possible pathways [259]. The presence of the ring electrode provides extra information, and thus the RRDE is a more sensitive instrument for mechanism analysis. An example is the distinction between the RR and the RS dimerization mechanisms for CS_2 radical anion [269]. It has been pointed out, however, that even with this electrode setup the working curves do

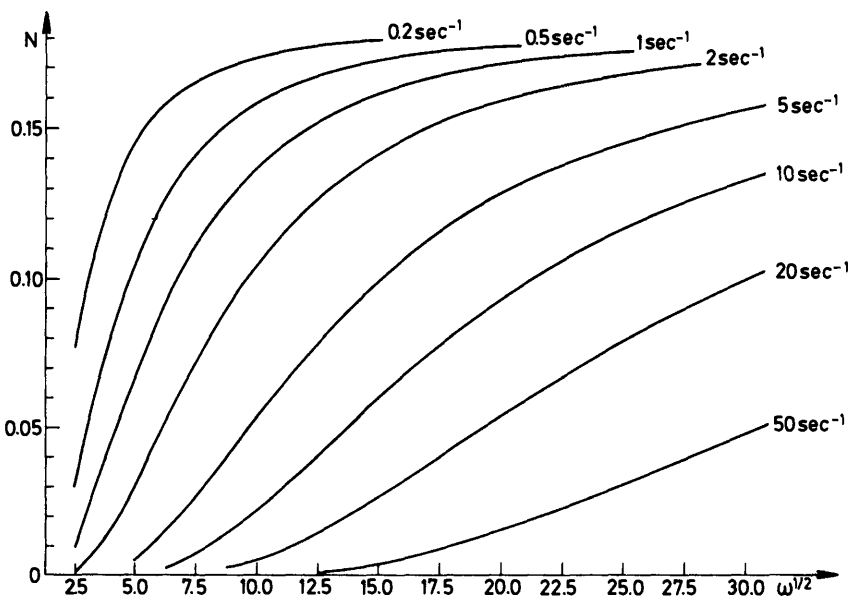


Figure 40. Rotating ring-disk electrode working curves for the eCe mechanism at different values of the first-order rate constant k for the chemical step. The value of N corresponding to k = 0 is 0.184 for this particular electrode.

not allow the unequivocal discrimination between, e.g., eCe type (Scheme 2) and catalytic mechanisms (Scheme 7) [265], or the different dimerization mechanisms (Scheme 3) [266]. A solution to this problem has been found that takes advantage of the possibility of varying the relative fluxes of A and B from the disk via the current density [266,270–272].

The RRDE technique can provide quantitative information for reactions having rate constants in the ranges given by Eqs. (96) and (97). The limits are dependent on the dimensions of the RRDE, in particular the size of the gap between the ring and the disk.

$$10^{-1}\,s^{-1} < k < 10^{3}\,s^{-1} \quad \text{(first-order rate law)} \tag{96}$$

$$10^{1}\,M^{-1}\,s^{-1} < k < 10^{8}\,M^{-1}\,s^{-1} \quad \text{(second-order rate law)} \tag{97}$$

VII. METHODS FOR DETERMINATION OF THE NUMBER OF ELECTRONS TRANSFERRED PER MOLECULE OF SUBSTRATE

An important parameter in all kinds of electrochemical work, including mechanism analysis, is the number of electrons n transferred per molecule during the electrochemical reaction.

Values of n may be obtained by almost any electrochemical technique, provided that a number of other parameters are known as illustrated, for example, by the relations between n and i given in Eqs. (13), (61), (64), (74), and (88). However, it is the exception rather than the rule that all the necessary parameters are known for a particular experiment. This applies especially to the effective electrode area A and diffusion coefficient D_A, which is known only for few substances in the solvent systems commonly used in electrochemical studies. A simple solution to this kind of problem is based on the quantitative comparison of, for instance, LSV and CA [273]. From Eqs. (13) and (64) it is easily seen that the ratio $R = (i_p/\nu^{1/2})/(it^{1/2})$ is given by the simple expression of Eq. (98), since all other parameters cancel.

$$R = \frac{i_p/\nu^{1/2}}{it^{1/2}} = 4.92n^{1/2} \tag{98}$$

Thus, it is possible to estimate n values without the prior knowledge of D_A and A, provided the same working electrode is used for both experiments. The experimental values of R for systems with known n were found to agree with the theoretical values (4.92 for $n = 1$ and 6.96 for $n = 2$) within 6%. This approach for the determination of n has been discussed in more detail elsewhere [274].

A different way of determining n values is based on the measurement of the amount of charge necessary for the exhaustive electrolysis of a known amount of substrate. This type of experiment, traditionally called coulometry, may be carried out either at constant potential or at constant current.

During coulometry at constant potential, the amount of charge is obtained by integration of the current-time curve (Fig. 41).

The advantage of potential control during the coulometry experiment has to be paid for by a rather long electrolysis time. The endpoint, $i = 0$, is in principle not reached until infinite time has elapsed. In practice, however, the electrolysis is stopped when the current has decayed to a few percent of the initial value. The error introduced in this way can be neglected for all practical purposes.

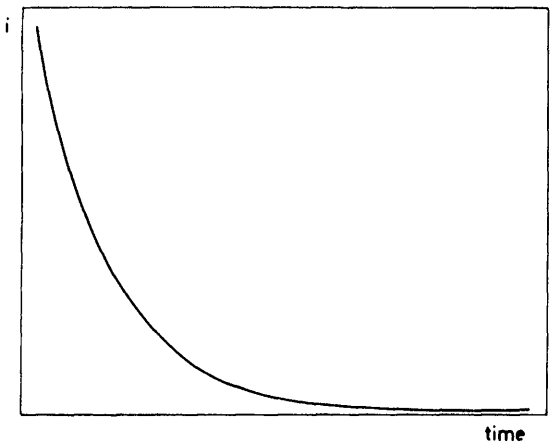


Figure 41. The current i as a function of the time t in constant potential electrolysis. The current is given by $i = i_{t=0} \cdot 10^{-kt}$, where k is a constant depending on the construction of the electrochemical cell (see Ref. 275.)

Coulometry at constant current is often considered as being less attractive than coulometry at constant potential. Control of the current rather than the potential has, however, a number of advantages. First, the charge consumed during the reaction is directly proportional to the electrolysis time, and second, simpler electronic equipment may be used. It has been demonstrated [276] that when the current density is low, the potential of the working electrode stays almost constant until 90% of the substrate is consumed. The total conversion of, for example, 0.1 mmol of substrate at 25 mA requires an electrolysis time of 6.44 min for n = 1. The change in concentration during electrolysis is conveniently followed by LSV or CV. Cyclic voltammograms of a solution containing 0.1 mmol 3,4-diphenyl-1,2-dithiolylium ion [277], after constant-current (25 mA) reduction in 0, 1, 2, 3, 4, 5, and 6 min, respectively, are shown in Fig. 42. Extrapolation of the current

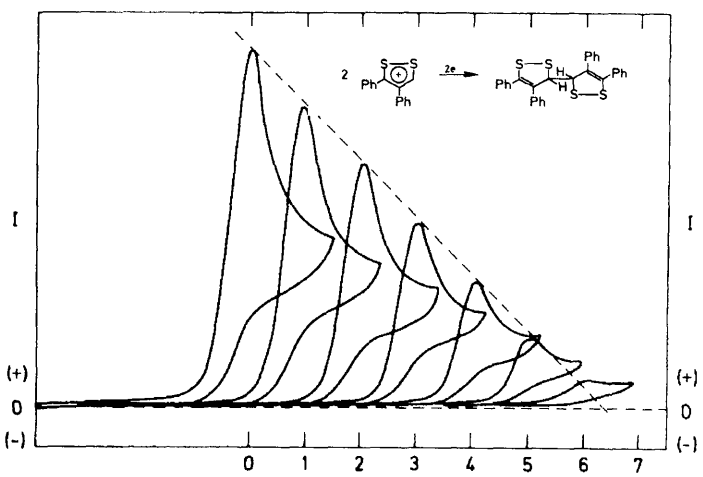


Figure 42. Constant current coulometry (25 mA) of 3,4-diphenyl-1,2-dithiolylium ion (0.1 mmol). Cyclic voltammograms, horizontally displaced, are shown after reduction for 0, 1, 2, 3, 4, 5, and 6 min, respectively.

to $i_p = 0$ gives the time for complete conversion, which in the present case was very close to the time, 6.44 min, predicted for n = 1

Under conditions where the primary electrode product undergoes a slow chemical reaction, that is, $t_{1/2}$ is of the order of seconds, the value of n determined by a relatively fast technique like LSV may differ from that obtained by a slow experiment like coulometry. This type of behavior was observed in the anodic oxidation of 2,3,5,6-tetraphenyl-1,4-dithiin in MeCN [278]. During CV the reversible oxidation to the radical cation is observed. However, when constant-current coulometry was carried out as described earlier, this time at i = 50 mA, 6.44 min was required to oxidize completely 0.1 mmol of the substrate to a product electroinactive in the potential region of interest, indicating an overall two-electron process (Fig. 43). Thus, apparently contradictory results may be obtained due to the difference in time scale between the two types of experiment.

The equipment necessary for the determination of n by coulometry as described earlier does not in principle differ from that used for a microscale preparative electrolysis. Therefore, in addition to the determination of n, it is possible also to investigate the voltammetric properties of the product and, for example, whether the starting material may be regenerated by electrolysis after the direction of the current has been changed.

VIII. METHODS BASED ON THE COMBINATION OF ELECTROCHEMICAL AND OPTICAL TECHNIQUES

Spectroelectrochemistry takes advantage of the possibility of characterizing and monitoring spectroscopically the intermediates and products formed as the result of the heterogeneous electron transfer reaction [1,4,279]. The major experimental problems met concern both the preparation of suitable electrodes and cells and the electronic detection of the absorptions, which are often weak.

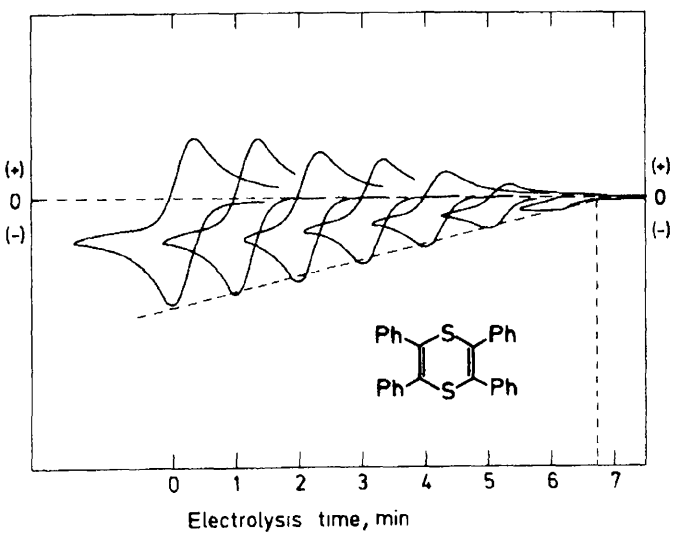


Figure 43. Constant current coulometry (50 mA) for 2,3,5,6-tetraphenyl-1,4-dithiin (0.1 mmol). Cyclic voltammograms, horizontally displaced, are shown after oxidation for 0, 1, 2, 3, 4, 5, and 6 min, respectively.

Within the fields of organic electrochemistry and mechanism analysis the interest is centered mainly on absorptions in the ultraviolet (UV)-visible (Vis) region. This obviously is related to the fact that the primary intermediates of electrochemical processes, radical ions and radicals, often absorb in the visible region where the solvent-supporting electrolyte-substrate mixture usually is transparent, which facilitates the recording of the spectral data. Several reviews have been published dealing with both the theoretical and practical aspects of the technique [280–285], which recently has been extended to include also circular dichroism [286] and fluorescence spectroscopy [287]. Attention has to some extent been focused also on the application of infrared (IR) [288–292] and Raman spectroscopy [293–296]. However, the recording of spectral data of, for instance, a radical ion in the IR region requires rather elaborate experimental setups and data-handling procedures because of the (often strong) absorptions caused by the solvent-supporting electrolyte-substrate mixture itself. Spectroelectrochemical techniques offer also the possibility for studying the electrode surface, in particular adsorbed organic species, and the interfacial region. However, this type of work is beyond the scope of the present text. Recently, a set of IUPAC recommendations concerning the names and abbreviations of the various spectroelectrochemical techniques has appeared [297].

A. The Techniques and Cells for Spectroelectrochemistry

Spectroelectrochemistry can be performed in a number of ways depending on the type of electrode employed [1,4,279,285,288,289]. Transmission spectroscopy by which the analyzing beam is passed through an optically transparent electrode (OTE) is illustrated in Fig. 44(a). The OTE may consist of a transparent material, usually glass or quartz, covered with a thin metal film, for instance, Pt or Au. Transparent conducting materials such as oxides of Sn and In have been used as well. A variant of the OTE is the minigrid electrode, which is made from a wire mesh, usually between 50 and 1000 wires per centimeter. The transparency of such electrodes is due to the holes in the metal grid. Although convenient to work with, the OTE technique originally suffered from the necessity of passing the light beam through the entire cell; that is, only a fraction of the solution in the light beam had been affected by the electrochemical process. This problem has been overcome by the application of various designs of thin-layer cells, usually referred to as optically transparent thin-layer electrodes (OTTLE). The thin-layer cells also have the advantage that only a small volume of the electrolyte solution is needed [298–303].

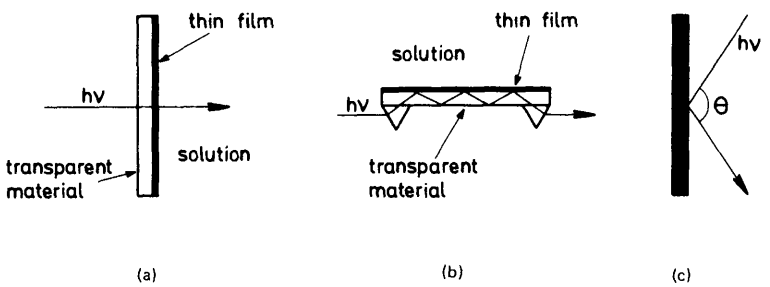


Figure 44. Electrode systems for spectroelectrochemistry: (a) optically transparent electrode, (b) electrode for internal reflection spectroscopy, and (c) electrode for specular reflectance spectroscopy.

Another approach, internal reflection spectroscopy (IRS) or attenuated total reflectance (ATR) spectroscopy, takes advantage of the total reflection observed when a light beam is directed to the back of the OTE at an angle greater than the critical angle. Since the reflection takes place at the electrode–solution interface, the light beam is attenuated only by molecules close to the electrode surface. The penetration depth is about 1000 Å in a typical experiment. Because of this very small effective cell length, the electrode is most frequently used in a multiple reflection mode [Fig. 44(b)].

Conventional electrodes for voltammetry, such as Pt electrodes, when polished to mirror quality, can be used in spectroelectrochemical work. The light beam is reflected at the electrode surface and passes the solution of interest twice, which causes an improvement in the sensitivity [Fig. 44(c)]. The sensitivity of this method, called specular reflectance spectroscopy (SRS) [1,304,305], can be further enhanced by increasing the angle θ to almost 180° (glancing incidence reflectance spectroscopy) [306]. In the limit, the light beam traverses the solution parallel to the electrode without reflection (parallel incident or grazing incidence spectroelectrochemistry) [307–309]. This is the basic idea behind the so-called long optical path thin-layer cells [310–313]. When a highly collimated light beam is used—for instance, as generated by a laser—this method may also provide spectroscopic information about the concentration-distance profiles in voltammetric experiments [307].

Many of the designs just referred to suffer from the problem that the electrochemical characteristics of the resulting spectroelectrochemical cells are not always good. In particular, many cell designs result in nonideal potential distributions, large ohmic resistances, and complicated diffusion patterns [314], which make the recording of high-quality voltammetric data impossible. In the cases where the electrogenerated intermediates or products have long lifetimes this problem has been solved by obtaining the spectral information using a so-called dip probe fitted into a conventional electrochemical cell [253,315].

Finally, mention should be made of a new generation of channel flow cells, in which the electrochemically generated species are transported by a laminar flow from the working electrode to an optically transparent part of the cell [316–318].

As it appears from the preceding discussion, much effort has been put into the design of suitable cells. Some of the classical setups are depicted in Fig. 45, and many other solutions to special needs have been reported, in particular during the last decade [285,291,300–303,309,312,316,319–321].

B. Modes of Operation and Applications

1. Recording of Spectral Data

Spectra of stable electrogenerated species are conveniently obtained by using, for instance, a cell equipped with an OTE (or OTTLE) [322–326]. An example is the reduction of 1,1′-dibenzyl-4,4′-bipyridinium dication to the radical cation (Fig. 46) [322]. If the current efficiency is 100%, the concentration of the electrogenerated species can easily be determined from the amount of charge passed through the solution, which enables the calculation of the extinction coefficient for the compound in question. The same experimental setup is useful for the measurements of spectral characteristics of species for which the heterogeneous electron transfer is so slow that the direct conversion at the electrode is either inconvenient or impossible. In such cases advantage can be taken of the presence of an electron carrier (a mediator), which is capable of exchanging electrons rapidly with the electrode as well as the substrate. This approach was taken in a study of the formal

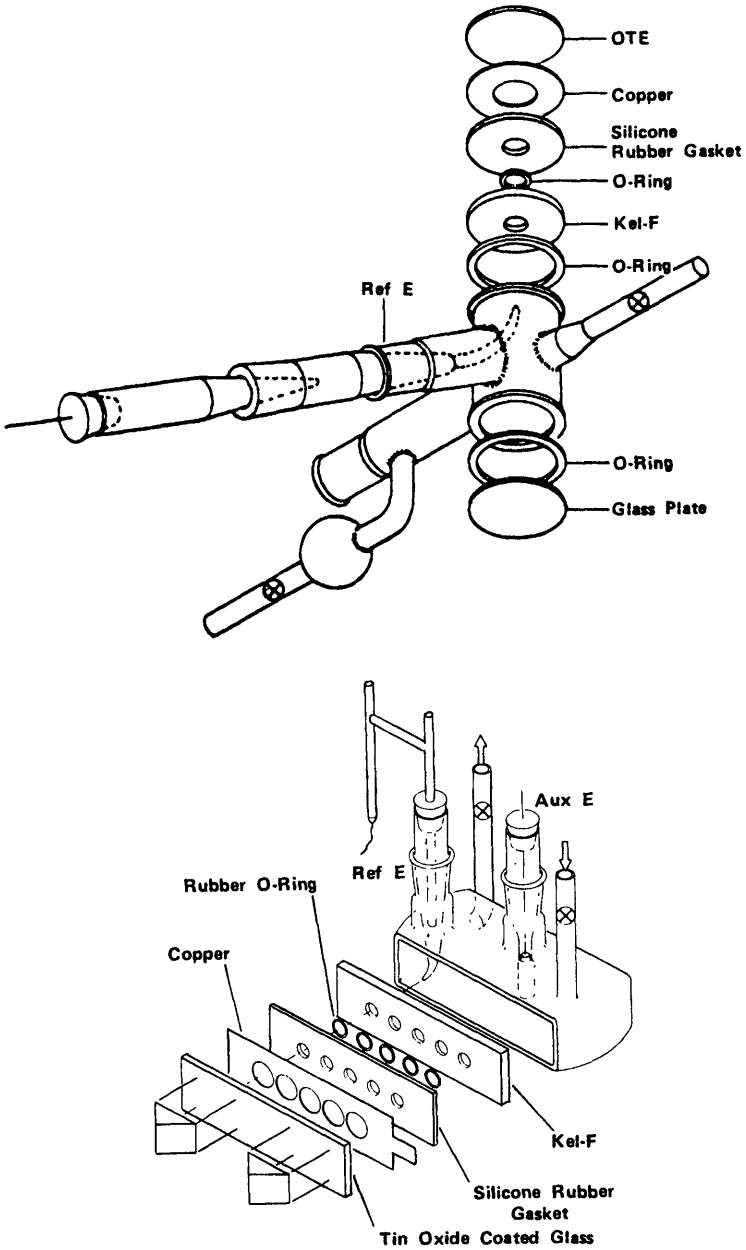


Figure 45. Examples of spectroelectrochemical cells for use in transmission spectroscopy (top) and internal reflectance spectroscopy (bottom). (From Ref. 281.)

potentials and number of electrons associated with the reduction of cytochrome c and cytochrome c oxidase [323]. Spectral changes could be observed after consecutive coulometric generation of as little as 5 nanoequivalents of the electron carrier, which in this particular case was the 1,1′-dimethyl-4,4′-bipyridinium radical cation.

Owing to the experimental difficulties already mentioned, few studies addressing the spectroscopic properties of stable ion radicals in the IR region have been published.

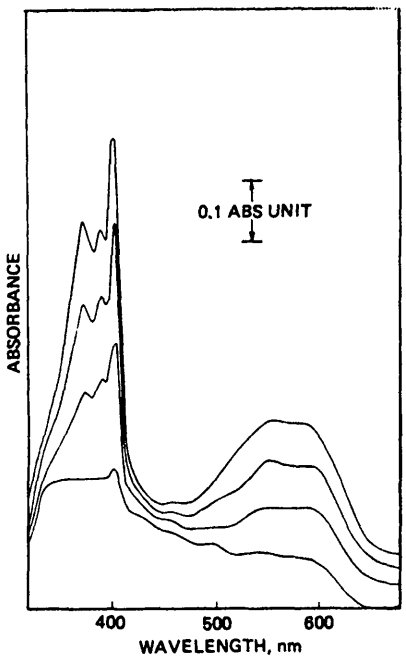


Figure 46. Spectra of 1,1′-dibenzyl-4.4′-bipyridinium radical cation taken after equal incremental reductions of the corresponding dication at an SnO_2 OTE. (From Ref. 322.)

Examples include the radical anion of tetracyanoethylene [327] and the radical cation derived from heptyl viologen [328].

2. Spectra of Rapidly Reacting Species and Kinetic Measurements

When the heterogeneous electron transfer is followed by a chemical step, the registration of spectral data becomes more complicated unless the rate of the chemical reaction is very low. Rapidly reacting species—for instance, radical ions—can be characterized spectroscopically by the application of rapid scan spectroscopy (RSS), modulated specular reflectance spectroscopy (MSRS) and, more recently, diode array spectrometers.

In the first of these techniques, RSS [329] the rapid scan may be obtained by using a vibrating mirror that allows a spectral region of approximately 400 nm to be covered in 1 ms. Coupled with a signal-averaging technique and computer control of the spectrometer and the data acquisition system, the relative sensitivity can be extended to 10^{-4} s for a 5-ms scan [330]. Kinetic and mechanistic information can be gained from the analysis of the time-dependent spectra obtained when a repetitive scan technique is used. Examples of the application of RSS for the determination of spectral data of rapidly reacting intermediates are found in studies of the oxidation of 4-methoxyphenylethylenes [330], tetraphenylethylene [331], and 3,3′-dimethylnaphthidine (Fig. 47) [332], and the reduction of 2,2′-diquinoxalyl [333].

The development of fast spectrometers has opened the possibility of studying, for instance, the spectral changes (UV-Vis and IR) associated with a single CV scan [334–336] or spectra of short-lived intermediates [337,338]. The first approach was taken in a study of the initial steps of the electropolymerization of aniline in aqueous sulfuric acid [335].

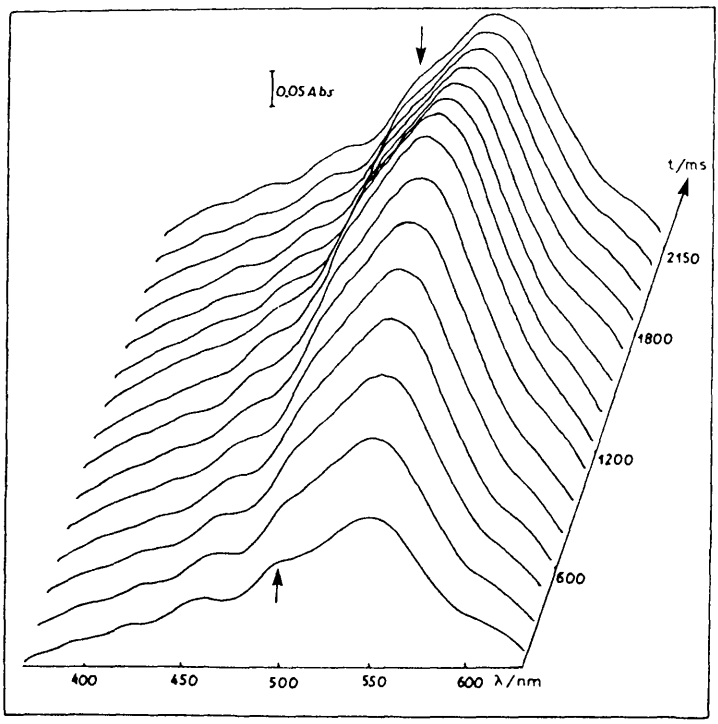


Figure 47. The spectra of 3,3′-dimethylnaphthidine products recorded during chronoamperometric measurements at an SnO_2 OTE. (From Ref. 332.)

The new UV-Vis absorption band at 425 nm (Fig. 48) was taken as evidence in support of participation of benzidine, the tail-to-tail dimer, in the polymerization process.

The details of the electrohydrodimerization of dimethyl maleate in methanol has been studied using Fourier transform infrared (FTIR) spectroscopy [339]. Spectra were recorded as a function of time at a constant applied potential (−1.5 V versus Ag/AgCl) with the reference spectrum being obtained at 0 V. The result is shown in Fig. 49(a) as plots of dR/R versus the wavenumber (cm^{-1}), where R is the reference spectrum and dR is the sample spectrum minus the reference spectrum. Thus, positive dR/R values indicate loss of chromophore, while negative dR/R values indicate gain of chromophore. The analysis of the spectral data showed that the formation of the hydrodimer, 1,2,3,4-butane tetracarboxylic acid, is accompanied by isomerization of dimethyl maleate (the *cis* isomer) to dimethyl fumarate (the *trans* isomer). This is nicely illustrated by Fig. 49(b), from which it is seen that the loss of chromophore at 1390 cm^{-1} (*cis* isomer) proceeds more rapidly than the gain in chronomophore at 1288 cm^{-1} (*trans* isomer).

A different approach, MSRS, involves modulation of the electrode potential by a periodic function, e.g., a sine wave or a pulse [340–345]. Absorbance variations other than those that are synchronized with the modulation frequency are discriminated by help of a lock-in amplifier, leaving the system almost insensitive to absorbance of products built up during the experiment. In this way it has been possible to obtain the visible spectrum of perylene radical anion in the presence of acetic acid (Fig. 50) and thianthrene radical cation in the presence of water [341]. Other examples include the oxidation of *N,N*-

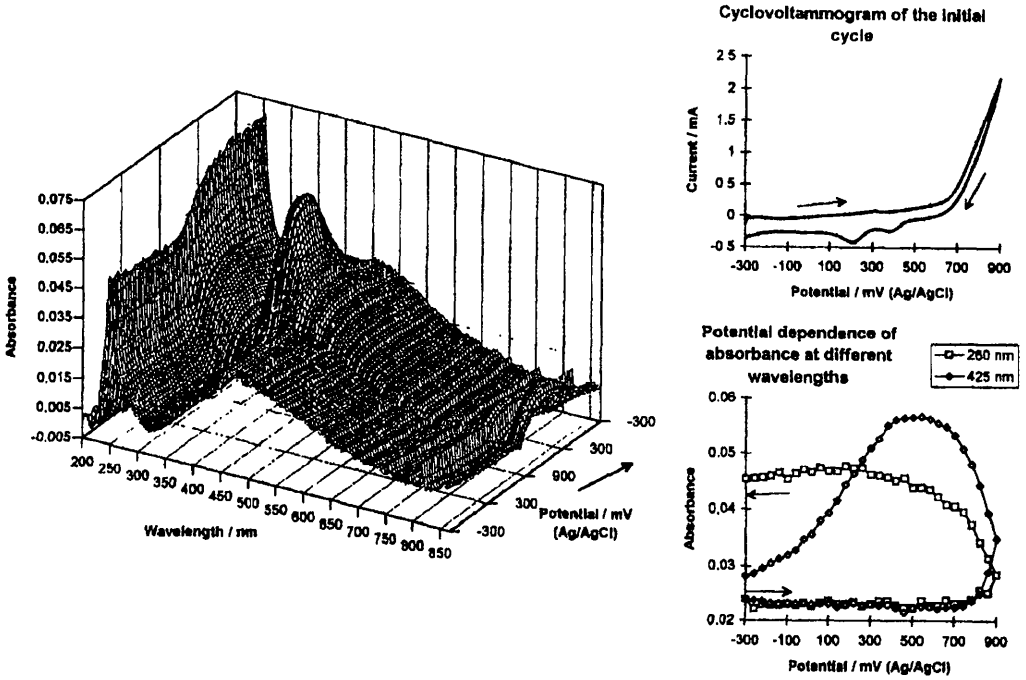


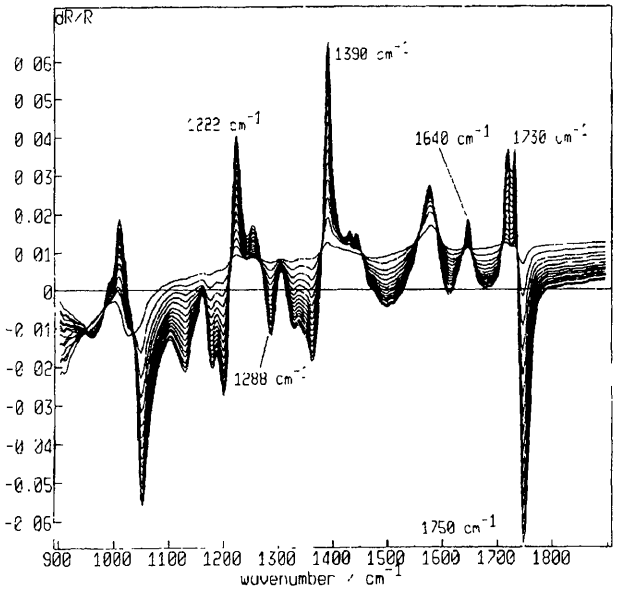
Figure 48. UV-Vis spectro-cyclic voltammogram corresponding to the first CV cycle for the oxidation of aniline (50 mM) in aqueous sulfuric acid (0.5 M) at $\nu = 0.2\,V\,s^{-1}$. The inserts show the voltammogram and the potential dependence of the absorbance. (From Ref. 335.)

dimethyl-*p*-phenylenediamine [342] and 2,6-di-*tert*-butylanilines [344] to the corresponding radical cations.

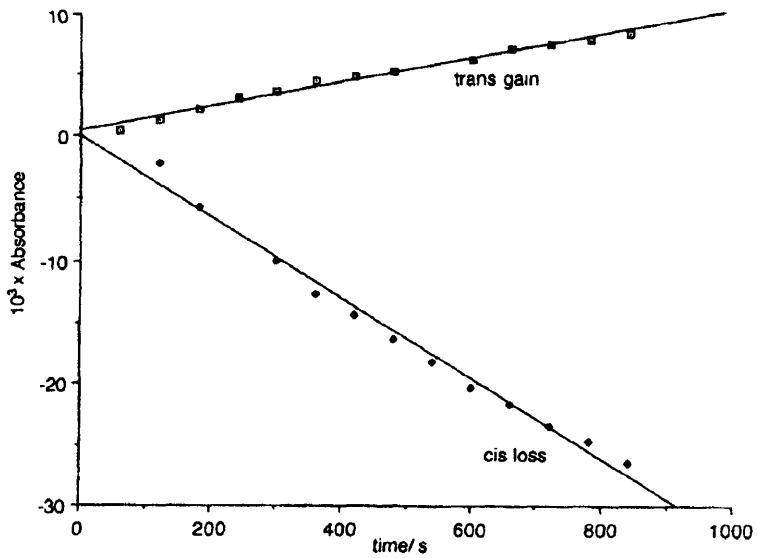
When spectroelectrochemistry is used as a tool in reaction kinetics, it is important to know accurately the rate of generation of reactive intermediates, that is, the accurate potential of the working electrode. This requirement becomes a particular problem when an OTE is the preferred electrode because of the ohmic drop in the electrode itself and the nonuniform current distributions often encountered. For the OTTLEs in particular, the accurate modeling of the diffusion in the cell also leads to rather complicated mathematical equations [346]. The most profitable way of operation is therefore to use a potential-step procedure where the potential is stepped to a value at which the heterogeneous electron transfer reaction proceeds at the diffusion-controlled rate. In transmission spectroscopy the absorbance, $A_B(t)$, of the initial electrode product B, in the absence of chemical follow-up reactions, is given by Eq. (99) [347,348], where ε_B is the extinction coefficient of B.

$$A_B(t) = \frac{2}{\sqrt{\pi}} \varepsilon_B C_A^* \sqrt{D_A t} \tag{99}$$

If B is unstable and disappears during the experiment, the absorbance measured will be smaller compared to that obtained in the absence of the chemical step. Expressions for $A_B(t)$ for a number of mechanistic perturbations have been calculated [348]. The results are most conveniently presented in terms of the normalized absorbance, Eq. (100), as a function of log(kt) (first-order rate law) or $\log(kC_A^* t)$ (second-order rate law).



(a)



(b)

Figure 49. (a) In situ FTIR difference spectra for the reduction of 5% (w/v) dimethyl maleate in MeOH (0.25 M NaOAc) recorded as a function of time at E = −1.5 V versus Ag/AgCl with 0.0 V as the reference spectrum, and (b) plots of the absorbance versus time for the loss and gain of bands at 1390 cm^{-1} and 1288 cm^{-1}, respectively. (From Ref. 339.)

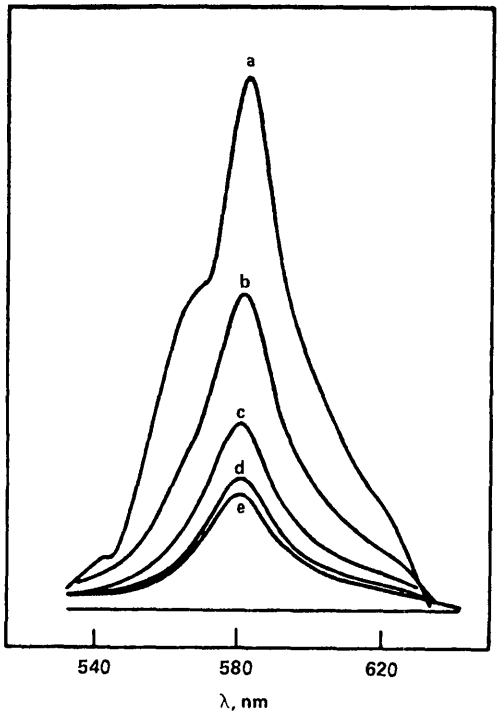


Figure 50. Visible absorption spectra of the perylene radical anion in DMF containing acetic acid (70 mM) measured by modulated specular reflectance spectroscopy at a, 3 Hz; b, 10 Hz; c 30 Hz; d, 60 Hz; and e, 80 Hz. (From Ref. 340.)

$$A_B^N = \frac{A_B(t)}{(2\epsilon_B C_A^* \sqrt{D_A t}/\sqrt{\pi})} \tag{100}$$

Obviously, A_B^N is unity when B is stable. The working curve for the eCe_h mechanism, which has been considered for the pyridination of 9,10-diphenylanthracene radical cation ($DPA^{+\cdot}$) [349], is illustrated in Fig. 51.

Performance of the experiment, usually termed chronoabsorptometry, includes the registration of the absorbance-time curves for $DPA^{+\cdot}$ in the absence and in the presence of pyridine from which data for the normalized absorbance-time dependence is obtained. The rate constant can be estimated by fitting these data to the working curve. In the present case [349] the rate constant for the nucleophilic attack of pyridine on $DPA^{+\cdot}$ was calculated to be $1.86 \times 10^4\ M^{-1}\ s^{-1}$.

By analogy to the extension of CA to DPSCA (Sec. IV), chronoabsorptometry has also been applied in a double potential-step version [350,351], and working curves for a large number of mechanisms have been calculated [352].

IRS and SRS may be used by analogy to chronoabsorptometry for the investigation of kinetic and mechanistic details (Fig. 52) [353–355]. In the absence of chemical follow-up reactions, the absorbance-time dependence, again assuming diffusion-controlled heterogeneous electron transfer, for IRS is given by Eq. (101), which at times greater than approximately 1 ms reduces to Eq. (102), where $a = \sqrt{D_B}/\delta$, b_{eff} is an efficiency factor, and δ is the diffusion layer thickness [Eq. (55)].

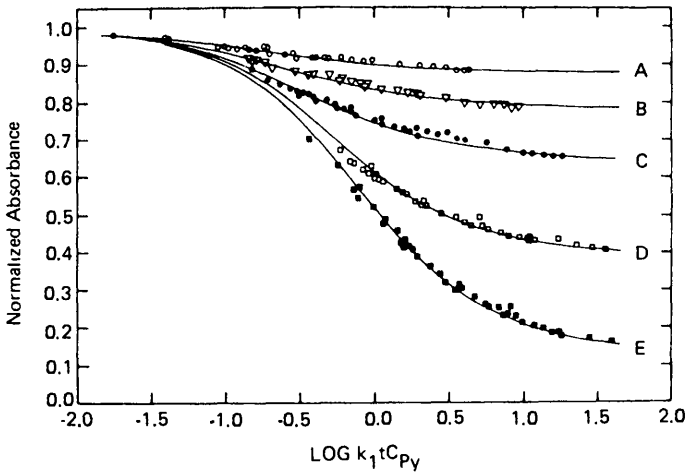


Figure 51. Chronoabsorptometry working curves for the eCe_h mechanism. The experimental points are for the reaction between the 9-10-diphenylanthracene radical cation and pyridine at different concentration ratios (From Ref. 349.)

$$A_B(t) = \varepsilon_B b_{eff} C_A^* \sqrt{\frac{D_A}{D_B}} \left[1 - e^{a^2 t} \operatorname{erfc}(a\sqrt{t})\right] \tag{101}$$

$$A_B = \varepsilon_B b_{eff} C_A^* \sqrt{\frac{D_A}{D_B}} \tag{102}$$

The simplification, Eq. (102), arises from the fact that the penetration depth of the light beam is only of the order of 1000 Å, and shortly after the potential has been switched on,

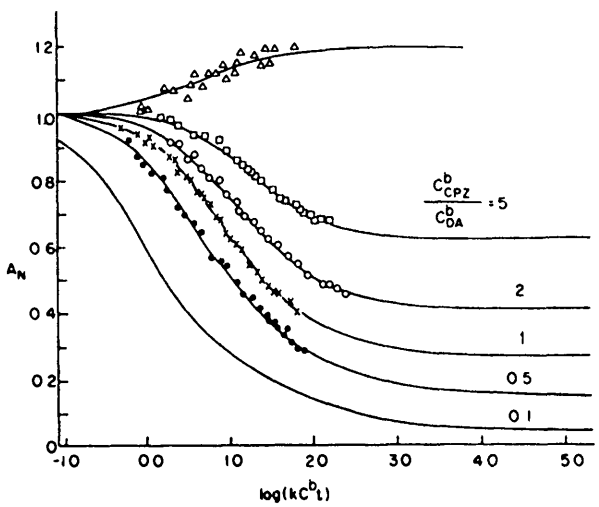


Figure 52. Normalized absorbance A_N versus $\log(kC^*_{CPZ}t)$ for the reaction between chlorpromazine (CPZ) radical cation and dopamine (DA) (from Ref. 354.)

the concentration profile close to the electrode is essentially in a steady-state condition, rendering the absorbance independent of time.

In potential-step chronoabsorptometry the absorbance of the electrogenerated species is followed during the electrochemical perturbation. Additional information may be gained by open-circuit relaxation (OCR), in which the absorbance decay is followed as a function of time after the working electrode has been disconnected from the potentiostat. When the electrode is connected, there is a continuous, though decreasing, generation of the reactive species, and both solution and heterogeneous processes can take place during the reaction to products. However, after the electrode has been disconnected and the generation of the reactive species stops, only solution electron transfer can occur. OCR spectroscopy has been discussed in detail in a number of papers [350,356–358]. The absorbance-time curve obtained in a typical experiment, the generation of perylene radical anion in the absence (a) and in the presence (b) of phenol [359], is illustrated in Fig. 53. The stability of the perylene radical anion in the absence of the proton donor is demonstrated by the time independence of the absorbance after the electrode has been disconnected at $t = 400$ ms. The pulse length may be varied between approximately 100 ms and several seconds. Since the average concentration of the reactive intermediate is dependent on this parameter, pulse-length variation is important in OCR experiments. The disconnection of the electrode is usually performed using an electronic switch. The lower limit for applicable pulse lengths is not set by the electronics, but by the time necessary to discharge the double layer. However, by application of charge injection [360] together with a special diode switching technique [359], the problem arising from the double layer discharging can be partly overcome and measurements can be performed in the microseconds range.

Working curves have been calculated for a number of reaction mechanisms. The experimental data are normalized by the absorption measured at the time of electrode

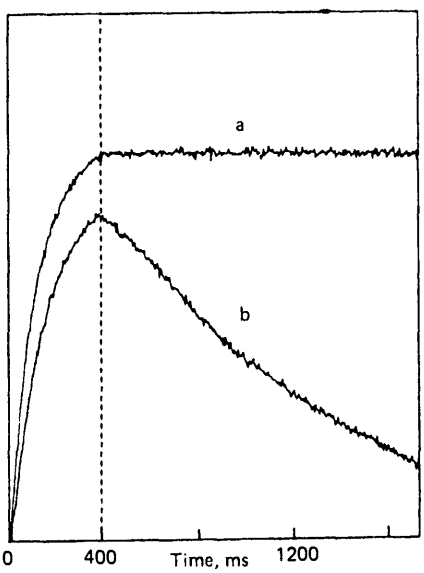


Figure 53. Absorbance-time curves for the spectroelectrochemical generation of perylene radical anion at 570 nm in DMF; (a) without and (b) with addition of phenol. The time to open circuit (dashed line) is 400 ms. (From Ref. 359.)

disconnection, and the mechanism analysis and calculation of rate data then follow essentially the procedure already described for chronoabsorptometry. An illustrative example of the application of OCR is the study mentioned earlier, the intramolecular cyclization of tetraphenylethylene radical cation [331]. Although it may be difficult or even impossible to distinguish between the eCe and eCe_h, the disproportionation, for which the rate law is second order in radical cation concentration, is clearly different from the other two and allowed the conclusion that this mechanism is indeed the most likely. The OCR technique has also played an important role in studies of the anodic oxidation of 4,4′-dimethoxystilbene [361] and the reaction of thianthrene radical cation with various nucleophiles [362].

IX. THE APPLICATION OF ESR SPECTROSCOPY

Since the primary intermediates in organic electrode reactions are usually radical ions or neutral radicals, the combination of electrochemical equipment with an electron spin resonance (ESR) spectrometer is a desirable possibility. The major practical problem encountered in designing an adequate experimental setup arises from the physical restrictions imposed on the electrochemical cell by the shape and size of the resonance cavity. Two different approaches have been taken to meet the requirements. One involves the formation of the radical species outside the magnetic field in a streaming solution that carries the electrode products into the ESR cavity. By the other technique the radical species are formed by electrolysis in a small cell placed directly in the cavity. Both techniques have for many years been used extensively in qualitative and semiquantitative work, and the design and construction of cells have now reached a high level of sophistication [363–377].

When a flow system is being used in quantitative work, the transport conditions must be such that the distribution of radicals in the cell can be exactly calculated. This is most easily obtained when a simple and highly symmetrical cell is employed. A satisfactory solution to the problem is the use of a cylindrical cell in which a ring electrode was placed in such a way that the electrode surface was flush with the inner wall of the cell [365]. The ESR cavity was placed immediately below the electrode. Provided that the flow is sufficiently slow that laminar conditions prevail, the associated transport equations may be solved and equations relating the intensity of the ESR signal to the flow rate and a kinetic parameter containing the rate constant may be obtained. It was proposed that rate constants for radical decay, disproportionation, or dimerization, up to $10^8\ M^{-1}\ s^{-1}$, can be measured using a cell of this type.

A cell (Fig. 54) that allowed the precise control of potential and current was designed by Goldberg and Bard, who also demonstrated the advantage of combining ESR spectroscopy with electrochemical techniques such as CA, CV, and chronopotentiometry [366]. The latter approach was taken in a study of the reduction of cyclooctatetraene (COT) in which it was demonstrated that the COT radical anion is stable in the presence of tetrabutylammonium ion, which had been a matter of dispute in previous work [378] (Fig. 55).

Another design for the electrochemical formation of radicals directly in the cavity involved the flow-through channel cell shown in Fig. 56 [370]. The cell was constructed in synthetic silica to avoid interference with the microwave field. The flow through this cell was demonstrated to be laminar up to Reynolds numbers less than 10^2, which allowed for the derivation of quantitative relations between the ESR signal, the flow rate, and the current.

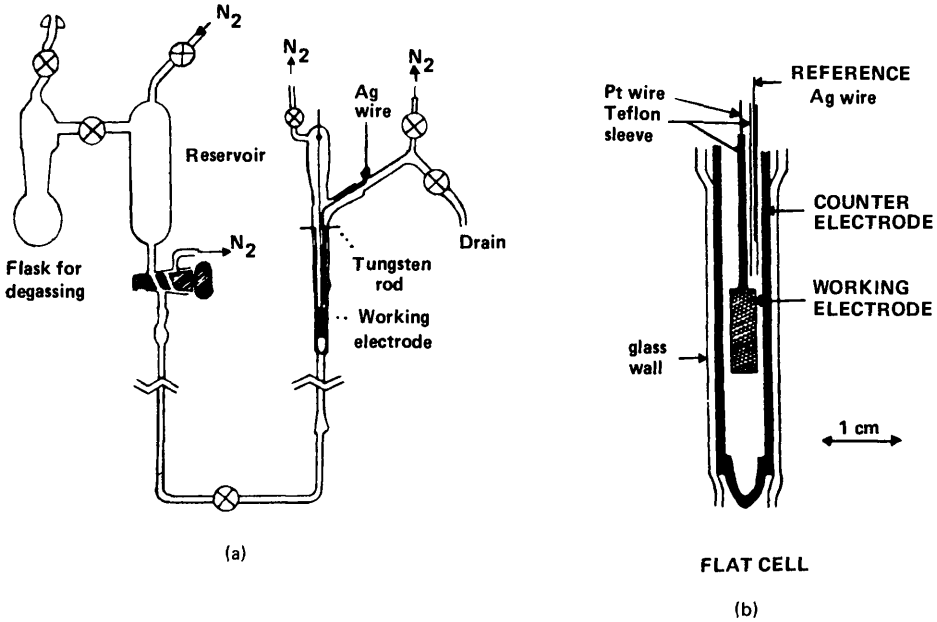


Figure 54. (a) Electrochemical ESR cell and reservoir assembly and (b) detail of the flat part of the cell. (From Ref. 366.)

Of particular interest is the recent development of an electrochemical cell (Fig. 57) that allows for the simultaneous recording of both ESR and UV-Vis spectra of electrogenerated intermediates [374]. This type of cell was used in a study of the initial steps of the electropolymerization of aniline in acidic DMSO [379].

An important application of combined electrochemistry and ESR spectroscopy is the characterization and identification of intermediates and products of electrode reactions [334,336,379–391]. For instance, the ESR technique is particularly useful to measure the degree of protonation under conditions where the radical ions take part in acid–base equilibria [380,381]. Such information may be obtained only with difficulty by other methods, but the coupling pattern of the ESR spectrum may often give the answer directly. An illustrative example is found in the anodic oxidation of 2,4,6-tri-*tert*-butylaniline, which, as expected, gives the radical cation as the initial electrode product [380]. In an aprotic solvent like MeCN or CH_3NO_2 the radical cation is stable and the ESR spectrum observed is in accordance with the reversible one-electron transfer indicated by CV. However, when the electrolysis is carried out in the presence of diphenylguanidine as a base, the ESR spectrum changes drastically and can be attributed to the presence of the neutral free radical formed by deprotonation of the radical cation.

The reductive cleavage of the carbon–halogen bond has been one of the most extensively studied reactions in organic electrochemistry (see Chapter 8). For the reduction of 4-iodonitrobenzene [392] and 4-chloroacetophenone [393] in the presence of cyanide ion, ESR evidence has been presented for the ultimate formation of the corresponding 4-cyanoarene radical anions. These reactions were proposed to proceed via the formation of aryl radicals trapped by cyanide ion. Additional evidence for this reaction pathway was gained through a spin trap experiment [390,394–396], by which the postulated aryl radical was trapped by α-phenyl-*N*-*tert*-butylnitrone, resulting in formation of the corresponding

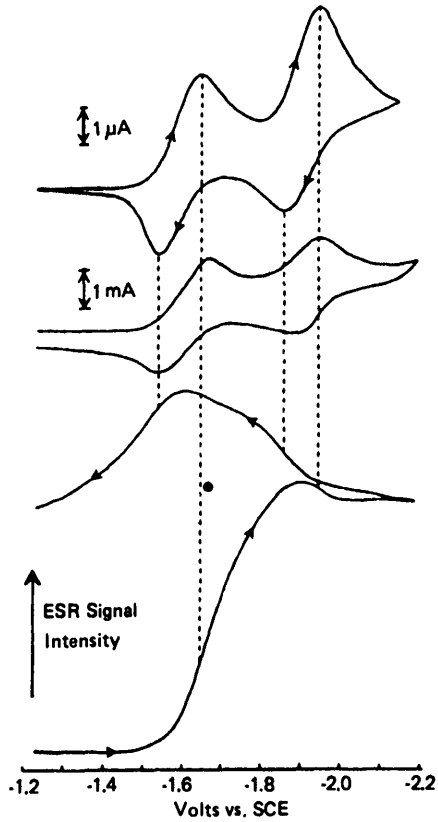


Figure 55. Cyclic voltammogram of COT in HMPA on a hanging mercury drop electrode (uppermost curve). Cyclic voltammogram of COT on a 15-cm^2 amalgamated gold electrode in an ESR cell (central curve). ESR-potential curve recorded simultaneously with the central curve (lowermost curve). (From Ref. 378.)

nitroxide. The proposed mechanism thus resembles the $S_{RN}1$ scheme [397]. Another illustrative example is the study of the electrochemical reduction of dimethyl benzene-1,3-dicarboxylates [391], which on a preparative scale proceeds to the monocarboxylate ion in a 1 F process. However, by application of a combination of CV and ESR spectroscopy it was possible to show that the radical ions formed primarily dimerize reversibly.

Further examples that illustrate the application of ESR spectroscopy in electrochemistry can be found in papers concerning the reduction of phosphonium and ammonium salts [382], 2,5-diphenyl-1,3,4-oxadiazole [336], and bianthrone [388], the electron transfer

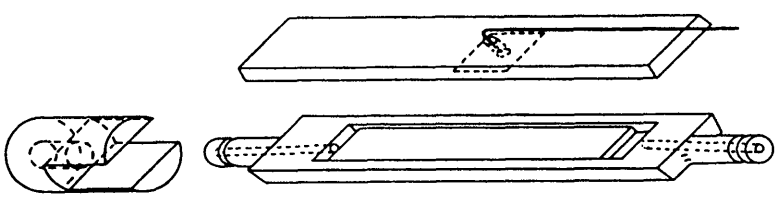


Figure 56. View of a flow-through channel cell (unassembled), showing cover place with electrode and lead-out wire, channel plate, and one of two PTFE mounting spacers. (From Ref. 370.)

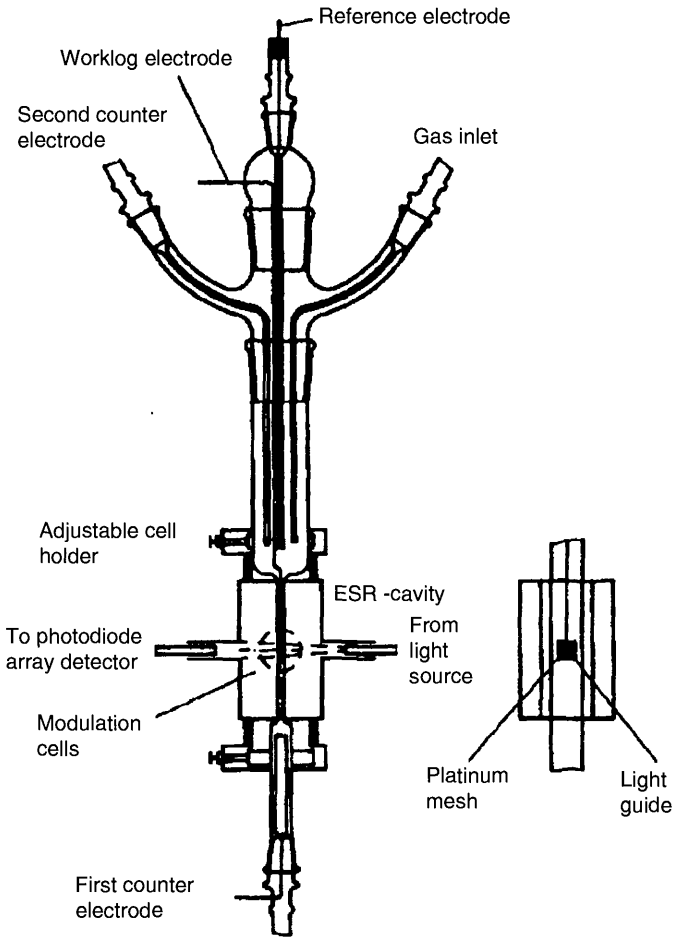


Figure 57. View of an electrochemical cell for the simultaneous recording of ESR and UV-Vis spectra (From Ref. 374.)

reactions of a series of Weitz-type systems [383], the formation of radical ions from 1,4-dimethoxybenzene [334] and bis(2,4,6-tri-*tert*-butylphenyl)-1,3-diphosphaallene [389], and the oxidation of Ph_3CCOOH [384] and Ph_3COH [385], resulting in the intermediate formation of Ph_3C^+, which could be reduced to the ESR-detectable $Ph_3C^{\cdot}$ radical.

Only a few kinetic studies in which ESR spectroscopy was used to monitor radical decay have been published [371,373,398–400]. For example, decay curves have been used to gain kinetic information about the reactions of the radical anions of aliphatic nitro compounds [371,399] and thienonaphthoquinones [400].

Signal-time behavior of the ESR response following a current pulse has been calculated by Goldberg and Bard [367] for a number of mechanisms, including first-order decomposition, radical ion dimerization, and radical ion-substrate coupling, and working curves from which rate constants can be calculated were presented. Application of this approach, which is very similar to that taken, for example, in transmission spectroelectrochemistry, was demonstrated for the reductive dimerization of a series of activated olefins (Fig. 58), a reaction that has been studied by a number of different electrochemical

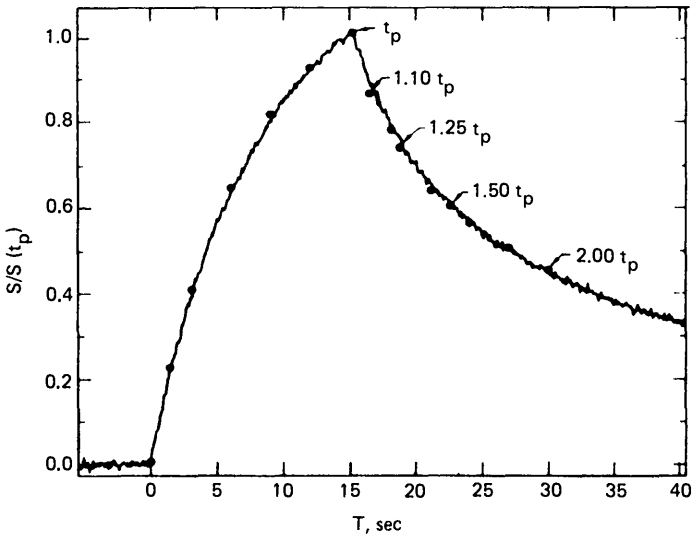


Figure 58. ESR signal-time dependence for 7.5 mM diethyl fumarate. Current pulse time $t_p = 15$ s, $i = 0.21$ mA. (From Ref. 368.)

techniques (see Chapter 21). It was proposed that the major reaction pathway involved the dimerization of two radical anions. The rate constant for dimethyl fumarate was found to be equal to $160 \pm 26\,M^{-1}\,s^{-1}$, which should be compared with the value obtained by other techniques: RRDE, $110 \pm 20\,M^{-1}\,s^{-1}$; double potential-step chronocoulometry, $117 \pm 6\,M^{-1}\,s^{-1}$; and CV, $160 \pm 40\,M^{-1}\,s^{-1}$. Thus, it can be concluded that ESR spectroscopy combined with electrochemical techniques provided results in satisfactory agreement with those obtained by other methods.

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3

Relations Between Micro- and Macrophenomena

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> Chemical reaction, like politics, is the art of the possible; electrochemical reaction, like military tactics, is the art of overriding the impossible by applying electrical force.
>
> R. B. MacMullin

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1. INTRODUCTION

In Chapter 1, our presentation of electrochemical concepts was focused mainly on the specific aspects related to the electrode and to the solution in its close vicinity. Indeed, as soon as kinetics is considered, the bulk solution may often be regarded as a concentration buffer whose only role is to maintain constant or known reactant concentrations at the external diffusion layer boundary. Obviously this is not the case when preparative electrochemistry is considered. Indeed, the goal is then to change the solution composition. Yet this composition change is effected through the relay of the diffusion layer, which "transmits" the modifications achieved at the electrode to the bulk solution. Since chemical reactions may take place within the diffusion layer, as discussed in Chapter 1, the way the bulk solution is affected depends largely on the microphenomena occurring in the thin solution layer (5–20 μm, usually) adjacent to the electrode. This results in an extensive coupling between micro- and macrophenomena at electrodes, which is one of the reasons why kinetics, the study of microelectrolysis phenomena, is so developed in electrochemistry.

Yet these important relations should not conceal the large differences between micro- and macroelectrolysis. These differences, which were discussed briefly in Chapter 1, have their main origin in the necessity of passing a current through the solution between the working and auxiliary (or counter) electrodes. Obviously, the ensuing problems are quite different when one considers currents in the microampere (or even nanoampere for ultramicroelectrodes) range or in the ampere range as in macroscale laboratory electrolysis.* Other changes are also introduced that originate from the differences in dilution. Under microelectrolytic conditions very dilute (usually 0.1–10 mM) solutions are considered. Thus activities and diffusion coefficients, for example, are close to their values at infinite dilution. This is not the case in macroelectrolysis since rather concentrated solutions are used. This may introduce large changes in mass transfer rates as well as in chemical reactivity, and also in such specific factors such as migration [2]. These changes in concentration, as well as the larger current densities and electrolysis times, may also result in an increased importance of adsorption, coatings, or pollution phenomena at the electrodes. This is particularly true in aqueous media in which adsorption or chemisorption may play a decisive role in the distribution and selectivity of the products as a function of the electrode material.

As understood from this discussion it is generally unrealistic to believe that microelectrolytic results transpose exactly to macroelectrolytic conditions.† However, provided one keeps these difficulties in mind, microelectrolysis results and approaches constitute extremely useful guides in tackling macroscale electrolysis. Amazingly, data obtained at ultramicroelectrodes (i.e., of micrometric or smaller dimensions) should transpose with the least difficulty since they may be obtained with concentration or current density (a few amperes per square centimeter) conditions matching those found in preparative-scale electrolysis. Moreover, they allow meaningful results to be obtained in the presence of strong migrational contributions [3,4].

II. BASIC PRINCIPLES

A. Homogeneous Chemical Equivalent of Electrolysis Rates

As explained in Chapter 1, the bulk concentrations are affected by the phenomena occurring within the diffusion layer (which is identified, in this chapter, with the stagnant layer imposed by hydrodynamics) through the general relationship in Eq. (1):

$$\frac{dC}{dt} = -\frac{DA}{V}\left(\frac{\partial C}{\partial x}\right)_{x=\delta} + \left(\frac{dC}{dt}\right)_{chem} \tag{1}$$

This equation derives from the conservation of mass fluxes at the diffusion layer/bulk solution interface [compare Eqs. (155) and (156) in Chapter 1 and Fig. 1]. In Eq. (1), dC/dt is the overall rate of the concentration variations considered, whereas $(dC/dt)_{chem}$ is that arising from possible consumption or production of the species within the bulk solution. The electrochemical rate of production or consumption is given by the first term on the

*Note that in the following we do not discuss the ultraspecific aspects of industrial-scale electrolysis, which generally cannot be dissociated from a particular process [1].

†But this is not particular to electrochemistry, since most of the above difficulties (with the exception of those related to the current) are encountered when transferring any physical organic result to preparative conditions.

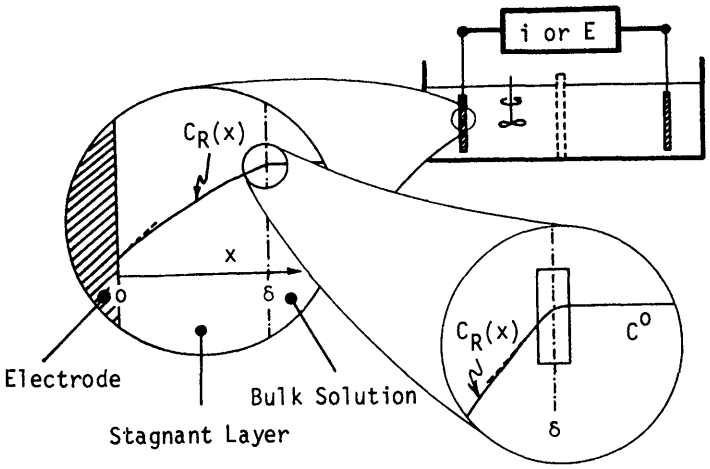


Figure 1. Schematic representation of the electrochemical cell. First insert: concentration profile of the reactant in the stagnant layer in the vicinity of the electrode. Second insert; mass transfer "black box" at the boundary between the stagnant layer and the bulk solution ($x = \delta$).

right-hand side of Eq. (1). It depends on the concentration gradient of the species at the end of the diffusion layer, that is, at $x = \delta$, as well as on the ratio of the electrode surface area to the solution volume, A/V. The larger the absolute value of this rate, the smaller the duration of the electrolysis, which is the reason that generally large electrode surface areas and high stirring rates (i.e., small stagnant layer thickness) are used for electrolysis.

Note that in Eq. (1), a single space coordinate is considered, x, the distance normal to the electrode. This necessarily implies that all electrode locations behave identically. In practice this may be approximated by using symmetrical electrode geometries, with the auxiliary electrode (or separator in divided cells) parallel and of nearly identical size to that of the working electrode (see Chapter 5). This results in a "concentration field" as uniform as possible at the electrode surface(s). Note that this field is conveniently visualized when thinking in terms of the electrostatic field that would establish if the electrodes were those of a large capacitor, since both fields obey analogous laws [5]. However, in practice, ideal electrochemical geometries are only with difficulty compatible with other experimental constraints, so that the potential and current distribution at electrode surfaces may not be uniform. This is also true for the thickness of the stagnant layer since a uniform fluid velocity is difficult to achieve at the electrode surface. For these reasons, the first term on the right-hand side of Eq. (1) is merely considered as resulting from an averaging over the electrode surface; this is also true for the "electrode potential" E or the "electrode current density" i/A. Nevertheless, to maintain some generality and simplicity in the following presentation, we assume that the concentration profiles depend only on the distance x from the electrode surface.

The problem is then to relate the concentration gradient $(\partial C/\partial x)_{x=\delta}$ at the stagnant layer boundary to that $(\partial C/\partial x)_{x=0}$ at the electrode surface (compare Fig. 1). This is done via the integration of the differential equations, such as Eq. (175) in Chapter 1, which control the concentration profiles within the stagnant layer. In the most simple situation, the species whose bulk concentration is given in Eq. (1) undergoes no chemical reaction within the stagnant layer. Then from Eq. (175) (Chapter 1), its concentration flux is constant within the layer, and thus $(\partial C/\partial x)_{x=\delta} = (\partial C/\partial x)_{x=0} = (C - C_{x=0})/\delta$, where $C_{x=0}$

is the concentration of the species at the electrode surface. Thus Eq. (1) is transformed into Eq. (2),

$$\frac{dC}{dt} = -\frac{DA}{V\delta}(C - C_{x=0}) + \left(\frac{dC}{dt}\right)_{chem} \tag{2}$$

where the constant factor $DA/V\delta$ has the dimensions of a first-order rate constant (s^{-1}). Most of the time one is interested in exhaustive electrolysis and thus imposes an electrode potential so that $C_{x=0} = 0$, which in most cases simplifies Eq. (2) to Eq. (3) for the reactant.

$$\frac{dC}{dt} = -\frac{DA}{V\delta}C + \left(\frac{dC}{dt}\right)_{chem} \tag{3}$$

Interestingly, under such circumstances the electrochemical consumption of the species is equivalent to a pseudo-first-order chemical reaction taking place into the bulk solution, with a rate constant k_{elec} in Eq. (4) [6].

$$k_{elec} = \frac{DA}{V\delta} \tag{4}$$

Note that it may be surprising that a chemical term is considered in Eq. (3), whereas we have supposed that no chemical reaction term was involved within the stagnant layer. As explained in Chapter 1, this stems from the fact that the effect of any chemical reaction within the diffusion layer depends on the relative magnitude of $k\delta^2/D$ versus unity. For usual laboratory conditions, $\delta \approx 10^{-3}$ cm and $D \approx 5 \times 10^{-6}\,cm^2\,s^{-1}$ and then δ^2/D is of the order of 0.2 s. Thus, provided k is less than approximately $1\,s^{-1}$ it has no tangible effect on the concentration profiles of the species, whereas it has a definite effect in the bulk solution due to the long reaction times (usually longer or comparable to half an hour). In practice it is important to decide when the simplification in Eq. (2) or (3) applies to a given experimental situation. The discussion just presented affords a simple answer to the problem. Indeed, consider the electron transfer reaction in Eq. (5), possibly followed by a chemical step in Eq. (6).

$$R + ne \rightleftharpoons P \quad (E^\circ) \tag{5}$$

$$P \longrightarrow P' \quad (k) \tag{6}$$

The simplification in Eqs. (2) and (3) is equivalent to saying that k is much smaller than the mass transfer rate D/δ^2, which is of the order of $5\,s^{-1}$. From Chapter 1, this implies that the R/P redox couple gives a chemically reversible cyclic voltammogram at a scan rate corresponding to the same mass transfer rate. From a dimensionless analysis and Table 5 in Chapter 1, this corresponds to a scan rate v such as $Fv/RT \approx D/\delta^2$, that is, v of the order $0.1\,V\,s^{-1}$. Thus, observation for identical or close experimental conditions of a chemically reversible cyclic voltammogram at $v \approx 0.1\,V\,s^{-1}$ for the redox couple of interest is sufficient to prove the validity of the assumptions leading to the homogeneous equivalent rate laws in Eqs. (7) and (8),

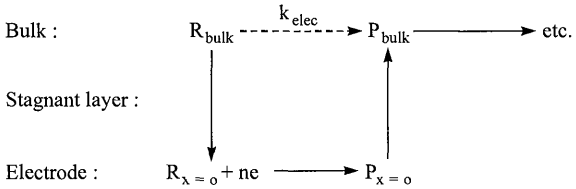
$$\frac{d[R]}{dt} = -k_{elec}[R] \tag{7}$$

$$\frac{d[P]}{dt} = +k_{elec}[R] + \left(\frac{d[P]}{dt}\right)_{chem} \tag{8}$$

with k_{elec} given in Eq. (4). In the converse situation, this is, when a totally irreversible cyclic voltammogram is observed, Eq. (7) still applies for R, which is not chemically affected in the sequence considered, but Eq. (8) does not reflect the variations in the bulk concentration of the product P [7]. Indeed, the observation of a chemically irreversible cyclic voltammogram shows that P is too short-lived to have any possibility of escaping that stagnant layer. However, because of mass conservation within the stagnant layer, the outgoing flux of P′, the product of chemical reaction of P in Eq. (6), is identical to the incoming flux of R. Equation (8) is then replaced by $[P] \approx 0$, and Eq. (9) results, which is tantamount to the steady-state approximation in homogeneous chemistry:

$$\frac{d[P']}{dt} = +k_{elec}[R] \tag{9}$$

From this analysis and presentation it is seen that when single chemical pathways are followed, that is, when no competitive route interferes in the reaction of intermediate(s) within the diffusion layer, the electrolysis affects the different bulk concentrations in a way similar to a first-order chemical reaction, as outlined in Scheme 1. This analogy affords an extremely simple way to handle the various problems that may arise during electrolysis. Indeed, they then become exactly identical to those that would be observed for homogeneous chemistry, that is, as if the R/P redox reaction were performed using a homogeneous redox reagent in excess.



Scheme 1

B. Coulometry: Apparent Number of Electrons Consumed

In the preceding section we have presented the analogy that exists between electrolysis and homogeneous chemistry in terms of an equivalent rate constant $k_{elec} = DA/V\delta$. Yet it may be surprising that this rate constant does not include a term related to the current. However, the current corresponds to a number of moles consumed per unit of time, that is, to an instantaneous rate, and therefore not to a rate constant. From the description outlined in Scheme 1 and Eq. (141) in Chapter 1, the current exchanged at the electrode at any time is given in Eq. (10):

$$i = nFAD\left(\frac{\partial[R]}{\partial x}\right)_{x=0} = -nFAD\left(\frac{\partial[P]}{\partial x}\right)_{x=0} \tag{10}$$

When R undergoes no significant chemical reaction within the diffusion layer, its concentration profile is linear, as established previously, and Eq. (10) is rewritten as in Eq. (11):

$$i = \frac{nFAD}{\delta}([R]_{bulk} - [R]_{x=0}) \tag{11}$$

Again, when one considers the most frequent situation in which the electrode potential is such as $[R]_{x=0} = 0$, Eq. (12) is finally obtained:

$$i = \frac{nFAD}{\delta}[R]_{bulk} \tag{12}$$

Comparison to the definition of k_{elec} [Eq. (4)] affords the relationship in Eq. (13) between the instantaneous current and the equivalent rate of electrolysis [6].

$$i = nFVk_{elec}[R]_{bulk} \tag{13}$$

Note that Eqs. (12) and (13) are independent of the eventual chemical fate of R or P in the bulk solution but suppose only that R undergoes no chemical reaction within the stagnant layer.

The overall quantity of electricity Q_t consumed after a duration t of electrolysis is given by the integration versus time of Eq. (13), which affords Eq. (14):

$$Q_t = \int_0^t i\,dt = nFVk_{elec}\int_0^t [R]_{bulk}dt \tag{14}$$

In Eq. (14), $[R]_{bulk}$ is obtained as a function of time in Eq. (15), which follows directly from Eq. (3).

$$\frac{d[R]_{bulk}}{dt} = -k_{elec}[R]_{bulk} + \left(\frac{d[R]_{bulk}}{dt}\right)_{chem} \tag{15}$$

When the last term in Eq. (15) is negligible, R is consumed only at the electrode. Thus the charge consumption is easily obtained by considering that each mole of R converted consumes nF coulombs, that is, Q_t is given in Eq. (16), where C^0 is the initial bulk concentration of R.

$$Q_t = nFV(C^0 - [R]_{bulk}) \tag{16}$$

On the other hand, from Eq. (15), $[R]_{bulk}$ decays exponentially with time as in Eq. (17):

$$[R]_{bulk} = C^0 e^{-k_{elec}t} \tag{17}$$

At the end of electrolysis, that is, for $t \gg 1/k_{elec}$, one obtains the overall charge consumption in Eq. (18). In practice, Eq. (18) allows the experimental determination of n, the number of electrons consumed per molecule of R, as in Eq. (19):

$$Q = nFVC^0 \tag{18}$$

$$n = \frac{Q}{C^0 FV} \tag{19}$$

But when experimentally possible, one does not proceed from Eq. (19), because when the R concentration becomes small, that is, near the end of electrolysis, residual currents arising from other electroactive species may contribute significantly to the current and then alter the charge measured. It is then preferable to rely on the plot of Q versus $[R]_{bulk}$, according to Eq. (16). Thus a linear plot should be obtained as in Fig. 2a, in which extrapolation at $[R]_{bulk} = 0$ allows a more accurate value of Q to be determined. Note that the ensuing value of n should be identical to that determined from transient or steady-state methods.

However, it happens frequently that the two figures do not agree, which is a proof that the chemical term in Eq. (15) is not negligible in preparative-scale electrolysis. Indeed, when the latter is positive, that is, corresponds to a production of R in the bulk solution, as by a regenerating sequence as in Eq. (20),

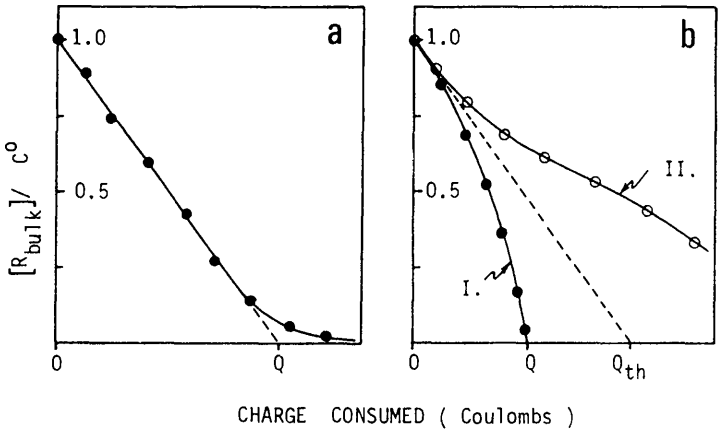


Figure 2. Variations in the bulk concentration of the reactant as a function of the charge consumed: (a) in the absence or (b) in the presence of chemical reaction(s) consuming (I) or regenerating (II) the electrolyzed species (initial concentration of the reactant C^0).

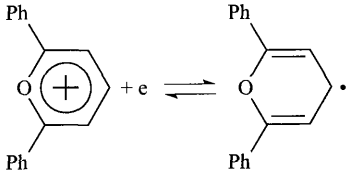
$$\begin{aligned} &R + ne \longrightarrow P \qquad \text{stagnant layer} \\ &P + Z \longrightarrow R + \cdots \qquad \text{bulk solution} \end{aligned} \tag{20}$$

the instant R concentration is larger than predicted by Eq. (17). From Eq. (14) it is seen that Q is then larger than determined via Eq. (18), which results in a larger number of electrons consumed n_{ap} during the electrolysis, when compared with the net electron exchange n at the electrode identified in microelectrolysis.

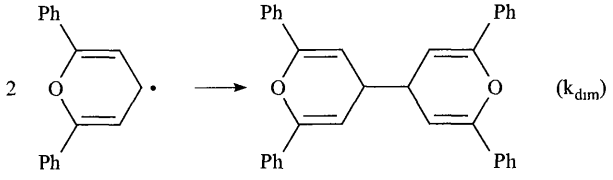
$$n_{ap} = \frac{Q}{FVC^0} \tag{21}$$

Conversely, when R is consumed in the bulk solution, Q and therefore n_{ap} are smaller than predicted in Eqs. (18) and (19).

A typical example of such behavior is given by the reduction of pyrylium cations. Under steady state or moderate-scan cyclic voltammetry, their reduction involves the net consumption of one electron per molecule, which corresponds to the fast radical dimerization in Eq. (23).



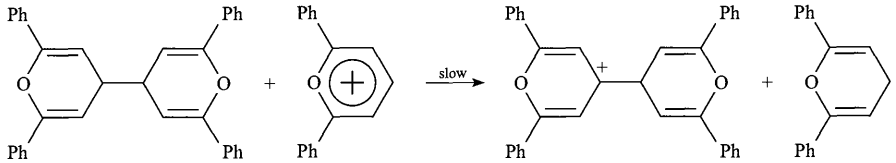
(22)



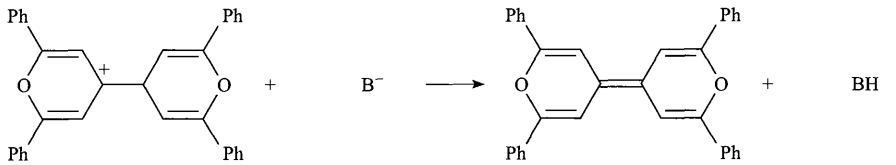
(23)

The corresponding rate constant k_{dim}, close to the diffusion limit, has been determined in acetonitrile using ultrafast cyclic volammetry in the low million volts per second

[8a]. However, bulk electrolysis and coulometries indicate an overall consumption of 2/3 electrons. This was shown to correspond to the involvement of the slow hydride transfer sequence outlined in reactions (24) and (25) [9].

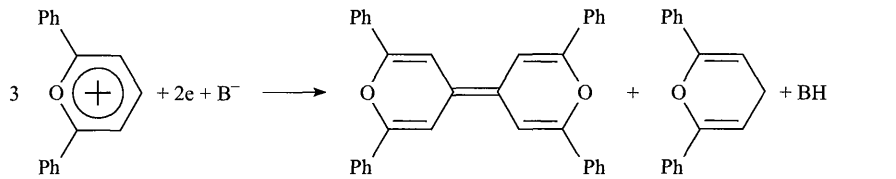


(24)



(25)

Reaction (24) is too slow to be detected in cyclic voltammetry, yet it takes place during the electrolysis to afford finally a 4H-pyran and a bipyranylidene as summarized in the balanced Eq. (26).



(26)

Thus three pyrylium molecules are consumed for only two electrons exchanged, resulting in $n_{ap} = 2/3$.

In this discussion we have considered the involvement of a slow follow-up reaction of the reactant as a cause for the difference between n and n_{ap}. Yet this is not the only situation possible. In most cases such disagreements are due to the involvement of an ECE kind of sequence such as that featured in Eqs. (27) through (29),

$$R + ne \longrightarrow P \quad (E^\circ) \tag{27}$$

$$P \longrightarrow R' \quad \left(\text{slow versus} \frac{D}{\delta^2}\right) \tag{28}$$

$$R' + n'e \longrightarrow P' \quad (E^{\circ\prime}) \tag{29}$$

as well as to their homogeneous analogs in which the heterogeneous electron transfer is replaced by a homogeneous electron transfer (disproportionation sequences). When the interposed chemical step or the disproportionation is slow enough to make no contribution within the diffusion layer, the apparent number of electrons observed in microelectrolysis is n, that is, reflects the redox process in Eq. (27). However, the chemical step may be sufficiently rapid when compared with the electrolysis duration to convert quantitatively the primary product P into R′. Thus, provided that $n(E^{\circ\prime} - E^\circ) > 0$, R′ is coelectrolyzed and the apparent number of electrons exchanged is $n_{ap} = n + n'$. The absolute value of n_{ap} may then be larger than that of n when both have the same sign, or smaller when of opposite signs. Similarly, slow disproportionation reactions pulled by a fast

protonation step, for example, may affect the n_{ap} value, as outlined in the following sequence:

$$R + ne \longrightarrow P$$
$$2P \rightleftharpoons R + P'$$
$$P' + Z \longrightarrow \cdots$$

These examples illustrate some of the difficulties that may be encountered when comparing the numbers of electrons exchanged in micro- or macroscale electrolysis. In a few instances these chemical complications may be detected by important curvatures of the Q versus $[R]_{bulk}$ plots as sketched in Fig. 2b. Such curvatures are observed when the degree of involvement of the follow-up chemical steps increases during electrolysis. Indeed, because of concentration effects the effective rate of the chemical step may be slow at the beginning of the electrolysis, and thus a slope corresponding to $n_{ap} = n$ is observed. However, when the pertinent concentrations of intermediates increase, the rate of their chemical reaction may become sufficient so that the intermediates reach steady-state behavior, which results in a tendency to reach a slope corresponding to $n_{ap} = n + n'$ while electrolysis progresses. Yet this supposes that the degree of participation changes during the electrolysis, which obviously is not a general fact. Thus the absence of curvature in the Q versus $[R]_{bulk}$ plots cannot be taken as evidence of no chemical complication, that is, of the fact that $n = n_{ap}$. This is important to remember when using coulometric results, that is, n_{ap} values, in the rationalization of electrochemical mechanisms.

C. Separation of Waves and Selectivity in Electrolysis

It is often alleged that the fine-tuning of electrode potential allows high selectivity in electrolysis. This is certainly true for a wide variety of electrochemical situations but may turn out totally inexact in others, as is shown in the following discussion. Indeed, let us consider from steady-state or transient electrochemical data two successive reduction waves* at E_1 an E_2 for a compound involving two reduction sites A and R: A–R. Let us assume, in addition, that electrolysis of related molecules, but without the R center, is known to occur at potentials lying in the same range where the first wave is observed. Thus an "evident" rationalization of the observed waves consists in ascribing them to the successive reductions in Eqs. (30) and (31):

$$A - R + e \longrightarrow {}^{\cdot}A - R - \cdots \rightarrow B - R \quad (k_1) \quad \text{first wave} \tag{30}$$

$$B - R + e \longrightarrow B - R^{\cdot} - \cdots \rightarrow B - P \quad (k_2) \quad \text{second wave} \tag{31}$$

When the lifetime of the anion radical formed upon the electron transfer in step (30) is extremely short, the mechanism in Eqs. (30) and (31) is certainly valid and the electrolysis product obtained at $E = E_1$ is B – R. Yet when this is not the case, a combination of A – P and B – R products may be obtained although the electrolysis is performed at the first wave [11,12]. Indeed, an alternative route is now offered to the ${}^{\cdot}A - R$ anion radical formed in Eq. (30), which involves a possible intra- or intermolecular electron transfer to the R site to afford the $A - R^{\cdot}$ anion radical.

*Transposition to oxidations is obvious, so that the discussion hereafter is developed only for a cathodic process.

$$^{-}A - R \rightleftharpoons A - R^{-} - \cdots \rightarrow A - P \tag{32}$$

If the latter is not highly unstable, a back electron transfer occurs to regenerate the $^{-}A - R$ anion radical. In the converse situation, $A - R^{-}$ may evolve directly to the A – P product, which corresponds to the overall reduction of the R moiety although the first electron transfer has occurred at the A group. The observed phenomenon is thus tantamount to indirect electrolysis [13], where the A group plays the role of an intramolecular electron mediator for the reduction of the R group. Although not explicitly recognized as such, this is the case for the reduction of aromatic halides, for example, since the initial electron is transferred to the aromatic ring and then internally transferred to the carbon-halogen antibonding orbital, resulting finally in the overall reduction of the carbon–halogen bond.

In such situations the exact nature of the B – R or A – P product obtained depends on the relative chemical stabilities of the A^{-} and R^{-} moieties [rate constants k_1 and k_2 in Eqs. (30) and (31)], as well as on the difference between the standard reduction potentials of the two groups, as explained later. Indeed, in a general case, one must consider that the mechanism occurring at the first reduction wave is not as in Eq. (30) but may involve the sequence in Eqs. (33) through (35).

$$A—R + e \longrightarrow {}^{-}A—R \tag{33}$$

$$\overset{k_1}{\cdots\cdots\rightarrow} B—R \tag{34}$$

$$^{\cdot}A—R \underset{K}{\rightleftharpoons} A—R^{\cdot-} \overset{k_2}{\cdots\rightarrow} A—P \tag{35}$$

When the homogeneous electron transfer is sufficiently fast to be equilibrated (with an equilibrium constant K), the formation rate constant of A – P product is k_2K when related to $^{-}A - R$.

$$\frac{[B - R]_{yield}}{[A - P]_{yield}} = \frac{k_1}{k_2K} \tag{36}$$

$$\frac{[B - R]_{yield}}{[A - P]_{yield}} = \frac{k_1(k_2 + k_b)}{k_2k_f} \tag{37}$$

Thus the relative yields of the B – R and A – P products are given in Eq. (36), and, it is noteworthy, are independent of the electrode potential. In a more general case, the forward k_f and backward k_b rate constants of the homogeneous electron transfer must be considered, and the relative yields are given in Eq. (37)* and are again independent of the electrode potential, provided it is kept on the first wave.

*Note that in Eq. (37), k_f and k_b may include a concentration term when the homogeneous electron transfer is bimolecular as in Eq. (38):

$$^{-}A - R + A - R \rightleftharpoons A - R + A - R^{-} \tag{38}$$

III. COMPETITIVE REACTION SCHEMES: OPTIMIZATION OF PREPARATIVE-SCALE ELECTROLYSIS

A. Slow Reaction Schemes

In electrochemistry, as in other chemical methods, situations in which a single product is obtained are seldom encountered. In most experimental cases the target product is often accompanied by unwanted side products formed along competitive pathways. Under such conditions, optimization of the target product yield is obviously desirable. Frequently this optimization is sought on the basis of chemical intuition and of "blind tests" of supposedly critical parameters. Yet is difficult to be certain (except when a 100% yield is obtained!) that the best yield obtained is the maximum. In the following we want to show that semiquantitative predictions can be made on the basis of very simple considerations. The goal of these approaches is not to replace the necessary tests, but to provide useful guidelines for the selection of the parameters that affect the yield of the target product.

From the preceding presentation it is easily inferred that different behaviors are obtained when the "key species," that is, that at which the different chemical routes are branched, exists only within the stagnant layer or exists in the bulk solution, as schematized in Fig. 3. In the latter case, the competition problem is analogous to the homogeneous chemical situation, owing to the equivalences established previously. For example, let us consider a reaction sequence like that in Fig. 3 (case a or b):

$$A + e \longrightarrow B \quad (E^\circ) \tag{39}$$

$$B \longrightarrow C \quad (k_1) \tag{40}$$

$$C \overset{+e}{\rightleftharpoons} \begin{matrix} P_1 \quad (k_2) \\ P_2 \quad (E^{\circ\prime} > E^\circ) \end{matrix} \tag{41, 42}$$

For a potentiostatic electrolysis on the plateau of the A/B reduction wave, the reaction sequence in Eqs. (39) through (42) is equivalent to the homogeneous mechanism in Eqs. (43) through (46), where $k_{elec} = DA/V\delta$:

$$A \longrightarrow B \quad (k_{elec}) \tag{43}$$

$$B \longrightarrow C \quad (k_1) \tag{44}$$

$$C \rightleftharpoons \begin{matrix} P_1 \quad (k_2) \\ P_2 \quad (k_{elec}) \end{matrix} \tag{45, 46}$$

Thus, the yield of species P_1 vis-à-vis P_2 is simply expressed as in Eq. (47).

$$\frac{[P_1]_{yield}}{[P_1]_{yield} + [P_2]_{yield}} = \frac{k_2}{k_2 + k_{elec}} \tag{47}$$

From Eq. (47) it is easily seen that maximizing the yield of P_1 amounts to decreasing the ratio k_{elec}/k_2, that is, of $DA/V\delta k_2$. Thus it obviously follows that one must decrease the electrode surface area and the stirring rate (i.e., increase δ), increase the bulk solution volume, and when possible, increase k_2. The opposite changes are needed when the target compound is P_2. Similarly, when B is the compound sought, one wants $k_{elec} \gg k_1$, that is,

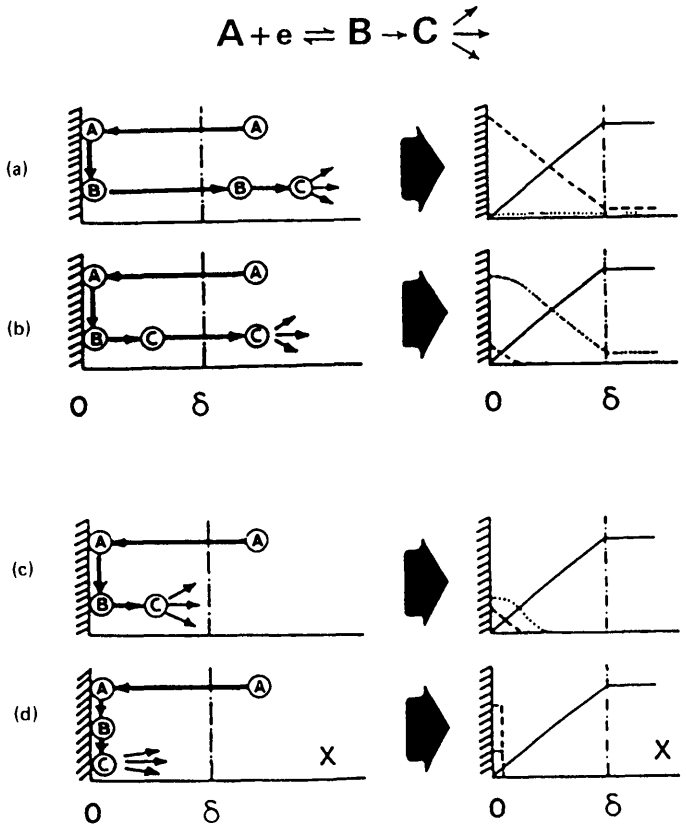


Figure 3. Schematic representation of the localization of the "branching point" for an ECC competitive sequence and resulting concentration profiles for (—) A, (- - -) B, and (· · ·) C. (a, b) Slow production of the intermediate "key species"; (c) fast production of the key species; (d) reaction in the adsorbed phase.

a large surface area for the electrode, small bulk solution volume, and high stirring rates (small δ).

Thus, owing to the equivalent homogeneous formulation, there are no specific particularities associated with optimization in electrochemistry, as soon as the branching point takes place in the bulk solution. As explained earlier, this is generally easy to decide on the basis of cyclic voltammograms of the system of interest.

Conversely, when the key species exists only in a thin reaction layer adjacent to the electrode (case c in Fig. 3), the degree of competition between the various routes is greatly influenced by the local concentration profiles of the different species involved. In such cases, general theories have been established that allow a complete and quantitative description of the optimization procedure. However, in the following we want to present a very simple approach to the problem.*

*Note that case d in Fig. 3, which relates to surface reactions between adsorbed or chemisorbed species, is not considered here because of the too specific nature of the electrode–species interactions involved.

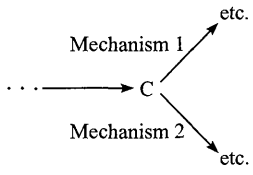
B. An Elementary Method for Fast Competitive Kinetics

1. Presentation of the Method

All the results presented in the following discussion derive from the simple consideration* that when a species is involved in a branched kinetic scheme, the major pathway is the fastest; that is, the main product is that formed according to the pathway corresponding to the highest rate of consumption of the key species.

On the other hand, when the key species is formed at a given rate, the faster its consumption, the smaller its concentration. Taking into account these two obvious statements leads to the following conclusion: When two or more pathways compete for the consumption of a given species, the major pathway is that leading to the smallest concentration of this species, when each pathway is considered alone under identical experimental conditions.

When two competing mechanisms are considered, for example, a competition parameter may thus be defined as the ratio of the average concentration of the key species obtained when each of these mechanisms is considered alone. Let us denote by C_1 and C_2 the corresponding concentrations for mechanisms 1 and 2 in Scheme 2, when they do not interfere. The competition parameter $p = C_1/C_2$ is then such that $p \ll 1$ favors the occurrence of mechanism 1 as the main pathway since this condition corresponds to $C_1 \ll C_2$, whereas mechanism 2 is observed when $p \gg 1$. In the general case the dependence of both C_1 and C_2 on the experimental conditions (concentrations of the reactants and of the coreactants, stirring rate, and so on) and intrinsic factors (rate constants and diffusion coefficients, for example) may be determined, thus leading to the expression of p as a function of these factors. The effects of the latter on the overall product distribution are then readily given with the direction and magnitude included in the p expression.



Scheme 2

Table 1 gives the average concentrations to be used for the various intermediates involved in the most basic schemes of electrochemical mechanisms† which may allow the simple derivation of the competition parameters p for most of the possible experimental situations.

In the preceding discussion we have considered for simplicity that only two pathways were possible for the key species. Thus a single parameter p is defined. However, when more routes are branched for the same species, the situation is a priori more difficult to handle. For three competitive routes, for example, Table 1 affords three concentrations C_1, C_2, and C_3, and thus three parameters $p_1 = C_1/C_2$, $p_2 = C_1/C_3$, and $p_3 = C_2/C_3$ are defined, which are all affected by the experimental and intrinsic parameters. Thus it is a

*Yet they are based and supported by a rigorous physicomathematical analysis. See, for example, Refs. 7a and 14–20.

†Note that each of the reactions presented in Table 1 may consist of true elemental reactions or of a kinetically equivalent series of elemental steps.

Table 1 "Average Concentrations" of the Different Intermediates Involved in the Main Electrochemical Mechanisms[a,b]

Mechanism[b]	Scheme	Average concentration[c]
EC	$A + ne \rightleftharpoons B$	$[B] = C^0/(k\theta)^{1/2}$
	$B \xrightarrow{k} C$	$[C] = C^0$
ECE	$A + ne \rightleftharpoons B$	$[B] = C^0/(k\theta)^{1/2}$
	$B \xrightarrow{k} C$	$[C] = C^0/(k\theta)^{1/2}$
	$C + ne \rightarrow D$	$[D] = C^0$
DISP	$A + ne \rightleftharpoons B$	$[B] = C^0/(2k\theta)^{1/2}$
	$B \xrightarrow{k} C$	$[C] = k/k_d$
	$B + C \xrightarrow{k_d} A + D$	$[D] = C^0$
ECC	$A + ne \rightleftharpoons B$	$[B] = C^0/(k_1\theta)^{1/2}$
	$B \xrightarrow{k_1} C$	$[C] = (C^0/k_2)(k_1/\theta)^{1/2}$
	$C \xrightarrow{k_2} D$	$[D] = C^0$
Dim 1	$A + ne \rightleftharpoons B$	$[B] = C^{02/3}(3/4k\theta)^{1/3}$
	$2B \xrightarrow{k} C$	$[C] = C^0/2$
Dim 2 (ECE)	$A + ne \rightleftharpoons B$	$[B] = C^{02/3}/(k\theta)^{1/3}$
	$B + A \xrightarrow{k} C$	$[C] = C^{02/3}/(k\theta)^{1/3}$
	$C + ne \rightarrow D$	$[D] = C^0/2$
Dim 2 (DISP)	$A + ne \rightleftharpoons B$	$[B] = C^{02/3}/(2k\theta)^{1/3}$
	$B + A \xrightarrow{k} C$	$[C] = (kC^0)^{2/3}/(k_d\theta^{1/3})$
	$B + C \xrightarrow{k_d} A + D$	$[D] = C^0/2$
Dim 3 (DISP)	$A + ne \rightleftharpoons B$	$[B] = (3C^0/4kK\theta)^{1/3}$
	$B + A \rightleftharpoons C$ [K][d]	$[C] = C^0K[B]$
	$B + C \xrightarrow{k_d} A + D$	$[D] = C^0/2$
ECDim	$A + ne \rightleftharpoons B$	$[B] = C^0/(k_1\theta)^{1/2}$
	$B \xrightarrow{k_1} C$	$[C] = (C^0/2k_2)^{1/2}(k_1/\theta)^{1/4}$
	$2C \xrightarrow{k_2} D$	$[D] = C^0/2$

[a]The concentrations are given for an electrolysis on the plateau of the A/B wave. C^0, bulk concentration of A; $\theta = \delta^2/D$.

[b]Usual names, or taken from the nomenclature developed in Savéant's group.

[c]These concentrations are valid provided each resulting figure is lower than approximately $C^0/10$ (except for the final product).

[d]Rapid equilibrium; K, equilibrium constant.

priori difficult to appreciate the effect resulting of the variation of one of the experimental parameters on the overall competition. Yet it is first noticed that the consideration of only two parameters suffices to describe the competition since they are all given by ratios or products of the two others, as $p_3 = p_2/p_1$. Thus a convenient presentation of the competition problem consists in the construction of a diagram in which $\log p_1$ is the ordinate axis and $\log p_2$ is the abscissa axis, as in Fig. 4. In such a diagram, "kinetic zones" corresponding to the predominance of one of the three possible mechanisms may be defined in a similar way as "thermodynamic stability zones" corresponding to the predominance of a species are defined, for example, as a function of the solution potential and pH (Chapter 1). Thus mechanism 1, which corresponds to $p_1 \ll 1$ and $p_2 \ll 1$, is located in the lower left corner of Fig. 4, that is, $\log p_1 < 0$ and $\log p_2 < 0$. Mechanism 2 is observed for $p_1 \gg 1$ and $p_3 = p_2/p_1 \ll 1$, and its kinetic zone is then such that $\log p_1 > 0$ and $\log p_1 > \log p_2$. Similarly, the kinetic zone corresponding to the predominance of mechanism 3 is such that $p_3 \gg 1$ and $p_2 \gg 1$, that is, $\log p_2 > 0$ and $\log p_2 > \log p_1$. Then three boundary lines delimiting the zone of predominance of each mechanism are constructed in Fig. 4. Near one of these boundaries the two delimited mechanisms compete without interference from the third. The general competition, that is, that involving the three mechanisms, is observed near the intersection of the three boundary lines in the central region of Fig. 4. When such a diagram has been constructed, the effect of each experimental parameter is easily seen by construction of a "compass card," such as that shown in the upper right corner of Fig. 4. For example, let us assume that $p_1 \propto C^0\delta^2/C_y$ and $p_2 \propto C^0C_z/\delta$. Thus a multiplication of δ by 10, for example, results in an increase of 2 in $\log p_1$ and a decrease by 1 in $\log p_2$. A vector corresponding to the "δ effect" can then be constructed in the diagram, which has a projection -1 in the abscissa and $+2$ in the ordinate. Similarly, other vectors can be drawn for C^0, C_y, and C_z to constitute the compass card shown in the upper right corner of Fig. 4. Such a compass allows easy visualization of the effect of any variation in the experimental parameters. For example, it is seen in Fig. 4 that when the system is at point A, an increase in δ results in a trend to shift from mechanism 3 to mechanism 2, whereas the same variation results in a tendency to pass from mechanism 3

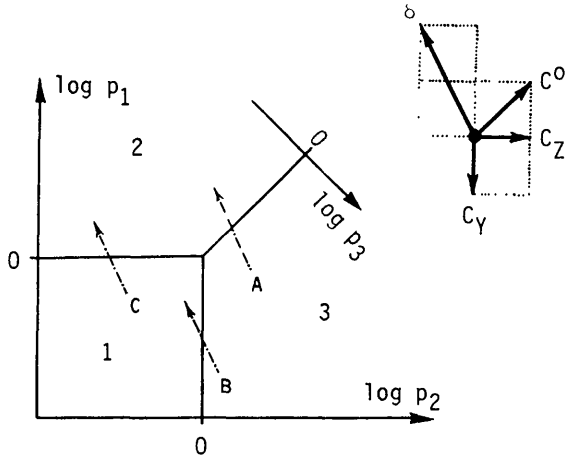


Figure 4. Kinetic zone diagram and corresponding "compass card" for a competition between three hypothetical mechanisms, as discussed in the text.

Table 2 Competition Parameters for an ECDim/ECE/DISP Competing Sequence

Average concentration of Ar[a]		Competition parameter		Major pathway[d]	
Mechanism	$[Ar]^{b,c}$	Sequence	Competition parameter	$p_i \ll 1$	$p_i \gg 1$
ECDim	$(C^0/2k_{dim})^{1/2}(k_1/\theta)^{1/4}$	ECDim/ECE	$p_1 = (Ar)_{ECDim}/(Ar)_{ECE}$ $p_1 = k_1^{3/4}\theta^{1/4}/(2k_{dim}C^0)^{1/2}$	ECDim	ECE
ECE	$C^0/(k_1\theta)^{1/2}$	ECDim/DISP	$p_2 = (Ar)_{ECDim}/(AR^{\cdot})_{DISP}$ $p_2 = k_dC^{01/2}/k_1^{3/4}(2k_{dim})^{1/2}\theta^{1/4}$	ECDim	DISP
DISP	k_1/k_d	DISP/ECE	$p_3 = (Ar)_{DISP}/(Ar)_{ECE}$ $p_3 = p_1/p_2$	DISP	ECE

[a] Taken from Table 1.

[b] k_1, rate constant of the aromatic halide anion cleavage; k_{dim}, dimerization rate constant of the σ-aryl radicals; k_d, homogeneous electron transfer rate constant (usually $k_d = k_{dif}$, the diffusion-controlled rate constant).

[c] C^0, ArX bulk concentration; $\theta = \delta^2/D$.

[d] Both pathways are observed when the value of p_i is close to unity (i.e., when $\sim 0.1 \leq p_i \leq 10$).

to 1 when starting from location B or from mechanism 1 to 2 when starting from point C. Such different effects induced by the same experimental variation would have been puzzling and difficult to rationalize, whereas they are easily understood from the kinetic zone diagram and its associated compass card. Similarly, a compass card showing the effect of each intrinsic parameter may be constructed.

In the following discussion we want to show how this simple method may be used in practical situations, either to rationalize a series of results or to decide a priori the worthiness of an experimental strategy. To maintain some homogeneity in the presentation, the two aspects are discussed on the basis of examples pertaining to the electrochemistry of aryl halides.

2. Predictive Value of the Method

This aspect is developed by addressing the following question: Is there any chance that biaryls may be formed, via aryl radical dimerization, during the reductive electrolysis of aryl halides?

The reduction of aryl halides is known [21] to afford a frangible anion radical $ArX^{\cdot -}$, which yields a σ-aryl radical by cleaving off the halide ion in Eq. (49).

$$ArC + e \longrightarrow ArX^{\cdot -} \quad (E^\circ) \tag{48}$$

$$ArX^{\cdot -} \longrightarrow Ar^{\cdot} + X^- \quad (k_1) \tag{49}$$

Although these σ-aryl radicals are prone to undergo a facile reduction at the electrode [Eq. (50)] or in solution as in Eq. (51), one may think of the possibility of impeding these normal pathways to favor their radical dimerization [Eqs. (48), (49), and (53)].

$$Ar^{\cdot} + e \longrightarrow Ar^- \qquad (E^{\circ\prime} > E^\circ) \tag{50}$$

$$Ar^{\cdot} + ArX^{\cdot -} \longrightarrow Ar^- + ArX \quad (k_{dif}) \tag{51}$$

$$Ar^- + BH \longrightarrow ArH + B^- \tag{52}$$

$$2\,Ar^{\cdot} \longrightarrow Ar - Ar \qquad (k_{dim}) \tag{53}$$

Indeed, the dimerization of these σ radicals is expected to be extremely fast and possibly close to diffusion control. Then owing to its bimolecular nature, a concentration effect should favor this step vis-à-vis the reduction at the electrode. On the other hand, increasing the rate of the anion radical cleavage in Eq. (49) should decrease its concentration with a concomitant increase in the radical concentration, both effects being in favor of the duplicating step.*

The average concentrations for the key species Ar to be used in the following analysis are obtained from Table 1, where the role of $Ar^{\cdot}$ is symbolized by C in the three competing sequences: ECE [Eqs. (48) through (50) and (52)], DISP [Eqs. (48), (49), (51), and (52)], and ECDim [Eqs. (48), (49), and (53)]. This allows the three competition parameters to be obtained as in Table 2: p_1 = (ECDim/ECE), p_2 = (ECDim/DISP), and $p_3 = (p_1/p_2)$ = (DISP/ECE) from the ratios of the respective average concentrations. Following this procedure, a kinetic zone diagram and a compass card are then constructed

*Note that $Ar^{\cdot}$ is prone to undergo other facile reaction paths (see later). The concurrent routes in Eqs. (50) through (52) then constitute the minimal competitive sequence to be considered.

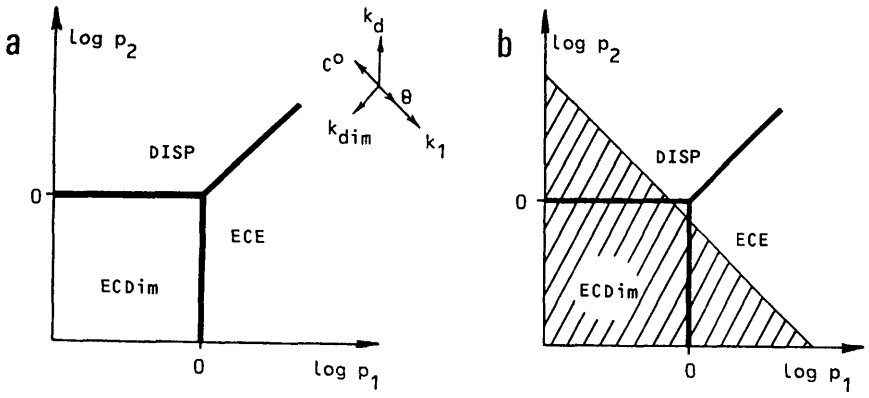
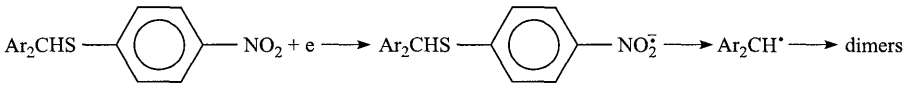


Figure 5. Kinetic zone diagram for an ECDim/ECE/DISP competitive sequence [see text, Eqs. (48) through (53), and Table 2 for definitions of p_1, p_2, and p_3; note that for the example discussed in the text $k_d = k_{dif}$]. The hatched zone in b corresponds to the region without experimental validity.

in Fig. 5a. Such a diagram shows that these considerations on the effect of C^0 or of the cleavage rate constant k_1 of $ArX^{\cdot-}$ are valid only when the point representing the system is in the ECE zone (C^0 effect) or in the DISP zone (k_1 effect). When starting from and ECDim zone, however, an increase in C^0 results in a tendency to shift toward the DISP zone and an increase in k_1 favors reduction via an ECE mechanism. The concentration effect is difficult to predict on an intuitive basis, yet that of k_1 could have been intuitively guessed. Indeed, when k_1 increases, Ar is produced closer and closer to the electrode surface and then has less and less possibility to dimerize before reaching the electrode to be reduced. As for C^0, the effect of the mass transfer rate (i.e., of $\theta = \delta^2/D$ in the compass card) was almost impossible to predict on an intuitive basis.

To illustrate a further useful aspect of the method, let us discuss the experimental validity of the ECDim zone in Fig. 5a. Indeed, the representation in Fig. 5a supposes that any values are possible for p_1 and p_2. Yet in an actual case this is not true since the product $p_1p_2 = k_{diff}/2k_{dim}$ is necessarily larger than 1/2 because k_{dim} cannot exceed the diffusion limit k_{dif}. This implies that the hatched zone in Fig. 5b, which corresponds to $p_1p_2 < 0.5$, has no experimental validity. Thus, no system can be located in this zone regardless of the values of the experimental (C^0, θ, and δ) or intrinsic parameters (D, k_{dif}, k_{dim}, or k_1); this shows that almost all the ECDim zone has no experimental significance. Although this method does not allow the maximum yield of biaryl to be determined, it leads to the conclusion that it is necessarily poor and requires extremely precise conditions to be achieved. A complete and accurate analysis [17] of the problem establishes that this maximum yield is of the order of 10–20% at best, which is in complete agreement with the maximum experimental yields in the range of 7%.

However, this does not mean that biaryls cannot be obtained via aryl halide reduction but only that this strategy is not experimentally valid as soon as $Ar^{\cdot}$ is more easily reducible than the parent halide. Yet other approaches to the synthetic problem may be found. An obvious one consists in suppressing the facile reductions of $Ar^{\cdot}$ by using an electrophore as the leaving group X^-, which will be the site of the initial electron uptake [Eq. (48)]. $Ar^{\cdot}$ may not then be reducible at the reduction potential of the parent pseudohalide, as in reaction (54), which is shown in benzylic series [22].

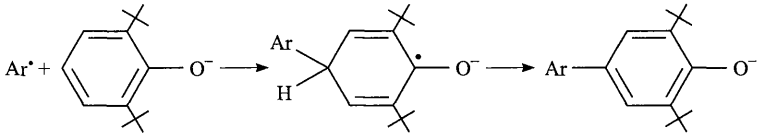


(54)

Another approach consists, for example, in using an ArX or a coreactant Ar′X, prone to react with Ar· via the Ullman kind of reaction in Eq. (55) [23,24]:

$$Ar + ArX \longrightarrow [Ar - ArX]^{\cdot} \longrightarrow \cdots \tag{55}$$

Naturally, each of these possible approaches, as well as many others that may be conceived, may be tested "on paper" following this method to decide its possible validity and the best experimental conditions to favor it. For example, application of this "on paper" strategy shows that only moderate yields are obtained for the process in Eq. (56) when directly reducing the aryl halide at the electrode, whereas interesting yields (i.e., from 80 to 70%) are possible by using a redox mediator for performing the initial ArX reduction [24c]:



(56)

3. Rationalization of a Series of Results

Figure 6 presents the variations in the yield in monodeuterated arene obtained when an aromatic halide is reduced in acetonitrile in the presence of 10% D_2O [25].

$$ArX + 2e \xrightarrow{ACN,\ 10\%D_2O} yArD + (1 - y)ArH \tag{57}$$

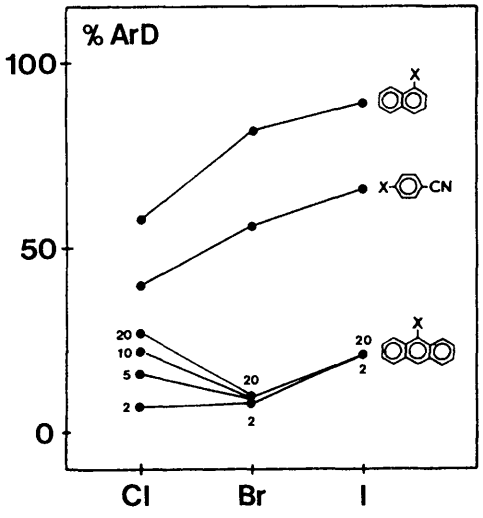


Figure 6. Experimental variations in the yield of monodeuterated arene ArD as obtained by reduction of the corresponding halide in acetonitrile in the presence of 10% D_2O and 0.1 M $LiClO_4$. The number on the curves are the initial concentration (mM) of the halide. (Data from Ref. 25.)

The overall stoichiometry of the reaction shown in Eq. (57) corresponds to the formation of ArD and ArH via two competitive pathways. ArD is obtained along the sequence presented in Eqs. (48) through (51), the resulting σ-aromatic anion being deuterated by D_2O, as in eq. (58):

$$Ar^- + D_2O \longrightarrow ArD + DO^- \tag{58}$$

ArH is formed via an H atom transfer from the ACN solvent to the aryl radical formed upon the mechanism in Eqs. (48) and (49), as outlined in the following sequence [25]*:

$$Ar^{\cdot} + CH_3CN \longrightarrow ArH + {}^{\cdot}CH_2CN \quad (k_H) \tag{59}$$

$${}^{\cdot}CH_2CN(+e \text{ or } ArX^{\cdot-}) \longrightarrow {}^-CH_2CN \tag{60}$$

$${}^-CH_2CN + D_2O \rightleftharpoons CH_2DCN + DO^- \tag{61}$$

The data in Fig. 6 show that for the 1-halonaphthalene or 4-halobenzonitrile series a continuous variation is observed; that is, the yield in ArD increases in the series $Cl \ll Br < I$, in agreement (at least for the monotonic variation) with usual chemical expectations. But for the 9-anthracene series a nonuniform variation is observed as a function of the halide. Moreover, the ArD yields obtained for the 9-chloroanthracene are extremely dependent on the concentration or the stirring rate, whereas the effects of these factors are minimal for the bromo derivative and totally negligible for the iodo derivative or for the 1-halonaphthalene or 4-halobenzonitrile series. Such a priori puzzling experimental results may, however, be easily rationalized through the preceding method.

From Table 1 the two parameters corresponding to the competition between ECE [reactions (48), (49), (50), and (58)] or DISP [reactions (48), (49), (51), and (58)] sequences and the ECC sequence [reactions (48), (49), and (59) through (61)] are obtained as follows†:

$$p_1 = \frac{k_1}{k_H} \qquad \text{ECC/ECE} \tag{62}$$

$$p_2 = \frac{C^0}{\theta^{1/2}} \frac{k_{dif}}{k_H k_1^{1/2}} \qquad \text{ECC/DISP} \tag{63}$$

$$p_3 = \frac{p_1}{p_2} \qquad \text{DISP/ECE} \tag{64}$$

This allows the construction of the kinetic zone diagram in Fig. 7a according to the previously explained procedure. The location of the experimental systems considered in Fig. 6 indicates that the benzonitrile or naphthalene derivatives undergo an ECE/ECC competition without interference from the DISP route. Thus, as indicated by the compass card in Fig. 7a or by the formulation of p_1 in Eq. (62), C^0 or $\theta = \delta^2/D$ has no effect on the

*The scrambling in Eq. (61) has been shown to play a minimal role during the electrolysis on the basis of experimental isotopic studies [25].

†Note that for the H atom transfer pathway, steps (60) and (61), which occur after the branching point [Eq. (59)], play no role in the ArD yield. Thus the sequence of reactions (48), (49), and (59) through (61) behaves like an ECC sequence in regard to the competition between the H versus (+e, $+D_2O$) routes.

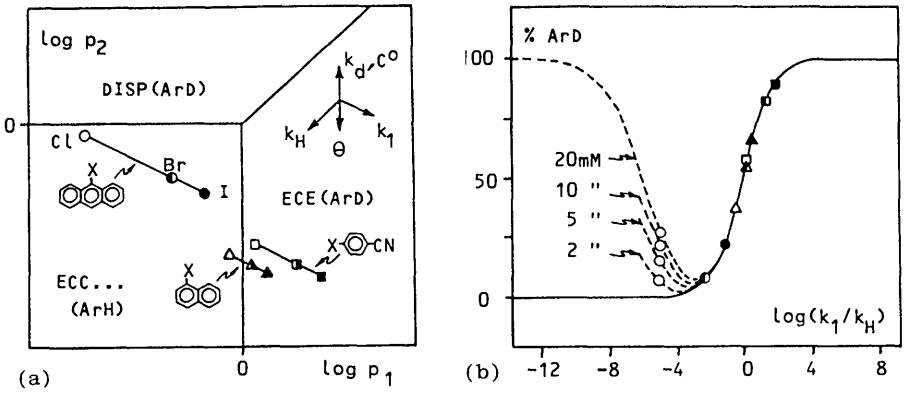


Figure 7. (a) Kinetic zone diagram for the ECC/ECE/DISP competitive sequence in the ArD versus ArH formation under the experimental conditions of Fig. 6 [see text and Eqs. (48) through (51) and (58) through (61); note that for the example discussed $k_d = k_{dif}$]. (b) Theoretical variations in the yield of ArD as a function of the concentration of ArX (numbers on the curves) and of the rate constants ratio k_1/k_H. (Experimental data from Ref. 25.)

overall ArD yield, in agreement with the experimental observations. Moreover, for a given aromatic moiety, k_H is constant and does not depend on the halide, whereas k_1 increases in the order $Cl \ll Br < 1$. Thus $p_1 = k_1/k_H$ increases monotonically in the series, which explains the uniform variations in Fig. 6. The 9-iodo anthracene also undergoes an ECC versus ECE competition, whereas an ECC/DISP competition is observed for the 9-chloro derivative. From the compass card in Fig. 7a it is then seen that C^0 or θ considerably affects the ArD yield for the 9-chloroanthracene, whereas there is no effect of these parameters on the iodo derivative. For the bromide, an intermediate situation is observed but more shifted toward predominance of an ECC than for the iodide or chloride cases, which explains the minimum observed in Fig. 6 as well as the small variations in the ArD yield with concentration or stirring rate changes. It is thus seen that the simple approach presented here is sufficient to rationalize qualitatively all the a priori puzzling observations in Fig. 6. But a correct and thorough analysis of the problem on a physicomathematical basis [15] may be achieved and leads to a more quantitative description of these facts. The result of such an analysis is shown in Fig. 7b, under the form of predicted variations in the ArD yield, for the systems in Fig. 6. Although more quantitative information is then obtained, it is seen that all the trends observed in Fig. 7b have been qualitatively predicted via the above approach, which requires no sophisticated derivations and can be handled "on the back of an envelope."

IV. CONCLUSION

This presentation was designed to discuss the relationships between micro- and macroscale electrolysis. Besides the intrinsic factors arising from scaling-up problems (larger concentrations, larger current densities, and longer reaction times), we have tried to show how the results of microscale electrolysis could be used with large profit, either in devising adequate experimental conditions or in the rationalization of product distributions. However, it is important to decide in such cases if the branching point leading to the different products

takes place in the bulk solution or occurs in the very close vicinity of the electrode. Indeed, in the first case the problem must be examined in terms of its homogeneous equivalent, the electrolytic reactions being replaced by first-order reactions. Conversely, in the second case an electrochemical analysis taking into account the concentration profiles in the vicinity of the electrode must be performed to solve quantitatively the distribution problem. However, in such cases, and when only semiquantitative predictions are needed, a very simple approach based upon competition parameters and kinetic zone diagrams proves to be considerably useful.*

ACKNOWLEDGEMENTS

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4

Comparison Between Electrochemical Reactions and Chemical Oxidations and Reductions

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I. Introduction
II. Comparison of Electrochemical Reactions with Chemical Oxidations and Reductions with Regard to their Mechanism
  A. General considerations
  B. More detailed comparisons of electrochemical reactions with chemical oxidations and reductions
III. Comparison of Electrochemical Reactions with Chemical Oxidations and Reductions in Synthesis
  A. Introduction
  B. C,C-Bond-forming reactions
  C. Functional-group interconversions
  D. Some general comments
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1. INTRODUCTION

Electrochemistry is the combination of a heterogeneous electron transfer at an electrode with a chemical reaction. The electron transfer leads to the reactive intermediates: carbocations [1], carbanions [2], radicals [3], and radical ions [4]. The differences in comparison to chemical reactions are due to the way in which these reactive intermediates are generated. In electrochemistry, the electrode transfers the electron; in chemical reactions, chemical reductants or oxidants are used. Furthermore, carbocations, radicals, and carbanions are chemically generated by dissociation, homolysis, or deprotonation. The reaction conditions, the solvents, and the reactants encountered by the electrochemically or chemically formed intermediates can differ substantially and thus can lead to diverse reaction pathways and products.

Electrochemistry is also an esteemed method in organic synthesis [5]. Sometimes, when common synthetic methods fail, electrochemistry is chosen as a last possibility, which often leads to success but also to disappointment due to the high expectancy. To

achieve a more realistic picture the advantages and disadvantages of chemical and electrochemical conversions are compared in Sec. III on synthesis.

Additionally, there are features of organic electrochemistry that cannot be compared with organic chemistry because they are unique to this field and have no counterpart elsewhere in common chemistry. They result from the combination of electron transfer with a chemical reaction. This way reactive intermediates can be generated, which in another way are not or only in a limited extent accessible, such as radical ions. Mechanisms can be studied in otherwise not accessible depth from time-resolved electrical signals of starting materials, products, or intermediates (see Chapter 2) [6].

II. COMPARISON OF ELECTROCHEMICAL REACTIONS WITH CHEMICAL OXIDATIONS AND REDUCTIONS WITH REGARD TO THEIR MECHANISM

A. General Considerations

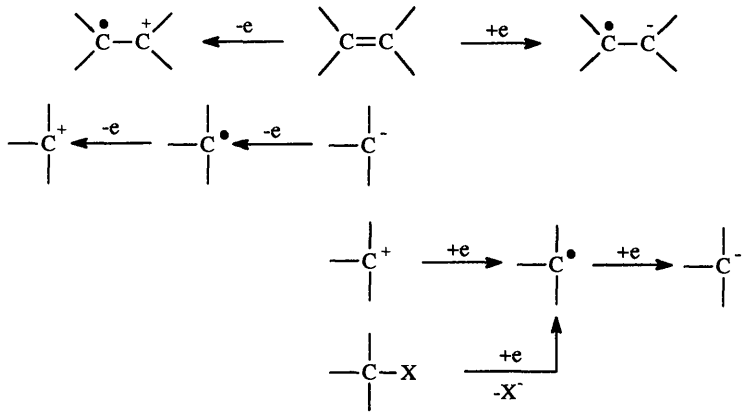
If one looks at a chemical and an electrochemical reaction, general steps can be distinguished:

1. In a chemical reaction the approach of the substrate to the chemical oxidant or reductant by forming covalent or ionic bonds, in electrochemistry the diffusion to and sometimes adsorption at the electrode,
2. In the chemical reaction reductive or oxidative elimination to the product (inner sphere electron transfer) [7] or in electrochemistry generation of the reactive intermediate by electron transfer (outer sphere electron transfer) [7], and follow-up reaction of the intermediate to the product.

In chemical oxidation or reduction the redox reagent and the substrate often form a covalent or ionic bond, for example, an ester in chromic acid oxidation [8], a sulfonium methylide in the Swern oxidation [9], cyclic esters in the *syn* dihydroxylation with OsO_4 [10], or in the selenium dioxide oxidation of ketones and aldehydes [11]. In electrochemical processes the substrate must diffuse from the bulk of the solution to the electrode and compete there with other components of the electrolyte by competitive adsorption for a position at the electrode surface [12]. The next step is then generation of the reactive intermediate by electron transfer at the electrode that reacts with a low activation energy to the products. In chemical oxidations or reductions one finds a reductive or oxidative elimination of the intermediate with a higher activation energy.

The transition states of the latter are therefore more sensitive to stereochemical and electronic influences, which also leads to a higher selectivity than in analogous electrochemical conversions. At some oxide electrodes, such as the $Ni(OH)_2$ electrode [13], the oxidation occurs as inner sphere electron transfer by hydrogen atom transfer. Also at doped titanium anodes this seems to be partially the case [14]. It cannot be definitely excluded that also in some oxidations at platinum anodes, higher valency oxides at the surface act as inner sphere electron transfer agents. "Electrochemical" inner sphere electron transfers are intentionally used in indirect electrochemical conversions where selective chemical oxidants or reductants are regenerated by electron transfer from the electrode [15]. They are also immobilized by attaching polymer-bound electrocatalysts as mediators to the electrode surface [16].

By electron transfer radical ions, anions, cations, and radicals can be generated as reactive intermediates. Radical ions are mostly products of outer sphere electron transfer [Eq. (1)]:



(1)

Carbanions can alternatively be generated by deprotonation [2], carbocations by S_N1 or A_E processes [1], and radicals by homolysis [3].

Distinctions in the follow-up reactions of electrochemical and chemical conversions are due to different concentrations of the reactive intermediates, different reaction media and additives, and the possibility of further oxidation or reduction. In electrochemical reactions the intermediates generated at the electrode surface diffuse into the bulk solution. Owing to their high reactivity, they react in a fairly thin reaction layer that adheres to the electrode and thus their concentration is higher than in homogeneous reactions [17], where they are uniformly spread over the medium. This can influence the product distribution. Radical additions initiated by electron transfer often lead in homogeneous solution to polymers [18], but in electrochemical reactions the termination step of a radical polymerization, that is, the formation of additive monomers and dimers, preponderates [19]. In electrochemical reactions the electrode surface can be depleted of the electroactive substrate at high current densities. This way reactions between the reactive intermediate and the educt can be decreased [20]. The adsorption of supporting electrolyte or other additives can create a special microenvironment in the reaction layer near the electrode that can favor distinct pathways. Thus the use of tetraalkylammonium ions as supporting electrolyte depletes the electrode surface of water and thus favors the hydrodimerization of acrylonitrile [21]. The enrichment of alkaloid salt at the electrode surface promotes an enantioselective reduction of 2-acetylpyridine [22] or of 4-methyl coumarine [23].

The proximity of the electrode to the reaction layer can lead to follow-up oxidations and reductions of intermediate products. These are much less pronounced in homogeneous solution.

Each electron transfer generates a proton or Lewis acid at the anode and a hydroxyl ion or Lewis base at the cathode. This creates strongly acidic or basic media in the reaction layers adhering to the anode or cathode, whereby acid- [24] or base-catalyzed reactions [25] can be induced (see Chapter 30).

These more general considerations are subsequently illustrated by some studies in which data for electrochemical reactions and chemical oxidations and reductions are available.

B. More Detailed Comparisons of Electrochemical Reactions with Chemical Oxidations and Reductions

1. Oxidative Nucleophilic Aromatic Substitution

Eberson has compared the isomer ratios for the acetoxylation of aromatic substrates at the anode with those obtained from different oxidants (Table 1) [26]. The anodic reaction proceeds by an initial electron transfer, thus forming a radical cation, which is then attacked by acetate ion. The homogeneous reactions, which come closest to the results of the anodic oxidation, are the Co(III)$W_{12}O_{40}^{5-}$ and the Ag(II) oxidation. These and also the Ce(IV) oxidant, which still exhibits some similarities in the isomer distribution, have been characterized as electron transfer oxidants, whereas the Pd(II)-catalyzed acetoxylation has been shown to proceed via organopalladium species [27]. The isomer distributions in the latter, where predominantly *meta* orientation is being observed, are drastically different from those of ET-mediated reactions.

Table 1 Isomer Ratios for Oxidative Acetoxylation or Aromatic Hydrocarbons

	Anisole		Naphthalene,	Nuclear/side chain	
Oxidant	o/p	m/p	1-/2-	Mesitylene	*p*-Xylene
Pt anode[a]	2.3	0.12	24	4.4	0.9
Ag(II)[b]	2.2	0.032	19	2.3	—
Co(III)W[c]	1.3	0.1	99	0.41	< 0.01
Ce(IV)[d]	0.82	< 0.01	24	0.7	
Pd(II)[e]	0.5	49	1.3	< 0.01	0.66

[a] In HOAc, 0.5 M NaOAc, 20°C,
[b] In HOAc, 0.5 M NaOAc at 40°C,
[c] Co(III) $W_{12}O_{40}^{5-}$ in HOAc/H_2O (4:1), 0.1 M KOAc at 102°C,
[d] Ce(IV) ammonium nitrate or acetate in HOAc at 20–70°C,
[e] In HOAc at 115°C.

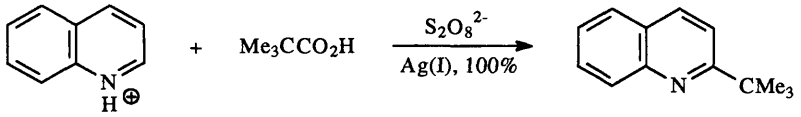
2. The Oxidative Decarboxylation of Carboxylic Acids

Kolbe electrolysis also allows some comparisons with analogous homogeneous reactions with regard to dimerization, substitution, or addition reactions of the generated radicals. Photolytic or thermal decarboxylation of diacylperoxides is a source of alkyl radicals similar to those afforded by the Kolbe electrolysis. The anodic oxidation of propionate has been compared with the thermal decomposition of dipropionyl peroxide [28]. Examination of the yields shows that reaction between radicals is favored in the electrochemical process, whereas in peroxide decomposition hydrogen atom abstraction from the solvent or the substrate occurs to a higher extent. This illustrates the effect of the higher radical concentration at the electrode.

Photolysis at lower temperatures and in the solid state decreases the extent of the hydrogen atom abstraction due to its higher activation energy compared to radical dimerization. Additionally, the lower mobility of the radicals in the solid state increases the cage reaction of the pairwise generated radicals. This way unsymmetrical diacylperoxides form unsymmetrical dimers with less than 1% of the symmetrical product [29]. Peroxides from carboxylic acids, being optically active at the α-carbon, couple photochemically in the solid with only a minor loss of optical activity [30].

In Kolbe electrolysis, coupling of the radicals generated from different carboxylates occurs statistically [31], and the chirality at the α-carbon is totally lost [32,33].

The easy follow-up oxidation of intermediates at the electrode is illustrated by the oxidation of trimethylacetic acid. The decarboxylation of carboxylate by peroxidisulfate/Ag(I) is a good way to simulate the Kolbe anodic oxidation in a homogeneous solution [34]. The oxidation of trimethylacetic acid with $S_2O_8^{2-}$/Ag(I) in the presence of protonated quinoline affords by reaction of the intermediate *t*-butyl radicals in an S_RAr substitution a high yield of *t*-butylated product [Eq. (2)] [35].



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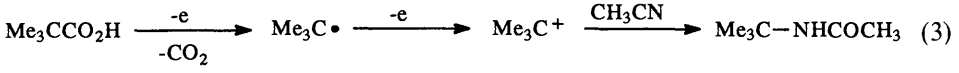
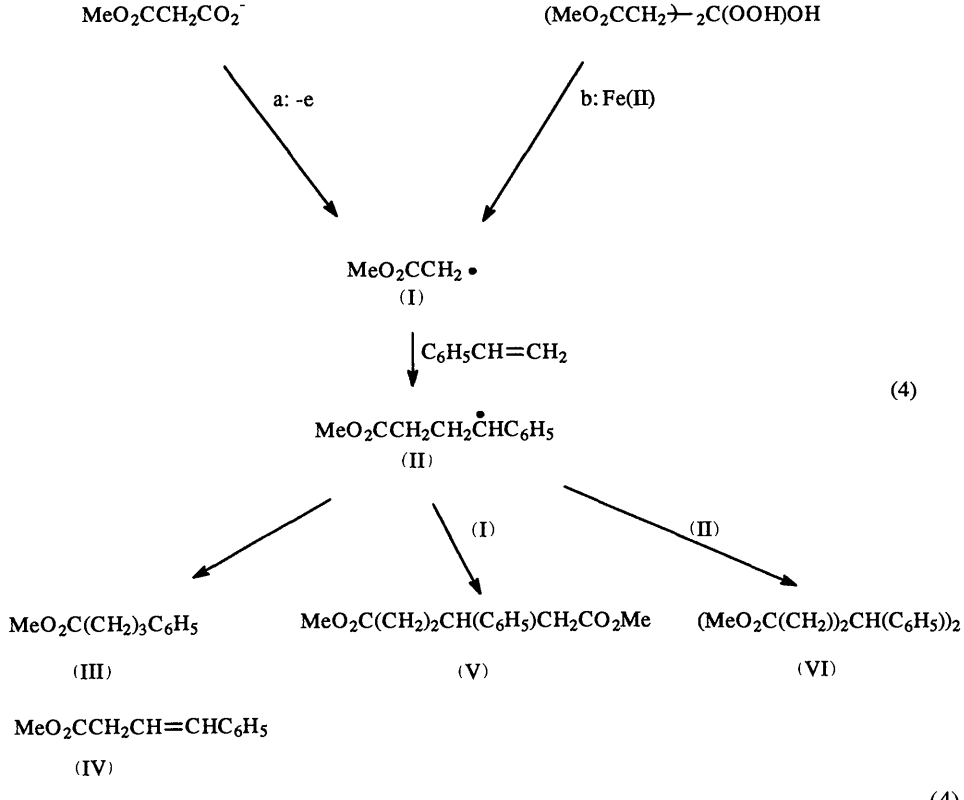


(3)

The anodic oxidation of trimethylacetic acid in acetonitrile, however, leads to *t*-butylacetamide owing to further oxidation of the intermediate *t*-butyl radical to the *t*-butyl cation and its Ritter reaction with MeCN [Eq (3)] [36].

The reaction of styrene with carbomethoxymethyl radicals generated in homogeneous solution and by Kolbe electrolysis has been compared [Eq. (4)] (Table 2) [37]:



(4)

(4)

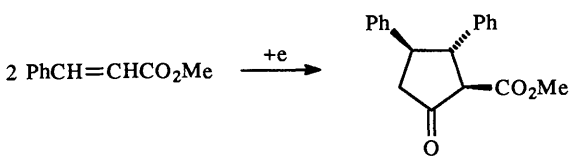
Table 2 Addition of the $MeO_2CCH_2^{\cdot}$ Radical Generated by Kolbe Electrolysis and Homogeneous Chemical Reaction to Styrene

Method [Eq. (4)]	Relative Yields (%)				Total yield (%) of III–VI
	III	IV	V	VI	
a	16.3	15.1	5.7	62.9	43
b	13.0	14.8	1.8	70.4	38.4

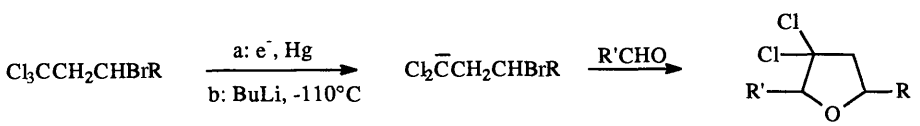
The methoxycarbonylmethyl radical I is obtained by Kolbe electrolysis from methylmalonate [Eq. (4, path a)], and in homogeneous solution by reductive fragmentation of the hydroperoxide of dimethyl acetone dicarboxylate [Eq. (4, path b)]. Radical I forms with styrene the adduct II, which reacts by disproportionation to III and IV, by coupling with I to V and by dimerization to VI. The yields and product ratios for the electrolysis and the reductive fragmentation correspond surprisingly well, and no extensive polymerization was found for the homogeneous reaction.

The Birch reduction of aromatic hydrocarbons or of double bonds with alkali metals in liquid ammonia or amines [37] resembles in yield and selectivity the cathodic reduction with lithium halide as supporting electrolyte (for example, Ref. 38).

In reductive acylation and dimerization, the cathode is often superior to dissolving metal or radical anions reductants. So α, β-unsaturated ketones or esters can be acylated in high yield to 1,4-dicarbonyl compounds at the mercury cathode [39], but the corresponding reaction with sodium in tetrahydrofuran (THF) fails [40]. On the other hand, reductive acylation of double bonds becomes possible in high yield, when vitamin B_{12} is used as mediator [41]. Here cobalt–alkyl complexes play a decisive role as intermediates.



(5)



(6)

In the reductive dimerization of methyl cinnamate to a cyclopentanone [Eq. (5)], similar yields are found at the cathode [42] and with metals (sodium, THF, and TBAI, −78°C) [40]. Because of the potential selective conversion at the electrode, halides can be reduced at the cathode to carbanions in the presence of carbonyl compounds, which are reduced at more cathodic potentials. This way labile carbanions can be obtained and reacted under conditions in which the same species generated by a metalorganic route would decompose. For example, trichlorobromoalkane can be cathodically converted in the presence of aldehydes to a dichloromethyl anion 0°C [route a, Eq. (6)] and be trapped to form a dichlorotetrahydrofuran, but for the metallorganic route [route b, Eq. (6)] a reaction temperature of −110°C is necessary [43].

III. COMPARISON OF ELECTROCHEMICAL REACTIONS WITH CHEMICAL REDUCTIONS AND OXIDATIONS IN SYNTHESIS

A. Introduction

For the synthesis of organic compounds, two types of reaction are used: C,C-bond-forming reactions for the construction of large structures from small units, and functional group interconversion for introduction of the functionality into the target molecule and for activation of the building blocks [44].

B. C,C-Bond-Forming Reactions

The C,C-bond-forming reactions can be classified as *polar reactions*, in which an activated donor reacts selectively with an acceptor or vice versa; *radical reactions*, which are increasingly applied in coupling or addition reactions because they do not interfere with polar groups in the molecule and thus save steps as no protections are needed [43]; *pericyclic reactions*, especially cycloadditions, for the construction of ring compounds with high stereoselectivity [45]; and *transition metal-catalyzed reactions* [46].

The first two reaction types involve reactive intermediates, namely, radical ions, carbocations, carbanions, and radicals, that can be prepared in a broad variety at the electrode. Therefore, the electrode is well suited for these two types of reaction.

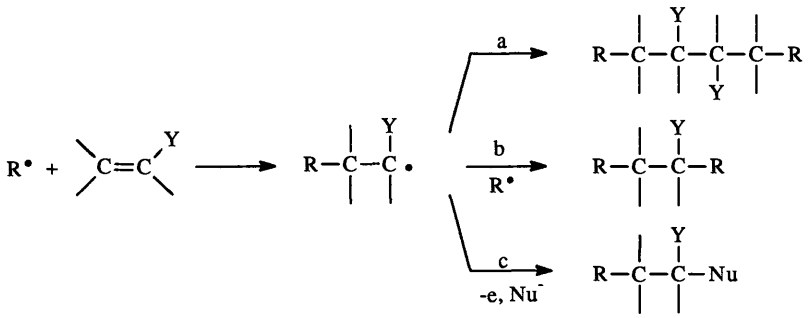
Pericyclic electrochemical reactions are increasingly developed. They involve chain reactions with a radical cation as chain transferring step or the generation of reactive dienophiles (see Chapter 22, Sec. V). Transition metal complexes are increasingly applied in electrochemistry as electrocatalysts for reductive carboxylation [47], acylation or alkylation [41], or activation [51].

Reactive acceptors are anodically available as radical cations in a wide variety by the oxidative "Umpolung" of donors. This way two donors can be coupled in one step, if one of them is converted to an acceptor by electron transfer. Chemically, two or more steps are required for this operation. Thus electrochemistry can save steps in synthesis. Of general synthetic value is the generation of latent immonium ions for electrophilic addition [48] and the oxidative coupling of olefins [49] and Chapter 22. In common chemical synthesis there is, on the other hand, a highly developed experience and a large arsenal of reagents to execute selective S_E and A_E reactions with a wide choice of substrates.

Reactive donors can be generated cathodically by reductive cleavage of halides to carbanions or by the reduction of double bonds to radical anions. By reductive "Umpolung," two acceptors can be dimerized in one step, such as acrylonitrile to adipodinitrile, a reaction that in common chemistry is not possible. Two different acceptors can be selectively coupled either by controlled potential electrolysis (cpe) [39,55] or with cobalt complexes as mediators [41]. On the other hand, highly developed chemical techniques are available to generate activated donors with different functionality and carbon structure by hydrogen-metal, halide-metal, or metal-metal interchange [2]. Furthermore, in these cases low temperatures and inert solvents, necessary to handle reactive and labile carbanions and to achieve high selectivities, can be applied.

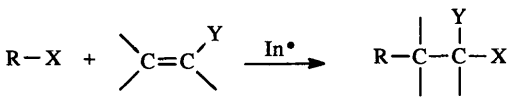
Radicals can be generated at the anode by oxidation of carbanions, alkyl borates, alkoxides, and carboxylates (see Chapter 22, Sec. V) and at the cathode by reduction of protonated carbonyl compounds or onium salts (see Chapter 10). Thereby, a wide choice of different radical structures can be mildly and simply obtained from readily available precursors. These radicals are especially suited for coupling and additive coupling reac-

tions in nonchain processes because these are favored by the high radical concentrations at the electrode. Compared with these possibilities, chemical methods for radical coupling are less general and limited to less easily accessible starting materials, such as azo and peroxy compounds. On the other hand, radical chain reactions with tandem sequences are highly developed in chemical synthesis [3]. The electrogenerated radicals can be trapped by olefins to yield additive dimers and additive monomers. The product distribution can in part be controlled by the current density and olefin concentration [Eq. (7), paths a and b] and by the electrode potential or the substituent Y of the olefin [Eq. (7), path c] (see Chapter 22, Sec. V).



(7)

In common chemistry these types of adducts are not or are much less easily accessible. The products are different from those of a radical chain addition [Eq. (8)] [3]. There, one C,C and one C,H or C,heteroatom bond is formed, while in the electrochemical generation of the radicals two carbon–carbon bonds can be obtained [paths a, b, eq. (7)].



(8)

C. Functional-Group Interconversions

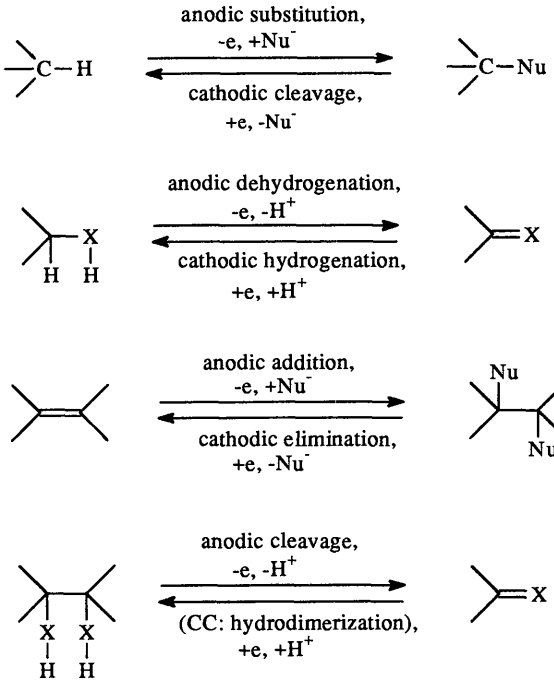
Electrochemical functional-group interconversions can be classified into four groups [Eq. (9)]:

1. Anodic substitution and its cathodic counterpart, cathodic cleavage.
2. Anodic dehydrogenation and cathodic hydrogenation.
3. Anodic addition and cathodic elimination.
4. Anodic cleavage, where the cathodic reversal would be a C,C-bond-forming reaction, such as hydrodimerization.

For the anodic substitution of unactivated CH bonds, some fairly selective reactions for tertiary CH bonds in hydrocarbons and γ–CH bonds in esters or ketones are available [51,52]. However, in some cases a better control of follow-up oxidations remains to be developed. Chemically a number of selective reactions can be used, such as ozone on silica gel for tertiary CH bonds [53], the Barton or Hoffmann-Loeffler-Freytag reaction for γ-CH bonds [54], $(i\text{-prop})_2CNCl/H^+$ [55], fatty acids adsorbed on alumina and chlorine [56], and template-directed oxidations for remote CH bonds [57].

For activated CH bonds a wealth of chemical methods is available, such as singlet oxygen, *N*-bromosuccinimide, $Br_2/h\nu$, $Pb(OAc)_4$, or SeO_2 [58]. Anodically fair yields are obtained for CH bonds activated by a vinyl, phenyl, or alkoxy group, although sometimes

problems of regioselectivity occur [59]. The α-oxidation of *N*-acyl-*N*-alkylamines, which leads to synthetically very interesting precursors of immonium cations [48], has no chemical counterpart.



(9)

For the nucleophilic substitution of aromatic CH bonds, electrochemistry has a clear advantage over chemical conversions. While at the anode, nucleophiles like OR, OCOR, Br, and CN can be introduced simply and in one step [60], chemically multistep procedures are necessary to achieve the same goal.

Carboxylic acids can be regarded as compounds having a CH bond with an inserted CO_2 group. They can be converted by non-Kolbe electrolysis into products in which the CO_2H group is replaced by a nucleophile or a double bond (see Chapter 14) [61]. These conversions can be combined with specific rearrangements or fragmentations [62]. The comparable chemical conversions, such as the Kochi reaction [63] or the Hofmann degradation [64], have more limited applications.

The cathodic cleavage of C–X to C–H bonds can be applied to a variety of substituent X, such as Hal, NR_3^+, PR_3^+, OAc, OCH_3, OTos, $OPO(OEt)_2$, or epoxides. Generally good yields, an often high potential selectivity, and sometimes good stereoselectivities are encountered (see Chapters 8 and 23). Chemical reactions for similar conversions that are well worked out, especially with regard to yield and selectivity, are the reduction of tosylates with $LiAlH_4$ and of halides with Bu_3SnH [65] or radical deoxygenations [66].

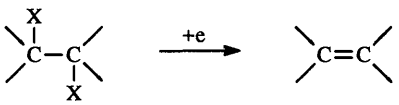
For the dehydrogenation of HC–XH bonds, for example, of alcohols to ketones, aldehydes to carboxylic acids, and amines to nitriles, is there is a wealth of anodic reactions for specific applications available, such as the nickel hydroxide electrode [13], indirect electrolysis [15] with I^-, NO_3^-, or thioanisole [67], RuO_2/Cl^- [68], and chemical oxidations [Cr(VI), MnO_2, MnO_4^-, $DMSO/Ac_2O$, Ag_2O/Celite, and O_2/Pt] [69]. The

advantages of the electrochemical conversion are a lower price, a more easy scale-up, and reduced pollutional problems.

The hydrogenation of C=X and C=C double bonds can be achieved cathodically and with a number of chemical reagents, such as catalytic hydrogenation, metal hydrides, and dissolving metals. Here the best method must be selected for each individual case. The advantages of the electrochemical method are the potential selective conversion at the cathode with e.g. the possibility of reducing carbon-heteroatom double bonds in the presence of C=C bonds, or the *trans*-hydrogenation of C=C bonds via radical anions in contrast to the synchronous *cis*-hydrogenation with catalytic hydrogen.

Anodic addition affords products, some of which are of industrial interest, such as propylene oxide [70], diols, or 1,4-dimethoxyfuran [71]. To improve the selectivity, sometimes mediators like Tl^{3+}, Pd^{2+}, Ce^{4+}, or Ru^{3+} are used (see Chapter 29) [15]. Chemical reagents that serve a similar purpose include MnO_4^-, OsO_4/*N*-methyl morpholinoxide, Hal_2, and peracids [72].

Reductive elimination can remove a variety of vicinal nucleophiles to form double bonds [Eq. (10)]:



(10)

X = Br, OAc, NO_2, CN, —OC(=O)—CO—

At the cathode, a chemoselective elimination depending on the degree of alkylation of the *vic*-dihalide is possible [73]. Chemically these reductions are more limited in scope; they can be conducted with I^- in DMF, with Zn, Mg, or Cr^{2+} [74]. The cleavage of 1,2-diols can be inexpensively achieved at the nickel hydroxide electrode [13], while chemically the more expensive reagents $Pb(OAc)_4$ or IO_4^- must be used.

The conversion of heteroatoms to different oxidation states, for example -S-, -SO-, $-SO_2-$, or NO_2, NHOH, NH_2 is possible at the electrode. Of advantage, especially in the reduction of nitro functions, is the potential selective conversion to certain oxidation states (see Chapters 9, 15–17).

By controlled potential electrolysis protecting, groups can be selectively removed. This makes electrochemical deprotection (see Chapter 23) [75,76] a valuable supplement to chemical deprotection [77]. Additionally, less interference with other functional groups is encountered than in chemical deprotection.

D. Some General Comments

The supposed need for sophisticated equipment is often the reason that electrochemistry is less frequently applied than it could be. However, more than 90% of preparative-scale electrolyses—especially first exploratory experiments—can be conducted with simple and readily available equipment [78]. A beaker with a stirring bar can serve as a reaction vessel. Quite often a diaphragm is unnecessary, as most anodic oxidations can be conducted in an undivided cell. Graphite plates, graphite felt, or a platinum foil fastened to an inert support is used as the anode and a steel or lead plate or a mercury pool as the cathode. The silver/silver chloride reference electrode is prepared by anodically chlorinating a silver wire. The cell voltage is supplied from an ac source, a voltage regulator, and a rectifier, and

the potential between the working and the reference electrode is read from a high-resistance voltmeter. The little knowledge necessary to conduct the electrolysis is easily obtained. The oxidation or reduction potential of the substrate is determined with the equipment just mentioned. The electrolyte is then chosen in such a way that its decomposition potential exceeds that of the oxidation or reduction potential of the substrate. The electrode material is selected so that it does not oxidatively or reductively dissolve at the applied potential. This procedure can be applied with only minor changes to a wide variety of substrates and conversions. In chemical reactions, the selective reagents are frequently applicable to only a limited number of substrates and are mostly considerably more expensive than the electrical current and the simple equipment.

Electrochemical preparations are often easier to conduct than chemical conversions. Solubility problems, which often occur with inorganic redox reagents in organic solvents, are not encountered. On the other hand, the inertness of solvents and the lower attainable temperatures in chemical reactions cannot be achieved to this extent in electrolysis. Polar and thus more reactive solvents are necessary for the electrolytes, and the temperatures for practical reasons cannot be lowered much below $-40°C$ in preparative scale electrolyses.

Workup of electrolyses is often easier as no products of chemical oxidants or reductants must be separated. Additionally, in electrolysis a similar workup can be used for a wide number of applications. Furthermore, the scale-up of electrochemical reactions is often easier to achieve than for chemical conversions.

The selectivity of electrochemical reactions with regard to a potential selective conversion of an electrophore is superior to that of chemical reactions. However, the chemoselectivity, the regioselectivity, and especially the stereoselectivity are often inferior to those of chemical reactions. The reasons are that chemical redox reactions involve inner sphere electron transfers, which by nature are more selective than outer sphere electron transfers at the electrode; lower temperatures are attainable in chemical conversions and a much more profound knowledge of the control of these reactions has been accumulated. With regard to the economy of synthesis, the electrode can be superior to chemical reactions. First, the redox "Umpolung" saves steps because it allows the one-step coupling of two donors or two acceptors. In comparable chemical conversions, two or more steps are necessary for that purpose. Second, at the electrode a synthetic building unit can be used with several reactivities because it can be changed via electron transfer. In chemical preparations, building units are usually designed for only one reactivity.

A great advantage of electrochemical reactions compared with chemical conversions is the effective contribution to pollution control. The direct electron transfer from the electrode to the substrate avoids the problem of separation and waste treatment of the frequently toxic end products of the chemical oxidants or reductants. Furthermore, by electrodialysis, organic acids or bases can be regenerated from their salts without the use of sulfuric acid or sodium hydroxide, for example, which lead to the coproduction of sodium salts or sulfates as waste [79]. At the same time, inorganic acids and bases, necessary for chemical production, are provided by this process. An application of electrodialysis has been demonstrated in the preparation of methoxyacetic acid by oxidation of methoxyethanol at the nickel hydroxide electrode [80]. Finally, unwanted side products can be converted into the wanted product, which increases the economy of the process and reduces the problem of waste separation and treatment. This is accomplished in the manufacture of chloroacetic acid by chlorination of acetic acid. There the side product dichloroacetic acid, formed by overchlorination, is cathodically converted to chloroacetic acid [81].

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5
Practical Problems in Electrolysis

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I. INTRODUCTION

An attractive feature of the electrolytic method is that it has the possibility of controlling the activity of the reagent, the electron, over a wide range. The success or failure of an electrolysis depends to a great degree on the proper selection of experimental conditions. An intelligent choice of these requires an understanding of the principles of controlling the reacation and of the properties of the different components, such as electrolytic cells, electrodes, solvents, and electrolytes, which are part of the electrolytic equipment.

In classic electrolytic reactions the current density, measured in amperes per square decimeter, was the quantity that was controlled, possibly because it was the easiest factor to measure and keep constant. For a long time nearly all electrolytic reactions were performed with control of the current density, although Haber, as early as 1898, in his famous papers on the stepwise reduction of nitro compounds, realized that the potential of the working electrode was the proper quantity to control.

The differences in the two ways of controlling the electrolytic reaction are illustrated in Fig. 1. In this figure, curve I depicts schematically the connection between the current through the cell and the potential of the working electrode. The initial solution contains two reducible compounds or one compound with two groups reducible at different potentials. When the potential at the cathode is between 0 and E_A, no electron transfer across the electrical double layer can take place and thus no current runs through the cell. If the cathode potential is made more negative, the electron transfer becomes possible; that is, the reduction of the most easily reducible compound or group starts. Between E_A and E_B the current rises in dependence on the potential, but when the value E_B has been reached, all the molecules that arrive at the electrode and that can undergo the first reduction are reduced as soon as they reach the electrode. In the potential interval E_B to E_C the current is limited by the transport of the reducible compound to the cathode. This current is called the limiting current i_d, and under fixed conditions it is proportional to the concentration of the electroactive compound.

A further change of the electrode potential in the negative direction results in the occurrence of the second electrode reaction and the current rises; a similar S-shaped curve results from this reduction. At more negative potentials a third-reacation or a reduction of the medium takes place.

If a suitable current i_o [$i_o < id(I)$] is sent through the cell, the cathode potential assumes the value $E_o(I)$, and when $i_o < i_d(I)$ this is well below the potential (E_C) at which the second electrode reaction starts; a selective reduction thus occurs at the beginning of the electrolysis. During the electrolysis the concentration of the reducible compound, and thus its limiting current, diminishes and after a while (curve II) the limiting

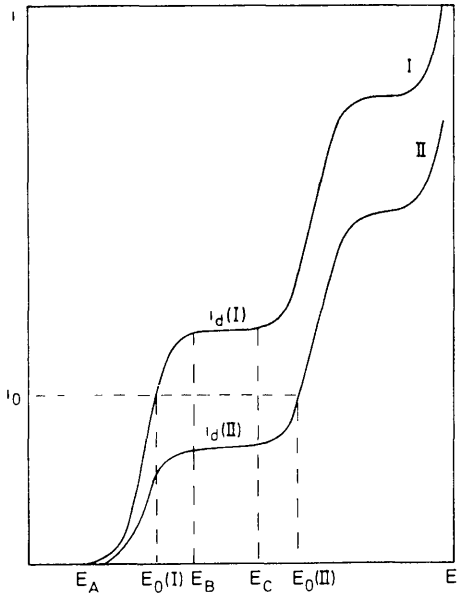

Figure 1. Schematic representation of the connection between the current and the potential of the working electrode in a solution containing a compound with two groups reducible at different potentials. Curve I, before electrolysis; curve II, after the passage of some current; I_0 is an applied current, E_0(I) and E_0(II) the potentials corresponding to i_0; i_d is the limiting current, and E_A, E_B, and E_C are applied potentials.

current becomes smaller than the applied current [$i_o > i_d$ (II)]. The cathode potential has then, by necessity, reached the value E_o(II), and at this potential the second electrode reaction also takes place; the electrolysis is no longer selective. However, if a current density reasonably low in relation to the concentration of the electroactive compound is used, the potential will remain constant for a large part of the electrolysis and the electrolysis is selective during that part of the reaction.

If the second electrode process does not interfere with the first (e.g., it may be due to the background), the method may still be acceptable in the laboratory (e.g., anodic methoxylation or an electrolytic reduction with simultaneous hydrogen evolution). For industrial processes, however, a high *current yield* (or current efficiency) is generally desirable and waste of current on the background is less tolerable. The current yield is the theoretical amount of electricity divided by the amount actually employed for the production of a particular substance (usually expressed as a percentage).

On the other hand, when the electrode potential is the controlled factor and is kept at a suitable value, such as E_B, the second electrode process cannot take place, and the reduction remains selective to the end. The current through the cell is never higher than the limiting current corresponding to the first electrode reaction. This means that the current decreases during the reduction and becomes very small toward the end of the reaction, as the limiting current is proportional to the concentration of the electroactive material.

Another way of keeping the potential constant is to maintain a certain concentration of the reducible compound, e.g., corresponding to the limiting current i_d (I) in Fig. 1. By

continuously adding substrate and removing product and by keeping the current at a constant value smaller than i_d (I), for example, I_0, the potential stays at E_0 (I) and the reaction remains selective. This way is preferred in large-scale electrolysis.

In some reactions the required potential lies outside the decomposition potential of the medium and a certain current density is necessary to force the potential to acquire that value; a competition between transfer of electrons to the substrate and to the electrolytic medium takes place. The outcome of this competition, the current yield, depends on such factors as electrode material, current density, specific adsorption, and concentrations of the reacting species.

If the current yield is of minor importance and no further oxidation or reduction than desired occurs (except reactions of the supporting electrolyte), constant current electrolysis is simpler to use than constant potential electrolysis, which is desirable especially for an introductory investigation.

A different way of making electrolytic reduction is through electrocatalytic hydrogenation, which is a kind of indirect electrolysis. Protons are reduced and the key intermediate is Me(H) (with Me being platinum, palladium, rhodium, or nickel), and the potential determining step is the formation of this reactive intermediate. Selective reductions may be performed by this method, and the potential used for the formation of Me(H) is often less negative than that required for the direct electron transfer to the reducible substrate. Hence, electrolysis occurs with a lower energy consumption. The selectivity of the reaction may depend on the support for the catalyst.

The information found in Chapters 1–3 and the considerations presented here can be translated into practical solutions of the problems of electrolysis in many ways, some of which are discussed in the next sections. Although the emphasis in this chapter is on laboratory-scale electrolyses and in Chapter 31 on industrial-scale work, it is clear that many of the factors that enter into consideration of cell design and choice of electrode, for example, are common to both.

II. CELLS FOR ELECTROLYSIS

A. General Considerations

Most of the industrial cells discussed in Chapter 31 have been developed from laboratory prototypes mentioned in this chapter. Polarographic cells and other cells for electroanalytical purposes discussed in different monographs [1,2] have been omitted; however, some electron spin and some electroanalytical cells can be found in Chapter 2. The problems connected with the scale-up of organic electrode processes and electrochemical engineering have been treated [3–5] and are discussed in Chapter 31. Fuel cells have also been omitted here; they are discussed in a special issue of Electrochimica Acta (nr 24, 1998).

A number of problems must be considered when designing a cell for electrolysis, such as potential distribution at the working electrode, position of the reference electrode, ohmic resistance in the circuit, mass and heat transfer, the need for a diaphragm, and the necessity of working in a closed system.

1. Potential Distribution

It is desirable that the potential gradient be the same all over the electrode surface so that a uniform current density distribution is obtained, provided the substrate (or depolarizer) concentration is equal at different parts of the electrode. (Depolarizer was the name given

by Heyrovsky for the substance that receives or gives away electrons at the electrode surface.) This can be achieved in two ways, by employing concentric, cylindrical electrodes or planar, parallel electrodes of equal size. Generally, only the electrode areas facing each other carry the current, so in the former arrangement only one side of the electrode is effective, whereas in the latter arrangement the working electrode may be placed between two auxiliary electrodes; this is of interest when the working electrode is of an expensive material whereas the auxiliary electrodes may be of cheaper material, as in the Kolbe reaction.

Mercury electrodes present special problems. It is more difficult to make electrodes of the required symmetry, and the inequalities in the distance to the anode introduced by stirring the mercury surface result in differences in the potential gradient along the electrode surface and uneven depolarization (see later). Amalgamated electrodes may be used in many cases instead of mercury.

Sometimes, especially in laboratory cells that carry only a small current, the required symmetry of the cell is overruled by other considerations, such as convenience of operation, as in the H cells (discussed later).

The use of small alternating voltage on a dc current, which has been claimed [6] to enhance the reaction rate and selectivity in some cases, does not require special considerations in the construction of the cell.

2. Position of Reference Electrode

Theoretical considerations and actual measurements of the working electrode potential under working conditions show that a uniform potential distribution is possible only with concentric electrodes of the same area [7, 8]. There is thus a limitation to how exactly the potential indicated by the potentiostat reflects the working potential at different parts of the electrode. In actual practice, a controlled potential electrolysis (CPE) is carried out in a small potential range around some average value. In the author's experience, a selective electrolysis requires a separation of 0.15–0.2 V in $E_{1/2}$ between the two reactions.

Special problems are found for mercury electrodes, especially in the widely employed H cells; the part of the electrode near the diaphragm has a higher current density than the rest of the electrode, and the stirring of the mercury introduces changes in the distance between the tip of the reference electrode and the working electrode, which affects the measured reference potential.

3. Ohmic Resistance

A low ohmic resistance of the cell is desired from several points of view; this may be achieved by having a small distance between anode and cathode, a large electrode surface, a compact cell, and a low-resistance diaphragm. A distance between anode and cathode as small as 0.1–0.2 mm has been reported [9], although usually larger distances are employed. A large electrode area may involve the use of many electrodes; a further development in this direction is the "fluidized bed" electrode (Chapter 31).

For laboratory experiments *electroosmosis* may be a problem, especially when working in nonaqueous solvents of high resistance. The resulting pumping through the diaphragm, most often from anode to cathode compartment, depends above all on the cell voltage [10,11] and thus on the resistance. In practice, it is not easy to predict when and how much pumping will take place.

4. Diaphragm

Since the electrode reaction or its products at the auxiliary electrode may interfere with the desired product or the electrode reaction of the working electrode, it is very often necessary, especially in reductions, to separate the cell into anode and cathode compartments by some kind of diaphragm that allows the current to pass but suppresses mixing of anolyte and catholyte. Cells of this kind are called *divided cells*.

The design of the cell is simpler and the ohmic resistance is lower in an undivided cell, and diaphragms should be used only when unavoidable. In some cases the mixing of the catholyte and anolyte may be lowered sufficiently simply by pressing a porous material, such as porous plastics, against the counterelectrode and thereby dampening convection mass transfer [12].

A review has been published on the application of ion-exchange membranes as separators in electrolytic reactions [13] and on bipolar ion-exchange membranes for the production of acids and bases from neutral salts [13,14].

The use of a "quasi-divided cell" with a working electrode much larger than the auxiliary electrode may in some cases make a diaphragm less necessary; the much higher current density at the auxiliary electrode than at the working electrode forces the major electrode reaction to be a reduction (oxidation) of the solvent rather than of the substrate [15]; in aprotic media the use of a diaphragm may be avoided by employing a sacrificial counterelectrode.

5. Mass Transfer

For small cells, stirring, either mechanical or magnetic, may be sufficient to obtain a reasonable mass transfer. Pumping the substrate between the electrodes is a procedure suitable for large-scale electrolysis, as it allows a favorable position of the electrodes and the use of high current densities. Besides stirring and pumping, mass transfer may be enhanced by ultrasound and by an applied magnetic field.

The effect of ultrasound is ascribed to promotion of cavitation, which is the rapid generation and collapse of microbubbles within the medium; this cavitational collapse results in dramatic pressure and thermal differentials on a microscopic scale, which accelerate mass transport and enhance energy transfer [16]. The enhanced mass transport has also been used to increase the sensitivity of voltammetric analysis [17]. Besides the enhanced mass transport, heating and interfacial cleaning due to the asymmetric collapse of the bubbles at the solid/liquid interface may influence electrolysis.

Ultrasound may influence the outcome of competing reactions; thus, for example, on electrolyzing cyclohexanecarboxylate at a platinum electrode in methanol, a switch from one-electron "Kolbe products" to two-electron "non-Kolbe products" was observed. Reviews of the use of ultrasound in electrochemistry have recently appeared [18].

It has been found [19,20] that applying a magnetic field during an electrolysis enhances the limiting current; this is generally interpreted as a consequence of the magnetohydrodynamic effect. The enhancement factor of the limiting current in an unstirred solution may be 2–3 for a magnetic field of 8000 G. The stationary limiting diffusion current on a steady electrode has been found to vary with $B^{1/3}C^{4/3}$ where C is the concentration of the electroactive species and B is the magnetic field intensity [21]. It has been reported that during the anodic oxidation of phenylacetic acid the yield of benzaldehyde increased about 40% in the presence of a magnetic field [20].

At ultramicroelectrodes at high substrate concentrations and relatively low concentration of supporting electrolyte, an enhancement of the limiting current is observed when

the magnetic field is parallel to the electrode surface. The enhancement, which seems not to be a magnetohydrodynamic effect, is roughly proportional to the strength of the magnetic field; when the field is perpendicular to the surface, a slight decrease in the limiting current is observed [22].

It has been claimed [23] that ketoacids may be reduced in dilute acetic acid buffer (pH 3.8) under the influence of a magnetic field (>300 Oe) perpendicular to the Hg electrode to the hydroxyacids with a significant excess of one of the enantiometers. However, later attempts to reproduce the results have failed [24–26].

Special forms of mass transfer operate at the wicking electrode [27] and with foaming electrolytes [28]. In the former, that some substrates "creep" on the electrode surface is exploited to transport the substrate to the working electrode. The latter may be useful when electrolyzing gaseous substrates. If a gas evolution process occurs at the working electrode, this gives very efficient stirring. Stirring by gas bubbles may also be achieved with porous electrodes and a gaseous depolarizer in excess.

6. Heat Transfer

For removal of the heat generated during electrolysis, the cell may be surrounded by a cooling bath or provided with a water jacket and/or internal cooling spiral; this also permits electrolysis at constant temperature. In larger cells with metallic electrodes, the electrodes can be made hollow to allow for a direct water cooling of the electrode itself. However, it is often more advisable to pump the electrolyte through an external heat-exchanger system, thus making a flow cell.

7. Closed System

It is simplest to use an open cell, but often it is necessary to apply a closed system—either because oxygen or water must be excluded or high pressure is necessary, or because the reaction involves poisonous reactants.

Often oxygen can be removed to a sufficient degree by bubbling an inert gas through the solution, but when working in systems in which even traces of oxygen must be avoided, all manipulations of substances must occur on a vacuum line and the cell constructed to meet this requirement.

8. Space–Time Yield

The space–time yield is defined as the amount of desired product divided by time and cell volume, and it is important for the economy of a process (Chapter 31). For laboratory cells, space–time yields as such are of minor importance, but if a cell is designed for a process in which commercialization is a possibility, one might just as well have the conception in mind from the beginning, and it is advisable early in such an investigation to use experimental conditions akin to those to be used industrially. The passage of the current through the cell is always associated with two simultaneous electrode processes: an oxidation at the anode and a reduction at the cathode. From an economic point of view, it is of course desirable that both processes be engaged in the preparation of useful products. This is, however, difficult to realize with purely organic systems.

The actual design depends on the type and number of electrodes and operational principle and scale, and on the actual process. Once the relevant parameters of the electrode reactions are known, it is often possible to use a simpler cell with only two electrodes and a minimum of additional facilities for that special reaction. For exploratory work,

however, it is more desirable to have a very flexible construction with many additional facilities so that a broad range of experiments can be carried out in the same cell.

It may often be advisable (for cathodic processes especially) to have in the cell the possibility of including an indicator electrode and a pH control system.

In the following, some representative examples have been selected for more detailed discussion. Supplementary hints may be found in books by Allen [29], Weinberg [30], Beck [31], and Pletcher [3]. A comparison has been made between the performance of some types of cells in a selected reaction (oxidation of organic anions) [32].

The presentation of the cells has been organized according to the following criteria: two- or three-dimensional electrodes, batch or continuous operation, and absence or presence of a diaphragm.

B. Cells with Two-Dimensional Electrodes

In "classic" preparative electrochemistry and in most research work, two-dimensional electrodes have been used, partly because it is simpler to control the different parameters at such electrodes and partly because time–space yield is not a deciding factor for laboratory cells.

1. Batch Cells

a. Undivided Cells. A simple piece of equipment for the performance of a simple electrolysis may consist of a beaker to contain a conducting solution of the substrate and two working electrodes connected to some dc source. The vessel is usually made of some rigid indifferent material, such as glass, but the inner wall of the container can also be made of a conducting material to serve as one of the electrodes. An undivided cell may be used when the products from the electrode reactions do not react with the other electrode or the other products. The classic Kolbe electrosynthesis is an example of a reaction that goes well in such an extremely simple "beaker cell." In aprotic media a sacrificial counterelectrode or a hydrogen gas diffusion electrode may eliminate the need for a diaphragm.

Solid electrodes may be used in the form of wires, rods, sheets, bars, plates, or gauze, or a liquid, such as mercury, may be placed at the bottom of the container; electrode materials are treated in Sec. IV. The distance between the electrodes should be kept as small as possible to minimize the ohmic resistance of the cell and thus the heat generated during the passage of the current. To get a larger working area, several electrodes [33] may be connected in parallel in the same manner as in a conventional storage batter, thus comprising a "tank cell." In cases (e.g., Kolbe electrolyses) in which a film may be formed on the electrode surface during the electrolysis, both electrodes may preferably be made of platinum and the surface cleaned by occasionally changing the direction of the current [34] or using pulse techniques [35,36].

In more elaborate electrolytic experiments it is often desirable to use a closed cell [37] with accessories for working under an inert atmosphere, or in vacuum [38], at elevated pressure, with reflux, or to allow the identification of gaseous products; a stirrer and a thermometer are also conveniently added. For the performance of controlled potential electrolyses with external control of the working electrode potential by a potentiostat, it is necessary to include a reference electrode, which should then be placed as near the working electrode surface [39] as possible. However, reference electrodes are not so much used in undivided cells, and it must be stressed that CPE may be realized without the use of a

three-electrode system and a potentiostat by having a sufficiently high concentration of the electroactive substance during electrolysis at constant current with partial conversion or by adding another redox system to transfer the electrons to or from the compound under investigation (see Chapter 29). Various kinds of reference electrodes are treated in a separate section.

An overview of dynamic and the stady state analysis for design and modeling of the continuously stirred tank electrochemical reactor has been published [40].

Electrolytic fluorination of organic compounds is usually done in undivided cells with several alternating cathodes and anodes; the corrosive nature of the HF medium presents special technological problems.

b. Divided Cells. H cells. In principle an H cell consists of two containers placed beside each other and connected through a diaphragm; the actual design depends on the types of electrodes and diaphragms used. The prototype for cells with mercury electrodes is the well-known Lingane cell [41] developed for use with a three-electrode system and later modified by Pasternak [42]. Figure 2 shows a modification that is easily constructed from common glassware by a skilled glassworker and has been used for several years in the author's laboratory [43,44]. It may also be used with a solid working electrode; for nonaqueous work the working electrode compartment may be closed and provided with standard joints. An indicator electrode or a device for measuring the optical properties of the solution [45,46] may be included to monitor the concentration of the substrate, intermediates and/or products. A good description of an all-glass disconnectable H cell construction has been given by Peltier and coworkers [47]. Glass H cells are available commercially, e.g., from Techno-Sigma Co, Ltd.

H cells with solid plane parallel electrodes of the same area have been used rather often for work in anhydrous media. They give a uniform current distribution. An example of one such cell with a reference electrode is shown in Fig. 3 [48]. It has a small distance between the electrodes, which is suitable for work in media of low electrical conductivity.

In an H cell for electrolysis in liquid ammonia, a connection between the anode and cathode chamber above the level of the solution is necessary to equilibrate the pressure in the system [49].

Cylindrical Cells. From the preceding discussion it should be clear that it is difficult to realize a preparative cell with a strictly uniform current and potential distribution,

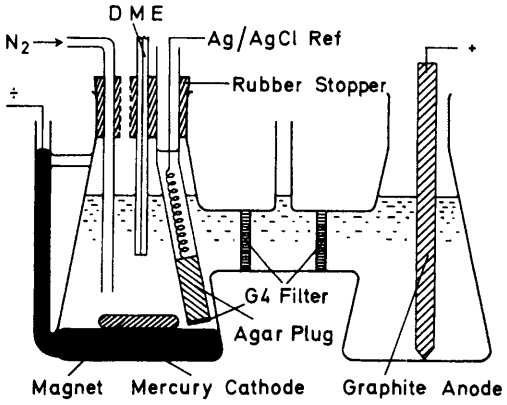

Figure 2. Semimacroscale electrolytic cell. (From Ref. 44.)

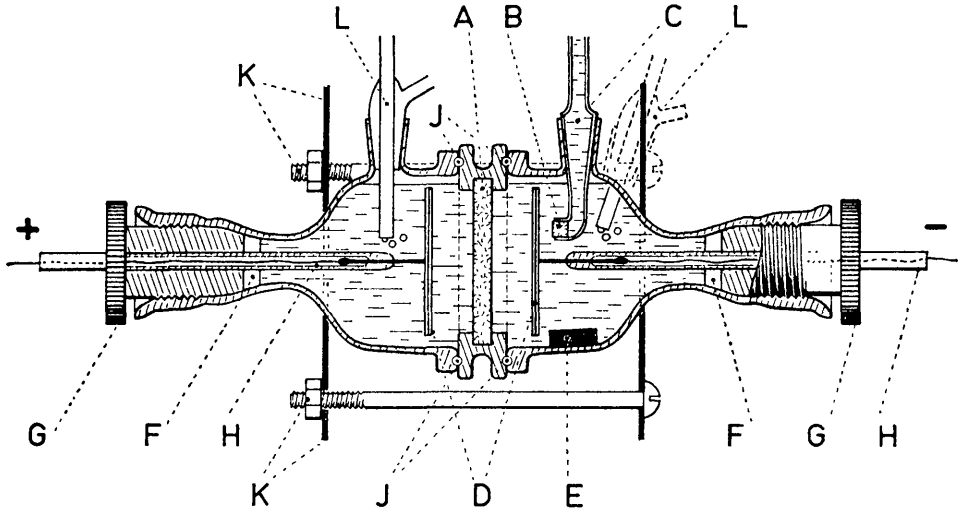

Figure 3. Electrolysis cell. A, B, fritted glass disks; C, electrolytic junction between solution and reference electrode; D, platinum grid; E, magnetic stirrer (in Teflon); F, Teflon gasket; G, Torion stopper, H, glass tube; J, ground glass surfaces; K, locking screw; L, bubbler. (From Ref. 48.)

especially with a mercury electrode with which the condition of parallel electrode surfaces of same area is not easily fulfilled. A good approach has been given by Moinet and Peltier [8], and a schematic representation of the construction is shown in Fig. 4. Special attention has been paid to the problem of renewing the mercury electrode surface with minimal variation in the distance to the reference electrode. This has been done by stirring at moderate speed with a magnetic mounted on a Teflon cross turning on a short axis centered at the bottom of the vessel. Good thermal stability is secured by a cooling coil through the anode compartment connected in series with the outer bath. The cells have been proved to work satisfactorily with currents up to 3 A in a well-conducting aqueous medium. A cell for preparative electrolyses on a 0.1–1 mol scale with anolyte flow has been described [50].

To increase mass transfer the solution is generally stirred; alternatively, the working electrode may be rotated [51,52] or vibrated [9]. Rotation works well for laboratory cells but is less suited for industrial cells.

c. Flow Cells. In principle a batch cell can easily be changed to a cell with flow operation simply by adding an external loop with a pump to recirculate the electrolyte. Such a loop also enables the cell to work with a larger reservoir of electrolyte and substrate. An external heat exchanger can also conveniently be included. However, this does not change the basic concept of the cell; only the batch size may be increased.

A cell for continuous flow operation must be designed with a high electrode surface-electrolyte volume ratio, provided with a feeding system, and, last but not least, connected with suitable auxiliary equipment for continuous removal of the product(s) of electrolysis and reestablishment of the electrolyte composition. The continuous workup procedure during electrolysis is somewhat inconvenient in the laboratory, and consequently small continuous flow cells have mostly been operated with recycling to a reservoir before scaling up. Large cells and their industrial applications are discussed in Chapter 31.

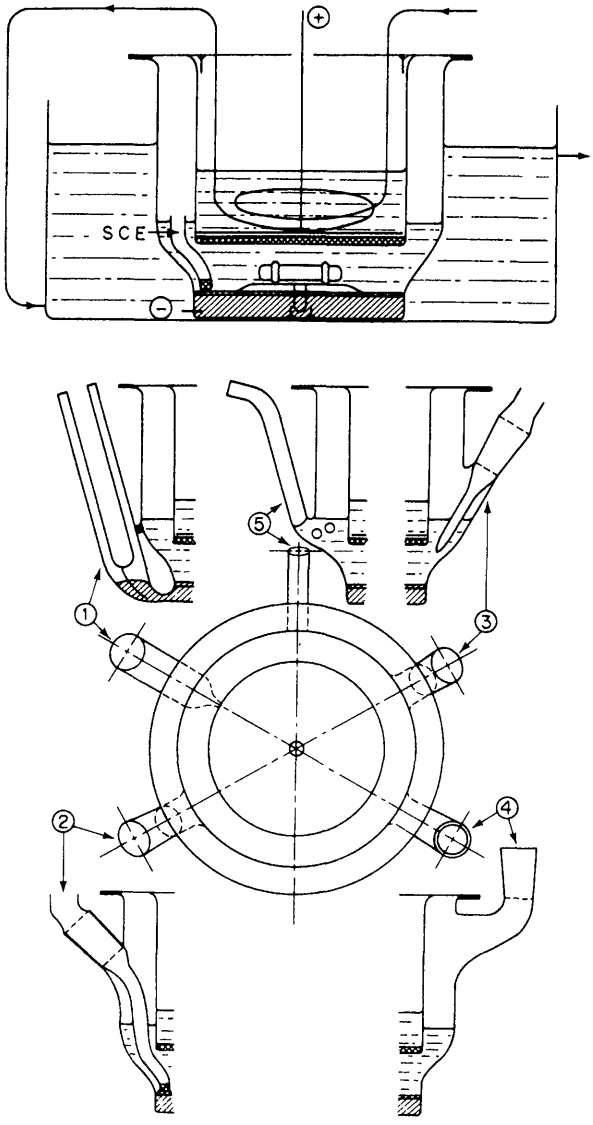

Figure 4. 1, Cathode connection; 2, SCE reference electrode; 3, thermometer; 4, available, for example, for reflux condenser; 5, gas inlet. (From Ref. 8.)

Undivided Flow Cells. A simple cell for large-scale laboratory electrolysis of organic compounds is shown in Fig. 5, and this concentric capillary gap cell has been used for many anodic reactions [53].

The cathode (A) is a 2-mm-thick stainless-steel tube 300–500 mm long with inner diameter 44 mm. The anode is a cylindrical graphite rod 40 or 43 mm in diameter; the distance between cathode and anode is thus 0.5 or 2 mm. The solution is pumped in at C_2 and leaves the cell at C_1

A somewhat similar cell design has been used in the equipment for electrolytic reductions in liquid ammonia for both static and circulating media; in this case the center electrode is a sacrificial magnesium anode [54].

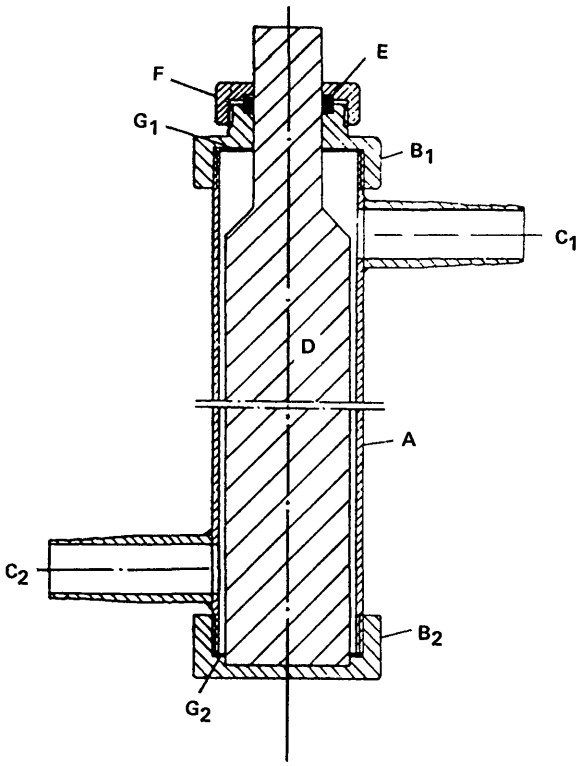

Figure 5. Cross section of concentric capillary gap cell. A, cathode; B_1 and B_2, anode support; C_1, outlet; C_2, inlet; D, anode; E, silicon rubber seal. (From Ref. 53.)

Divided Flow Cells. Filter press (plate and frame) (Fig. 6) cells may be used with and without diaphragm: this type of cell is treated in Chapter 31. Filter press cells for laboratory-scale work are now available commercially. It might be pointed out that when commercializing a process is a possibility, it might save time to switch early to a cell type akin to those usually employed in large-scale operations.

The various configurations for a reference electrode in such a parallel plate cell have been analyzed; a convenient way is to place the reference electrode in the feed line and compensate for ohmic potential drop [55].

The importance of high rates of mass transport for a clean and efficient electrosynthesis using a filter press reactor has been stressed, and the effect of inclusion of a platic mesh turbulence promoter considered [56]. A multipurpose filterpress cell for continuous electrolysis of organic compounds has been described [57], and a mathematical model of the startup of a continuous parallel-plate reactor has been published [58].

The possibility of studying the hydrodynamic of a filter press laboratory cell by impedance spectroscopy and, together with voltammetry, the kinetics of an electrochemical system has been explored [59].

Laboratory and industrial parallel plate cells (filterpress cells) are commercially available from ICI [60], Electrocell AB/Electrosynthesis [61], Reilly Tar and Chemical [62], and Electricity Company [63].

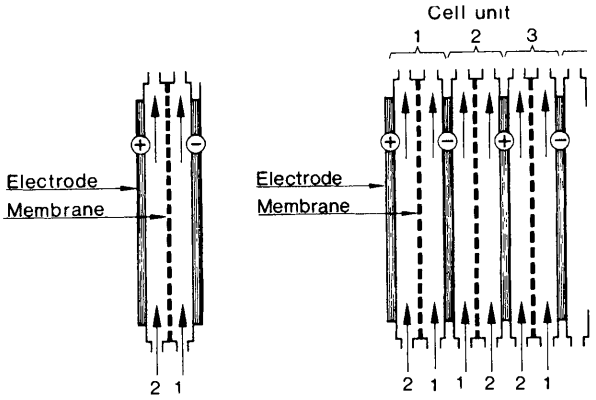

Figure 6. Filter press (plate and frame) cell: 1, catholyte; 2, anolyte.

d. Cells With Porous Electrodes. Porous electrodes have certain advantages and disadvantages. An advantage is that a single flow through the electrode may be sufficient to reduce the substrate completely; a disadvantage is that a control of the effective potential is difficult. Cells with porous electrodes may be used with or without a diaphragm [64–67]. In Fig. 7 is shown a cell that may be used with one, two, or three electrical circuits; it has been used for the preparation of nitroso compounds by reduction of nitro compounds to phenylhydroxylamines and oxidation of the latter. To balance the different requirements for the cathodic and anodic reactions, one or two extra electrical circuits were employed.

A special kind of porous electrodes is gas diffusion electrodes which mostly have been used in fuel cells. A gas diffusion anode for hydrogen [68–73] may consist of three layers: a metal current collector, a hydrophobic gas-porous layer, and a catalyst layer. The hydrophobic layer is often based on polytetrafluorethylene, which is made electric con-

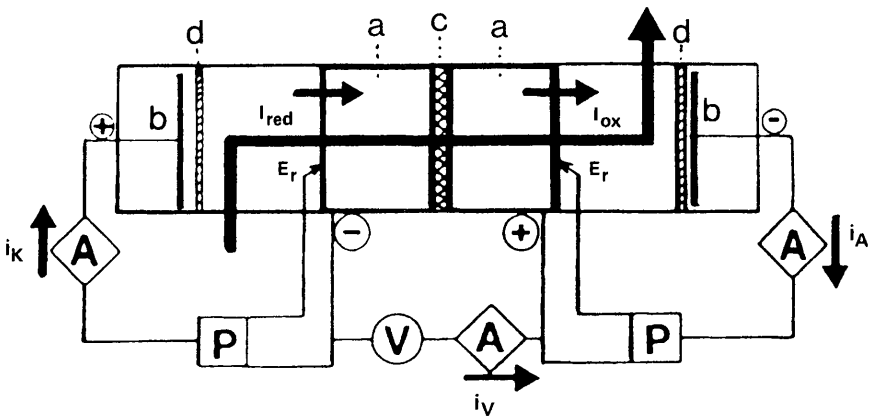

Figure 7. Schematic diagram of the cell and current distribution with one ($i_K = i_A = 0$), two ($i_K \neq 0$ and $i_A = 0$), or three ($i_K \neq 0$ and $i_A \neq 0$) electrical circuits. A, ammeter; P, potentiostat; V, power supply; a, porous working electrode; b, auxiliary counterelectrode; c, porous insulator; d, fritted glass separator; E_R, reference electrode, →, electrode flow circuit. $i_{red} = i_k + i_v$; $i_{ox} = i_A + i_v$. (Reprinted from Ref. 67 by permission of Chapman and Hall.)

ductive, e.g., with acetylene black. The three layers can be prepared separately and then pressed together. The pressure used is critical. The gas diffuses through the porous backing into the catalyst layer, where the electrolyte is present and the electrochemical reaction takes place. An example of the construction of a gas diffusion anode and a cell equipped with one is shown in Fig. 8 [70].

Gas diffusion electrodes have not been used much in organic electrochemistry, but using hydrogen in a gas diffusion electrode as the anode may have several advantages, such as low anode potential for the anode reaction (oxidation of hydrogen to protons) and the elimination of the need of addition of acids for supplying protons for the reduction of an organic compound by the formation of protons in the anode reaction; furthermore, oxygen evolution at the anode is avoided and gaseous by-products may escape through the gas diffusion electrode. In the reduction of 3-hydroxybenzoic acid to the alcohol using a lead cathode and a gas diffusion anode, the cell voltage was about 40% less for this undivided cell compared to the traditional divided cell [71].

A reaction in which two gas diffusion electrodes were employed is the simultaneous reduction of carbon dioxide and nitrate with various metal catalysts at the gas diffusion and a hydrogen diffusion electrode as anode [72].

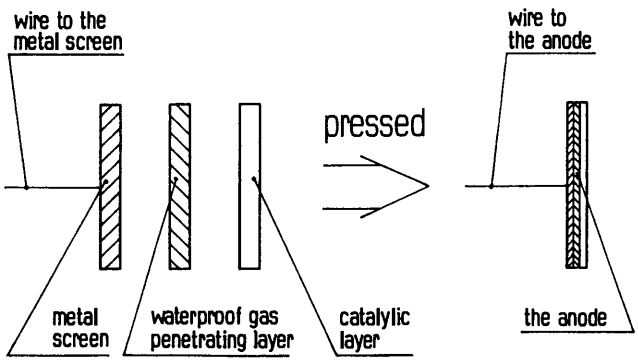

Figure 8a. Construction of a gas diffusion electrode. (Reprinted from Ref. 70 by permission of Chapman and Hall.)

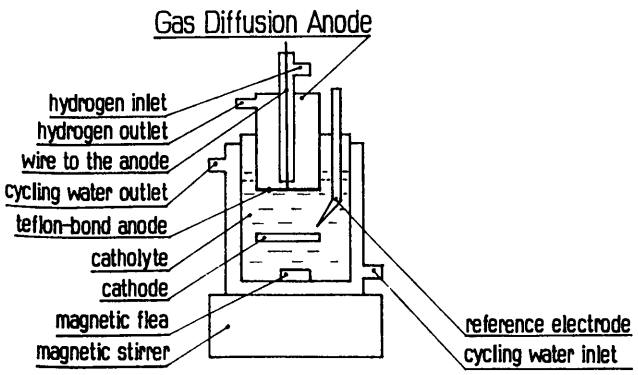

Figure 8b. Cell with a gas diffusion electrode as anode.

e. SPE Cells. Solid polymer electrolytes (SPE) may be used in organic electrosynthesis [9,74–78]. The electrode material, usually platinum or gold, may be deposited on one or both sides of a membrane [74], such as Nafion, or a metal grid is pressed against the membrane [75], The deposited metal may be modified by deposition of other metals to increase the hydrogen overvoltage, for example [76].

An advantage of the use of SPE is that no supporting electrolyte is required, so reduction can be made in other solvents than are usually employed, and one of the electrodes may even be in contact with gas phase rather than with a solvent [78].

A cell using solid polymer electrolyte (SPE) is depicted in Ref. 79.

C. Cells with Three-Dimensional Electrodes

Cells with three-dimensional electrodes have bipolar electrodes; such electrodes are characterized by the feature that one part of the electrode is anode and another part cathode. This can be realized in different ways, such as the pile capillary gap cell (Beck/Guthke cell, Chapter 32) [9,80], the "Swiss roll cell" [81], and packed- and fluidized-bell cells (Chapter 32) [82–84]. These cells are developed to meet economic demands, such as high space–time yield and simplicity in construction; they are discussed in Chapter 31.

D. Special-Purpose Cells

A number of cells described in the literature are not aimed primarily at preparative electrolysis, but as means of generating intermediates to be investigated by some physical-chemical method, generally some sort of spectroscopy; such cells are not discussed here.

For certain purposes, electrolysis of thin layers is advantageous; a cell with a well-defined thin layer and a uniform potential distribution has been described [85]. Cells for electrochemistry at very low temperatures have been constructed [86].

Optically transparent electrodes (OTE) have been used for many kinds of spectroelectrochemical investigations; several aspects of this type of research have been covered in reviews [87].

Cells for electroanalysis in supercritical and near-supercritical liquids have been described [88,89], including one in which the pressure can be varied independently of the temperature [90].

A cell for sonoelectrochemistry with a variable distance between the electrode and the ultrasonic horn has been published [91].

III. DIAPHRAGM MATERIALS

A. General Considerations

Although an undivided cell is favored from an economical point of view, it is often necessary to separate the anode chamber from the cathode compartment by some kind of diaphragm. The ideal material should be an electric insulator chemically inert to and preventing the interdiffusion of the anolyte and catholyte components while presenting only a little resistance to the electric current. For practical reasons, the material should also possess reasonable mechanical strength and good dimensional stability. No real material can fulfill all of these demands simultaneously, and it is generally necessary by

trial and error to find a suitable compromise with which the deviations from the ideal can be tolerated for the given process. Fortunately, there is a rather wide selection of available refractories, membranes, and woven materials, especially for laboratory cells, for which the engineering demands are less strict than for production cells.

The diaphragm materials can be divided into two categories according to the mechanism by which the electric current is carried through the medium: porous materials and ion-exchange membranes [or nonpermselective and permselective materials (Chapter 31)]. With porous materials a more or less tight barrier is offered to the diffusion of both ions and uncharged species, and the electrical resistivity generally increases drastically with decreasing pore size. Thus there is no change in the transport number of the ions as in the case of ion-exchange membranes, which are able to discriminate between ions of opposite charge to a very high degree according to the type of membrane material. A seepage of neutral compounds through an ion-exchange membrane is often unavoidable [92].

B. Porous Materials

Porous materials have mostly been used when ion-exchange membranes are less suited or cannot be employed, for instance, in aprotic media. Most common are sintered glass (especially suitable for all-glass cells) and ceramic refractories, such as Alundum, unglazed porcelain, and pottery. These materials are available in many different sizes, shapes, and porosites, which is convenient for laboratory purposes. A serious drawback is that for greater pieces of material the wall thickness must be considerably increased to obtain a satisfactory mechanical strength; this, however, results in a higher voltage loss in the diaphragm, with consequent unproductive heat generation, and limits the cell size in practice. The ceramic materials are also less suitable for diaphragms for prolonged operation in alkaline media, as the ceramic matrix that holds the grains together is attacked.

Materials of more or less broad utility, reported in the literature, include the following: filter paper [93], asbestos [51, 94, 95], cellophane [96], nylon cloth [52], and porous plastic [97]; other potential candidates are listed in Chapter 31. The porosity of the medium may be decreased by partially filling the voids with another material, such as agaragar, silica gel [9], or magnesium hydroxide.

C. Ion-Exchange Membranes

Ion-exchange membranes are classified according their function as follows: cation exchange membrane, anion exchange membrane, amphoteric ion exchange membrane, bipolar ion exchange membrane, and mosaic ion exchange membrane.

In most cases the cation-exchange type (H^+ form) of membranes [98–100] has been used in electrolytic cells, but membranes enabling the anions to pass are also available. It must be remembered that if the membrane is not of completely homogeneous polymeric structure (it may be finely dispersed in some binding matrix), channels usually exist through the matrix, making it less permselective. When the product of electrolysis or the starting material is an ion with a charge opposite to that of the working electrode (e.g., reduction of trichloroacetic acid in ammonium buffer), it is especially advantageous to use an ion-exchange membrane as diaphragm to avoid loss of depolarizer or product due to electrical migration out of the working electrode component. In some cases [74–79] the ion-exchange membrane serves both as a diaphragm and as an electrolyte.

The polyelectrolyte membranes are often the material of choice for production cells, and hence a more detailed discussion of their properties is naturally postponed to Chapter

31. Several examples of cells employing ion-exchange membranes have been given in the section on cell construction. Ion-exchange membranes are also used for electrodialysis.

Reviews have been published on the application of ion-exchange membranes as separators in electrolytic reactions [101] and on bipolar ion-exchange membranes for the production of acids and bases from neutral salts [101,102].

IV. ELECTRODE MATERIALS

A. General Considerations

The electrode material is an important factor in directing the course of an electrode reaction, but the influence of the electrode material is one of the least understood points in organic electrolysis. It is known that hydrogen or oxygen overvoltage, catalytic effect, adsorption of substrate to the electrode, the nature of impurities and added components, and the physical state of—and even the history of—the electrode may influence a branching of an electrode process. Efforts have been made to clarify the situation, and although some knowledge has been gained, research in this area is very much needed. Besides the factors already mentioned, the resistance of the electrode toward corrosion must be considered when the electrode material is chosen. A review on electrode materials has been published [103].

The *hydrogen overvoltage* of an electrode material is an important factor in reduction in protic solvents, as it determines how negative the potential may be before the reduction of the medium starts to compete seriously with the electrode reaction of the substrate. Metals can be divided into low-, medium-, and high-overvoltage materials. In the first group is platinized platinum; in the second one, smooth platinum, nickel, palladium, rhodium, nickel, and copper; in the third group, tin, lead, cadmium, and mercury. An electrode with high hydrogen overvoltage is also obtained at a nickel-poly(tetrafluoroethylene) composite-coated electrode [104–106]. The values of hydrogen overvoltage of different materials in tables depend on the current density at which they are measured.

Hydrogen overvoltage is caued by a slow step during the electrolytic evolution of hydrogen; the reaction involves the following main steps:

$$H^+_{solv} + e^- \rightleftharpoons H_{ads} \tag{1}$$

$$H_{ads} + H^+_{solv} + e^- \rightleftharpoons H_{2_{ads}} \tag{2}$$

$$H_{2_{ads}} \rightleftharpoons H_{2_{gas}} \tag{3}$$

The first reaction [107] (1) is believed to be the slow step on mercury and other high-overvoltage metals. This means that no appreciable concentration of adsorbed hydrogen atoms is present on mercury and implies that at mercury cathodes the reduction occurs by a transfer of electrons directly to the substrate not via adsorbed hydrogen atoms. This implication has been tested [108] and confirmed in the reduction of acrylonitrile in the presence of hydrogen ions.

At electrodes of low hydrogen overvoltage, reaction (2) is considered [109–111] the slow step, which implies that the electrode surface is covered to a certain extent with adsorbed atomic hydrogen. This is consistent with the finding that reduction at such electrodes in many cases occurs by the electrocatalytic reaction [112,113], which in many respects is similar to the well-known catalytic hydrogenation reaction.

Oxygen overvoltage plays a similar role in anodic reactions as hydrogen overvoltage in reductions, but the choice of anode materials with different oxygen overvoltages is very

restricted as the overriding consideration is the corrosion resistance of the material. Smooth platinum, gold, lead dioxide, and glassy carbon are among the resistant anode materials with high oxygen overvoltage.

The *catalytic effect* of the electrode material on the branching of an electrode reaction is most often apparent at cathodes with low overvoltage but may also be observed at materials with high hydrogen overvoltage. In the reduction of acetone in 6 N H_2SO_4 at a platinized platinum electrode, two independent paths are accessible: One leads to propane and the other to isopropyl alcohol. The rate of formation of these two products depends on the voltage and on the history of the electrode.

The catalytic effect of high-overvoltage electrode materials may be exemplified by the reduction of ketones in hydrochloric acid at mercury and cadmium or amalgamated zinc electrodes; at mercury, alcohols, pinacols, organic mercury compounds, or sometimes hydrocarbons may be formed (Chapter 10), whereas at cadmium, the reaction is to some degree analogous to the Clemmensen reduction and yields methylene compounds [114].

Some examples of the effect of the electrode material on the branching of reactions are the reduction of benzyltriethylammonium nitrate in dimenthylformamide (DMF) to bibenzyl or toluene at aluminum or platinum electrodes [115] and the reduction of aliphatic aldehydes [116] or alkyl arylketones [117] at different materials.

Chemical modification of the electrodes may change the catalytic effect of electrodes.

Adsorption of the substrate at the electrode plays an only partly understood role, predictable only with difficulty, in organic electrochemistry. An example of the influence of adsorption is found in the Kolbe reaction in an aqueous acetate solution at smooth platinum and gold electrodes. Although both materials have high oxygen overvoltage, the Kolbe reaction takes place only at platinum and at a potential higher than that of the oxygen evolution. Addition of indifferent electrolytes that compete with the acetate ions in the adsorption at the electrode lowers the yield of the Kolbe product. In methanol, in which adsorption is less important than in water, the Kolbe reaction proceeds both at platinum and gold anodes.

The *surface* may influence the catalytic activity of the electrode and the adsorption of the substrate. Sometimes in the reduction of certain nitro compounds at a tin electrode, for example, the surface changes during the electrolysis as if some of the metal has been dissolved and reduced again [118]. Such a phenomenon is also observed during the reduction of *m*-nitrobenzenesulfonic acid in a fluidized bed electrode [119]. The role of stannous salts (Chapter 29) added to the catholyte in certain reductions has a bearing on this problem.

Porous electrodes may be used to achieve a high space–time yield, as they possess a large internal surface. A consequence of using such electrodes is, however, that interior mass transfer and ohmic resistance effects may lead to a nonuniform potential distribution, which affects the selectivity of the reaction. The cell design and the adjustable parameters must thus be optimized for each reaction [64–67,120].

Porous electrodes for hydrogen gas diffusion electrodes were discussed earlier. The main advantage of such electrodes are a low anode potential, elimination of the need of adding protons for the reduction, and avoidance of dioxygen evolution. The advantage of a low anode potential can be illustrated by the observation that in the reduction of glucose to sorbitol the cell voltage could, by employing a hydrogen-diffusion anode, be decreased by 50% compared to the conventional cell. The reduction could be made without a diaphragm, which reduced both the cell voltage and the cost of the cell [69–73].

Impurities in the electrode material may modify its properties both in negative and positive directions; the latter may be exploited by using *alloys*, *adatoms*, or *additions*. The

desired modification may be an enhanced mechanical strength, a higher catalytic activity of the electrode material, or a greater resistance toward corrosion. In some cases, however, the amount of side products is increased by the presence of impurities.

An illustration is the increased rate of the electrocatalytic reduction of 4-methylstyrene on deposition of small amounts of platinum or gold on a palladium cathode [121].

B. Cathode Materials

The choice of cathode materials is less restricted by corrosion considerations than the choice of anodes; so few metals react readily with the medium that their use is impractical. Some of the most popular electrode materials are mercury, lead, tin, copper, iron, aluminum, platinum, nickel, and carbon.

1. Mercury

Mercury has been used extensively in electrochemistry in the past because of its many good properties, but its use is declining due to health and environmental problems. Mercury is not used in industrial cells anymore.

Mercury has a very high hydrogen overvoltage. It is obtained commercially sufficiently pure for electrochemical purposes. Stirring of a mercury electrode provides a clean, reproducible surface, which is one of the major advantages of mercury. Another is that in electrolysis at a mercury cathode, results obtained from polarography can be used for selecting the optimal conditions. On the other hand, the liquid state of mercury places certain restrictions on the design of cells employing mercury cathodes. In some cases, amalgamated copper or lead electrodes may be used, with the amalgamation being done either by treating the solid electrode with a solution of mercuric chloride or simply by rubbing mercury on its surface.

A mercury cathode mostly functions only as an electron donor; numerous examples of such simple reductions have been reported. In some cases, however, the electrode is attacked with the formation of organic mercury compounds, e.g., by radicals during the reduction of a halide. When using mercury, suitable precautions must be taken to avoid mercury poisoning and environmental pollution.

As an anode, mercury has a very limited use as it is attacked at rather low anodic potentials. It has been used as an anode in the preparation of mercury salts of weak acids [122]; other metals may be used similarly.

2. Lead

Lead has been much used as a cathode material ever since the beginning of organic electrochemistry; it has a high hydrogen overvoltage and is easy to work mechanically. The purity of the material is important in some, but not in all, cases, and different procedures involving successively anodic and cathodic treatments have been recommended in order to obtain a pure, reproducible surfaces. Sometimes a lead cathode becomes deactivated during electrolysis, and a continuous addition of Pb^{2+} to the catholyte may prohibit such a deactivation [123]. It has been observed that the chemistry of freshly deposited lead and copper is markedly different from that of bulk metal [124].

In many reductions a lead cathode yields the same kind of product as a mercury electrode, but in some cases it is either inferior or superior to mercury. The latter is found in the reduction in sulfuric acid of aromatic acids to the corresponding alcohols. In such cases, specific adsorption of the substrate at the electrode may partly exclude the discharge

of hydrogen ions and thus promote transfer of electrons to the substrate, but the nature of this (assumed) adsorption is only partly understood.

If the potential of a lead electrode becomes too negative in a solution of NaOH, formation of Pb(Na) is observed; at high current densities it is visible as a black cloud coming from the electrode. Even under other conditions, corrosion of a lead cathode should be considered.

The mechanical strength of lead is low, which may be a problem in large cells. Lead plated on titanium may be used.

3. Tin and Copper

Tin and copper electrodes have been used mostly in reductions of nitro compounds. It has been noticed that the electrode surface of tin may change structure during an electrolysis. This has been interpreted [118] as showing that the electrode material reacts "chemically" with the substrate and the stannous (or stannic) ions are discharged subsequently. The negative potential of the cathode would counteract the dissolution of the tin metal, but no investigations using modern electroanalytical techniques have been made to settle the question. It has been observed that the chemistry of freshly deposited copper is markedly different from that of bulk copper [124] and may catalayze, e.g., a dehalogenation reaction.

4. Cadmium and Magnesium

The hydrogen overvoltage of cadmium is rather large and cadmium may be used, plated on steel, as an alternative to lead. Cadmium has been used as cathode material in the hydrodimerization of acrylonitrile (Chapter 31). Magnesium may be used in reductive dimerization of aliphatic esters [459].

5. Silver

Silver electrodes have been employed in form of an expanded silver sheet on a plastic plate in the dehalogenation of polyhalogenated heterocyclic compounds; examples are given in Chapter 18.

6. Aluminum and Iron

Aluminum and iron (steel) have not been used widely in laboratory cells but are preferred in technical installations when possible (Chapter 31).

7. Carbon

Several forms of carbon has been used as cathode, the most common being glassy carbon, carbon cloth, and graphite. Carbon cloth electrodes are convenient when a large surface is essential. The surface of graphite (and to a lesser degree glassy carbon) contains different oxidized groups, such as carboxyl, hydroxyl, carbonyl, and quinones. In some cases, such groups catalyze a specific reaction [125]; they are also essential for a chemical modification of a carbon electrode.

8. Composite Electrodes

Such electrodes have mostly been used as anodes, but cathodic redox catalysis is also possible. In Ti/TiO_2 composite cathodes, prepared by the ceramic method, $Ti(OH)_4$ is

reduced to $Ti(OH)_3$, which "chemically" reduces the substrate, such as aromatic nitro compounds [126], in an "inner sphere" electron transfer reaction.

9. Electrodes for Electrolytic Hydrogenation

Nickel (Raney nickel) [113,127–130], Devarda copper [131], ruthenium on nickel [132], palladium on felt [133], and platinum have a low hydrogen overvoltage with the formation of the catalytically active metal-bonded hydrogen atoms, Me(H), as the potential-determining step. These metals are used for electrocatalytic hydrogenations. Deposition of platinum or gold on a palladium sheet may increase the rate of hydrogenetion of some compounds [121]. As other hydrogenation catalysts, these materials can be poisoned; regeneration of poisoned Raney nickel electrodes has been described [134]. A discussion of the formation of nickel hydride in alkaline solutions has recently appeared [135].

Addition of a low concentration of a non-micelle-forming surfactant may strongly increase the adsorption of an organic compound, which favors the hydrogenation reaction over the hydrogen evolution. [136].

10. Sacrificial Cathodes

Phosphorus [137], sulfur [138–140,143], selenium [141,143], and tellurium [142,143] electrodes may be used for incorporation of these elements in organic compounds. Sulfur and selenium are used in a mixture with graphite, whereas white phosphorus may be used melted or in contact with carbon or mercury; tellurium has sufficient conductivity to be used directly or applied on a platinum electrode.

A convenient arrangement of a sacrificial selenium cathode is the "tea bag" method, in which a graphite cloth bag is filled with selenium pearls [143]. Other forms of sulfur or selenium electrodes have been described [144].

A somewhat similar approach has been used by mixing a finely dispersed, slightly soluble organic solid into a paste with graphite powder; an aqueous electrolyte was employed. Thus, *p*-dinitrobenzene has been reduced to *p*-nitrophenylhydroxylamine by this method [145].

C. Anode Materials

The choice of anode material is very limited because most metals are attacked in the anodic reaction. In laboratory experiments, platinum, gold, and carbon are most widely used; lead containing a small percentage of silver and lead dioxide can be employed in dilute sulfuric acid and iron and nickel in alkaline solution.

1. Platinum

Platinum is used both as microelectrode and in macroscale electrolysis; for larger electrodes platinum plated on titanium may be useful. Platinum is in aqueous solvents probably covered with an oxide at potentials more positive than about 0.75 V (SCE) [146,147], so the electrode material may actually be a platinum oxide.

In some anodic reactions, especially in aprotic media, the products obtained form a layer of tarry material on the electrode surface that (by covering it) insulates it electrically from the solution. The removal of this layer and the attainment and maintenance of a clean, reproducible surface are often a major problem in the use of noble metal anodes. Sometimes it is possible to avoid fouling of the electrode by using pulse electrolysis.

2. Carbon

Graphite electrodes are very useful as anodes; electrodes of natural graphite, however, are not as resistant toward corrosion as platinum electrodes and thus have a limited lifetime. Graphite is available in many forms, one resembling cloth, which is convenient for laboratory purposes, and another one being glassy carbon. Glassy carbon (vitreous carbon) can be used in many cases in which platinum previously was used. The properties of glassy carbon depend above all on the temperature at which it is made [148,149].

On electrooxidative pretreatment in aqueous media of glassy carbon the surface is modified; the anodization results in a higher background current, increased reversibility, and decreased oxidation potential of some compounds. The effect depends on pH and the supporting electrolyte [150].

Oxidation of organic substrates at a graphite anode often results in products other than oxidation at a platinum electrode; the tendency to further oxidation of a primarily produced radical to a carbocation seems higher at carbon than at platinum. Products obtained at graphite, glassy carbon, or other forms of carbon may differ considerably [148–151]. Glassy carbon is difficult to work mechanically.

In voltammetry it is important to secure the reproducibility of solid electrodes. In the carbon paste electrode the problem of contamination of the surface is solved by producing a fresh surface for each run.

3. Lead and Lead Dioxide

Pure or alloyed lead may be employed as anode in sulfuric acid; addition of 1% silver, 0.3% tin, and a little cobalt raises its resistance toward corrosion. Other metals may improve the yield of a given electrode process. Thus, addition of antimony and cadmium to a lead anode [152] is advantageous in the oxidation of *o*-toluenesulfonamide to *o*-benzoylsulfonimide (saccharin). The same effect may be obtained, however, by using an uncoated, unalloyed lead anode if Sb_2O_3 is added to the anolyte [153]. It seems possible that the dissolution of some antimony from the alloyed lead anode takes place and produces the same effect as the Sb_2O_3 in the anolyte.

In many cases the surface of the anode is oxidized to lead oxide, which thus is the real anode material. Titanium anodes coated with lead oxide have been found to have a long lifetime [154,155]. In some cases the lead dioxide, a strong oxidant in acid solution, reacts chemically with the substrate [156] and is continuously regenerated whereas it acts as an inert electrode in other oxidations. A review of the basic electrochemistry of PbO_2, mainly in relation to the lead battery, has been published [157].

4. Nickel

A nickel anode is in alkaline solution protected against corrosion by a layer of nickel oxides. Ni^{+3} oxide (NiOOH) is capable of oxidizing a number of functional groups; primary alcohols may be oxidized to carboxylic acids [158–161], which is of interest for the technical production of an intermediate for vitamin C production [162]. NiOOH chemically oxidizes the substrate and is regenerated electrochemically; a large anode surface, which is realized in the Swiss-roll cell (Chap. 31), is thus advantageous. NiOOH electrodes in form of nickel foam electrodes has been found to be useful for the oxidation of diacetone L-sorbose to diacetone 2-keto-L-gulonic acid in the vitamin C synthesis [163].

5. Dimensionally Stable Anodes (DSA) and Composite Anodes

These materials [164–166], consisting of precious metal (e.g., ruthenium) oxides coated on baser metals (e.g., titanium), have already had a major impact on the chloralkali industry as replacements for graphite. Sometimes an inactive oxide (e.g. TiO_2) is mixed with the catalyst to improve corrosion resistance [167]. These types of electrodes may in many cases be used where previously only platinum could be employed and may thus make a number of organic electrosyntheses possible that were not considered industrially viable due to the price of platinum.

Titanium/chromium oxide ($Ti/Cr_2O_3 + TiO_2$) composite electrodes, fabricated by a ceramic method [168], may be used for oxidation of organic compounds. The chromium is oxidized to CrO_3, which chemically oxidizes the substrate. The lifetime of the electrode may be improved by doping with Sb_2O_3.

Ebonex is a conducting ceramic material mainly composed of the Magnéli-phase titanium oxides, Ti_4O_7 and Ti_5O_9, resistant to anodic corrosion in a wide range of media. Electrodeposition of a metal changes the low electron transfer rates of the ceramic material to that of the bulk metal [169].

6. Sacrificial Anodes

Anodes of magnesium, aluminum, or zinc may be used as sacrificial anodes [170–179]; in most cases DMF has been used as solvent, but other dipolar, aprotic solvents may be employed. A main advantage of the use of sacrificial anodes in aprotic medium is the lack of need for a diaphragm, which often is a problem in such solvents. Another advantage is that only a small concentration of supporting electrolyte is needed, as the Me^{n+} formed during the electrolysis helps carry the current. Furthermore, Me^{n+} may play a special role (e.g. salt formation during carboxylation and with other anions to avoid unwanted further reactions, replacement of a mediator cation with Mg^{2+}, e.g., exchange with samarium ions, or furthering a dimerization) during the reaction. The choice of metal depends among other considerations on the redox properties of the substrate and products; zinc is convenient for reactions with compounds having reduction potentials higher than about -1.3 V (SCE), whereas magnesium and aluminum may be used in reactions where the substrate is reduced at potentials higher than about -2.8 V (SCE). An electrochemical reactor with a consumeable anode with the active metal in a granular form has been described [174].

Application of zinc as a sacrificial anode often overcomes the difficulties with activation of zinc in the Reformatsky reaction and the problems with uncontrolled exothermic reactions. When zinc or indium is employed for the reaction, the amount of electricity used is less than the theoretical, and this suggests that the anode acts as activated metal and reacts with the bromo compound [175].

When using sacrificial magnesium anodes in DMF, an overconsumption of metal is observed; it has been shown that electrochemically scouring of magnesium induces a chemical reduction of DMF, possibly primarily involving a reductive dimerization [176].

A catalyst of the Friedel–Craft type, which promotes the acetylation of aromatic compounds, has been prepared using aluminum as sacrificial anode [177,178].

In some older papers the reduction of some compounds by anodically generated Mg^+ [180,181] has been described. It has not been investigated whether Mg^+ (or finely divided Mg?) plays any role during electrolysis using sacrificial magnesium anodes.

7. Hydrogen

The oxidation of hydrogen to protons as anode reaction is conceptionally attractive, and the use of a hydrogen diffusion anode should be considered in more cases of electroorganic reductions than has been done until now [68–73].

8. Mercury

Mercury is generally not useful as an anode, however, it has been used as anode in the preparation of mercury salts of weak acids [122]; other metals may be used similarly.

D. Electrodes with Chemically Modified Surfaces

Recently, considerable interest has been shown for electrodes on which the surface has been modified chemically (CME, chemically modified electrodes). The emphasis in the investigations has mainly been on studying the preparation, properties, and mechanism of the electron transfer, but gradually the emphasis in the field is shifting to applications; the use of CME for induction of chirality is treated in Chapter 26.

Electrodes may also be modified by deposition of metal adatoms at potentials several hundred millivolts positive to the reversible potential for metal deposition. A submonolayer of adatoms may lower overpotentials for electron transfer processes or improve the selectivity of an electrocatalytic surface. Underpotential deposition and electrocatalysis have been discussed in a review [182].

V. REFERENCE ELECTRODES

A. General Considerations

A reference electrode [183–185] is a half-cell that defines a potential to which all other measurements are referred. The primary standard electrode is the standard hydrogen electrode (SHE), but as this electrode is inconvenient for practical work, other reference electrodes are used. Such reference electrodes must have a potential that changes very little and is known to within 1 mV or so. In some cases of controlled potential electrolysis, it is sufficient to know the potential of the working electrode during the electrolysis within 10–20 mV, because the potential variations between different points of the electrode are of this magnitude (see earlier), and less precise electrodes may be termed comparison electrodes. In principle, any electrode at the surface of which an electrochemical reaction with a large exchange current can take place may be used as a reference electrode.

Several problems are encountered when potentials in different solvents are sought compared to the potential scale in water. A variety of approaches [186–194] have been followed to attack this problem; usually the approach has been to introduce some kind of nonthermodynamic assumption, such as the supposition that certain large, monovalent ions (Rb^+, CS^+) [191] or redox systems [186–188] of the charge type n/n + 1 (preferably 0/ + 1 [186,187]) have a nearly equal free energy of solvation in the two solvents so that the free energy of a transfer of the reference ion is small. The redox couples [194] ferrocenium/ferrocene and bis(biphenyl)chromium(I)/bis(biphenyl)chromium(O) (BCr^+/BCr) have been recommended as reference redox systems for measurements in nonaqueous solvents; however, an investigation concluded [195] that the electrochemistry of ferrocene in MeCN at microelectrodes was far from ideal, as some film formation may occur.

Liquid junction potentials may be a problem. For electroanalytical work it is essential that the potential values are not made uncertain by unknown liquid junction potentials, and the use of an internal standard such as ferrocene is recommended. In preparative reactions the reference electrode has to be separated from the medium, but as long as the liquid junction potential can be held reasonably constant it is not a serious problem.

The contact between the reference half-cell and the test solution requires some consideration. The ohmic reistance of the electric contact should preferably be kept low and contamination of the test solution by the reference electrode and vice versa must be avoided. Usually some kind of salt bridge with or without a diaphragm is employed. The liquid junction potential is lowered if a salt, such as KCl, with nearly equal mobilities of the cation and anion is used. The diffusion between the two half-cells is discouraged by introducing some kind of diaphragm, such as a salt-saturated agar gel, a fritted glass plate, asbestos fibers, a fritted glass membrane, cracked soft glass [196], or a Teflon roll junction [197]. A considerable ohmic resistance may be introduced simultaneously, which puts certain requirements on the internal resistance of the potential-measuring device.

The ideal reference electrode is indefinitely stable, unpolarizable, easy to handle, temperature independent, has a low resistance, and does not cause contamination of the test solution.

A stable potential of a reference electrode is very important. Instability may be caused by several factors. One of the components may be unstable in the solvent. Thus, mercurous chloride is unstable in acetonitrile and a calomel electrode is unreliable in this solvent. Evaporation of solvent from a standard solution, the concentration of which determines the potential, changes the potential. A liquid junction potential may change; this is observed when an aqueous calomel electrode, connected to the test solution through a diaphragm, is used for measurements of potentials in acetonitrile for periods longer than about 5 min (see later).

An unpolarizable electrode is an electrode the potential of which does not change significantly when a small current passes through it. Most of the potential-measuring devices used draw a small current from the reference electrode, depending on the resistance of the circuit. Polarization is diminished by employing a reference electrode with an electrode reaction with a high exchange current, with a large area, and with a sufficiently high concentration of the potential-determining species, so its concentration is not changed appreciably by the passage of the current.

In some reference electrodes the concentration of the potential-determining species is kept constant by maintaining a saturated solution of a suitable compound. The solubility of a compound is generally temperature dependent, and the potential dependence on temperature of such electrodes is thus higher than for other kinds of reference electrodes.

The reference electrodes have been divided according to the electrode reaction responsible for maintaining the constant potential: In electrodes of the first kind, the potential of the metal electrode is determined by the concentration of the metal ions; in electrodes of the second kind, the potential is determined by the concentration of an anion that forms an insoluble salt with the metal cation; and in redox electrodes, the potential of an indifferent electrode is determined by the relative concentrations of the two components of a redox system.

B. Electrodes of the First Kind

Metal electrodes of this kind require that neither the metal nor the metal cation reacts chemically with the solvent; reactive metals may, however, be used as their amalgams.

Electrodes of the first kind require a standardized solution in the half-cell, which makes such electrodes less convenient to employ than most electrodes of the second kind.

The *silver/silver ion electrode* is a widely used reference electrode [198] in nonaqueous solvents, such as acetonitrile [199]. The electrode consists of a silver wire immersed in a solution of $AgClO_4$ or $AgNO_3$. It is connected to the test solution through a salt bridge containing $NaClO_4$ or a tetraalkylammonium perchlorate and equipped with some kind of device to diminish diffusion.

The Ag/Ag^+ electrode is reversible [200] in many solvents. The main advantage of this and similar reference electrodes is that it allows working in a system containing a single solvent. Silver ions react with certain organic solvents, such as DMF, and other metal electrodes must then be used; however, a silver cryptate electrode [Ag/0.005 M Ag Cryp(2.2)ClO_4] is stable in DMF [201].

Silver perchlorate is hygroscopic and has a tendency to explode. Handling $AgClO_4$ may be avoided by its electrolytic preparation in the reference electrode [202]: Current is passed through a silver anode in an anolyte containing a soluble perchlorate until the desired silver ion concentration is reached. Silver nitrate may be used instead of silver perchlorate, although it is not as fully dissociated in acetonitrile [203]. The influence of the ion pairing on the potential has been discussed [204].

A *zinc amalgam electrode* has been employed as reference electrode in dimethyl sulfoxide (DMSO) [205] and ammonia [206]. The saturated zinc amalgam was prepared [207] by electrolytic deposition of zinc into a layer of pure mercury from an aqueous $ZnSO_4$ solution. The solution in equilibrium with the Zn(Hg) consisted of a saturated solution of $Zn(ClO_4)_2$, 4DMSO or $ZnCl_2$, $6NH_3$.

The use of a *sodium amalgam electrode* [Na(Hg)/$NaClO_4$(s)] in DMF has been reported [205] and a similar *lithium amalgam electrode* has been employed in DMSO [207]. The potential of the cell, $Li(Hg)/Li^+Cl^-$ (DMSO), has been measured for LiCl concentrations from 0.01 to 1.0 M and the Nernst relation was verified within 1 mV; the Li(Hg) electrode obeys the Tafel equation with the transfer coefficient $\alpha = 0.5$ over a current density range from 10^{-7} to 2×10^{-3} A/cm_2 [207].

A special reference electrode is the *electron electrode*, which can operate in solvents capable of solvating electrons, such as ammonia. A sheet of platinum suspended in a solution of sodium metal in ammonia may be used as a reference electrode [208]. The concentration of the reference solution can be varied over relatively wide limits without a change in the potential of the electrode. A sodium concentration of 0.001 M was found suitable [208].

C. Electrodes of the Second Kind

An electrode of the second kind may be used if the metal cation forms an insoluble salt with an anion, but from the point of establishing a satisfactory reference electrode of this kind, the most interesting constant is not the solubility constant, but the equilibrium constant for the reaction

$$MeX_{(s)} + X^- \rightleftharpoons MeX_2^-$$

1. Calomel Electrode

The saturated calomel electrode (SCE) is probably the most widely used reference electrode. It consists of a mercury electrode in contact with a solution saturated with respect to both Hg_2Cl_2 and KCl. The half-reaction is

$$Hg_2Cl_2 + 2e^- \rightleftharpoons 2Hg + 2Cl^-$$

The activity of the potential-determining mercurous ion is maintained constant through the solubility product Hg_2Cl_2 by the constant activity of Cl^- in the saturated KCl solution, which is in equilibrium with solid KCl. The passage of current thus just changes the quantities of the solid salts, Hg_2Cl_2 and KCl, but not the composition of the solution. The solubilities of Hg_2Cl_2 and KCl change with temperature, and the potential of the aqueous SCE versus NHE is $E = +0.242 - 7.6 \times 10^{-4} \times (t^\circ - 25)$.

The "normal calomel electrode" (NCE), which employs a 1 N KCl solution instead of a saturated solution, has a smaller temperature coefficient [$E = +0.280 - 2.4 \times 10^{-4} \times (t^\circ - 25)$ versus NHE], but because it requires a standardized solution it is less convenient than the SCE. The potential change of SCE with temperature is less than 1 mV/degree and is of no importance for controlled potential electrolysis.

Many designs of calomel electrodes exist, and several types are commercially available. Some of these are constructed for voltammetric work, whereas others are used in connection with glass electrodes. The latter type generally has a high resistance, which must be considered when the choice of voltmeter or potentiostat is made.

The use of SCE presents only a few problems in aqueous solution. For measurements in nonaqueous solvents it can be employed in two fashions: The aqueous SCE can be connected to the nonaqueous solvent through some device that hinders contamination of the solvent, or an electrode analogous to the aqueous SCE may be constructed in the nonaqueous solvent.

In many nonaqueous solvents a calomel electrode is inapplicable. In acetonitrile, mercurous chloride, although insoluble, undergoes a disproportionation reaction in the presence of excess chloride ion according to

$$Hg_2Cl_2 + Cl^- \longrightarrow Hg^\circ + HgCl_3^-$$

It is often possible to employ an aqueous SCE that is connected through a conventional aqueous KCl–agar bridge to a suitable salt solution in the nonaqueous solvent, which in turn dips into the solution under investigation. In such cases gradual deposition of KCl and/or dehydrated agar at the tip of the salt bridge may cause the liquid junction potential to change and thus the potential of the electrode to drift. The drift is often negligible when the measurement is completed within about 5 min [209].

If chloride ions must be avoided, a *mercury/mercurous sulfate electrode* [Hg/Hg_2SO_4(s), K_2SO_4(s); E = 0.621 V versus NHE] may be employed. In alkaline solution a *mercury/mercuric oxide electrode* (E = 0.098 versus NHE) may be useful.

The saturated *silver/silver chloride electrode* [Ag/Ag(Cl(s), KCl(s); E = 0.197 V versus NHE, E = −0.045 V versus SCE] is especially convenient as it can be constructed by placing a silver wire in a solution of saturated potassium chloride, separated from the test solution by an agar plug and a glass filter. An analogous electrode may be employed in certain nonaqueous solvents, e.g., nitromethane]202], acetic acid [210], and DMF [211], but is does not work well in others, such as ammonia or acetonitrile [212], in which complexes are formed that cause the potential to drift.

Often a silver wire in the medium may serve as a convenient comparison electrode, the potential of which afterward is measured against added ferrocene.

The *copper fluoride electrode* has been found to be a convenient reference electrode in hydrogen fluoride [213].

The *thallium amalgam/thallium chloride electrode* [Tl(Hg)/TlCl(s), LiCl] is a stable and reversible reference electrode in such solvents as DMSO and DMF [211, 214]. Similarly, the *lead amalgam/lead chloride electrode* [211,215] may be employed, but this electrode takes a longer time to reach a stable potential than the Tl(Hg)/TlCl electrode.

In dimethylformamide, a *cadmium amalgam electrode* [211,216] gives a reproducible potential that is stable and well poised. The cadmium amalgam was prepared [216] by heating cadmium with pure mercury for several minutes and adding, after cooling, sufficient mercury to make a slurry, which was filtered through a pinhole in filter paper. The half-cell was: $Cd(Hg)/CdCl_2(s)$, $CdCl_2$–$H_2O(s)$, NaCl(s), DMF. The variation of cell potential with water content has been examined.

D. Redox Electrodes

In a redox electrode both components of the redox system are in solution, and their relative concentrations determine the potential of an inert electrode immersed in the system. Such electrodes have been used as reference electrodes only in special cases, because the potential is dependent on two concentrations, the ratio of which must be kept constant. The primary standard reference electrode, the hydrogen electrode, has been used as practical reference electrode in certain case, as in HF [217,218].

1. Fc^+/Fc and BCr^+/Bcr

Ferrocenium ion/ferrocene (Fc^+/Fc) and bis(biphenyl)chromium(I)/bis(biphenyl)chromium (O) (BCr^+/BCr) have been proposed [194] as reference redox systems for nonaqueous electrochemistry. Both materials have been found suitable for practical referencing, for example, in THF [219], covering complementary potential ranges.

2. Poly(vinylferrocene) Electrode (PVF)

A platinum electrode coated with a film of poly(vinylferrocene), which was electrodeposited in its oxidized form and later partially reduced, was found to be a stable reference electrode in MeCN (but not in DMF) [220]. Polymer films containing other redox systems may also be used.

A similar electrode based on $Fe(CN)_6^{3-/4-}$ adsorbed on a cross-linked polymer (polyethyleneimine/1,4-dibromobutane) has been proposed as a reference electrode in organic solvents [221].

3. Chloranil Electrode

The tetrachloroquinone (chloranil)/tetrachlorohydroquinone system has been used as a reference electrode in alcohols and acetic acid [222], often in the presence of an excess mineral acid. The half-cell consisted of a platinum electrode in a solution saturated with respect to both chloranil and the hydroquinone. The electrode is well poised, and at constant temperature and constant hydrogen ion activity the potential is stable.

4. Triiodide/Iodide Electrode

The triiodide/iodide electrode ($Pt/I_3^-/I^-$) has been recommended as reference electrode in MeCN and propylene carbonate [223]. It was found to have a higher exchange current

than the Ag^+/Ag electrode; the exchange current was highest at Pt, lower at glassy carbon, and lowest at stainless steel. A Teflon salt bridge [197] was recommended.

Table 1 summarizes the suitability of the various reference electrodes in different solvents. Reviews on reference electrodes have been published recently [224].

VI. SOLVENTS FOR ELECTROLYSIS

A. General Considerations

Electrolysis can occur only at the boundary between an electrode and a medium that conducts the electric current, and the nature of the solvent is important for the course of electrolytic reactions. Such factors as proton activity, usable potential range, dielectric constant, ability to dissolve electrolytes and substrates, ion pair formation, accessible temperature range, vapor pressure, viscosity, toxicity, and price must be taken into consideration when the choice of solvent is made.

1. Proton Activity

The availability of protons is one of the most important properties of a medium by which it can influence an electrolytic reaction, especially a reduction. Anodic reactions are generally less susceptible to the proton activity, but both the stability of cation radicals and the reactivity of some nucleophiles in anodic substitution reactions depend on proton activity.

At high proton activity a protonation of the substrate may occur prior to the charge-transfer step. A protonated molecule is reduced at a less negative potential than an unprotonated one. At medium proton activity the unprotonated molecule is reduced to a radical anion; this is rapidly protonated to a radical, which generally is more easily reduced than the unreduced substrate. In aprotic media the radical anion formed in the charge transfer step may be so long-lived that it can be regarded as the product. The radical anion is normally more difficult to reduce than the unreduced substrate. The substrate itself may act as a proton donor ("father/son reaction") [253,254].

A high proton activity generally makes an oxidation occur at more positive potentials; it also diminishes the tendency to lose protons from cation radicals, which thus may have reasonable stability under strongly acidic conditions.

In aqueous solution (1) a change in pH may alter the sequence of reducibility of different "electrophores"; (2) the degree of reaction of an "electrophore" may be different in acid and alkaline solutions; (3) a branching of a reaction may be influenced by the availability of protons; and (4) the stereochemistry of the product may be pH dependent. As examples can be given (1) the reduction of isonicotinic amide in which the carboxamide group is reduced in acid solution whereas the pyridine ring suffers reduction at high pH (Chapter 18); (2) the reduction of aromatic nitro compounds, which at low pH at a suitable potential yields an amine and, in alkaline solution, a phenylhydroxylamine (and its condensation products; Chapter 9); (3) the reduction of acrylonitrile may yield the two-electron reduction product, propionitrile, or the one-electron reaction product, adiponitrile, depending on the availability of protons (Chapter 21); (4) the stereochemistry of the product mixture of pinacols formed on electrolysis of aromatic ketones is pH dependent (Chapters 10 and 26).

When considering an aprotic solvent, it must be recalled that it is difficult to obtain a strictly anhydrous medium. Especially in voltammetric experiments in which the concen-

Table 1 Reference Electrodes in Different Solvents [a,b]

	SCE (aqueous)	$Hg/Hg_2\lambda_2$	Ag/AgCl	Ag/Ag^+	$Li(Hg)/Li^+$	$Na(Hg)/Na^+$	$Tl(Hg)/Tl^+$
CH_3CN	+[225, 226][c]	–	(–)[212]	+[185, 226]			
DMF	+	(+)	(+)[211]			+[205]	+[211]
NH_3	–	(+)[225]	–	–			
$(H_2NCH_2)_2$	+	(+)[246]					
C_5H_5N		+		+[229, 230]			
$((CH_3)_2N)_3PO$				+			
DMSO	+	–	(+)[211, 231]		+[208]		+[211, 214]
CH_3OH	+	+	+	+			
CH_3COOH		+[232]	+[210]				
$(CH_3CO)_2O$		+[234]		+[235]			
H_2SO_4		+[236]					
FSO_3H		+[239]		+[237][e]			
PC	+			+[240]			(+)[211]
CH_3NO_2			+[202]	+[202]			
THF	+[243]			+[242]			
HFP			+[245]				
CH_2Cl_2	+						
THAB	+[244]						
HF		+[251, 252]					

[a]Symbols: +, stable reference electrode, (+), usable comparison electrode, (–), dubious comparison electrode, –, unsuitable electrode.

[b]DMF = dimethylformamide; DMSO = dimethyl sulfoxide; PC = propylene carbonate, THF = tetrahydrofuran, HFP = 1,1,1,3,3,3-hexafluoro-2-propanol; THAB = tetrahexylammonium benzoate; $TBAPF_6$ = tetrabutylammonium hexafluorophosphate.

[c]Reference numbers.

[d]Poly(vinylferrocene) electrode.

[e]Au/Au^{3+}

tration of the substrate is low, the residual water nearly always present in a "dry" solution may influence the results obtained. It must also be considered that the anodic limiting reaction of some anions, such as perchlorates [255–257], results in the formation of water. Protons may also be supplied by abstraction by an electrogenerated base from the nonaqueous solvent or from tetraalkylammonium ions, in the latter case by a Hofmann elimination. A convenient way to remove the major part of acidic impurities from "aprotic" solvents is to add active anhydrous alumina to the solution [258,259] or let the solution pass through a column of anhydrous alumina.

Acidity and basicity scales in polar solvents have been discussed [260] and it has been concluded that the most appropriate scales are the acceptor number AN or donor number DN introduced by Gutmann [261–263], although it does not directly allow one to estimate the basicity of a protic solvent.

A determination of water in a "dry" solution is thus often of interest. A gas chromatographic method has been employed [264] for determination of water in certain cyclic esters, but injection of electrolyte solutions causes accumulation of salts in the injection chamber and sometimes erratic results due to thermal decomposition of electrolytes. Analytical use of the 1.9-μm water band in the near-infrared [265] may be practical for certain solvents, such as propylene carbonate, but not for many of the commonly used solvents. A method has been described [266] in which the water reacts with lead tetra-

$Zn(Hg)/Zn^{2+}$	$Cd(Hg)/Cd^{2+}$	$Pb(Hg)/Pb^{2+}$	Cu/CuF	$H_2(Pt)/H^+$	Chloranil	I_3^-/I^-	Electrons (solvated)	PVF[d]
				−[247]		+[223]		+[220]
	+[211, 216]	(+)[211]						−[220]
+[227]		+[215]					+[211]	
+[229]								
				−[248]				
+[205]								
				−[249]				
				−[233]	+[222]			
				+[238]				
	−[211]	(−)[211]		+[241]				
				+[250]				
			+[213]	+[217, 218]				

acetate in benzene; the lead dioxide thus formed is determined spectrophotometrically at about 400 nm. As little as 2.5 ppm in a 2-ml sample can be measured. The method was found to be applicable to a wide range of solvents and to certain solutions commonly employed in electrochemistry.

The two one-electron reduction waves of 2,5-diphenyl-1,3,4-oxadiazole have been used as a criterion for estimating the degree of drying of aprotic solvents [267]. When $C_{H_2O} < 3–5 \times 10^{-3}$M the two waves had equal height and $E_{1/2} - 1.96$ and −2.33 V (SCE), respectively, whereas in insufficiently purified solvents, the height of the two one-electron waves were not equal and $\Delta E_{1/2}$ decreased.

The Karl Fischer method may be used in many cases. An extremely sensitive method using tritiated water as tracer for the determination of solvent water content has been developed [268] in which drying efficiency is determined by the addition of a specified amount of tritium-labeled water to a rigorously dried solvent and subsequent determination of the decrease in activity of the solvent after treatment with the drying agent.

Besides the ability to donate protons, the properties of the medium (solvent, supporting electrolyte) as hydrogen atom donor are of importance. Hence the strength of the available bonds to hydrogen must be considered. The ability as a hydrogen atom donor is $H_2O < NH_3 <$ MeCN ~ DMSO < DMF < THF.

2. Usable Potential Range

The useful potential range that can be obtained in a given system depends on the electrode material, the supporting electrolyte, the temperature [269], and the solvent; only the solvent is discussed here. Approximate values for the anodic and cathodic limits of some

Table 2 Dielectric Constants and Accessible Potential Range for Some Solvents[a,b]

	Dielectric constant	Working electrode	Reference electrode	Supporting electrolyte	Anodic limit (V)		Working electrode	Reference electrode	Supporting electrolyte	Cathodic limit (V)	
Water	80	Pt	SCE	$HClO_4$	1.5		Hg	SCE	TBAP	−2.	
Methanol	33						Hg	Hg pool	TEAB	−2.	
H_2SO_4 (96–99%)	>84						Hg	Hg pool	None	−0.7	[236]
CH_3COOH	6.2	Pt	SCE	NaOAc	2.0	[321][c]	Hg	SCE	TEAP	−1.7	
CH_3CN	37.5	Pt	Ag/Ag^+	$LiClO_4$	2.4	[362]	Pt	Ag/Ag^+	$LiClO_4$	−3.5	[362]
DMF	36.7	Pt	Hg pool	$LiClO_4$	1.5	[371]	Hg	Hg pool	TEAP	−3.5	[371]
NMP	32	Pt	Hg pool	$LiClO_4$	1.4	[371]	Hg	Hg pool	TEAP	−3.3	[371]
HMPA	30	Pt	Ag/Ag^+	$LiCO_4$	0.8	[362]	Hg	Ag/Ag^+	$LiClO_4$	−3.6	[379]
NH_3	23						Hg,Pt	Hg pool	TBAI	−2.3	[225]
$(H_2NCH_2)_2$	12.5	C	SCE	TEAP	0.1	[322]	Hg	SCE	TEAP	−2.65	[322]
Pyridine	13	Graphite	Ag/Ag^+	$LiClO_4$	1.4	[385]	Hg	Hg pool	$LiClO_4$	−1.7	[385]
DMSO	46.7	Pt	SCE	$NaClO_4$	0.7	[383]	Hg	SCE	TEAP	−2.8	[383]
Sulfolane	44	Pt	SCE	$NaClO_4$	2.3	[393]	Pt	SCE	$NaClO_4$	−4	[393]
PC	69	Pt	SCE	TEAP	1.7	[406]	Hg	SCE	TEAP	−2.5	[406]
CH_3NO_2	36.7	Pt	SCE	$LiClO_4$	2.7	[202]	Hg	SCE	$LiClO_4$	−1.2	[202]
THF	7.4	Pt	Ag/Ag^+	$LiClO_4$	1.8	[245]	Pt	Ag/Ag^+	$LiClO_4$	−3.6	
HFP	16.6	Pt	Ag/AgCl	$TBAPF_6$	2.1	[245]	Pt	Ag/AgCl	$TBAPF_6$	+0.4	[245]
CH_2Cl_2	8.9	Pt	SCE	TBAP	1.8	[289]	Pt	SCE	TBAP	−1.7	[289]

[a]The limit for the accessible potential for a solvent depends on many factors, such as supporting electrolyte, electrode material, and magnitude of permissible current density, and the numbers given are cited as illustrative values only.

[b]DMF = dimethylformamide; NMP = *N*-methylpyrrolidone; HMPA = hexamethylphosphotriamide; DMSO = dimethyl sulfoxide; sulfolane = tetramethylene sulfone; PC = propylene carbonate; THF = tetrahydrofuran, HFP = hexafluoro-2-propanol; TBAP, TBAI = tetrabutylammonium perchlorate or iodide, respectively; TEAP, TEAB = tetraethylammonium perchlorate or bromide, respectively; $TBAPF_6$ = tetrabutylammonium hexafluorophosphate.

[c]Reference numbers.

commonly used solvents are given in Table 2. The numbers can be taken only as a crude indication of the usable potential range, as the latter depends on the criteria used.

Many solvents are available that are so difficult to reduce that it is the discharge of the supporting electrolyte that sets the cathodic limit for the potential; on the other hand, only few polar solvents are resistant to anodic oxidation. The reason is that most polar groups have loosely bound nonbonding electrons on oxygen or nitrogen that are easily lost at the anode. The solvents useful for anodic reactions at high potentials contain electron-attracting groups, such as nitrile, carboxy, sulfone, or nitro groups. For more easily oxidized substrates, sulfoxides or dialkylamides may be used, whereas water, alcohols, and aliphatic amines have a very limited useful potential range for anodic reactions.

3. Dielectric Constant

The dielectric constant is of interest primarily because it influences the ohmic resistance of the medium. Solvents with high dielectric constant are preferable because salts dissociate better in such media. The dielectric constants for some solvents commonly used for electrolysis are listed in Table 2. These solvents can be divided roughly into three main groups: those with high dielectric constant ($D > 60$), those with medium dielectric constant ($20 < D < 50$), and those with low dielectric constant ($D < 13$). In the first group are solvents like water, formamide, *N*-methylamides, and propylene carbonate; the second one comprises compounds like acetonitrile, dimethylformamide, dimethyl sulfoxide, methanol, nitromethane, and ammonia; whereas in the last group belong solvents like acetic acid, ethylenediamine, methylamine, tetrahydrofuran, dioxane, and methylene chloride. The solvents in the last group require a higher concentration of supporting electrolyte in order to acquire a reasonable conductivity.

For acetonitrile, propylene carbonate, 4-butyrolactone, DMSO, DMF, and similar amides, the maximum conductance for fully ionized salts occur at approximately 1 M concentration and is about $10^{-2}\ \Omega^{-1}\ cm^{-1}$, comparable to an aqueous salt solution of 0.5–1 M.

The rate constant for the heterogeneous electron transfer to aromatic compounds is usually somewhat higher in MeCN than in DMF, which indicates that not only the dielectric but also the dynamic properties of the solvents influence the rate of radical anion formation [270].

4. Dissolving Power

The choice of solvent is often a result of a series of compromises. Very few solvents have good dissolving power for both organic substrates and inorganic salts. The good electrochemical properties of water are marred by the lack of its ability to dissolve many organic systems. This ability may be raised by using water in a mixture with an organic solvent like ethanol, acetonitrile, dimethylformamide, or dioxane, or by using a "hydrotropic" supporting electrolyte [271] like tetraalkylammonium *p*-toluenesulfonate. Tetraalkylammonium salts are soluble in most polar solvents and even in less polar liquids, such as chloroform and methylene chloride. Some polar solvents, such as acetonitrile, DMSO, and DMF, combine good dissolving power for both organic compounds and a variety of salts.

Besides the dissolving power of a solvent toward substrate and supporting electrolyte, the ability to solvate intermediate cations and anions is also important. The chemical properties of charged species are dependent on whether there are formed tight ion pairs, solvent-separated ion pairs, or symmetrically solvated ions. Redox potentials of ions are

thus dependent on solvent (see, e.g., Ref. 272). A knowledge of the donor and acceptor values [262,263] of a solvent is thus helpful in predicting its properties as medium. Also, the autoprotolytic constant of a solvent is of interest in this respect.

A combination of the good conductivity of water and the dissolving power of an organic solvent may be exploited by using an emulsion [273–284]. A simple emulsion is useful only if the substrate has a reasonable solubility in water and thus only a limited advantage compared with a suspension of the substrate. For reactions in which the product is much more soluble in an organic phase than the reactants, an emulsion may continuously extract the product and protect it against further reaction. Emulsions are made from an aqueous phase, an organic phase, and a surfactant; they may be "water in oil," "oil in water," or a bicontinuous microemulsion. The first two types have one continuous phase, whereas the bicontinuous microemulsion has both the aqueous and the organic phase as continuous phases; it consists of a dynamic intertwined network of the two phases with a surfactant monolayer at the interphase [280–282]. Bicontinuous microemulsions are nontoxic, have a large interfacial area facilitating an intimate mixing of polar and nonpolar reactants, good solubilization of polar and nonpolar compounds, and high conductivity. Bicontinuous microemulsiosn could thus be useful for electrochemical synthesis as an alternative to the use of organic solvents [280–282].

Utilization of a mediator and a phase-transfer catalyst may enhance the reaction rate considerably; in a bimolecular reaction the rate may be enhanced by preconcentration of a mediator by adsorption to the electrode in a microemulsion [281,282]. When a desired bimolecular reaction involves ions (including radical ions), the nature of the surfactant (cationic, anionic, neutral) may play a role in the product distribution [283].

Ultrasound-assisted electrolytic reduction of emulsions of activated unsaturated systems provides a method for hydrogenation of water-insoluble materials in an aqueous environment [284]. The effect of ultrasound on electrochemical reactions in emulsions may vary depending on the reaction; in some cases solubilization of an insoluble reaction product is furthered, whereas in other cases the heterogeneous rate constant is influenced [284].

When cells with solid polymer electrolytes (SPE) are used, no electrolytes need to be dissolved in the medium, and solvents, which usually cannot be employed in electrolysis, may be used [74–79].

5. Temperature Range and Other Factors

It is desirable that the solvent be a liquid in a convenient temperature interval and that the *vapor pressure* be not too high at the working temperature to avoid excessive loss of solvent. This is not an important point since the electrolysis is often carried out in a closed system anyway. The vapor pressure may also sometimes be lowered considerably by working with a high salt concentration. Two low a vapor pressure of the solvent is inconvenient, as it may be difficult to remove the solvent during the workup.

The *viscosity* of the medium influences not only the mass transfer, but also the rate constant of the heterogeneous electron transfer [285]. A low viscosity is preferable both from the point of view of diffusion and from considerations of pumping in flow cells. For some kind of electroanalytical work, however, a high viscosity is preferable. Diffusion coefficients in some solvents useful for electrolysis have been published [286].

The *toxicity* and *odor* of the solvent warrant consideration. Proper design of the apparatus and careful handling of the solvent make these properties less objectionable.

The *chirality* of a solvent, *S*, *S*$^{-}$(+)2,3-dimethoxy-1,4-bis(dimethylamino)-butane (DDB), has been used to induce chirality in reduction products [287].

6. Purification

Few, if any, organic solvents are obtained commercially pure enough for electrochemical work. However, when selecting a method for purification of a chosen solvent, one should realize that it is seldom necessary to lower the concentration of all impurities. An aprotic solvent used for a reduction should especially be purified for electrophiles, whereas nucleophiles (bases) should be removed from a solvent for oxidations.

Solvents obtained from different sources may have different impurities, and even in solvents from the same source the kind and concentration of impurities may change from batch to batch.

Water is always an impurity in an organic aprotic solvent. The influence of a given water concentration depends on the stability of the complexes between water and the solvent; water is, for example, less firmly bound to MeCN than to DMF or DMSO.

When one wants to remove a given impurity, there is always a danger that the reagent or method introduces other impurities or decomposition products; some solvents, such as DMF, decompose somewhat on distillation at ambient pressure.

The storage of a solvent is important, and ideally one should use the solvent immediately after purification. Some solvents are decomposed by light, and most solvents absorb some water if given the chance.

Methods for purification of some aprotic solvents and tests for impurity recommended by IUPAC have been published [288].

B. Protic Solvents

It is practical to divide solvents into two groups, protic and aprotic solvents. Protic solvents are those that have protons bonded to heteroatoms and include acids, neutral solvents, and some bases. A review of solvents useful for electrochemistry has appeared [289]. Electrochemical reactions in nonaqueous systems [290] and the chemistry of nonaqueous solvents [291] have been treated in monographs.

1. Acid solvents

The electrochemistry of a protonated organic compound differs in many cases from that of the neutral molecule, and the strength of the acid necessary for protonation of the substrate must be considered. Sulfuric acid and acetic acid, often containing some water, have generally been used. When high acidities are desired, fluorosulfonic acid may be used.

a. Sulfuric acid. Concentrated or slightly diluted sulfuric acid is in many respects an excellent medium for electrolysis. It dissolves many organic compounds, and it is sufficiently dissociated to make the addition of foreign electrolytes unnecessary.

Sulfuric acid can protonate even very weak bases, such as aromatic ethers or some aromatic hydrocarbons; it may promote the formation of carbocations either by dehydration of hydroxyl compounds or by addition of a proton to a double bond. These properties are still more strongly developed in the "superacids."

Sulfuric acid has certain disadvantages: It cannot be removed by distillation during the workup. It is, therefore, often most practical to dilute the medium with water and extract the product. If neutralization is necessary, concentrated ammonia is preferable. Another disadvantage is that sulfuric acid may oxidize or sulfonate the substrate.

Most of the electrolyses in sulfuric acid have been performed without control of the potential. In polarographic work the mercury pool has been used for anodic and cathodic reactions: As anode, platinum or lead dioxide have been employed; as cathode, lead, mercury, or platinum.

A 1:1 mixture of sulfuric acid and ethanol was a very popular medium for electrolytic reductions around 1900. The mixture dissolves many organic compounds, but the leveling effect of the alcohol lowers its protonating ability considerably.

b. Fluorosulfonic Acid. This solvent is a very strong acid and may be used when stabilization of cationic species is required [237,292–298]. It has above all been used as medium for the oxidation of alkanes. It is rather resistant toward anodic oxidation, the oxidation product being peroxydisulfuryldifluoride [296].

Fluorosulfonic acid is not a conducting medium, and it is necessary to add a supporting electrolyte, such as $NaSO_3F$ or KSO_3F, or a ionizable organic compound, such as acetic acid, which acts as a strong base and forms CH_3CO^+. Antimony pentafluoride acts as an acid in FSO_3H.

In fluorosulfonic acid containing sulfuric acid anodic dissolution of platinum is reported to take place; in anhydrous FSO_3H an oxide layer is formed, which protects the platinum electrode [298].

As reference electrode the hydrogen electrode [238], the $Au(s)/Au^{+3}$ electrode [237], and $HgSO_4/Hg$ in HSO_3F [230] have been used, but an internal reference system, such as $perylene^+/perylene^{2+}$, has been recommended [268] to avoid unknown liquid junction potentials.

Perfluorosulfonic acids may be used similarly [299]. They may be purified by distillation and treatment with H_2O_2 [300]. Trifluoromethanesulfonic acid has been used as solvent for CV with sodium trifluoromethanesulfonate as supporting electrolyte, glassy carbon as indicator electrode, platinum as counterelectrode and a silver wire as pseudoreference electrode. At $v = 100$ mV s^{-1} the accessible potential window was from +0.4 to +3.0 V vs NHE (calibrated against $Ru(bpy)_3^{3+/2+}$) [301].

c. Hydrogen Fluoride. Hydrogen fluoride has been used for electrochemical fluorination of organic compounds [302–305] and is a promising solvent for electrochemical studies. It has a high dielectric constant (80 at 0°C), is less viscous than water, is transparent for UV light to 165 nm, and is difficult to oxidize. It dissolves many metal fluorides, giving highly conducting solutions; it also dissolves many organic substances. The main disadvantages are its poisonous effect, its ability to attack glass, and its relatively low boiling point, 19.5°C. The low boiling point gives it a tendency to form bubbles, which must be taken into account in the construction of cells. This and other practical problems have been discussed [306].

Hydrogen fluoride can be handled in apparatus of suitable metals (copper, nickel, magnesium, or aluminum, which all form a protective fluoride coating, or platinum), or plastic materials [especially polypropylene, Teflon, and polyvinylidene fluoride (Viton)]; polychlorotrifluoroethylene (Kel-F) can be made into transparent windows. A capillary for a dropping mercury electrode may be made from Teflon [307]. Hydrogen fluoride is obtained commercially in steel cylinders in a purity of 99.5%. The impurities may be removed by distillation [308] or electrolysis [309]. During the electrolytic removal of water the explosive F_2O is formed, which must be taken into consideration [305].

The useful potential range in the cathodic direction is rather limited owing to the evolution of hydrogen, whereas the anodic limit is about 2.6 V (SCE). Sodium or potassium fluoride as supporting electrolyte may be used; the addition of these salts lowers the protonating power of the solvent. The solubility of NaF is about 30 g NaF per 100 g HF;

other fluorides, such as LiF, KF, CsF, NH_4F, AgF, and TlF, are very soluble in liquid HF. The acidity of HF may be enhanced by the addition of BF_3 or SbF_5.

The addition of amines to hydrogen fluoride makes the fluoride ion a better nucleophile and reduces the acidity of HF; $Et_3N/3HF$ and pyridine/HF are commercially available. $ET_3N/3HF$ may be used as such or mixed with MeCN as a medium for electrochemical fluorination (Chapter 25) [310,311].

Several types of reference electrodes may be used. The hydrogen electrode has been shown to behave reversibly in HF [217,218] and has been employed as reference electrode both in electroanalytical and preparative work [218], and mercury fluoride [251,312] and copper fluoride [213,306] have also been used as such. A comparison of these reference electrodes pointed to the hydrogen electrode (H_2/Pd) as the most convenient [313].

d. Trifluoroacetic Acid. Trifluoroacetic acid has mainly been used as a medium for oxidations [314]. It has a dielectric constant of 8.4 [315,316] and a boiling point at 72.5°C; although it has a low conductivity, it is possible to conduct electrolysis in it without using a supporting electrolyte [317]. Its main advantage is that many cation radicals show considerable stability in this medium. Sometimes it is used in mixture with its anhydride and methylene chloride [318].

e. Acetic Acid. Acetic acid is a good solvent for many organic compounds and some inorganic salts. It has a rather low dielectric constant, which makes it necessary to have a considerable electrolyte concentration (≥ 0.5 M) to obtain a reasonable conductance.

Acetic acid may be considered as solvent for acetoxylations [319–321] and for reactions that require an acidic medium other than sulfuric acid. The acidity may be enhanced by adding perchloric acid to acetic acid containing a suitable amount of acetic anhydride, which reacts with the introduced water.

Usable supporting electrolytes include NaOAc, NH_4OAc, LiCl, HCl, H_2SO_4, $HClO_4$, $NaClO_4$, Bu_4NClO_4, and Bu_4NBF_4. The choice of supporting electrolyte may influence the product distribution. Thus, anodic acetoxylation gives different results in NaOAc/HOAc and in Bu_4NBF_4/HOAc. Several types of reference electrodes work well in acetic acid. The chloranil electrode [222] behaves reversibly in this medium and so does the analog of SCE [322] [Hg/Hg_2Cl_2(s), LiCl(s), HOAc]; the mercury pool [323] and the Ag/AgCl electrode [210] can also be used.

The cathodic limit is about -1.7 V (SCE), and the limiting reaction is evolution of hydrogen. The anodic range ends at about 2.0 V (SCE) when NaOAc is electrolyte [321]. The limiting reaction is probably the discharge of acetate ions.

Acetic acid may be purified by partial freezing [321] or by distilling it from CrO_3 [322,323] in the presence of acetic anhydride. CrO_3 oxidizes impurities and acts as an acid catalyst for the reaction between water and acetic anhydride. An excess of acetic anhydride is necessary to force the equilibrium $2AcOH \rightleftharpoons Ac_2O + H_2O$ sufficiently to the left [324]. Modifications of the method have been described [232,323].

f. Other Acids. Methanesulfonic acid [325] and formic acid have also been used as solvent for electrolysis; superacids offer possibilities for unusual electrode reactions.

2. Neutral Solvents

This group comprises water, mono- and polyvalent alcohols, and monoehters of polyvalent alcohols. Often mixtures of water and alcohols are used. Such mixed solvents retain to some degree the favorable characteristics of water but raise its ability to dissolve organic substrates.

a. Water. Water is the solvent of choice for electrolysis, unless some of its properties are undesired or inadequate. An aprotic solvent is sometimes preferable to water since a reaction mechanism of an electrode reaction in an aprotic, organic solvent is often simpler to elucidate than in water. Adsorption phenomena are often a complicating factor in aqueous solution, but much less so in many organic solvents. The usable potential range of water in the anodic direction is quite limited, and the most important factor, the solubility of many organic compounds in water, is quite unsatisfactory. The use of "hydrotropic" salts (Sec. VII.A.) may enhance the solubility of organic compounds in an aqueous medium. Another way of combining the good conductivity of aqueous solutions with the better dissolving power for organic substrates is the use of emulsions [273–284], preferentially with a mediator and a phase transfer reagent.

b. Methanol. The electrochemical behavior of methanol is rather similar to that of water. Methanol is well suited for anodic reactions of the Kolbe type and for methoxylations; for reductions it may be used when the solubility of the substrate in water is too low. The dielectric constant of methanol is fairly high ($\varepsilon = 33$); its liquid range (−98 to 64° C) is convenient, and it is easy to remove during the workup.

Quite a few electrolytes are soluble in methanol, such as NH_4Cl, LiCl, HCl, KOH, KOMe, $NaClO_4$, and tetraalkylammonium salts. For reductions a solution of HCl in MeOH is convenient as it has a high conductance and both components are easy to get rid of during the isolation of the product.

Reference electrodes that can be used in water work in most cases also in MeOH; thus the Hg/Hg(I) and Ag/Ag(I) electrodes may be used. The useful potential range for large-scale electrolysis is about the same as for water, but methanol is less satisfactory for electroanalytical work. Methanol can in general be used as received; it can be dried by treatment with magnesium [326].

It has been reported that methanol oxidized at the anode may diffuse to the catholyte and react with nucleophiles or EGB [327].

c. Other Alcohols. Ethanol and the higher alcohols have lower dielectric constants and poorer ability to dissolve electrolytes. They have been used mostly in mixture with water or sulfuric acid. 2,2,2-Trifluoroethanol is more acidic than ethanol and can be used when strong bases are undesired [328].

3. 1,1,1,3,3,3-Hexafluoropropan-2-ol

1,1,1,3,3,3-Hexafluoropropan-2-ol (HFP) is a solvent [245] with unusually low nucleophilicity; it has a high ionizing power, a high hydrogen bonding strength, and a low hydrogen bonding acceptor strength, which makes it a good solvent for investigations of cation radicals. It may be useful for electropolymerization. It dissolves many polar compounds, but is less good in dissolving nonpolar substrates.

It has a liquid range from −5 to 58.6°, a dielectricity constant of 16.7, pK_A in water 9.30, and pK_A in DMSO 18.2. It is rather volatile and should be handled in a well-ventilated hood. Tetrabutylammonium hexafluorophosphate or tetrafluoroborate has a sufficient solubility in HFP to give a good conductivity. Aqueous Ag/AgCl or SCE has been used in connection with a suitable low-leaking salt bridge. The reversible potential ferrocenium/ferrocene couple in HFP was found [245] to be 0.05 V versus Ag/AgCl, to be compared with that in CH_2Cl_2, 0.43 V vs Ag/AgCl. The potentials in HFP generally differ appreciably from those in e.g., MeCN.

HFP of highest quality may be used as received; it is rather expensive as a solvent for electrochemistry and regeneration of the solvent could be attractive, but as HF might be

formed during regeneration, the procedure should be carefully considered. However, in the author's laboratory solvents from CV (HFP/TBABF$_4$), depending on the substrates, have been regenerated by destillation at 30°C/1/2 atm after use with a loss of 10–15 %.

4. Basic Solvents

Basic, protic solvents include ammonia and primary and secondary amines. These solvents are primarily of interest for an organic electrochemist because of their ability to solvate electrons, and solvated electrons have special reducing properties (Chapter 29). They also permit reductions in a protic medium in the presence of a very strong base, the conjugate base of the solvent.

a. Ammonia. The use of ammonia as solvent for electrochemical reactions presents some problems due to its inconvenient liquid range (−77.7 to −33.4°C); this difficulty can be coped with in different ways. The electrolysis may be made in a suitable low-temperature thermostat [329], the cell can be equipped with an efficient reflux condenser [330], a high-pressure apparatus can be used [331] (ammonia has even been used in its supercritical phase as a medium for electrochemical investigations [332]), or strong solutions (5–10 M) of various salts, such as NH_4SCN, NH_4I, $LiNO_3$, $LiClO_4$, NaSCN, and NaI, can be used [333] as they form a medium in which the vapor pressure of ammonia at ambient temperature is below 1 atm. The easy purification and low price of ammonia compared with the alternative amines favor the choice of ammonia for large-scale preparations.

When using a divided cell, a tube must connect the anode and cathode compartments for equilibration of the pressure.

Ammonia has a medium-high dielectric constant (23.7 at −36°C) and good dissolving power toward inorganic salts, but less for nonpolar organic compounds. It can act as both an acid and a base; the strongest possible acid in ammonia is ammonium ion and the strongest base the amide ion. The pK values of some weak acids have been determined in NH_3 at −60°C [334].

The combination of low proton availability together with the low temperature usually employed makes ammonia a suitable medium for electrochemical investigations of strongly basic species, such as dianions [49,335]. The low tendency to donate hydrogen atoms, due to the strength of an N–H bond, is important for many investigations [336–338].

Besides the electrolytes mentioned earlier, such salts as NH_4Cl, NH_4NO_3, KNO_3, and $NaClO_4$ may be used as supporting electrolyte; the tetraalkylammonium salts are generally rather sparingly soluble in ammonia. Most electrolyses in ammonia, except in voltammetric studies, have been performed without a reference electrode; as such, a $Zn(Hg)/ZnCl_2$ [206] or Pb/Pb^{2+} electrode [225,329,339] may be used. In polarography the mercury pool electrode has been applied [225].

Ammonia has been employed mostly for cathodic reactions, but some oxidations [330,333] have been carried out in this medium, although the potential range in the anodic direction is quite small. The anodically limiting reaction is oxidation to nitrogen and protons [340]; the cathodically limiting reaction is the transfer of electrons to the solvent, which occurs at about −2.3 V (versus Hg pool electrode) in a saturated solution of TBAI. In the elecltrolytic generation of solvated electrons the potential is determined by the surface concentration of electrons and no external reference electrode is needed.

Ammonia is purified by distilling it after treatment with sodium; the distillation from sodium may have to be repeated.

The threshold limit value (TLV) is 25 ppm.

b. Methylamine. Methylamine behaves electrochemically much like ammonia but has a somewhat more convenient liquid range (−93.45 to −6.3°C), although its odor and low boiling point require special considerations. Its dielectric constant is rather low (11.4 at −10°C), but sufficient conductivity for large-scale electrolysis can be obtained using LiCl as supporting electrolyte. Like ammonia, it is both an acid and a base.

Methylamine has mainly been used in large-scale electrolysis [341,342], and no reference electrodes have been employed so far. Reference electrodes such as the $Zn(Hg)/Zn^{2+}$ electrode, which work both in ammonia and ethylenediamine, would be assumed to be applicable to methylamine solutions.

Methylamine has been employed only for reductions, especially as solvent for electrolytic generation of solvated electrons. It would be of very limited use for anodic reactions. It may be purified by distillation from sodium. Its TLV is 10 ppm.

Ethylenediamine. Ethylenediamine (EDA) is a primary amine with a more convenient liquid range (11–117°C) than methylamine. Its dielectric constant ($\varepsilon = 12$) is about the same as that of methylamine. It dissolves many inorganic salts and is a better solvent than ammonia for many organic substrates.

LiCl, $NaNO_3$, and tetraalkylammonium salts can be used as supporting electrolytes. For the electrolytic generation of solvated electrons mainly LiCl has been employed [343,344]. A reversible reference electrode in EDA is the $Zn(Hg)/Zn^{2+}$ electrode [345], but the Hg pool [246] or the aqueous calomel electrode, fitted with a suitable salt bridge, is also applicable.

EDA is oxidized rather easily anodically but is resistant to reduction; the cathodic limiting current is the discharge of cations or the donation of electrons to the solvent. EDA may be purified by repeated refluxing and distillation from sodium [346]. It is extremely hydroscopic. The TLV is 10 ppm.

Other primary or secondary, aliphatic or cyclic amines may be used with similar results.

C. Aprotic Solvents

The use of aprotic solvents is of interest in many cases in which aqueous solutions lack desired or have undesired properties. The scarcity of protons makes it generally simpler to elucidate the mechanism of an electrode reaction for several reasons. The intermediates (e.g., radical anions) are more stable in the absence of protons, and the reaction scheme becomes simpler.

The scarcity of protons in aprotic solvents also makes it possible for added reagents (e.g., electrophiles) to compete successfully with protons for the intermediates.

"Dry" aprotic solvents usually contain some water, which is especially of importance in voltammetric studies in which the concentrations of water and substrate are about equal. The influence of a certain molar concentration of water depends on the solvent, the supporting electrolyte, and the substrate.

In certain solvents, such as dimethylformamide and dimethyl sulfoxide, water is a rather poor proton donor [347], and other impurities may be responsible for the protonation of the basic intermediates (radical anions, anions, and dianions). During preparative experiments the impurities may be reprotonated by water or, in case tetraalkylammonium salts (except tetramethylammonium salts) are used as supporting electrolyte, by attack on the cations (Hofmann elimination). Treatment of the medium with active alumina may lower the concentration of such protonating impurities [38,260].

When choosing a drying agent one must take into account that its affinity to water is different in vacuum and in a solvent, so the activity of a drying agent may be different in various solvents.

When deuterium oxide is added to an aprotic solvent containing tetraalkylammonium salts to promote incorporation of deuterium in the product, the base-promoted Hofmann elimination may become a problem, as the deuterium oxide becomes diluted with water. This can largely be avoided by running the reduction in the presence of a suspension of dry silica, which prevents the medium from being basic enough for the elimination to occur; the deuterium oxide adsorbed on the silica is in most cases sufficiently acidic to prevent Hofmann elimination. However, when the parasitic reaction is hydrogen abstraction from the solvent or supporting electrolyte, silica has no effect.

Controlled addition of a suitable proton donor or electrophile (reductions) or nucleophile (oxidations) is often useful in determining a reaction mechanism. The strength of a proton donor may vary from perchloric acid through acetic acid and a phenol to an alcohol; C acids, such as malonic ester, or N acids, such as urea, may also be used. Used as bases may be pyridine, carboxylate ions, alkoxides, or salts of malonic ester. Sometimes it is of interest to determine whether it is the basic or the nucleophilic properties of the compound that are important. The use of two bases with approximately the same pK values but widely differing in nucleophilicity, such as pyridine and a 2,6-dialkylpyridine, might answer the question.

In the absence of proton donors the "aprotic" solvent may act as a proton donor; the conjugate base of the solvent may act as a nucleophile toward substrate or intermediates.

Electrochemical phenomena may also be simplified in organic solvents, compared with aqueous solutions, because of the less important role adsorption plays in organic solvents.

1. Acetonitrile

Acetonitrile (MeCN) is one of the most used polar aprotoc solvents for both anodic and cathodic reactions. It is an excellent solvent for many organic substrates and quite a few organic and inorganic salts; it is miscible with water. Salt solutions show a reasonably high conductivity due to its rather high dielectric constant ($\varepsilon = 37$). MeCN is somewhat toxic, with a recommended maximum air concentration of 20 ppm.

Besides having good electrochemical properties, acetonitrile is an unusually good solvent for UV spectrosocpy, being transparent until about 190 nm. It is furthermore a convenient solvent for electron spin resonance (ESR) spectroscopy, which is valuable for the investigation of radicals produced during electrolysis. For use in preparative electrochemistry its liquid range (−45 to 82°C) is sufficient for most purposes and its relatively low boiling point makes the removal of the solvent easy. On gas-liquid chromatography (GLC), tailing may occur, unless a suitable polar column is used.

Acetonitrile has a wide, usable potential range in both the anodic and cathodic directions. The limit is set by the electrode reaction of the supporting electrolyte in both directions. In the presence of sodium or lithium ions their discharge sets the limit; the sodium subsequently reacts with acetonitrile, whereas lithium does not. Quaternary ammonium ions are reduced with dealkylation. Perchlorate ions, a widely used supporting electrolyte, are discharged to perchlorate radicals, which probably rapidly form oxygen and chlorodioxide radicals [259]. Transfer of protons in acetonitrile is a rather slow process. Its autoprotolysis constant is 33.2. In DMSO MeCN has $pK_A = 31.3$ [348]. MeCN is less apt to donate hydrogen atoms than DMF. Anhydrous perchloric acid in

MeCN has been prepared by oxidation of H_2 to H^+ at a platinized platinum electrode in a solution of $TBA^+ClO_4^-$ in MeCN [349].

Useful supporting electrolytes in acetonitrile are $NaClO_4$, $LiClO_4$, tetrabutylammonium salts, as well as other tetraalkylammonium salts. $AgNO_3$ and $AgClO_4$ are very soluble in acetonitrile; AgCl is somewhat soluble, especially in the presence of an excess of chloride ions. It is possible to make CV in MeCN with $TEACF_3SO_3$ or CF_3SO_3Na as supporting electrolyte near the supercritical conditions, but the resistance is too high for preparative reactions [350].

The Ag/Ag^+ electrode [198,199], which is reversible in acetonitrile, may be used as reference electrode. Quite often an aqueous calomel electrode with a suitable liquid junction is used [225]; a comparison of different reference electrodes has been made [226]. The Hg/Hg(I) is not stable in acetonitrile, as Hg(I) decomposes [351]. A platinum electrode coated with a film of poly(vinylferrocene) is a stable reference electrode in MeCN [203].

Commercial acetonitrile usually contains impurities, such as acrylonitrile, acetic acid, aldehydes, amines, and water. Several methods of purification [352–354] have been proposed: one is to distill it several times from P_2O_5 followed by fractionation from K_2CO_3 (200); a pure product may be obtained, but the procedure is time consuming and wasteful due to polymerization of MeCN; polymerization may be avoided by using B_2O_3 instead of P_2O_5 [355].

CaH_2 treatment of MeCN has been recommended [338], but it does not remove traces of aromatic hydrocarbons and is a surprisingly ineffective drying agent in MeCN [355]. For removal of acrylonitrile, which boils 4°C lower than MeCN, treatment with NaH [357] or azeotropic distillation with ethanol [358] has been recommended.

Removal of impurities by reaction in turn with benzoyl chloride and $KMnO_4$ followed by careful distillation gives a product suitable for both electrochemical and spectroscopic work [359]. Alternatively, acetonitrile is treated with N_2O_4, then with CaH_2, fractionated under N_2 from CaH_2, and the product further purified by letting it run through a column of activated alumina [260,358,360].

Water may be removed from commercial MeCN by azeotropic distillation [361,362] or by treatment with molecular sieves 3A; 3A is much more efficient than 4A for drying MeCN [355].The procedures recommended by IUPAC for purification are described in Ref. 363.

As is the case for other relatively inert solvents, it is unlikely that an all-purpose purification procedure can be devised that will give optimum results in all possible applications. Consequently, purification should be tailored to the intended use of the solvent.

Pure acetonitrile is not particularly hygroscopic. The product obtained by these procedures can be stored for several months without deterioration; the water content is approximately 1 mM. It is advisable to use the same glass apparatus repeatedly for the purification and storing of acetonitrile.

Electrolysis in MeCN, in the absence of added proton donor may produce the anion of MeCN $(CH_2CN)^-$, which may act as a nucleophile toward electrophilic centers [364].

At a Pt anode the solvent system $MeCN/TBABF_4$ breaks down to an adduct, CH_3CNBF_3, whereas the cathodic breakdown mainly gives the anion of 3-amino crotonitrile; in the presence of water the anion of acetamide is also formed and the breakdown commences at much less negative potentials [365].

Other nitriles, aliphatic and aromatic, have been investigated as solvents for electrolysis. Butyronitrile has been suggested as the solvent of choice for low-temperature electrochemistry [86], and propionitrile has in some cases been employed, as it is less

hygroscopi than MeCN [366]. Benzonitrile might be considered when hydrogen atom abstraction from the solvent is undesirable.

2. Dimethylformamide

Dimethylformamide (DMF) is a polar solvent with a dielectric constant ($\varepsilon = 37$) comparable to that of acetonitrile. It is a good solvent for most organic compounds and also for many organic and inorganic perchlorates and organic fluoborates. Owing to these properties, DMF has been widely used in electrochemical work. DMF is, however, susceptible to hydrolysis, which yields the easily oxidizable dimethylamine and the reducing agent formic acid.

DMF has an acceptable liquid range (−61 to 153°C), although the boiling point is near the upper limit for its convenient removal by distillation during the workup. DMF is inferior to acetonitrile as a solvent for UV spectroscopy. Contact with the skin and vapor concentrations over 10 ppm should be avoided.

For reductions DMF has a usable potential range comparable to that of acetonitrile, but it is inferior for oxidations. In the presence of inorganic ions their discharge is the cathodic limiting reaction, whereas it is more uncertain whether it is the solvent or the cation that is reduced in solutions of tetraalkylammonium ions. The anodic limiting reaction at a Pt electrode is an oxidation of DMF, which involves the removal of an electron from the amide nitrogen. Its autoprotolysis constant is 29.4. DMF is a better hydrogen atom donor than MeCN and DMSO.

As supporting electrolyte, tetraalkylammonium perchlorates or fluoroborates are mostly used, but LiCl or $NaClO_4$ may also be employed. The reference electrode may be a modified Ag/AgCl electrode [211,216], a $Cd(Hg)/Cd^{2+}$ electrode [211,216], $Na(Hg)/Na^+$ electrode [205], or silver/silver cryptate electrode [201].

For many purposes the commercial reagent-grade DMF, dried with molecular sieves, can be used; DMF decomposes on distillation at atmospheric pressure. The most convenient way to purify DMF is probably to let it pass through a column [358] of alumina (e.g., ICN Alumina N-Super I). Other methods involve drying ($CuSO_4$ [367], which also removes amines), azeotropic distillation with benzene, or percolation through molecular sieves [368] followed by fractional distillation at reduced pressure. DMF is difficult to obtain in an anhydrous form, but for most purposes a small water content is not critical. An impurity of *N*-methylformamide may act as a proton donor or otherwise interfere in the follow-up reactions [369]. DMF should be stored in the dark under nitrogen. The different purification methods have been compared and discussed [370].

3. *N*-Methylpyrrolidone

DMF has certain disadvantages that can be traced to its hygroscopic properties and rather easy hydrolysis; *N*-methylpyrrolidone (NMP), which is an *N*-disubstituted amide just like DMF, is less apt to hydrolyze owing to its cyclic structure. Furthermore, the product of hydrolyxis is not a reducing agent as is formic acid formed from DMF. Although only a limited number of experiments in NMP have been done [371,372], it seems probable that NMP will replace DMF in a number of cases because of its higher stability [373]. Vapor concentrations over 100 ppm should be avoided.

Like DMF, NMP is of limited value for oxidations but useful for cathodic reactions. Its dielectric constant is 32, and it is able to dissolve the same types of salts and organic compounds as DMF. NMP has a liquid range of from −24 to 205°C; the useful potential range is approximately the same as for DMF. Mercury in contact with its oxidation

products has been used as reference electrode; it is more stable than the Ag/Ag^+ electrode [371,372].

Other organic amides, such as formamide, *N*-methylformamide, *N*-methylacetamide, and tetramethylurea, have been investigated as solvents for electrochemical use primarily due to their high dielectric constant; none of them, however, seem to offer distinct advantages over DMF or NMP and in some respects they are inferior. *N*,*N*-Dimethylacetamide may be purified by destillation in vacuum [374].

4. 3-Methyl-2-Oxazolidinone (3M2O)

3M2O is a colorless, nonvolatile (kp_1 87–90°C) solvent with a high dielectric constant (77.5). It may be purified by vacuum distillation over BaO. With TBAP as electrolyte the cathodic limit is −2.9 V (aqueous SCE); the anodic limit at a Pt anode is +1.3 V. The suitability of 3M2O for voltammetry has been investigated [373].

5. Hexamethylphosphoramide (HMPA)

HMPA is a polar solvent that is remarkable for its ability to solvate electrons. Even in a mixture with ethanol (67 mol% ethanol and 33 mol% HMPA), reductions via solvated electrons may take place [373–377]. It has been suggested that HMPA is selectively adsorbed at the electrode, thus providing a layer of low proton activity near the electrode.

The liquid range of HMPA is 7.2–235°C; its dielectric constant is 30 (20°C). HMPA solvates cations strongly, whereas anions are less solvated. Unlike carboxamides, such as DMF, it is not attacked by aqueous alkali at $t < 80$°C, and it is very resistant toward nucleophilic attack [377] but forms peroxides under the influence of light and oxygen [376].

HMPA is completely miscible with water; it can be extracted from water by chloroform, which forms a complex with HMPA [204], $K(CHCl_3/H_2O) = 5.5$ [378]; HMPA is somewhat more basic than DMF. HMPA dissolves such salts as LiCl, $LiClO_4$, $NaClO_4$, and R_4NClO_4; the Ag/Ag^+ may be used as reference electrode [379]. The solvation effect of the cation of the supporting electrolyte in HMPA has been investigated [380]. Using R_4NClO_4 the accessible potential range is from +0.14 to −3.35 V (Ag/Ag^+) at a mercury electrode [376]. HMPA can be purified by fractionation under vacuum, boiling point 88–92°C (3 mm), 68–70°C (1 mm).

Reflux over BaO, followed by fractionation under vacuum, reflux over sodium, and finally vacuum distillation has been recommended for the purification [380]. Alternatively, fractional distillation over CaH_2, followed by purification through a column of activated alumina and standing over pyrene and sodium, produced a product that after distillation on a vacuum line contained only a negligible amount of impurities [381]. The purification of HMPA has been critically discussed [382].

Just like DMF, HMPA is not suitable for anodic reactions, since the amide nitrogen loses an electron easily. For cathodic reactions the useful potential range extends, in the presence of LiCl, to the value at which electrons are given off to the solution. HMPA has not been used widely in electrochemical experiments, and although its special properties are useful in electrochemistry, it should be used only when sufficient precautions have been taken with regard to its carcinogenic and other toxic properties [383]. Tetramethylurea (TMU) may in some cases be used as a nontoxic replacement for HMPA [384]. TMU may be purified by distillation from CaH_2.

6. Pyridine

Pyridine is a reasonably strong base and a good nucleophile. Although its dielectric constant is rather low ($\varepsilon = 12$), many salts are soluble in pyridine and the solutions have good conductivity. In contradistinction to most bases, pyridine, which is a π-electron-deficient heteroaromatic compound, is rather resistant toward oxidation.

Pyridine has a liquid range from −41 to 115°C; it is miscible with water and a good solvent for many organic compounds. Such salts as $LiNO_3$, LiCl, $LiClO_4$, NaI, KSCN, and tetraalkylammonium salts are soluble in pyridine. As reference electrode the Ag/Ag^+ [230] or the Hg pool electrode can be employed. Solute-solvent interactions have been discussed [385].

The useful potential range is from about −2.3 V [230] (versus Ag/Ag^+ electrode, DME, Bu_4NI) to + 1.4 V versus Ag/Ag^+, graphite electrode/$LiClO_4$ [385]. The cathodic limiting reaction might be the discharge of the cation, whereas an electron abstraction from pyridine is the anodic limiting reaction, in which probably 2-pyridylpyridinium ion is formed.

Besides being used as a solvent, pyridine has been employed as a nucleophile that is oxidizable with difficulty [199]. Reagent pyridine is satisfactory for most purposes; it may be dried with molecular sieves, type 5A. A recommended procedure for obtaining pure pyridine has been published [386]. The TLV is 5 ppm.

7. Dimethyl Sulfoxide (DMSO)

DMSO is an excellent solvent for many inorganic salts and organic compounds. It is difficult to reduce and fairly resistant to electrolytic oxidation. Its dielectric constant is high ($\varepsilon = 47$). It thus has many of the qualities desirable for a solvent for electrolysis, and it shows promise of being one of the most important electrochemical media [387]. The liquid range is from 18 to 189°C, which makes it somewhat inconvenient to get rid of DMSO in the workup. When used as solvent for electrolysis it must be considered that DMSO is not always inert but has a fair reactivity in certain reactions. DMSO is unfit for UV spectroscopy. Its autoprotolysis constant is 31.8.

DMSO has low toxicity; it is, however, transported through the skin very rapidly. Thus, minutes after applying a drop of DMSO to the palm of the hand its sweetish taste can be detected in the mouth. It may carry with it dissolved toxic materials that otherwise would be unable to penetrate the skin.

Many salts are soluble in DMSO, so the choice of supporting electrolyte is less restricted than in most other nonaqueous solvents. In general, perchlorates, even $KClO_4$, nitrates, and halides, are soluble, whereas fluorides, cyanides, sulfates, and carbonates are not; thus not only $NaClO_4$, LiCl, $NaNO_3$, and tetraalkylammonium salts can be used but also such salts as NH_4PF_6 and NH_4SCN. The ability of DMSO to solvate ions is also of importance in the indirect electrolytic hydrodimerization of, for example, acrylonitrile using Na(Hg) [388].

The equililibrium constant of the self-ionization of DMSO is 5×10^{-8} (25°C); the conjugate base $(CH_3SOCH_2)^-$, which is formed when DMSO acts as a proton donor during a reduction, is a rather strong base and a fairly good nucleophile, which may attack electrophilic centers or radicals [389].

The potential range of DMSO in the cathodic direction is at a Hg electrode limited by the discharge of the cation. Potassium and sodium react with DMSO, whereas lithium does not; tetraalkylammonium ions are reduced about −2.8 V (SCE) [390]. The anodic

limiting reaction at a Pt electrode is the oxidation of DMSO; probably one of the nonbonding electrons is lost, but the limiting reaction has not been investigated yet.

As reference electrode [211] for polarographic work, an aqueous or methanolic calomel electrode, connected to the DMSO solution with a suitable salt bridge to avoid contamination, has been used. The most stable reference electrodes in DMSO seem to be the amalgam electrodes, such as Tl(Hg)/TlCl [214] or Li(Hg)/LiCl [207].

DMSO is somewhat hygroscopic, and the main impurity in a good commercial grade of DMSO is water; the odor is due to dimethyl sulfide. For many purposes DMSO can be used as received or after drying either by shaking with CaO–MgO or passing through a column of molecular sieves. For further purification, fractional distillation or crystallization may be used. It has been recommended [391] that a fractional crystallization be done followed by two fractional distillations in vacuo, one through a column packed with activated carbon and one through a spinning band column. The pure DMSO must be handled without contact with humidity.

The different purification procedures have been discussed [392].

8. Sulfolane

Among sulfones, sulfolane (tetrahydrothiophen-1,1-dioxide, tetramethylene sulfone) shows promise for electrochemical use. It has a wide liquid range (28.6–285°C); on dissolving 0.1 M salts in sulfolane, its melting point is depressed below 25°C. Sulfolane has a relatively high dielectric constant (43 at 20°C), it is chemically stable toward both reducing and oxidizing agents, and it has a fair dissolving power for inorganic salts. One of its drawbacks is that it is rather hygroscopic.

The accessible potential range is large in both the anodic and cathodic directions. The limiting cathodic reaction seems to be the discharge of the supporting electrolyte, whereas the limiting anodic reaction probably is the oxidation of the solvent. With $NaClO_4$ as supporting electrolyte the anodic limit at a Pt electrode is about 2.3 V and the cathodic limit about −4 (versus Ag/Ag^+ electrode) [393].

As supporting electrolyte, $NaClO_4$, $LiClO_4$, NH_4PF_6, and quaternary ammonium compounds can be used. The Ag/Ag^+ [393,394] or Ag/AgCl [395] electrode or an aqueous SCE [396] with a suitable salt bridge can be used as reference electrode.

Sulfolane may be purified by fractional crystallization followed by fractional distillations at reduced pressure [396]; alternatively, treatment with aqueous hydrogen peroxide, followed by extraction with CH_2Cl_2 and fractional distillation, may be employed [393]. The purification procedures have been discussed [397].

Sulfolane is an alternative to acetonitrile or nitromethane as a solvent for anodic reactions; in reductions it generally offers no advantages over such solvents as MeCN, DMF, or DMSO, but for anodic fluorination sulfolane might be better than MeCN, as a competing acetamidation is avoided (Chapter 25).

Among other sulfones, dimethyl sulfone has been used as electrochemical medium [398,399]; its high melting point, 109°C, makes it less suitable for organic compounds.

9. Propylene Glycol Sulfite

A series of other sulfur-containing solvents has been investigated for electrolytic use. Of these, *propylene glycol sulfite* [400], a derivative of 1,3,2-dioxthiol, was found most suitable. It has a dielectric constant of 33, forms solutions with good conductivity with such salts as $LiClO_4$, and does not react with lithium. It has not yet been used for organic electrolysis.

10. Nitromethane

Nitromethane is one of the few solvents useful for anodic reactions, among them anodic coupling of aromatic hydrocarbons. Its application for cathodic reactions is limited, but in some cases in which its unreactivity toward certain active halogen compounds is valuable it may be used. The liquid range of nitromethane is −29 to 101°C; its dielectric constant is 37, but the dissociation of salts is not as high as could be expected.

Nitromethane dissolves rather few inorganic salts; $LiClO_4$ [403], $Mg(ClO_4)_2$, and tetrabutylammonium salts can be used as supporting electrolyte. The Ag/Ag^+ or Ag/AgCl electrode can be employed as reference electrode [202].

At a platinum electrode, potentials of about 3 V (versus Ag/AgCl) can be reached, and the limiting reaction is the discharge of the supporting electrolyte. The useful range in cathodic direction is very dependent on the water content.

Nitromethane has been purified by repeated washings with bicarbonate, sulfuric acid, and water, followed by drying and fractional distillation; the water content of the product is 5–8 mM. Alternatively, fractional distillation at reduced pressure followed by repeated fractional freezing may be employed [401]. The TLV is 100 ppm.

11. Nitrobenzene

Nitrobenzene has been used for electrolysis [402]; it was found that certain radicals were rather stable in this solvent. Nitrobenzene has a liquid range from 5.7 to 210.9°C; Bu_4NClO_4 may be used as supporting electrolyte. An aqueous SCE separated from the solution by a suitable bridge with porous glass has been used as reference electrode. Nitrobenzene may be purified by passing it through a column of alumina followed by a distillation in vacuo.

12. Propylene Carbonate (PC)

PC is of potential use in organic electrochemistry [404–406]. It has a high dielectric constant ($\varepsilon = 69$) and a wide liquid range (−49 to 242°C), but it is more reactive than acetonitrile, and the potential limit for anodic reactions is lower than for acetonitrile. It has so far been used mostly for electrochemical generation of cation radicals [406].

The cathodic limiting reaction of propylene carbonate containing $LiClO_4$ has been shown [407–410] to be a reduction to propene and carbonate. This reductive elimination is analogous to the reduction of vicinal halogen compounds to alkenes. The anodic reaction is an oxidation to CO_2 [409,410].

Propylene carbonate decomposes slowly on standing to allyl alcohol and CO_2; after standing for a year, small amounts of allyl alcohol could be detected. Protons increase the rate of decomposition [411].

With $LiAsF_6$ the oxidation limit of propylene carbonate is 4.0 V versus Li^+/Li [412].

As reference electrode, an Li/LiCl electrode, which in the presence of excess tetrabutylammonium chloride is an electrode of the second kind, may be used [413]. An $Ag/AgClO_4$ reference electrode with an $NaClO_4$ salt bridge has been used [414]; AgCl/Ag [415] and T1X/T1 [416] reference electrodes have also been employed. The purification of PC has been discussed [417].

13. Benzene and Chlorobenzene

It has been possible to use these nonpolar solvents for electroanalytical measurements by employing a minute working electrode [418], an ultramicroelectrode, or using a benzene solution containing a crown either (15-crown-5) and sodium tetraphenylborate [419].

Tetrahexylammonium perchlorate and tetrabutylammonium tetrafluoroborate have been used as supporting electrolyte in benzene and chlorobenzene, respectively. The latter was suggested [418] to be an excellent solvent for the study of reversible oxidations and reductions of aromatic compounds. The TLV for chlorobenzene is 75 ppm.

Benzene and even aliphatic hydrocarbons [74] have been used as solvents in SPE cells.

14. Ethers

Ethers, such as tetrahydrofuran and 1,2-dimethoxyethane, have low dielectric constants (7.4 and 7.2, respectively), and the choice of supporting electrolyte is very limited. The ethers are difficult to reduce and are inert toward many metalorganic reagents [243] that are soluble in the ethers. Ethers are thus suitable as medium for the anodic addition of Grignard reagents to olefins [420]. Dimethoxyethane and polyethylene glycol dimethyl ethers have the ability to solvate electrons [421]. Dissociation constants for some acids and the relative strength of some bases in THF has been determined [422].

As supporting electrolyte, $NaClO_4$ or $LiClO_4$ may be used in both solvents; TBAI in tetrahydrofuran and TBAP in dimethoxyethane have also been employed. As reference electrode the Ag/Ag^+ electrode functions satisfactorily [243]. Ferrocence and bis(biphenyl)chromium have also been used as reference electrodes in THF [423].

The ethers form peroxides. These can be removed by distillation from $LiAlH_4$. They must be stored under nitrogen or distilled from $LiAlH_4$ or Na directly into the electrolytic cell. If the water content of DME or THF is not neglible, the cathode may be passivated by a layer of a hydroxide formed during electrolysis, when an alkali metal salt is used as supporting electrolyte [424]. Purification of THF using sodium dianions of benzophenone and anthracene has been described [424a]. Protons and Lewis acids (EGA) can induce polymerization of THF; this may cause problems at the anode. The TLV for THF is 200 ppm.

15. Methylene Chloride and 1,1,2,2-Tetrachloroethane

Electrolysis may be carried out in methylene chloride. It dielectric constant is low ($\varepsilon = 9$), and only the larger tetraalkylammonium salts are soluble in methylene chloride.

Methylene chloride has been used for both anodic and cathodic reactions. The major advantages of using methylene chloride seem to be that certain cation radicals are more stable in methylene chloride than in the solvents usually employed in electrochemistry [425,426]. A disadvantage is that chloride ions produced at the cathode may diffuse to the anode compartment and interfere with the anodic reactions. This can partially be avoided by the addition of small amounts of acetic acid to the catholyte whereby the cathodic reaction becomes an evolution of hydrogen rather than formation of chloride ions.

In electrosynthesis in systems of two immicible liquids and a phase transfer catalyst, methylene chloride is in many cases preferred as the organic solvent.

The addition of trifluoroacetic acid (TFA) and its anhydride (TFAn) to CH_2CL_2 enhances the stability of cation radicals in the solution. A mixture of CH_2Cl_2–TFA–TFAn of 45:1:5 has been recommended [318]. TLV is 100 ppm.

1,1,2,2-Tetrachloroethane has been found to be a good solvent for anodic investigations of fullerenes (Chapter 7). It may be purified by refluxing over CaH_2 and dried over P_2O_5 under high vacuum [427].

16. Sulfur Dioxide

Sulfur dioxide is a solvent of low nucleophilicity and may be used when nucleophilic trapping by solvent is to be avoided. Its liquid range is somewhat inconvenient (−75 to −10°C), but its dielectric constant is reasonably high (17.6 at −20°C).

The SO_2 may be purified by washing with concentrated sulfuric acid, perculated through P_2O_5 and finally treated through a column of basic alumina [428,429].

As supporting electrolyte, Bu_4NClO_4 or Pr_4NPF_6 may be used [430–432]; at 0.2 M solution of these salts has a conductivity of about $9 \times 10^{-3}\ \Omega^{-1}\ cm^{-1}$ at −22° C. $CsAsF_6$ gives a potential window to about 5 V versus SCE, enough to oxidize methane; however, the solubility (and thus conductivity) of $CsAsF_6$ in SO_2 is too low to allow a preparative oxidation [428]; however, Bu_4NBF_4 has been used for preparative methylthiation [433].

As reference electrode, Ag/0.1 M $AgNO_3$ in acetonitrile has been used. The anodic range of perchlorates or hexafluorophosphates in sulfur dioxide is large. $AlCl_3$ may also be used as supporting electrolyte [434]; cation radicals are considerably stabilized in this medium.

D. Salts

In certain electrolytic media the concentration of salts is so high that the medium could be regarded as consisting of a solvated salt. This is thus the case in the strong solutions (10 M) of many salts in ammonia in which the vapor pressure of ammonia at ambient temperature is less than 1 atm. It also applies to the strong solutions of tetraalkylammonium *p*-toluenesulfonates in water, used sometimes in organic electrochemistry.

A genuine liquid salt is *tetrahexylammonium benzoate* (THAB) [244], which is a viscous liquid capable of acting as both solvent and supporting electrolyte; it has, however, a rather high resistance. Although it is a fairly polar solvent, THAB is miscible with benzene, toluene, and carbon tetrachloride; a mixture of THAB-toluene (75:25) has a rather low specific resistance of 3.8 kΩ and a much lower viscosity than pure THAB, which is about as viscous as glycerol. Relatively little water is miscible with THAB; addition of 1% by volume of water to tetrahexylammonium benzoate results in a two-phase system. THAB is soluble in acetone.

THAB is useful for reductions; the cathodic limit at a Hg electrode is about −2.6 V versus Ag/AgCl; at a platinum electrode the anodic limit is at about 0.3 V.

THAB has been prepared by neutralizing tetrahexylammonium hydroxide, obtained from the iodide by treatment with Ag_2O, with benzoic acid and evaporation of the water. The analysis of the dried product corresponds to a hemihydrate. The material is somewhat hygroscopic but can be dried by brief heating to 90°C.

Voltammetry has also been made in (toluene)$_3$tetrabutylammonium tetrafluoroborate; the resistance of the solution is between that of DMF and THF [435] but closer to that of DMF. On addition of proton donors, a low "buffer capacity" of the solvent is observed.

Aluminum chloride in mixture with an alkylpyridinium chloride, preferentially butylpyridinium chloride, has certain possibilities as a medium for studying electrochemi-

cally generated cation radicals. The 0.8:1 $AlCl_3$–$BuPy^+Cl^-$ mixture is molten at room temperature but has generally been used at 40°C [436].

A mixture of 1-methyl-3-ethylimidazolium chloride with aluminum chloride also gives an ionic liquid that may be used as electrolytic medium [437]. The medium is not quite inert; for example, quinone reacts with an excess of chloride to 2-chlorohydroquinone in an acid-catalyzed Michael addition [438]. As reference electrode an aluminum wire was used. 1-Methyl-3-ethylimidazolium chloride is in MeCN reduced at −2.35 versus Ag in 0.1 M TBAP [439].

At higher temperature certain quaternary ammonium salts (40–150°C) [440] may be used as media for electrolysis.

E. Supercritical Fluids

Supercritical fluids (SCF) have been used mainly for selective extraction of compounds; the solubility of a compound in a given solvent is in many cases vastly different under ambient and supercritical conditions. Thus supercritical water dissolves both polar and nonpolar compounds, which may be explored in electrochemistry. When temperature and pressure approach the critical values, the internal structure of the solvent is loosened and the viscosity, the dielectric constant, and the density diminish; the dielectricity constant ε of water thus diminishes from 80 at 25°C to 5.2 at 647°C at 221 bar [441].

Cyclic voltammetry in supercritical water–0.2 M $NaHSO_4$ [88] and ammonia–0.14 M CF_3SO_3K [88,332] of some organic compounds shows that this electroanalytical technique was applicable under these conditions. The behavior of phenazine in NH_3 at −40°C and under supercritical conditions, for example, was analogous; two reversible reductions were found in both cases [88]. Dimethyl carbonate has been prepared from CO and MeOH on anodic oxidation in a supercritical mixture of CO_2 and MeOH [89].

Supercritical carbon dioxide ($scCO_2$) has a dielectric constant $\varepsilon = 1.6$ (cyclohexane $\varepsilon = 2.0$), and even though tetrakis(decyl)ammonium tetraphenylborate has some solubility in $scCO_2$, the conductivity is too low for practical electrochemistry [442]. 1,1,1,2-Tetrafluoroethane (HFC 134a) has a higher polarity in the supercritically state, and well-behaved CV may be obtained; with $TBAClO_4$ a potential "window" of about 9 V has been obtained [443].

VII. ELECTROLYTES

The passage of electric current through a nonmetallic liquid is dependent on ions. The choice of electrolyte depends on such properties as its solubility, dissociation constant, mobility, discharge potential, and protic activity. It is desirable to employ a salt with high solubility, complete dissociation, high mobility of the ions, and a numerically high discharge potential. The role of adsorption of ions at the electrode is discussed elsewhere. The electrolyte may influence the rate constant for electron transfer from an electrode to a substrate.

A. Anions

The choice of anion is of most importance in anodic reactions in which the choice may influence the product distribution. Unless the oxidized anion is desired in an indirect electrolytic oxidation (Chapter 29), an anion that is oxidizable with difficulty, such as

perchlorate, tetrafluoborate, hexafluorophosphate, or nitrate, is chosen. In aqueous solution the choice of anion is less critical than in nonaqueous solvents. In cathodic reactions the choice of cation has highest priority, and the anion is generally selected on the basis of solubility of the salt or the ability of the anion to assist in dissolving the substrate.

1. Perchlorate

The perchlorate ion has a high anodic discharge potential, and only in a few solvents, such as acetonitrile or nitromethane, is the perchlorate ion oxidized in preference to the solvent. When oxidized, the primarily formed perchlorate radical decomposes into oxygen and chlorodioxide radical [259].

Caution must be exercised when handling perchlorates. Silver perchlorate is explosive; grinding it in a mortar should be avoided. For use in reference electrodes, it may be prepared by anodic dissolution of silver in a perchlorate medium [202]. Evaporation of solutions of organic perchlorates is discouraged but, if necessary, must occur in vacuo and at moderate temperatures. Even sodium perchlorate, which can be dried at 100°C without undue risk, may cause explosions when heated with an organic solvent.

Sodium perchlorate is soluble in many organic solvents. It is hygroscopic but can be dried at 110°C. Drying $NaClO_4,H_2O$ often results in a sintered mass that must be broken and dried. By recrystallization of $NaClO_4$ at temperatures about 80°C the anhydrous salt can be obtained, which can be dried without difficulty. Lithium perchlorate is very hygroscopic. Tetraalkylammonium perchlorates are less hygroscopic, and some of them may be recrystallized from water; they are useful for voltammetric studies in organic solvents.

2. Tetrafluoroborate

The discharge potential of the tetrafluoroborate ion is slightly more positive [444] than that of the perchlorate ion. Tetrafluoroborates do not have a tendency to explode, and they are recommended instead of perchlorates for use in preparative work when the solvent must be removed during the workup.

It has been reported that BF_4^- as anion in a supporting electrolyte in DMF gives in CV an anodic peak around 0.8 V versus SCE at a glassy carbon electrode [445].

Tetrabutylammonium tetrafluoroborate is only slightly soluble in water but is soluble in organic solvents. It is prepared by mixing solutions of $NaBF_4$ with a soluble tetrabutylammonium salt. Its solubility properties are convenient for its use in preparative electrolysis. During the workup the organic solvent may be diluted with water, whereby the salt precipitates and is recovered for future use. It may be recrystallized from toluene; the solution is dried by azeotropic distillation (or by molecular sieves A4); the compound crstallizes slowly on cooling [446].

3. Hexafluorophosphate, Hexafluoroarsenate

Hexafluorophosphates are slightly more resistant toward anodic oxidation than tetrafluoroborates and perchlorates [444]; in a 0.1 M solution of these salts in acetonitrile the potentials (versus Ag/0.1 M Ag^+ electrode) at a platinum disk electrode (0.12 cm_2) at 1 mA were for perchlorate, 2.48 V; for tetrafluoroborate, 2.91 V; and for hexafluorophosphate, 3.02 V [444]. Hexafluoroarsenates have been used in liquid SO_2 [432,433].

4. Trifluoromethanesulfonate

The trifluoromethanesulfonates have certain advantages over perchlorates (nonexplosive) and tetrafluoroborates (even less reactive toward oxidizing agents) [447]. The tetraalkylammonium trifluoromethanesulfonates are just as soluble or more soluble in the commonly used organic solvents than the corresponding perchlorates or fluoroborates. They can be prepared either by metathesis or by alkylation of a tertiary amine by an ester of trifluoromethanesulfonic acid.

5. Nitrate

Nitrate ion is not as resistant to oxidation as perchlorate or tetrafluoroborate; in nitromethane [448] solution it is oxidized anodically to NO_2^+ and oxygen, and the NO_2^+ reacts either with the water always present in "dry" organic solvents to form nitric acid or with nitrate ion to form N_2O_5. Nitrates, to a higher degree than perchlorates [449], form ion pairs in some solvents. Tetrabutylammonium nitrate can be prepared conveniently by mixing an aqueous solution of $NaNO_3$ with the commercially available tetrabutylammonium hydrogen sulfate. The salt is then extracted into methylene chloride, giving an almost quantitative yield of Bu_4NNO_3.

6. Aromatic Sulfonates

The use of aromatic sulfonates stems from their ability to assist the solution of organic substrates in an aqueous medium. This "hydrotropic" effect [270,450,451] is accentuated if a quarternary ammonium sulfonate, rather than an alkali metal sulfonate, is used.

The aromatic sulfonates have been employed mostly for reductions, but they would be expected to be reasonably stable toward oxidation. To obtain a reasonable hydrotropic effect, rather high concentrations are used; in the original hydrodimerization reaction of acrylonitrile, the medium may be regarded as either a solution of tetraalkylammonium *p*-toluenesulfonate in water or the salt containing some water.

7. Carboxylate Ion

In the Kolbe reaction and in anodic carboxylation reactions, salts of carboxylic acids function as both substrate and electrolyte. Usually the presence of other anions diminishes the yield of the Kolbe reaction, whereas the presence of anions that are oxidizable with difficulty, like bicarbonate or perchlorate ions, favors the related Hofer–Moest reaction.

For reductions in aprotic media, tetraalkylammonium salts of derivatives of oxalic and formic acid may be employed; in many cases the reaction may then be performed in an undivided cell, as the reaction at the counterelectrode (oxidation of the anion to carbon dioxide) generally does not interfere with the cathodic reaction [452].

8. Tetramethylaluminate and Tetraphenylborate

The sodium salts of these anions are soluble in tetrahydrofuran and have been found suitable as supporting electrolyte in this solvent [453,454].

B. Cations

The discharge potential of a cation determines whether it is useful, so in practice only alkali and alkali earth metal ions together with ammonium and tetraalkylammonium ions

are used. The nondischarge of a cation is a sine qua non, but in addition a choice of cation must take into consideration ion pair formation, solvation, and adsorption of particular species (e.g., see Refs. 455–457).

1. Lithium Ions

Many lithium salts, such as lithium perchlorate and the halides, are soluble in nonaqueous solvents. The reduction potential of Li^+ depends on the electrode and the solvent. At a mercury cathode amalgam formation takes place, whereas formation of lithium metal occurs at platinum in aprotic media. Lithium metal is less reactive than sodium, and in some solvents sodium attacks the solvent whereas lithium is unreactive. A small water content in an aprotic solvent may react with lithium (or Li^+ may react with hydroxyl ions formed at the cathode) to form lithium hydroxide, which may cover the electrode with an insoluble, insulating layer.

2. Sodium Ions

In aqueous buffers sodium ion is a common cation, but in nonaqueous solvents practically only $NaClO_4$ is useful. Even $NaBF_4$ is not suitable in most aprotic solvents.

3. Magnesium ions

Magnesium ions interact with radical ions in aprotic media, which may influence the course of the reaction; in some cases Mg^+ also stabilizes the product and thereby helps avoiding unwanted further reactions [458,459].

4. Tetraalkylammonium Ions

The most commonly used quaternary ammonium salts are tetrabutylammonium perchlorate (TBAP), tetrafluoroborate (TBAT), the halides (TBACl, TBAB, and TBAI), and the corresponding tetraethylammonium salts, such as the perchlorate (TEAP), but also the tetramethyl- or tetrapropylammonium salts have been employed; the former cannot undergo a base-promoted Hofmann elimination. However, evidence has been found for the formation of trimethylammonium methylide [460]. In nonpolar solvents it may be necessary to employ tetrahexyl- or tetraoctylammonium salts. The tetraalkylammonium ions are soluble in many nonaqueous media, and they may be extracted from an aqueous solution by means of chloroform or methylene chloride [461,462], and tetraalkylammonium salts may thus be prepared by ion extraction [462]. Tetrakis(decyl)ammonium tetraphenylborate is soluble even in hexane [442,443].

Reduction of R_4N^+ at a glassy carbon electrode in DMF yields an alkyl carbanion, which deprotonates residual water or R_4N^+ in a Hofmann elimination with formation of an alkene and a trialkylamine. Tetraethylammonium is attacked more easily than tetrabutylammonium [463].

The discharge potential becomes slightly more negative with increasing size of the ion, but in practice there is not much gained by going beyond tetrabutylammonium ions [464]. The reduction route of these ions is discussed elsewhere (Chapter 23).

In aqueous solution the tetraalkylammonium ions are adsorbed at the electrode, where they form a layer with a low proton activity. This property is used in the commercial production of adiponitrile from acrylonitrile (Chapter 31). The adsorption of the ions

depends on the potential of the electrode, the electrode material, the composition of the medium, and the size of the cation.

The rate constant for electron transfer from an electrode to a substrate decreases with the size of the cation; for instance, the rate constants for electron transfer at a mercury electrode in MeCN to a substrate were always smaller when tetra-*n*-heptylammonium perchlorate was the electrolyte than when tetraethylammonium perchlorate was it [465].

Quaternary ammonium salts are readily accessible; some are commercially available, and their preparation presents no problems [461,462]. Reducible impurities may be removed by electrolysis at a sufficiently negative potential. The production of tetraalkylammonium hydroxide using an anion [466] or cation [467] exchange membrane has been reported.

5. Sulfonium Salts

Tris(dimethylamino)sulfonium tetrafluoroborate ($TASBF_4$) has been investigated as a supporting electrolyte in MeCN and CH_2Cl_2. Compared with $TBABF_4$ the conductance of $TASBF_4$ in CH_2Cl_2 is slightly higher, suggesting a higher degree of dissociation of the latter [468].

6. Cryptates

Crown ethers and other cryptates form with several metal cations stable complexes, which generally are soluble in nonaqueous media, even in rather nonpolar solvents [394]. In some cases such complexes may be considered supporting electrolytes, especially when some of the special properties of a given cryptate are desirable also in other contexts. By complexing Ag^+ with a cryptate, the $Ag/AgCryp^+$ electrode becomes stable in DMF [201].

7. Polyelectrolytes

Polyelectrolytes having ion-exchange properties may be coated on one or both electrodes [9,74–78], which makes it possible to use virtually nonconducting liquids. This was discussed in Sec. II.B.

A copolymer of 4-vinylpyridine or styrene with a diaryl-4-(1-trifluoromethylvinyl)-aryl amine has sufficiently solubility and conductivity to serve as both supporting electrolyte and redox mediator; after use it can be recovered by ultrafiltration [469].

C. Buffers

Control of an electrolytic reaction often requires that the proton activity remains within acceptable limits during the electrolysis. For small-scale electrolytic preparations (less than about 10 g/liter of substrate), a sufficiently high initial concentration of buffer, acid, or base is adequate in aqueous solution; for large-scale electrolysis a controlled addition of protons during a reduction must be provided. This addition may be controlled by a pH-stat or coupled to the current integrator. In aprotic media a proton donor, electrophile, or nucleophile may play a similar role as buffers in aqueous media.

1. Acids

Hydrochloric acid is a convenient acid for laboratory-scale electrolysis; it is easy to remove during the workup by evaporation. The oxygen-containing acids, such as sulfuric or perchloric acid, must be neutralized before basic products can be extracted. Sulfuric acid is most conveniently neutralized by concentrated ammonia rather than by sodium hydroxide, whereby the precipitation of sodium sulfate is avoided.

Even in acetic acid perchloric acid is a strong acid. Anhydrous solutions are made by adding acetic anhydride equivalent to the water present in the acetic acid and introduced together with the perchloric acid. An excess of acetic anhydride should be avoided as this solution is a very strong acylating agent and it forms yellow condensation products on standing. Anhydrous perchloric acid in MeCN has been prepared by oxidation of H_2 to H^+ at a platinized platinum electrode in a solution of $TBA^+ClO_4^-$ in MeCN [349].

In aprotic media the addition of proton donors may be important. If the proton donor is too strong, protons may be reduced in preference to the substrate and a two weak proton donor may not furnish sufficient protons. Often a phenol is an acceptable compromise.

Extreme acidic conditions may be obtained in superacids, such as SbF_5 or BF_3 in HF or SbF_5 in FSO_3H.

2. Bases

Reductions in aqueous alkaline solution do not present many problems; the choice of cation was discussed earlier. In nonaqueous solvents bases may be generated electrolytically (Chapter 29) [490,491] or formed by reaction of the solvent with an alkali metal. The conjugate base of the solvent is the strongest base obtainable in any medium.

During oxidation in a nonaqueous solvent, the removal of a proton or an attack of a nucleophile on the oxidized substrate may be a chemical step in an ECE reaction. To explore which reaction is operating one can, in parallel voltammetric experiments, use two compounds that are equal in base strength but differ widely in nucleophilicity; such a pair is pyridine and 2,6-dimethylpyridine.

3. Buffer Systems

The use of buffers in electrolysis to maintain a desired pH warrants some consideration. During a reduction protons are consumed at the cathode surface, and unless they are replenished rapidly, the pH in the reaction layer is considerably higher than in the bulk of the solution. A high concentration of a buffer system, which exchanges protons rapidly, is required to maintain a desired pH.

In aqueous solution, phosphate, borate, and carboxylate buffers are applicable, but in mixed solvents the solubility of phosphate and borate buffers is low; in such mixtures, carboxylate buffers may be used in slightly acid, and amine buffers in slightly alkaline medium. To avoid excessive buffer concentrations it is advisable to maintain pH in the bulk of the solution constant by means of a pH-stat.

Buffering in an aprotic medium is sometimes a problem. Proton donors, such as a suitable phenol, malonic ester, or amine salt, together with the corresponding base, may be an acceptable solution. Guanidine perchlorate [472] has been proposed as an efficient proton donor (and supporting electrolyte) in aprotic solvents, as it brings the protons into the Helmholtz double layer.

VIII. VOLTAGE SOURCES AND COULOMETERS

A. Voltage Sources

To perform a simple electrolysis under constant conditions only a dc source, which may be a battery or a rectifier, is needed. Small ripples on the voltage usually do not harm in preparative work.

For experiments under controlled potential conditions the electrode voltage may be controlled manually following the reading of a dc voltmeter with high-input resistance or automatically by a *potentiostat*. This is a device that is able to keep the potential of the working electrode within a small range around a fixed value (versus the reference electrode), independent of the cell current. The apparatus thus reduces the cell current as the electroactive substance is consumed and also follows possible changes of the cell resistance.

B. Coulometers

Very often it is of great interest to determine the n value of an electrode reaction or the current efficiency of an electrosynthesis. Both involve a measurement of the electricity consumption, that is, an integration of the electric current over the time of electrolysis. In constant-current experiments this is, of course, an easy task. For controlled potential electrolysis, an integrating device is included in the circuit. Electronic integrators can usually be obtained from the companies that supply potentiostats.

IX. PRACTICAL HINTS

Besides the major features in electrolysis discussed here, there are smaller problems to be solved. It is, of course, easiest to consult an experienced electrochemist on such matters, but such a person may not always turn up when wanted, so the following items are briefly mentioned: circuit, counterelectrode reaction, removal of oxygen before electrolysis, removal of impurities, detection of intermediates, integration of current, and workup.

A. Circuit

For exploratory work, a cheap, manually controlled circuit, as shown in Fig. 9, may be assembled from components available in every organic laboratory. Although in some cases good results may be obtained by using a beaker and a circuit with just two electrodes and a 6 V battery as power supply [473], it is advisable in research work always to include a potential-measuring device. A potentiostat considerably facilitates the control of the electrolysis. Many different potentiostats are now commercially available. When choosing a potentiostat, such properties as output voltage, power, response time, and input resistance in the reference circuit must be considered. Electrolysis in nonaqueous solvents generally requires a higher voltage across the cell than electrolysis in water. Potentiostats for ordinary preparative electrolysis do not need as fast a response as those intended for pulse electrolysis. The input resistance of the reference circuit must be high compared with that of the reference electrode. The circuit should also include a coulometer and an ammeter.

When up-scaling a reaction the use of statistically designed experiments may facilitate the optimization of the reaction [474]; when the different parameters of the reaction

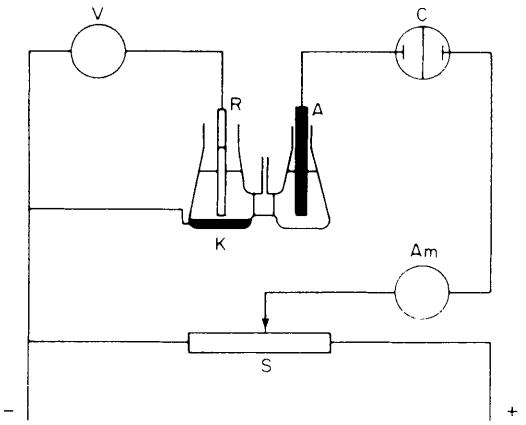

Figure 9. Circuit for constant potential reduction: K, cathode; A, Anode; R, reference electrode; V, potentiometer or pH meter; C, coulometer, Am, ammeter; S, voltage adjuster. (From Ref. 43.)

are known, the reaction can be performed without a reference electrode by a current-time program.

B. Counterlectrode Reactions

In divided cells the reaction at the counterelectrode is seldom a problem; in aqueous solvents, oxygen evolution at the anode is convenient; if chloride is desired as the anion, it is advisable to add ethanol to the anodic compartment as it reacts with the evolved chlorine. In oxidations, hydrogen evolution is a convenient counterelectrode reaction; it may also be used in nonaqueous solvents [68–73]. In methylene chloride it has been noted that chloride ion formed by reduction of methylene chloride at the counterelectrode could diffuse to the anode compartment and participate in the follow-up reactions [426]; this can be avoided by adding a little acetic acid to the cathode compartment.

In undivided cells the counterlectrode reaction must be chosen with care, as the products from it obviously must not interfere with the proper electrode reaction. This becomes a problem especially in nonaqueous solvents; in such media, hydrogen evolution is generally an acceptable counterlectrode reaction for oxidations; for reductions, the oxidation of oxalates and formates to carbon dioxide or azide to nitrogen [452] may be a solution to the problem.

In nonaqueous media, a sacrificial electrode or hydrogen gas diffusion electrode may be advantageous (discussed earlier).

The ideal solution is to have two useful electrode reactions, paired electrosynthesis.

C. Removal of Oxygen

Before electrolysis, most of the dissolved oxygen may be removed by bubbling an inert gas through the solution. It is advisable, especially for smallscale work in nonaqueous solvents, to saturate the gas with the solvent before it is introduced into the cell. The inert gas, nitrogen or argon, may be obtained commercially sufficiently pure, but if not, nitrogen may be purified by passing it through a tube containing a (commercially available) copper

catalyst. Previously, nitrogen has been purified by bubbling it through solutions of Cr(II) or V(II) salts or a Fieser solution.

Removal of traces of oxygen from a solution by bubbling an inert gas through it is virtually impossible; if such traces must be avoided, all manipulations must take place on a vacuum line and the cells constructed accordingly.

D. Determination of n Values

A direct determination of n values (n = F/mol in a reaction) can be made by microcoulometry. However, n values derived from electrolyses with macroelectrodes should be considered with some care because of the possibility of further reactions during the time of the experiment. A reliable procedure for compounds that can be dissolved fully is to follow the concentration of the electroactive substance analytically, plot corresponding values of the response and coulometer readings, and calculate the n value from the slope of the possibly straight line obtained during the first part of the electrolysis. If a straight line is not obtained, this indicates that secondary reactions take place.

E. Workup

Often, from the point of view of electrolysis, the choice of electrolyte or solvent is free within certain limits, and the workup may then be facilitated considerably by a suitable selection of experimental conditions. For example, the reduction of a nitroalkane [50] to a hydroxylamine requires an aqueous acid medium; sulfuric acid is just as good as hydrochloride acid for the electrolysis, but whereas hydrochloric acid may be removed in vacuo at a low temperature, leaving an alkylhydroxylamine hydrochloride, the sulfuric acid must be neutralized and the free, less stable base extracted.

Salts may be removed by electrodialysis using cation and anion exchange membranes [13,14] or bipolar membranes [13,14].

F. Removal of Impurities

To obtain a meaningful value of electricity consumption, it is necessary that electricity not be consumed by impurities. A convenient way to remove impurities is to preelectrolyze the catholyte at a potential somewhat more negative than that to be employed during the electrolysis of the substrate. When the background current has reached an acceptable value, the substrate is added and the electrolysis performed at the required potential.

Impurities of nucleophiles or electrophiles may be removed from aprotic solutions by passing the solution through a column of active, neutral alumina; the alumina may be activated at 400–450°C in vacuum and used immediately after.

G. Detection of Intermediates

During the electrolysis it is advisable to obtain some indication of what is going on in the cell. An indicator microelectrode in the electrolytic cell is valuable in order to follow the progress of the electrolysis and to detect intermediates. An intermediate more easily reducible than the substrate, for example, may be detected as a small prewave, and its half-wave potential or other voltammetric characteristics used for its identification. Polarographic or cyclic voltammetric curves measured during the electrolysis also present a means of monitoring the process. The combination of electrochemical and optical tech-

niques to detect intermediates was discussed in Chapter 2; an alternative is to use a fiber-optic spectrometer equipped with a transmission dip probe [45,46].

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6
Cathodic Reactions of Hydrocarbons

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I. INTRODUCTION

The electrochemical reduction of pure hydrocarbons without functional groups is almost exclusively restricted to unsaturated compounds. The reason is that aliphatic hydrocarbons have extremely low electron affinities, which render their reduction impossible, despite a gain of solvation energy within the stability limits of conventional solvent–electrolyte systems.

Thus, electrochemical data involving both thermodynamic and kinetic parameters of hydrocarbons are available for only olefinic and aromatic π-systems. The reduction of aromatics in particular had already attracted much interest in the late 1950s and early 1960s through the pioneering work of Hoijtink. The correlation between the reduction potentials and molecular orbital energies of a series of aromatic hydrocarbons was one of the first successful applications of the Hückel molecular orbital (HMO) theory, and allowed Hoijtink to develop a coherent picture of cathodic reduction [1]. The early research on this subject has been reviewed several times, emphasizing polarographic studies as well as physical chemistry [2–4].

Later, during the golden age of mechanistic chemistry, interest focused on the elucidation of reaction paths of cathodically generated species, including disproportionations [5] and chemical follow-up processes [6]. Techniques were developed and improved to

measure both the kinetics of coupled chemical reactions [7] and thermodynamic parameters such as redox potentials of higher charged aromatics [8]. The discovery of the redox properties of conducting polymers in 1979 and later of the fullerenes [9] gave new impetus to the electrochemistry of unsaturated hydrocarbons, initiating extended studies on the redox properties of these species [10].

We report here on the cathodic formation and follow-up reactions of anionic species of hydrocarbons. Other generation techniques, such as reduction by solvated electrons or indirect electrolysis, are discussed in detail in Chapter 29.

II. FORMATION OF RADICAL ANIONS, DIANIONS, AND POLYANIONS

A. Experimental Aspects

The first data on the electrochemical reduction of aromatic hydrocarbons were published by Wawzonek et al. [11]. They used polarography as a measurement technique and observed in most cases a series of one- and two-electron reduction waves, clearly indicating follow-up reactions resulting from the attack of the protic solvent mixture (75% dioxane–water) on the ionic intermediates. Later, electron spin resonance (ESR) spectroscopy revealed that charged species of aromatics generated by alkali metal reduction in ethers are stable and normally possess an unpaired electron [12]. Thermodynamic reduction potentials of numerous aromatics were first measured by Hoijtink und van Schooten in 96% aqueous dioxane, again using polarography [13]. These fundamental works were decisive tests of the HMO theory, showing that the polarographic half-wave potentials vary linearly with the HMO energies of the lowest unoccupied molecular orbitals (LUMO) of the hydrocarbons [1]. Hoitjink et al. had already noticed that most aromatics can be further reduced to their respective dianions [14]. They proposed a two-step reduction scheme, in which both redox potentials 1 and 2 are on average separated by about 500 mV:

$$A \overset{E_1^0}{\rightleftharpoons} A^{\cdot-} \tag{1}$$

$$A^{\cdot-} \overset{E_2^0}{\rightleftharpoons} A^{2-} \tag{2}$$

However, their careful analysis also showed that most of the dianions were not stable in the polarographic or voltammetric time scale, and even less so after bulk electrolysis, and underwent follow-up reactions with water or other electrophilic impurities, details of which are discussed in Sec. III.B.

Aprotic solvents such as acetonitrile [15,16] or dimethylformamide [17–20] considerably improved the stability of the radical anions but normally had little effect on the reactions of the more basic dianions [19–21]. The increased irreversibility of the dianion formation is probably due to the ability of dianions to abstract protons even from the solvent, or, by Hofmann elimination, from the tetraalkylammonium salts that are common supporting electrolytes in aprotic solvents [2].

Progress in electrochemical instrumentation soon stimulated the application of more elaborated measurement methods than simple dc polarography, which facilitated studies of heterogeneous kinetics and detection of follow-up reactions of the electrogenerated species. Thus, conclusions originally drawn from the shape and height of polarographic curves have been amply confirmed by straightforward diagnostic criteria in ac polarography [20,22] and above all in cyclic voltammetry [19,23–25], nowadays the standard method for mechanistic studies in organic electrochemistry [26].

Hoijtink et al. [27] also developed an alternative method of generating anionic species, which was improved by Szwarc et al. [28]. The technique involves potentiometric titration of aromatic compounds with a standard solution of Na-biphenylide. The extremely negative reduction potential of biphenyl assures that most of the common aromatics can be reduced to at least their respective radical anions. The values of the thermodynamic reduction potentials are generally obtained from the potentiometric titration curve. As all experiments are usually carried out in ethereal solutions, such as tetrahydrofuran (THF) or dimethoxyethane, problems of follow-up processes are less severe. Later, Gross and Schindewolf [29] reported on the potentiometric titration of aromatics using solvated electrons in liquid ammonia.

A fundamental improvement in the facilities for studying electrode processes of reactive intermediates was the purification technique of Parker and Hammerich [8]. They used neutral highly activated alumina suspended in the solvent electrolyte system as a scavenger of spurious impurities. Thus, it was possible to generate a large number of dianions of aromatic hydrocarbons in common electrolytic solvents containing tetraalkylammonium ions. It was the first time that such dianions were stable in the time scale of slow-sweep voltammetry. As the presence of alumina in the solvent–electrolyte systems may produce adsorption effects at the electrode, or in some cases chemisorption and decomposition of the electroactive species, Kiesele constructed a new electrochemical cell with an integrated alumina column [30].

Heinze modified the technique by purifying the solvent by transferring it under high vacuum from the electrochemical cell to superactive alumina in a separate vessel [26]. Such sophisticated methods made it possible to generate reversibly polyanions up to octaanions of aromatic and olefinic hydrocarbons [26,31] (Fig. 1).

Further progress in stabilizing highly charged anions was achieved by the application of unconventional solvents such as ammonia or dimethylamine at low temperatures. Using these solvents, it was possible to observe the reversible generation of supercharged anions at low scan rates in voltammetric experiments [32,33].

B. Thermodynamics

For purpose of description, the electrochemistry of hydrocarbons may usefully be classified in three categories: benzenoid, nonbenzenoid, and olefinic hydrocarbons, each of which exhibit characteristic properties upon reduction.

Benzenoid hydrocarbons have been studied in greatest detail [2,4,34]. In aprotic solvents they can be reversibly reduced to their respective anions without difficulties. Even the electrochemical reduction of benzene in dimethoxyethane has been described [35]. In many cases the electrogenerated radical anions are stable enough to allow the simultaneous measurements of their ESR spectra [36–38]. The most striking feature of benzenoid hydrocarbons is the excellent correlation between their thermodynamic reduction potentials and the predictions of semiempirical π-electron theories, especially of the Hückel approximation (HMO). As the thermodynamic reduction potentials are a measure of the electron affinities of the respective compounds, they can be compared with the theoretically calculated energies in the simple molecular-orbital (MO) picture, in which additional electrons have been added to antibonding MOs of the π-systems. Therefore, assuming that the solvation energies for a series of aromatic hydrocarbons are constant, there should be a linear correlation between the thermodynamic reduction potentials (half-wave potentials) and the energies m of the lowest unoccupied MO (LUMO):

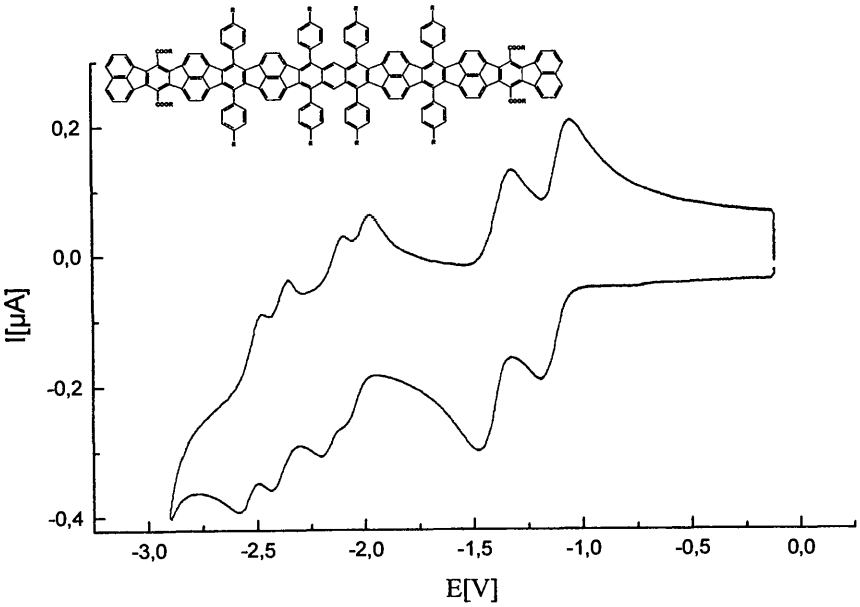


Figure 1. Cyclic voltammogram for the reduction of a polycyclic aromatic hydrocarbon (PAH) with 29 condensed 5- and 6-rings, indicating the formation of an octaanion (THF/$TBAPF_6$, T = −40°C, v = 200 mV s^{-1}) (see Ref. 31c).

$$E_{1/2} = -bm_{m+1} + C \tag{3}$$

Independent voltammetric and polarographic measurements carried out in different solvents such as 2-methoxyethanol, 96% dioxane, and dimethylformamide (DMF) confirm the relationship through excellent linear correlations with slopes b of approximately 2.40 [1,17,39,40]. Rather surprisingly, the differences in half-wave potentials of hydrocarbons from one solvent to another are very small. This constancy in energy values as well as slopes of correlation lines in widely varying solvents and supporting electrolytes implies that solvation energies, provided that they are not small, change in the same way from system to system.

As already observed by Hoijtink [14], nearly all benzenoid hydrocarbons can be reduced to their respective dianions—only benzene and naphthalene are exceptions. In all experiments, these second reduction steps appear approximately -0.55 ± 0.10 V negatively to the first reduction, provided that the supporting electrolytes used were tetraalkylammonium salts. Therefore, these reduction potentials were also correlated with the LUMO energies of the HMO model [3]. It was suggested that the energy difference of 0.55 eV corresponds to the repulsion energy between both electrons in the LUMOs of the dianions [1], despite the differences in their structures. On the other hand, quantum-mechanical calculations show that the repulsion energies are much larger. Dewar has calculated values in the range of 5 eV [41]. The discrepancy between experiment and theory results from the fact that ion-pairing effects and solvation influences have been neglected in the calculation. Experimental data clearly reveal that counterion effects that efficiently shield the negative excess charge have in the past been underestimated and are considerably stronger for di- and polyanions than for radical anions [42–44].

$$2A^{\cdot-} \rightleftharpoons A^{2-} + A \tag{4}$$

In polar solvents such as DMF or acetonitrile, the interaction increases in the order tetrabutylammonium < K < Na < Li and, consequently, reduction potentials shift in a positive direction [6,45]. Obviously, ion pairing is greatest for the small lithium ions, in agreement with the prediction of Born's equation [46]. In the case of solvents with low dielectricity constants the pattern is different, and ion pairing becomes dominant as the radius of alkali cations increases [44,47,48]. The reasons for this behavior have not yet been studied in detail, but it has been proposed that in ethereal solvents the solvation of small cations remains stronger than that of larger ones, and therefore ion pairing of potassium should be more pronounced than that of lithium.

Ion-pairing effects may considerably influence disproportionation mechanisms, which involve homogeneous redox reactions of anions to their respective dianionic and neutral species [49].

Disproportionation mechanisms have been proposed for protonation reactions and intramolecular rearrangements (see Sec. III.B and III.D) [50,51]. Their prominent feature is that follow-up processes at the level of the dianion can already take place at potentials corresponding to radical anion formation. In order to evaluate data for disproportionation reactions it is necessary to know the value of the disproportionation equilibrium constant,

$$K_D = \frac{[A^{2-}][A]}{[A^{\cdot-}]^2} \tag{5a}$$

$$\frac{RT}{nF} \ln K_D = E_2^0 - E_1^0 \tag{5b}$$

This can be determined from the difference in reversible potentials of the couples $A/A^{\cdot-}$ and $A^{\cdot-}/A^{2-}$.

In the case of benzenoid aromatics, K_D values range between 10^{-9} and 10^{-13}, provided that tetraalkylammonium salts have been used as supporting electrolytes [8b]. In solvents of low dielectricity constant, additional effects are observed, showing influences of the supporting electrolyte concentration and of the nature of the cations [6]. In the tetraalkylamonium series the strongest (contact) ion pairs are formed by $Et\ N^+$, and K_D is largest for that cation [8b,52].

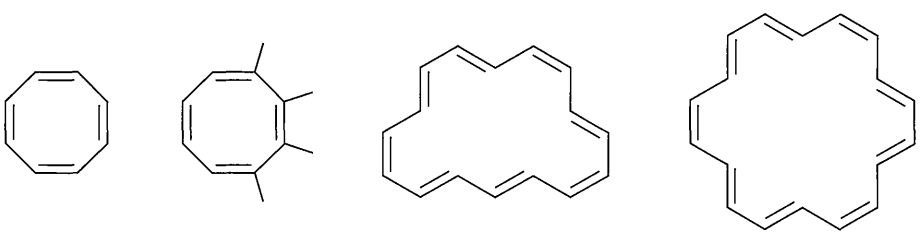
Drastic changes in the disproportionation constants occur when alkali cations are used instead of tetraalkylammonium ions. Typically, the potentials of the radical anion formation is less affected than that of the dianion formation. In the presence of alkali cations, ΔE^0 shifts may reach values of more than 600 mV, which correspond to an increase in the K constant of more than 10 orders of magnitude [49].

The electrochemistry of nonbenzenoid hydrocarbons has attracted much interest because their structures offer unusual insights into π-electron systems, which undergo geometric changes upon reduction and obey both the Hückel 4n and 4n + 2 rules.

The most widely studied examples are cyclooctatetraene (COT,I) and its derivatives. In such conventional aprotic solvents as DMF, dimethyl sulfoxide (DMSO), or acetonitrile containing tetraalkylammonium salts, two distinct one-electron reduction waves are observed at approximately −1.64 V and −1.80 V versus SCE, with ΔE^0 separations varying from −130 V to −240 mV [43,53–56]. In THF and NH_3, this separation reduces further [57–59], and in the presence of all alkali salts [60,61] even two-electron reduction waves with positive ΔE^0 differences were obtained, indicating large disproportionation constants. The unusually small separation of the two redox steps in comparison to the

data of benzenoid aromatics was ascribed to the fact that the planar COT dianion forms a 4n + 2 π-electron system that is stabilized by its gain in Hückel resonance energy [62]. Obviously, strong ion-pairing effects additionally favor the formation of the dianion [60,61]. On the other hand, it was argued that a negative shift of the first reduction step, leading to small ΔE^0 values, is caused by energy requirements accompanying the transition from the tube-shaped to the planar molecule. This is supported by electrochemical results obtained with methyl-substituted COT derivatives. Thus, all methyl-substituted derivatives due to a steric barrier are harder to reduce than I itself, and in 1,2,3,4-tetramethylcyclooctatetraene (II) reduction occurs at the extremely negative potential of −3.6 V (HMPA vs. SCE) [63]. In the case of phenyl-substituted COTs the steric demand is by and large energetically compensated through the planarization of the system and the subsequent resonance interaction between the phenyl moieties and the COT ring. Therefore, the reduction potentials are similar to that of unsubstituted I. In addition, the resonance-stabilizing effect upon the dianion is sufficient to shift the second redox potential E_2^0 positively to E_1^0, thus producing a single two-electron reduction wave [55]. It is interesting to note that electrochemistry of the doubly-decked [8]annulene (= 2_2(1,5)-cyclooctatetraenophane) also indicates some sterical strain [64]. The formation of the monoanion occurs at a potential of −2.43 V (DMA, Ag/AgCl). It can be reduced up to its tetraanion at a potential of −3.22 V.

The redox behavior of a number of higher annulenes than I has been studied during the past 25 years. The evaluation of their electronic properties has attracted much interest because it offers a good comparison of the fundamental differences between 4n and 4n + 2 π-systems. As predicted by the simple MO theories, the transfer of an electron to a [4n]annulene should be energetically favorable because the electron is inserted into a low-lying nonbonding orbital. The further reduction to the dianion leads to a stabilized (aromatic) 4n + 2 π-system, which therefore should be easily accessible. In contrast, during the reduction of an aromatic [4n + 2] annulene electrons are injected into a LUMO with high energy, and in the second reduction step an unstable 4n dianion is generated.



(I) (II) (III) (IV)

Consequently, the reduction of [4n]annulenes should be observed at relatively positive potentials with small ΔE^0 separations for the dianion formulation, while the reduction of the [4n + 2] annulenes should occur at more negative potentials with large ΔE^0 separations for the dianion formation. This is exactly what is observed in experiment (see Table 1). Although benzene [35], the classical Hückel aromatic with $4 \times 1 + 2 = 6$ π-electrons, is reduced at −3.42 V (vs. Ag/AgCl), the reduction of the [8]annulene COT occurs at −1.81 V. Similarly, the [16]annulene (III) [65,66] is more easily reduced than the corresponding [18]annulene (IV) [67], although the reduction of the larger π-systems should be more favorable for electrostatic reasons.

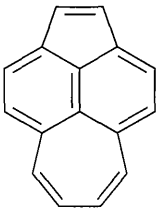
For larger annulenes, even the reduction to tetraanions is possible [44,48,69]. This is especially favorable for neutral 4n + 2 species, which, after the injection of four electrons, reform a stabilized 4n + 2 π-system. On the other hand, the existence of four excess

Table 1 Redox Potentials E^0 for the Reduction of Aromatic and Olefinic Hydrocarbons

Compounds	E^0_{R/R^-}(V)	$E^0_{R^-/R^{2-}}$(V)	$E^0_{R^{2-}/R^{3-}}$(V)	$E^0_{R^{3-}/-}$(V)	Reference
Benzene[a]	−3.42	—	—	—	33, 35
Naphthalene[a]	−2.53	—	—	—	33
Anthracene[a]	−2.04	−2.64	—	—	33
Chrysene[a]	−2.27	−2.77	—	—	8b
Corenene[b]	−2.07	−2.72	—	—	8b
1,2-Benzanthracene[b]	−2.05	−2.67	—	—	8b
Phenanthrene[a]	−2.49	−3.13	—	—	33
Triphenylene[a]	−2.42	−2.97	—	—	33
Pyrene[a]	−2.29	−2.91	—	—	33
Biphenyl[c]	−2.68	−3.18	—	—	10a
p-Terphenyl[a]	−2.40	−2.70	—	—	33
o-Terphenyl	−2.62	−2.72	—	—	232
Quaterphenyl[a]	−2.28	−2.455	—	—	33
Stilbene[a]	−2.26	−2.72	—	—	33
Bianthryl[a]	−1.92	−2.14	−2.82	−3.17	33
Biphenanthryl[a]	−2.35	−2.51	−3.23	—	33
Decacylene[c]	−1.74	−2.14	−2.35	−2.68(−2.88)	26
2,2′-Distyryl-biphenyl[a]	−2.12	−2.21	−2.81	−3.13	224
4,4′-Distyryl-biphenyl[c]	−2.30	−2.52	−3.06	—	224
p-Oligophenylenevinylene (n = 1)[a]	−2.00	−2.24	—	—	31b
(n = 2)[a]	−1.86	−1.97	−2.79	−3.10	31b
(n = 3)[a]	−1.85	−1.91	−2.46	−2.88	31b
Acepleiadylene[c]	−1.85	−2.51	−3.11	−3.14	44
COT[d]	−1.81	−1.94	—	—	55
[12] Annulene[e]	−1.35	−2.00	—	—	70
1,7-Methano[12]annulene[f]	−1.51	−1.84	—	—	78
15,16-Dihydropyrene ([14]Annulene)[g]	−2.22	−3.01	—	—	62
[16]Annulene[f]	−1.27	−1.56	—	—	65
[18]Annulene[f]	−1.60	−1.94	—	—	67
Heptalene[f]	−1.49	−2.19	—	—	78

[a]Cyclic voltammetry was performed at a Pt electrode with solutions of 10^{-3}–10^{-4} M in substrate. All potentials are expressed in V versus Ag/AgCl; solvent: dimethylamine–TBABr, temperature between −40 and −65°C.
[b]DMF–Me_4NBr, potentials versus Ag/AgCl (corrected from SCE).
[c]THF–$NABPh_4$ or $LiBPh_4$, potentials versus Ag/AgCl.
[d]ACN–TEAP, potentials versus Ag/AgCl (corrected from SCE).
[e]THF–$TBAClO_4$, potentials versus Hg pool.
[f]DMF–$TBAClO_4$, potentials versus Ag/AgCl (corrected from SCE).
[g]DMF–$TBAClO_4$, potentials versus Ag/0.1 M $AgNO_3$.

charges in one molecule gives rise to strong electron repulsion. It can be shielded only by ion pairing, which drives the formation of the tetraanion to a potential sufficiently positive for reduction to occur within the stability range of the solvent–electrolyte system. Thus, the electrochemical reduction of acepleiadylene (V) to its tetraanion was only achieved in THF in the presence of $LiBPh_4$ as supporting electrolyte [44]. Attempts to generate the same species in the presence of tetrabutylammonium ions were unsuccessful.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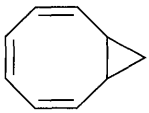
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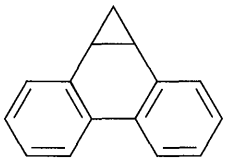
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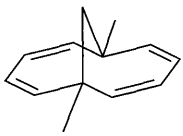
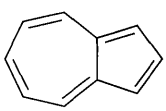

(IX)

Several studies have been published concerning the problem of homoaromaticity and its influence on reduction potentials. The term "homoaromaticity" is applied to cyclic resonance-stabilized systems in which a carbon–carbon double bond is replaced by a cyclopropane ring, or a saturated carbon atom is introduced into the conjugated chain. Paquette et al. investigated the reduction of *cis*-bicyclo-[6,1.0]-nona-2,4,6-triene (VI) and similar derivatives [71]. They found that it is reduced (−2.59, −2.79 V) more negatively than I but more easily than cyclooctatriene (VII) (−2.77 V), thus proving a degree of homoconjugative stabilization in the radical anion of VI. Analogously, dibenzonocaradiene (VIII) is easier to reduce than biphenyl, but harder to reduce than phenanthrene [72]. The electrochemical reduction of 1,6-dimethylbicyclo [4,4,1]undeca-2,4,7,9-tetraene (IX) was also interpreted in terms of homoconjugation in the anions. The reduction appears to proceed via an ECE scheme in which the initial reduction produces an unstable radical anion which undergoes a structural change, producing another radical anion with a conjugatively stabilized p-system. The second electron transfer occurs more easily than the first one, thus producing a typical "two-electron" reduction [73].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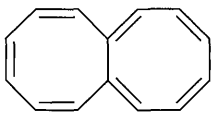
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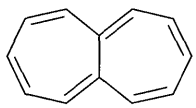
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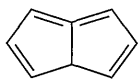
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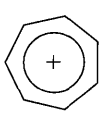
Of the condensed nonbenzenoid aromatics, azulene (X) has gained greatest popularity [74]. Although it is an isomer of naphthalene, its electrochemical behavior differs markedly from its benzenoid counterpart. Azulene is reversibly reduced at −1.62 V (vs. Ag/AgCl), while the reduction of naphthalene takes place at −2.53 V [33,75]. Furthermore, the anion of azulene is extremely stable against the attack of protons [76]. The bicyclus octalene (XI) has 14 π-electrons. H^1-NMR data show that it possesses a nonplanar structure with polyolefinic properties and therefore resembles its monocyclic relative COT. Polarography and cyclic voltammetry reveal that it is reversibly reduced to the radical anion at $E_{1/2} = -1.67$ V and, rather surprisingly, in a three-electron process at $E_{1/2} = -1.70$ V to its stable tetraanion [77]. This unusual behavior can be only explained by assuming that the energy gain from delocalization in the planar 18 π-system is higher than torsional and electronic repulsions. Other bicyclic systems such as heptalene (XII) [78] and pentalene (XIII) [79] can also be reduced to their respective anions. Nevertheless, in comparison with equivalent monocyclic π-systems such as I, their reduction behavior is still not properly understood.

(XIV)


(XV)

(XVI)

(XVII)

A further group of nonbenzenoid aromatics is the series of odd-membered cations and anions such as cyclopropenium (XIV) and tropylium cations (XV) as well as cyclopentadienyl (XVI) and cyclononatetracenyl anions (XVII). Regarding the arguments for the properties of Hückel-like 4n + 2 π-systems, all these molecules should be energetically stabilized. Obviously, this is not fulfilled in all cases. The tropylium cation (XV) can be reduced in a one-electron step to the tropyl radical even at E = +0.06 V versus SCE [80]. The radical is unstable and rapidly dimerizes to bitropyl. The heptaphenyl tropylium radical is stable on the voltammetric time scale, but decays slowly producing a dimeric species involving coupling via the phenyl groups [81]. Similarly, 2.3-diphenylethyl-cyclopropenyl is irreversibly reduced in CH_3CN at $E_p = -0.04$ V. On the other hand, the reduction of trimethylcyclopropenyl occurs at −1.32 V, which is in better agreement with the prediction of the Hückel theory [82–84]. Otherwise, relatively positive reduction potentials seem to be typical for most carbocations [85]. The easy reducibility is probably caused by the excess positive charge.

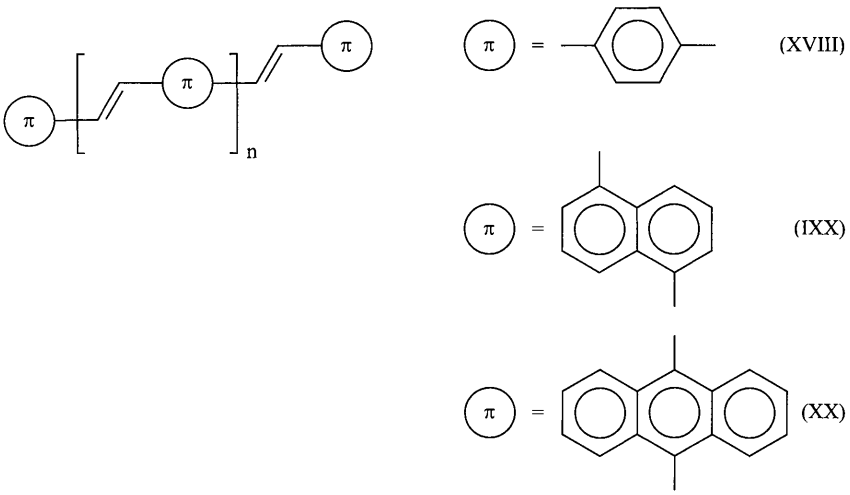
The discovery of the metal-like properties of conducting polymers has once again focused attention on the oxidation and reduction characteristics of aromatic systems. It turns out that most of these conducting materials consist of chainlike connected carbocyclic or heterocyclic aromatics (see Chapter 32) [86–88].

The simplest molecules in these series are dimers, followed by oligomers of increasing chain length and polymers. As the current–voltage curves of polymers are difficult to interpret, quantitative information on the redox properties of such systems was preferentially obtained from reduction experiments with dimers and defined oligomers. Redox data on dimers are available for biphenyl [10], bianthryl [49b,89], biazulenyl [90], bicyclooctatetraenyl [91] and dimeric [14]annulenes [92]. All species can be reduced to at least their respective dianions. In the case of bianthryl and bicyclooctatraene, even the formation of tetraanions has been observed. In general, the observed redox potentials of the monoanion formation differ significantly from those of the monomeric parent compounds and shift to less negative values. This is evidence of conjugative stabilization in the charged oligomeric unit [93]. On the other hand, large ΔE^0 separations between the redox potentials of the respective mono and dianions indicate strong electron repulsion between both electrophores. A typical example is biphenyl, which is reduced to the radical anion at −2.68 V and to the dianion at −3.18 V [10], whereas the reduction of the monomeric benzene occurs at −3.42 V [35]. Obviously, the biphenyl anion has gained a considerable amount of conjugative stabilization energy, while in the dianion strong electron–electron repulsion dominates.

During the last decade, the concept of the oligomeric approach has been developed, which includes electrochemical studies of a great number of monodisperse chainlike hydrocarbons. Voltammetric measurements carried out with several oligomers of the *p*-phenylenevinylene (XVIII, n = 1–6) [31a,b] and the *p*-phenylene [10] series, respectively, clearly demonstrate that the reduction properties of such oligomers and polymers depend on the chain length of the systems. Three effects are especially significant. First, the potentials of already existing redox states shift to less negative values when the next higher homologue is reduced. Obviously, the redox energies of different states gradually approach a common convergence limit with increasing chain length. Second, the redox states degenerate pairwise with increasing chain length, and third, in agreement with expectations, adding successive monomeric subunits in the molecular chain enlarges the number of accessible redox states. However, the energetic gap increases strongly between the lowest and the highest charged states. From these results, it becomes clear that in conducting polymers such as poly-*p*-phenylene a reasonable number of energetically low-

lying redox states are degenerated, followed by redox states with increasingly higher energies [10]. This explains the broad, plateaulike waves that are so often characteristic of the potential range following the peaklike main wave in voltammetric experiments.

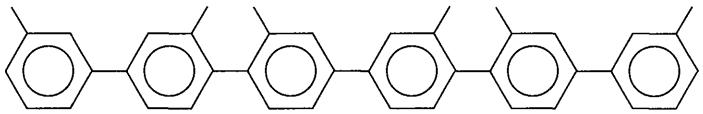
Quite a large number of publications that have appeared since that time support these findings, but have also introduced new aspects that show the complexity of redox mechanisms in such systems [94]. Very systematic studies have been carried out by the Müllen group, who have varied in chainlike oligomers the type and coupling position of the electroactive monomeric building blocks and the modes of linkage, using both saturated and unsaturated species with different lengths [95]. Their results clearly show that the size of the aromatic subunit, the overall number of π-electrons, the π-topology, and steric effects are important factors for the redox behavior of all these species. Thus in the series of oligoarylenevinylenes, replacement of the phenylene unit by larger arylene units enlarges the charge capacity of the respective systems. While the *p*-oligophenylenevinylene XVIII (n = 1) with three phenylene units can be electrochemically reduced up to a dianion, the corresponding naphthalene derivative IXX (n = 1) reaches a trianion level and the anthracene derivative XX (n = 1) even a hexanion state [95–98].



An important reason for this phenomenon is the fact that the better the excess charges in condensed aromatic units are stabilized, the larger the π-structure is. Of course, the energetic stabilization of an excess charge in a large aromatic unit diminishes the trend for its delocalization and Coulombic repulsion effects along the chain. Therefore, the shift of the first redox potential in dependence on the chain length is less pronounced for the naphthalene and anthracene derivatives than for the phenylene system or the pure oligoene chain, and, moreover, the separation between successive redox steps becomes substatially smaller as the number of π-subunits increases. A further influence on the redox properties results from the coupling pattern between the vinylene and the arylene units. Measurements on *para*-, *meta*-, and *ortho*-coupled phenylenevinylenes reveal that it is more difficult to charge *meta*- and *ortho*- homologs than the corresponding *para*-homologs. However, the conjugative uncoupling of two *meta*-groups in a phenylene ring diminishes Coulombic repulsion, and therefore the energetic separation between successive redox steps decreases [98].

The redox properties of oligo-*p*-phenylenes change when sterically relevant methyl groups exist in the central rings. Thus, in comparison with the unsubstituted oligomers in

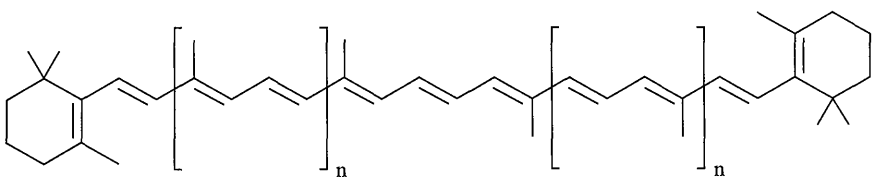
methyl-substituted homologs, e.g., XI, with four or more phenylene units, the first reductive redox step is shifted to a more negative potential and a two-electron wave appears in the voltammetric response [99]. This can be interpreted by assuming that, due to steric hindrance, additional energy is needed to planarize the phenylene chain for the first electron transfer, and that the second electron is able to enter the then flattened system at the same or even a more positive potential.



(XXI)

Within the hydrocarbons containing olefinic double bonds, polyacetylene (PA) is the most thoroughly studied system. The great interest results from its extremely high conductivity up to 100,000 S/cm, which emerges an oxidative or reductive charging of the polymer [86,87,100]. As already found by MacDiarmid [91], PA can be reversibly reduced to a polyanionic material. Its thermodynamically stable form is the *trans* configuration. In an electrochemical study [101] it was shown that *cis*-PA is irreversibly isomerized to the *trans* form upon reduction at $E_p = -1.80$ V versus Ag/AgCl (liquid NH_3, NaI). The voltammetric experiments prove that the isomerization only takes place via the charged *cis* segments of PA. The charged *cis* component is thermodynamically unstable and transforms through a fast chemical step to the *trans* form (EC mechanism), the redox potential of which is shifted in the positive direction ($E^0_{trans} > E^0_{cis}$). Similar stability conditions are also valid for monomeric olefins. The bestknown example is that of the dialkyl maleate/fumerate system [102]. Again, the reduction potential of the *cis* form is more negative than that of the *trans* form ($\Delta E^0 = 0.28$ V), and reduction of the *cis*-maleate induces the irreversible isomerization to the *trans*-fumarate. The redox potential of *cis*- and *trans*-stilbene with values of −2.18 V and −2.15 V versus SCE (DMF, TBAI) are almost equal, and therefore the electron-transfer-induced isomerization is slow (see Sec III.D) [103,104].

Despite the great interest in PA, there are only a few electrochemical studies of monodisperse oligoene systems. The reason is the high reactivity of doped alkyl-substituted oligoenes in the presence of nucleophiles or electrophiles. Normally, these oligomers consist of a carbon chain with alternating single and double bonds and two terminating groups, which are equal in most cases. Thus, a *t*-butyl group [105–107] or, in the case of α- and β-carotenoids, a cyclohexenyl group [108], has been used, while phenyl or other aromatic substituents have been used as end groups in the so-called arylpolyenes [109]. The chain length n (n = number of double bonds in the conjugated system) again determines the electronic properties of the oligomers.



(XXII)

(n = 0-4)

A series of carotenes [110] XXII (n = 4 and other) may serve as an illustration of this redox behavior. Cyclic voltammograms for the different species are shown in Fig. 2. As can be seen, the reduction for the oligomers with n = 5 starts with two well-separated one-electron redox steps, whereas its oxidation already involves a two-electron transfer. With

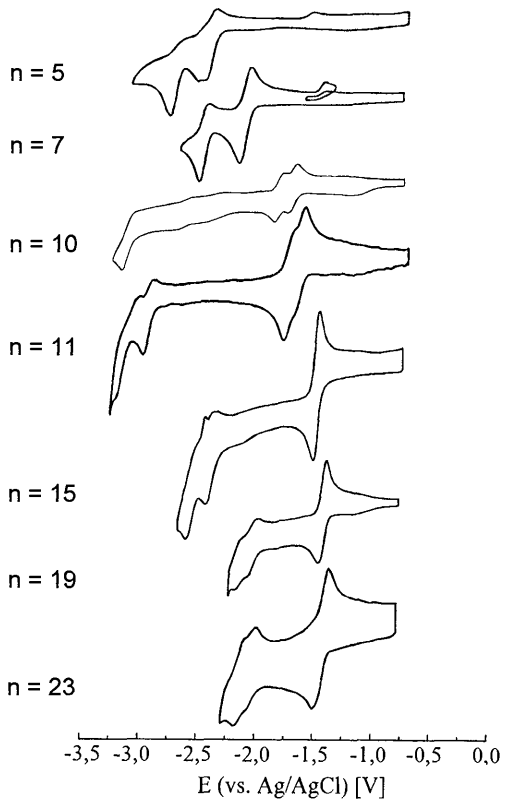


Figure 2. Voltammograms for the reduction of β-carotenoids (XXII) in dimethylamine/TBABr, T = 213 K, n = number of double bonds (see Ref. 110b).

increasing chain length, there are additional weakly separated redox pairs. The potential gaps in the single pairs and between them decrease. Thus, two-electron transfer steps are most likely to occur for the longer polyenes ($n \geq 19$).

A further interesting point concerns unusually small differences between the reduction potentials of mono- and dianions of some molecules containing olefinic double bonds. Although in *trans*-stilbene the formation of the dianion occurs approximately 500 mV negatively to the radical anion formation [33,104], for tetraphenylethylene the standard potentials for the R/R^- couple (E^0_{R/R^-}) and the R^-/R^{2-} couple ($E^0_{R/R^{2-}}$) are very closely spaced. The ΔE^0 separation amounts in HMPA to -138 mV, in DMF to -35 mV, and reaches in ACN even positive values of approximately 150 mV [111–113]. Consequently, the disproportionation constant K varies within five orders of magnitude, a phenomenon mainly ascribed to increasing ion pairing ongoing from HMPA to ACN [113]. Nevertheless, intermolecular phenomena alone are not sufficient to explain the dramatic decrease of the ΔE^0 separation in tetraphenylethylenes in comparison to stilbene. It is now generally accepted that structural changes involving twisting of the ethylenic bond and accompanying the dianion formation are the main reason for the enregetic stabilization of the dianion of tetraphenylethylene [114]. Similar effects also observed with 9,9′-bifluorenylidene [115].

A new class of conjugated hydrocarbons is the fullerenes [9b], which represent an allotropic modification of graphite. Their electrochemistry has been studied in great detail during the last decade (see Chapter 7). The basic entity within the series is the C_{60} molecule. Due to its high electron affinity, it can be reduced up to its hexaanion [10,116]. Solid-state measurements indicate that the radical anion of C_{60} reversibly dimerizes. NMR measurements confirm a σ-bond formation between two radical anion moieties [117].

C. Kinetics

Conversion of an oxidized species into the reduced form and vice versa requires the reorganization of the solvent in the immediate neighborhood of the reactant, together with some structural changes within the reactant. In the case of heterogeneous charge transfer, additional double layer effects are operative, which depend, inter alia, on type and concentration of the supporting electrolyte, but may be also influenced by the electrode material used as well as adsorption phenomena. Theoretical concepts have been developed by Hush, Marcus, and Dogonadze [118–120]. Applications of the Marcus theory to problems in organic electrochemistry have been discussed by Eberson [121]. As most studies on the reduction of hydrocarbons were carried out in aprotic solvents in the presence of excess supporting electrolyte, double-layer influences on electron transfer kinetics were usually regarded as less important [2,122]. Normally, the rates of heterogeneous electron transfer to aromatic and olefinic hydrocarbons are high. It is assumed that the activation barrier is mainly caused by the solvent reorganization. Such reactions are termed outer-sphere processes. Reductions of systems which require in addition a large conformational energy change in the transition state are rare [123]. The most widely discussed example from this class is the COT molecule (I), which exhibits a slow heterogeneous electron transfer for the anion formation, while the rate between the anion and the dianion is significantly faster [53,54,61]. In the literature it has been suggested that upon reduction the tube-shaped ring passes through at least a partially flattened transition state to form a planar anion radical. The experimentally determined activation energy (10–11 kcal/mole), which is similar to the activation energy of ring inversion (13.7 kcal/mole), has been interpreted as supporting evidence [122]. However, independent studies of Fry et al. [43] and Parker et al. [57] have shown that the rate constant for the first reduction step increased as the cation size of the supporting electrolyte decreased from tetraheptylammonium to tetramethylammonium. This contradicts the assumption of pure structural reorganization effects during the reduction of I and points to adsorption phenomena of the electrolyte cations. Moreover, in a very recent EPR investigation, homogeneous rate constants for the COT^{-}/COT electron self-exchange process were found to be close to the diffusion limit ($\sim 10^9\ M^{-1}\ s^{-1}$) [58b]. It seems that the influence of structural reorganization on the activation process was overestimated in earlier work. In a recent paper, Evans discussed electron-transfer reactions of some fully α-methylated cycloalkane-1,2-diones in which the contributions of internal reorganization are substantial [124]. In that case, both homogeneous (self-exchange) and heterogeneous electron-transfer rate constants are affected by the structural differences among these diketones.

Tetraphenylethylene is another example of a slow charge transfer. Here, the radical anion formation is fast, whereas the second charge transfer is slow [111]. In agreement with the thermodynamic findings, the second charge transfer suggests that considerable structural reorganization occurs at the activation barrier of the second reduction step. Nor

is it yet clear to what extent solvent reorganization as well influences the activation energy [111].

III. FOLLOW-UP REACTIONS OF THE REDUCED SPECIES

With one or even more electrons in antibonding orbitals, reduced hydrocarbons are highly reactive species capable of both inter- and intramolecular reactions. The preferred pathway of the follow-up reaction depends not only on the electronic and steric structure of the reduced species but also on its chemical environment, especially on the counterion and the solvent.

A. Homogeneous Electron Transfer

The most elementary follow-up reaction is the homogeneous electron transfer (ET) to another solution species, which may be identical with the donor molecule itself [49a]. The equilibria of homogeneous ET reactions are governed by the standard potentials of the involved redox couples and are easily calculated with given data according to Eqs. (6)–(9):

$$A_1^{\cdot-} + A_2 \overset{K}{\rightleftharpoons} A_1 + A_2^{\cdot-} \tag{6}$$

$$A_1 + e^- \overset{E_1^0}{\rightleftharpoons} A_1^{\cdot-} \tag{7}$$

$$A_2 + e^- \overset{E_2^0}{\rightleftharpoons} A_2^{\cdot-} \tag{8}$$

$$\frac{RT}{F} \ln K = E_2^0 - E_1^0 \tag{9}$$

The kinetics are much more complex and depend on the reorganization of the molecular framework [125], the solvation shell, and the electrostatic interaction. A semiquantitative estimation of rate constants may be obtained with the well-known Marcus equation [126]. The calculated data compare quite well with experimental values. Most of the experimental hydrocarbon data have been provided by Szwarc and his school [5]. The state of the art has been discussed in an excellent review [121].

Homogeneous ET has to be taken into account whenever dealing with electrode reactions, as was pointed out by Marcoux [127]. It is of special importance when the heterogeneous ET is slow, providing an additional and more effective pathway to reduced species. The homogeneous rate constant for the second charge transfer in I, similar to the heterogeneous charge transfer, is considerably larger than the first one. The difference greatly depends on the experimental conditions. It has been shown by cyclic voltammetry in superdry THF/TBAPF$_6$ that the first ET can be catalyzed by the dianion of COT itself in a homogeneous synproportionation, giving rise to a catalytic spike. The mechanism has been confirmed by digital simulation [58].

Quite often the resulting species undergoes a fast follow-up reaction. Thus, homogeneous ET becomes a crucial step in many electrode reactions: A well-known example is the cathodic reduction of organic halides. At mercury, heterogeneous electron transfer to most halides is slow. This kinetic barrier may be circumvented by addition of aromatic hydrocarbons such as phenanthrene [128], anthracene [129], and naphthalene [128]. These compounds are easily reduced at the cathode and transfer their excess electron to the

organic halide. The resulting halide anion radical undergoes a fast follow-up reaction. The whole reaction sequence is:

$$A + e^- \rightleftharpoons A^{\cdot-} \tag{10}$$

$$A^{\cdot-} + PhCl \rightleftharpoons A + PhCl^{\cdot-} \tag{11}$$

$$PhCl^{\cdot-} \rightarrow Ph^{\cdot} + Cl^- \tag{12}$$

$$Ph^{\cdot} + A^{\cdot-} \rightleftharpoons Ph^- + A \tag{13}$$

$$Ph^- + H^+ \rightarrow PhH \tag{14}$$

Regeneration of hydrocarbon in Eqs. (11) and (13) makes the process catalytic.

The reduction of organic halides in the presence of aromatic hydrocarbons has been the subject of detailed kinetic studies, which provide rate constants for the homogeneous ET [130] and the follow-up reaction [131]. The theoretical basis for this kind of experiment ("homogeneous redox catalysis") was laid by Savéant's group in a series of papers in 1978–1980 [132–134]. Homogeneous ET also plays an important role in the protonation of anion radicals [135], and it is also an essential step in the sigmatropic rearrangement in 1-arylindenes [136]. Both reactions are discussed here.

When an anion radical undergoes heterogeneous ET, formation of the neutral molecule in the ground state is strongly favored over formation of an excited state [137]. No such restriction applies to homogeneous ET, which, if sufficiently exothermic, may yield excited states of hydrocarbons. One may naively suppose that an electron is removed from the bonding molecular orbital of highest energy to give either the first excited singlet or triplet; electrochemiluminescence [138] may then occur.

The emission observed is usually the fluorescent band of the hydrocarbon, corresponding to the decay of the first excited singlet. The energy released by homogeneous electron transfer is given by the difference between the redox potentials of donor and acceptor plus a small entropy term [139], and in many case sof electrochemiluminescence falls short of the energy needed to populate the singlet state directly. In these "energy-deficient" cases there is sufficient energy to populate the lowest triplet state, and singlets can then be produced by diffusion-controlled triplet–triplet annihilation. Emissions observed at wavelengths other than that of the main singlet have been ascribed to excited dimers (eximers) [140,141], excited charge-transfer complexes (exiplexes) [142,143], and fluorescent products of radical-ion decay. Acceptors in electrochemiluminescence may be the corresponding hydrocarbon radical cations, added alkyl halides [144] or benzoyl peroxide [145], or adventitious impurities, which need be present at only 10^{-7} M levels. Experimental technique for the method is demanding [146]. Research attention is turning from the energy balance to the detailed mechanistic steps between electron transfer and photonic emission to the question of the quantum efficiency of the process.

B. Addition of Electrophilic Reagents and Related Reactions

1. Protonation

Under protic conditions, aromatic hydrocarbons and compounds with activated double-bonds usually undergo Birch-like reactions [11,147]. The reaction sequence has been elucidated by the classical work of Hoijtink [13,14,20,148,149], who used HMO theory to rationalize both chemical and electrochemical steps.

The anion radical produced by homogeneous ET is monoprotonated to give a Wheland-like π-radical. It readily accepts another electron because its bonding or non-

binding SOMO (single occupied molecular orbital) always has a lower energy than the antibonding LUMO of the single hydrocarbon. The second ET preferably occurs by disproportionation [135]. In a fast follow-up reaction the resulting carbanion takes another proton to eventually yield the final dihydro product:

$$A + e^- \rightleftharpoons A^{\cdot-} \tag{15}$$

$$A^{\cdot-} + H^+ \rightleftharpoons AH^{\cdot} \tag{16}$$

$$AH^{\cdot} + e^- \rightleftharpoons AH^- \tag{17}$$

or

$$AH^{\cdot} + AH^{\cdot} + A^{\cdot-} \rightleftharpoons AH^- + A \tag{18}$$

$$AH^- + H^+ \rightarrow AH_2 \tag{19}$$

If the reduction potential of the resulting dihydro product is sufficiently positive, it can undergo another reduction cycle. One of many examples is provided by the reduction of benz[a]anthracene in 75% aqueous dioxane [11,13,14,150].

Because of its general importance to organic electrochemistry, the reaction scheme just outlined has been the subject of detailed mechanistic studies [18,151–160]. As a model reaction, protonation of anthracene anion radicals by phenol in dimethylformamide has been selected. Of five limiting kinetic variants, ECE_{rev}, ECe_{irr}, DISP1, DISP2 and DISP3, the favored pathway was found to be DISP1 [135]. It involves the protonation of the anion radical and the protonated anion radical as the rate-determining step [Eq. (16)], followed by homogeneous ET between the anion radical and the protonated anion radical [Eq. (18)], yielding the monohydrogenated anion, which is itself rapidly and irreversibly protonated to the final dihydrogenated product. This mechanism has been disputed because of apparent deviations from predicted reaction orders [152–156]. Recently, it turned out that the inconsistencies are largely due to the formation of homoconjugated complexes between phenol and the phenolate anion [158,159]. Thus, DISP1 now seems to be generally accepted.

The rate-determining step of the DISP1 mechanism, the protonation of the radical anion, largely depends on its electronic structure. As a guideline, LUMO energies of the parent hydrocarbon may be used [39,161]. The attempt to correlate rate constants with highest local charge densities failed [162]. Therefore, Eberson suggested the application of the Dewar–Zimmermann rules [163].

Under highly protic conditions, the major products of cathodic reductions of cyclic conjugated hydrocarbons are usually dihydro derivatives [11,13,53,164]. In 2-methoxyethanol, for example, naphthalene yields 1,4-dihydronaphthalene [164] and COT provides mainly 1,3,6-cyclooctatriene [53].

These findings are in contrast to thermodynamics favoring in the case of naphthalene the formation of conjugated 1,2-isomers. Therefore, kinetic control has to be assumed. The site selectivity for the first as well as the second protonation step has been predicted by HMO theory. One approach refers to local charge densities [13,165]; the other one uses localization energies as a reactivity index [166]. In any event, the inductive effect of the methylene group, formed in the first protonation step, has to be taken into account if two sites provide comparable reactivity indices.

These techniques proved to be successful for the majority of the hydrocarbons, but they failed for some compounds such as phenanthrene, terphenyl, or quaterphenyl. The failure has been interpreted by the effect of the electric field on the charge distribution

[167]. Actually, these molecules have strongly anisotropic polarizabilities. In a more recent study, it was demonstrated that the isomeric ratio also depends on the counterion [168].

Under nominally aprotic conditions, 1,2-protonation dominates in naphthalene. Reduction of naphthalene in anhydrous acetonitrile containing tetraethylammonium *p*-toluenesulfonate yields 1,2-dihydronaphthalene, which is subsequently reduced to tetralin [169]. Similarly, reduction of I in anhydrous DMF gives 1,3,5-cyclooctatriene almost exclusively [53]. The formation of the thermodynamically more stable products is most probably due to base-catalyzed isomerization.

An interesting situation arises from the reduction of CH-acidic hydrocarbons because these compounds can undergo self-protonation. Actually, a voltammetric investigation of 1,3-diphenyl-2-methylindene and 4,5-methylenephenanthrene in DMF/TBAP or DMSO/TBAP clearly indicated a DISP1 mechanism, analogous to that described earlier [170a]. Similar results have been obtained for variously substituted indenes where the stoicheiometry is in perfect agreement with a two-electron, two-proton reduction process involving one-third starting material under self-protonation conditions, the remaining two-thirds acting as an proton donor [170b]. Generally, under self-protonation conditions the DISP1 pathway operates [Eqs. (20)–(23)], in which the protonation reaction between the radical anion ($AH^{\cdot-}$) and the neutral species (AH) is the rate-determining step.

$$AH + e^- \rightleftharpoons AH^{\cdot-} \tag{20}$$

$$AH^{\cdot-} + AH \rightleftharpoons AH_2^{\cdot} + A^- \tag{21}$$

$$AH_2^{\cdot} + AH^{\cdot-} \rightleftharpoons AH_2^- + AH \tag{22}$$

$$AH_2^- + AH \rightarrow AH_3 + A^- \tag{23}$$

On the other hand, reduction of fluorene [171,172] results in a homolytic cleavage of the CH bond (discussed later).

To study the stereochemistry of protonation reactions, substituted indenes have been cathodically reduced in DMF/TBAP with added water or phenol [170b,173,174]. In the presence of water, a formal "'anti" addition of protons was observed, whereas addition of phenol led to the prevalent formation of products, formally deriving from "syn" protonation. Obviously, steric effects and/or acidities of proton donor and the dihydroproduct play an important role. A detailed discussion of stereochemical aspects is found in Chapter 26.

Quite often, ion pairing causes a substantial positive shift of the reduction potential. For electrostatic reasons, the shift is especially large for the formation of higher valency ions. Therefore, with increasing interaction of the counterion, di- and polyanion formation becomes thermodynamically more favorable. Under these conditions, cathodic reduction immediately produces dianions via disproportionation and heterogeneous ET. Because of their high basicity, the dianions readily undergo protonation. Such a dianion mechanism was observed when tetraphenylethylene was reduced in a acetonitrile–TEAP in the presence of water or alcohols. Kinetic measurements led to a mixed-order rate low, rationalized by the existence of a hydrogen-bonded complex between the ion-paired dianion and the proton donor [113].

The classical Hoijtink, mechanism and the dianion mechanism have been observed at electrodes with a higher hydrogen overvoltage, such as mercury. If mercury is replaced by platinum with its low hydrogen overvoltage, a radical pathway seems to be favored [175a], which is closely related to catalytic hydrogenations of hydrocarbons. Spectroelectrochemical experiments provided evidence for an additional hydride mechanism [175b].

$$2H^+ + 2e^- \rightleftharpoons H_{2_{ads}} \quad (24)$$

$$H_{2_{ads}} + e^- \rightleftharpoons H^- + H^{\cdot}_{ads} \quad (25)$$

$$A + H^- \rightleftharpoons AH^- \quad (26)$$

These results illustrate that the reaction sequence and the stereochemistry of cathodic hydrogenations are controlled by the solvent, electrolyte, proton donor, electrode materials, etc. Thus, with increasing mechanistic knowledge, electrochemistry offers the chance to realize highly selective hydrogenations.

The addition of protons certainly is the most common "nucleophilic" reaction of reduced hydrocarbon species because of the almost ubiquitous availability of proton donors, which may be wanted or not. However, under strictly aprotic conditions it is also possible to add other electrophilic reagents such as alkyl halides, acyl halides, CO_2, and SO_2.

2. Alkylation

The addition of alkyl halides to aromatic anion radicals, generated by alkali metal reduction in etheral solvents, was already known in the 1950s [176] and was reviewed by Garst in 1971 [177]. The first electrochemical analogue was observed by Lund et al. [178]. These authors cathodically reduced hydrocarbons such as naphthalene, anthracene, stilbene [128,129], and perylene [130] in the presence of alkyl halides and isolated hydrogenated and alkylated products. Similar reactions are observed when the halides are replaced by ammonium or sulfonium [179].

These alkylations can be looked upon as aliphatic nucleophilic substitutions, usually thought to proceed via S_N1, S_N2, or hybrids of these mechanisms. However, in recent years more and more evidence for a single-electron transfer (SET) mechanism, represented in Eqs. (27)–(30), was obtained, and it was suggested that S_N2 and SET are just limiting cases of the same single-electron transfer mechanism [180]. The SET pathway involves first a transfer of an electron from the nucleophile to the electrophile followed by bond formation, whereas S_N2 reaction involves a synchronous shift of a single electron and bond formation [Eqs. (31)–(32)]. In addition, the generated anions may be protonated [Eq. (33)].

Because of these fundamental aspects, the mechanism of cathodically induced alkylations has been the subject of detailed studies [130,182]. In a stereochemical investigation it was found that racemization is much more effective than inversion. This result was interpreted as evidence of competition between the SET pathway and the S_N2 mechanism, with SET being the more important route [182]. The SET mechanism is represented in Eqs. (27)–(33):

$$A + e^- \rightleftharpoons A^{\cdot -} \quad (27)$$

$$A^{\cdot -} + BX \rightarrow A + B^{\cdot} + X^- \quad (28)$$

$$A^{\cdot -} + B^{\cdot} \rightarrow AB^- \quad (29)$$

$$A^{\cdot -} + B^{\cdot} \rightleftharpoons A + B^- \quad (30)$$

$$A^{\cdot -} + BX \rightarrow AB^{\cdot} + X^- \quad (31)$$

$$A^{\cdot -} + AB^{\cdot} \rightleftharpoons A + AB^- \quad (32)$$

$$B^-, AB^- + H^+ \rightarrow BH, ABH \quad (33)$$

The rate-determining step [Eq. (28)] of the SET mechanism consists of an electron transfer concerted with a cleavage of the carbon–halide bond in the alkyl halide, and

resulting in the generation of an alkyl radical. Numerous investigations have focused on the measurement of these rate constants [130]. As expected, the rate constant increases when the redox potential of the aromatic compound becomes more negative. The coupling step between alkyl radicals and aromatic anions is fast, with rate constants at the level of diffusion control. This indicates the lack of significant activation barriers, which consequently results in insensitivity to structural differences in the alkyl radical and in the aromatic radical anion [181]. Moreover, radical anions with very different redox potentials ($\Delta E_A^0 = 0.9$ V) couple with primary radicals with approximately the same rate constant. The competing S_N2 mechanism [Eqs. (31)–(32)] may be favored if the reacting species are not too sterically hindered, and the driving force for an electron-transfer reaction is low. In general, the more positive the redox potential of the aromatic compound is or the poorer the alkyl halide is an electron acceptor, the more important the S_N2 mechanism becomes [183].

3. Acylation

Formally related reactions are observed, when anthracene [184] or arylolefines [185] are reduced in the presence of carbonic acid derivatives such as anhydrides, esters, amides, or nitriles. Under these conditions, mono- or diacylated compounds are obtained. It is interesting to note that the yield of acylated products largely depends on the counterion of the reduced hydrocarbon species. It is especially high when lithium is used, which is supposed to prevent hydrocarbon species. It is especially high when lithium is used, which is supposed to prevent hydrodimerization by ion pair formation. In contrast to alkylation, acylation is assumed to prefer an S_N2 mechanism. However, it is not clear if the radical anion or the dianion are the relative species. The addition of nitriles is usually followed by hydrolysis of the resulting ketimines [185].

4. Addition of CO_2 and SO_3

In the pioneering papers of Wawzonek et al. [15,186] it was demonstrated that CO_2 can be added to cathodically reduced hydrocarbons to yield dihydrodicarbonylates. Examples of this kind of reaction include naphthalene [186,187], anthracene [15], 9,10-diphenylanthracene [15], phenanthrene [186], butadiene [187], stilbene [15], and diphenyl acetylene [187]. The mechanism is assumed to be analogous to that for protonation, with the essential steps being nucleophilic addition by an anion radical and subsequently by an anion [188]. 1,4-Addition to naphthalene suggests that carboxylation is kinetically controlled; formation of dihydromonocarboxylates indicates competition with protonation. Mechanisms involving CO_2 have to be considered for those hydrocarbons that are reduced at more negative potentials than CO_2^- [189], and for the electroinactive norbornadiene, which gives 3-nortricyclenecarboxylic acid [190]. Chemically formed CO_2^- is known to undergo typical radical addition reactions [191]. Like CO_2, SO_3 adds to reduced anthracene to give 9,10-dihydroanthracenebissulfonate [192].

C. Dimerization and Polymerization

Cathodically reduced hydrocarbons undergo not only homogeneous ET and nucleophilic attack but also coupling reactions resulting in hydrodimerization and polymerization.

Reduction of stilbene [15] or diphenylacetylene [186] in DMF yields 1,2,3,4-tetraphenylbutane, whereas phenanthrene [186] provides 9,9′10,10′-tetrahydro-9,9′-biphenanthrene. Hydrodimerization was also observed with benzalfluorene [193]. If DMF is

replaced by acetonitrile, protonation completely dominated hydrodimerization [15]. In carefully dried ethers, using alkali or alkaline earth metals salts as supporting electrolyte, 1,1-diphenylethylene can be reduced cathodically to give stable solutions of 1,1,4,4-tetraphenylbutane dianions [194]. These dianions can be cleaved by flash photolysis in the presence of excess 1,1-diphenylethylene to give transient anion radicals of 1,1-diphenylethylene. Kinetic analysis of the subsequent recombination confirmed the postulated radical–radical mechanism; the rate constant was found to be 0.5×10^9 M^{-1} s^{-1} [195]. 9-Cyanoanthracene undergoes a reversible electrodimerization with almost no side reactions, making a perfect model compound [196–200]. Again, it turned out that the dimerization follows a radical–radical mechanism. It is also interesting to note that water accelerates the dimerization. This effect was rationalized by specific solvation [200]. A careful study of the dimerization kinetics of 9-cyanoanthracene in different solvents and at low temperatures gives evidence that the coupling reaction is diffusion controlled and that its rate constant increases with increasing polarity of the solvent as predicted by the Debye–Smoluchovsky theory [201]. It should be noted that several authors have suggested a more complex reaction pattern, which at least involves a two-step mechanism [202]. A final decision on the validity of these different reaction paths will be a task of future research.

Many alkenes, activated by electron-withdrawing groups, readily undergo hydrodimerizations. The best known example is the electrodimerization of acrylonitrile, the base of the commercial Monsanto process [203]. This type of reaction was the subject of particularly active mechanistic investigations and is treated in detail in Chapter 31. Evidence is presented there that the essential step is a coupling of two radical anions (radical-radical route). In a very recent study, A. J. Bard has shown, using the SECM technique, that only the radical anions of acrylontrile dimerize (radical–radical route) [204]. Sterically less demanding arylalkenes and dienes undergo not only dimerization but also polymerization. Styrene is polymerized in ethers by alkali metal reduction [205] or addition of cumyl potassium [206]. The mechanism of ET-induced polymerization was extensively studied by Szwarc and his school [207]. It turned out that the first step is dimerization of the styrene anion radical, usually obtained by addition of sodium naphthalene. Under aprotic conditions, the resulting dianion adds to monomers, forming polymeric "living anions." It is interesting to note that the rate of the polymerization largely depends on the counterion.

With conventional techniques and electrolytes, it was not possible to obtain living anions because they are rapidly protonated by tetraalkylammonium salts and residual water. The first report of the production of living polymers by an electrolytic method has to be attributed to Yamazaki et al. [208], who used tetrahydrofuran as solvent, and $LiAlH_4$ or $NaAl(C_2H_5)_4$ as electrolyte for the polymerization of α-methylstyrene. A similar technique was used to polymerize styrene as well as derivatives [209–213]. The suggested mechanism agrees with the pathway described earlier.

D. Intramolecular Reactions

For many years, intramolecular reactions such as conformational changes, bond cleavage, bond formation, and valence isomerizations have been observed only when hydrocarbons were reduced with alkali metals in etheral solvents. In most electrochemical experiments these reactions were dominated by the electrophilic processes already described here. However, progress in experimental techniques [8,26,30] has made these reactions accessible to electroanalytical investigations, providing new mechanistic insight.

1. Conformational Changes

In recent years it has become more and more obvious that ET is frequently accompanied by conformational changes. The interconversion may preceed or follow ET; the majority of these processes have to be classified as CE (as yet this mechanism has not been observed in the hydrocarbon series), EC, EEC, or ECE mechanisms, whereas only a few systems follow an EE pathway. An example for an EC process is the interconversion of the anion radical of *cis*-stilbene, which is quite slow on the voltammetric time scale [103,104], whereas *cis*-azobenzene anion radicals isomerize very rapidly [214]. Tetraphenylethylene undergoes two closely separated reversible additions of one electron [112,215]. The small difference of standard potentials, equivalent to a high disproportionation constant [see Eq. (5)], has been interpreted as interconversion from an almost planar to an orthogonal conformation when going from the neutral molecule to the dianion [216]. The thermodynamics and kinetics of ET-induced interconversions of substituted tetraphenylethylenes have been studied in great detail [125]. Reduction of 1,6-dimethylbicyclo[4.4.1]undeca-2,4,7,9-tetraene appears to proceed via an ECE scheme in which the initial reduction gives an unstable radical anion, which undergoes a structural change, giving another anion with a conjugatively stabilized π-system [73]. Conformational changes concurrent with ET (EE pathway) are observed upon reduction of I, as cited earlier. This emerging field was reviewed by Evans and O'Connell [125].

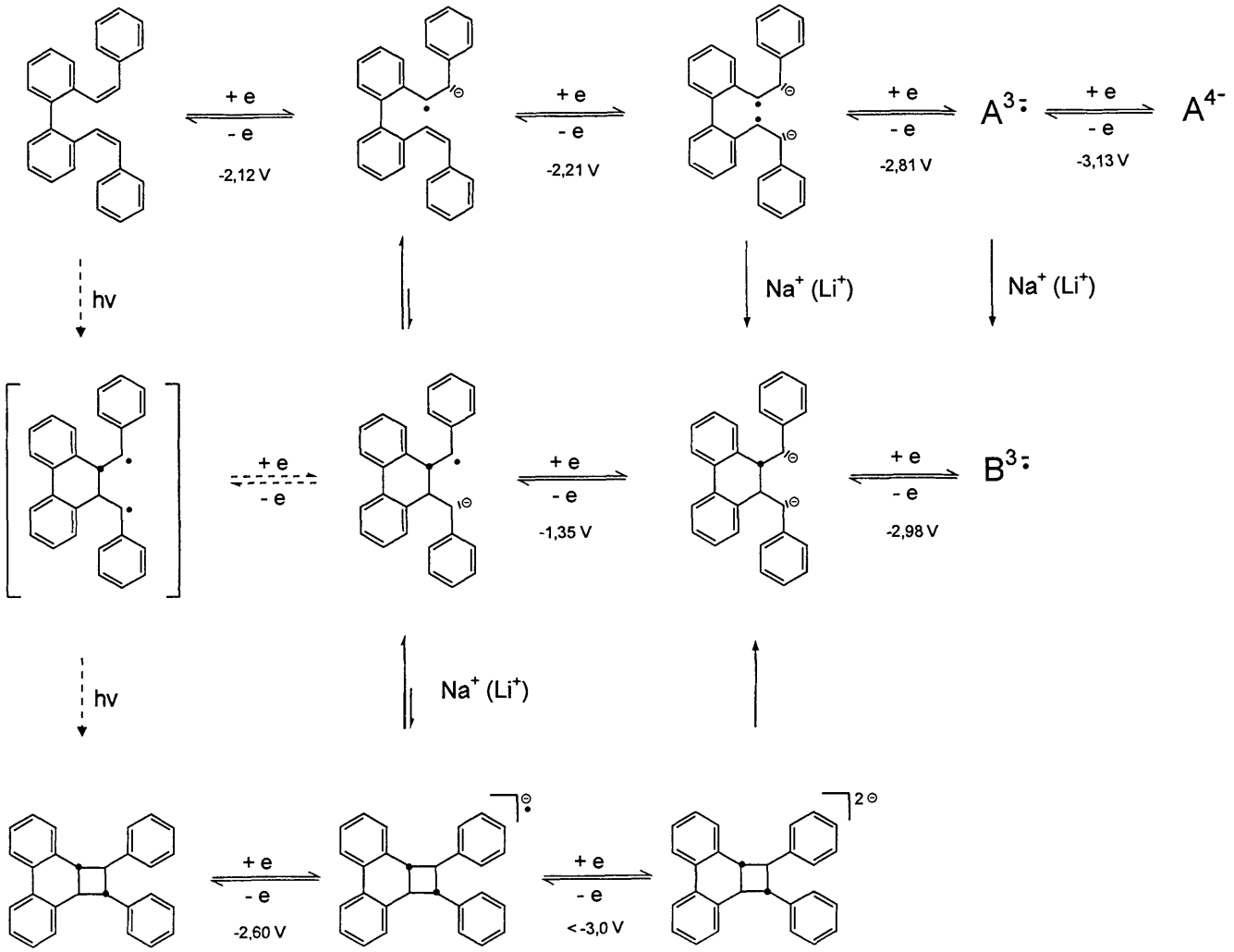
2. Bond-Breaking and Bond-Making Reactions

Reductive cleavage of carbon–carbon bonds was already observed in the 1920s by Ziegler and Thielemann upon alkali metal reduction of diarylalkanes in etheral solvents [217]. As was shown by Lagendijk and Szwarc [218] for 1,2-di(α-naphthyl)ethane, the primary anion radical undergoes homogeneous disproportionation which is supported by ion pairing. The resulting dianion decomposes by the fission of the CH_2–CH_2 bonds into the salts of α-naphthylmethyl carbanions. Similarly, 9,9′-bianthryl can be cathodically cleaved into anthracene and 9.9′-dihydroanthracene plus small amounts of reduced dimers. The dianion mechanism is quite slow, whereas the tri- and tetraanions are supposed to decay rapidly [219].

ESR spectroscopical investigations of the anion radical of fluorene indicated a first-order decay, and it was concluded that the CH bond undergoes homolytic cleavage [220]. Voltammetric studies of fluorene in DMF reached the same conclusion [171,172].

The thermal and photochemial ring opening reactions of cyclobutene are the classical examples of pericyclic processes [221]. In 1976, Bauld et al. described an ET-induced analog [222]. They observed that benzo- and phenanthrocyclobutene undergoes ring opening upon alkali metal reduction and suggested an ECE pathway. A voltammetric study of *cis*- and *trans*-tetrahydro-1,2-diphenylcyclobutanephenanthrene in THF–$NaBPh_4$ confirmed this mechanism. However, it turned out that the rate of the ring opening largely depends on the counterion. If ion pairing is prevented by addition of 15-crown-5, the reaction rate slows dramatically. At $-50°C$ the anion radical of the *Z* isomer becomes stable on the voltammetric time scale, whereas the dianion exhibits a fast ring opening [223].

Two-electron reduction [58a] or oxidation [224] of 1,3-dimethylidenecyclobutanes yields bicyclo[1.1.0]butanes. Cyclic voltammetry of 2,4-di-9*H*-fluoren-i-yliden-1,1,3,3-tetramethylcyclobutane in DMF at low temperatures demonstrated that bond formation proceeds via an EEC mechanism; the rate constant was found to be $20\ s^{-1}$ [58a].


+ e
- e
-2,12 V
+ e
- e
-2,21 V
+ e
- e
-2,81 V
A3:
+ e
- e
-3,13 V
A4-
hv
Na+ (Li+)
Na+ (Li+)
+ e
- e
+ e
- e
-1,35 V
+ e
- e
-2,98 V
B3:
hv
Na+ (Li+)
+ e
- e
-2,60 V
+ e
- e
< -3,0 V
2⊖

Scheme 1

ET-induced cycloadditions of polycyclic olefins and cycloreversions of cyclobutane species have been studied by ESR spectroscopy [225]. Upon chemical and electrochemical reduction, 2,2′-distyrylbiphenyl rearranges by intramolecular coupling into a "bis-benzylic" dihydrophenanthrene dianion, which can be either protonated to a 9,10′-dibenzyl-9,10-dihydrophenanthrene or oxidatively coupled to a cyclobutane species. It is interesting to note that the intramolecular bond formation takes place at the di- and triionic level, which is comparable with a radical–radical coupling (RR route, EEC mechanism) [223a]. The experiments are evidence that RS coupling is generally improbable for ionic dimerization reactions. At low temperatures, the coupling rate between the negatively charged stryryl units slows down and the tetraanion of the starting species can be obtained. Again, it turns out that ion-pairing effects favor the formation of the bis-benzyclic intermediate. Thus, the first-order intramolecular coupling step between the negatively charged styryl units is significantly faster in THF/$NaBPh_4$ than in the presence of additional 15-crown-5 or in DMA/TBABr [223a] (Scheme 1, Fig. 3).

1-Arylindenes undergo sigmatropic 1,5-shifts, induced oxidatively [226], thermally [227], photochemically [228], and reductively [229]. The reductive rearrangement of 1,1,3-triphenylindene, yielding the dianion of 1,2,3-triphenyl-2*H*-indene, has been the subject of

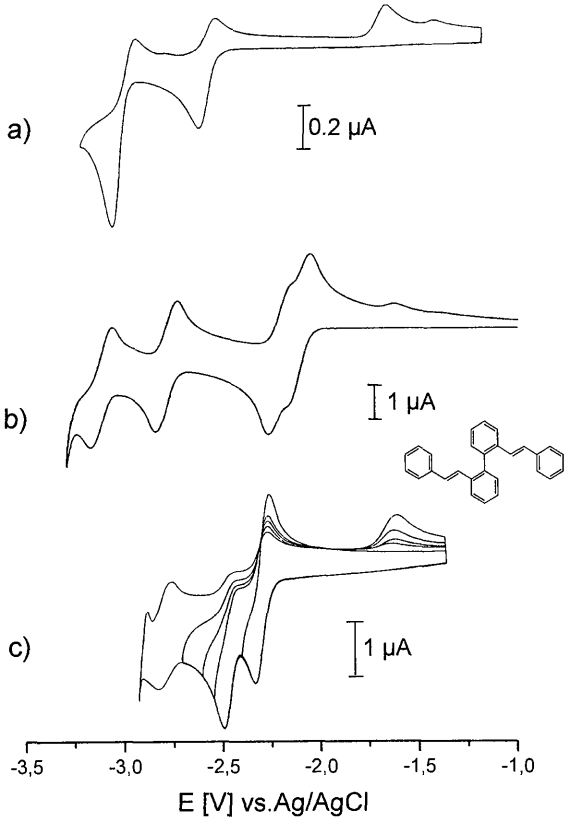


Figure 3. Reduction of 1,2-tetrahydro-1,2-diphenylcyclobuta[l]phenanthrene (a) and 2,2'-distyrylbiphenyl (b,c) (see Ref. 222a). (a), (b) In DMA/TBABr, v = 100 mV s^{-1}, T = 213 K. (c) In THF/$NaBPh_4$, v = 200 mV s^{-1}, T = 223 K.

a voltammetric investigations in "superdry" THF–$NaBPh_4$ [136] and in DMF–TBAP [230]. The reaction follows an EEC or EDispC pathway.

At room temperature in the presence of Na^+ cations, the rearranging dianion is formed via homogeneous disporportionation, thermodynamically favored by ion pairing and kinetically supported by the fast follow-up reaction. When ion pairing is suppressed by application of low temperatures or the addition of sodium complexing 15-crown-5, the anion radical becomes persistent and the reactive dianion species has to be generated via heterogeneous ET at much more negative potentials. The same results are obtained when the bulky tetrabutylammonium ion is used as counterion [230]. Replacing 1,1,3-triphenylindene with 1-methyl-1-phenylindene or 1,2-dihydro-1,1′-spiribiindene, the anion radical undergoes a quite unusual cleavage of the alkyl-aryl bond, whereas the dianion rearranges in the same manner as triphenylindene [231].

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7

The Electrochemistry of C_{60} and Related Compounds

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I. INTRODUCTION

Fourteen years ago, when buckminsterfullerene, C_{60} was discovered [1], it was impossible to predict the impact that this discovery would have in so many research laboratories around the world. Researchers in fields ranging from organic chemistry to cryogenic physics have been attracted to the incredibly symmetric molecule for different reasons. We believe that one particular property of C_{60} has been of particular interest to all the different fields: the ability of C_{60} to easily accept electrons. This property was theoretically predicted [2] soon after its soccer-ball structure was proposed but before it was confirmed by x-ray crystallography [3]. At that time, because of the possible implications in the field of chemistry, an active search for a method to produce the compound in reasonable quantities began, and shortly after, success was achieved [4]. The race began for those interested in confirming the theoretical predictions, as well as for those with the incredible insight to see the immense possibilities presented by an electrophilic molecule that not only could be easily derivatized in three dimensions but that, belonging to the family of carbon allotropes and being fully conjugated, offered the possibility of being a great conductor or perhaps even a superconductor [5].

In this chapter we concentrate exclusively on the most important aspects of the electrochemistry of C_{60} and the other pristine higher fullerenes, namely, C_{70}, C_{76}, C_{78}, C_{82}, and C_{84}. A vast number of derivatives of C_{60} and a few of C_{70}, C_{76}, and C_{78} have been prepared, and their redox properties have been studied using electrochemical techniques. However, due to space limitations, it is impossible to cover this subject here and to give it the justice that it deserves. Since several comprehensive reviews on fullerenes and their derivatives have appeared recently, the reader is referred to these for details [6]. Nevertheless, it has been recently discovered that controlled potential electrolysis can be used as a synthetic tool for the preparation of new fullerene derivatives, as well as for the separation of otherwise inseparable fullerene isomers. Thus, a short section covering electrosynthesis of fullerene derivatives is included at the end of this chapter.

II. REDUCTION AND OXIDATION OF C_{60}

The cathodic electrochemistry of C_{60} has been studied by cyclic voltammetry (CV), differential pulse voltammetry (DPV), and Osteryoung square-wave voltammetry (OSWV). Using any of the three techniques, the reduction of this fullerene is characterized by the appearance of up to six reversible waves [7–10], a fact that confirms the theoretical prediction of an energetically low-lying triply-degenerate LUMO (lowest unoccupied molecular oribtal) [2]. The number of waves observed as well as the reduction potentials are dependent on the solvent, supporting electrolyte, and temperature chosen [11]. Figure 1 shows the CV and DPV of C_{60} obtained under vacuum at $-10°C$ in the mixed solvent system toluene/acetonitrile (5/1) using tetra-*n*-butylammonium hexafluorophosphate ($TBAPF_6$) as supporting electrolyte. The resulting reduction potentials obtained under these conditions are presented in Table 1. Notice that, as predicted by the triply degenerate LUMO, the potential separation between any two successive waves is relatively constant,

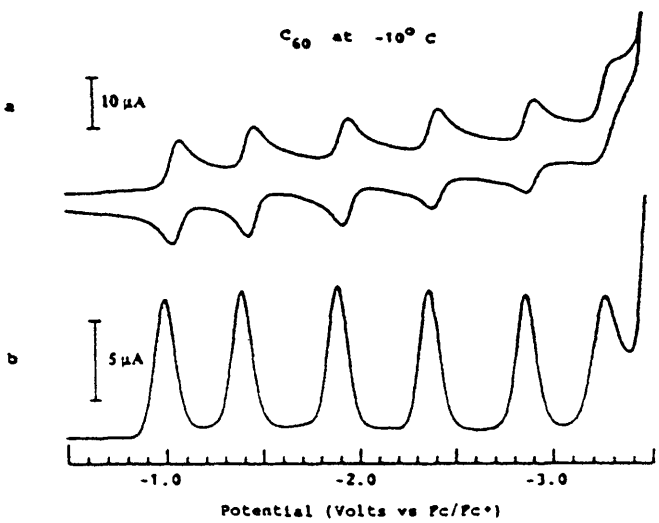

Figure 1. Reduction of C_{60} in acetonitrile/toluene using (a) cyclic voltammetry at 100 mV/s scan rate and (b) differential pulse voltammetry (50 mV pulse, 50 ms pulse width, 300 ms period, 25 mV/s scan rate). From Ref. 7.

Table 1 Half-Wave Reduction Potentials (in V vs. Fc/Fc^+) of C_{60} Using Various Solvents, Supporting Electrolytes, and Temperatures

Solvent	Supporting Electrolyte	Temp. (°C)	E_1	E_2	E_3	E_4	E_5	E_6	Reference
Ph/Me/MeCN[a]	$TBAPF_6$	−10	−0.98	−1.37	−1.87	−2.35	−2.85	−3.26	7
PhMe/DMF	$TBAPF_6$	−60	−0.82	−1.26	−1.82	−2.33	−2.89	−3.34[b]	8
Liquid NH_3[c]	KI	−70	−1.04	−1.56	−2.00	−2.37	−2.43	−3.03	9
Benzene	$THAClO_4$	+45	−0.83	−1.29	−1.89	−2.46	−3.07		10e
MeCN[d]	$TBAClO_4$	+22		−1.24	−1.73	−2.19	−2.78		11
Pyridine	$TBAClO_4$	+22	−0.86	−1.38	−1.80	−2.33			11
DMF	$TBAClO_4$	+22	−0.77	−1.23	−1.82	−2.36			11
PhCN	$TBAClO_4$	+22	−0.92	−1.34	−1.82				10e
THF	$TBABF_4$	−60	−0.96	−1.53	−2.11	−2.60	−3.13	−3.59	12
	$TBABF_4$	+25	−0.93	−1.52	−2.08	−2.57	−3.08		12
	$TBAClO_4$	+22	−0.90	−1.49	−2.06	−2.56			11
DCM	$TBAPF_6$	+22	−1.02	−1.41	−1.87				11
	$TBAClO_4$	+22	−1.00	−1.39	−1.84[e]				11
	$TBABF_4$	+25	−1.01	−1.40					10a
TCE	$TBAPF_6$	+25	−1.06						17

Note: DCM = dichloromethane; DMA - dimethylamine; DMF = dimethylformamide; MeCN = acetonitrile; ODCB = *o*-dichlorobenezene; PhCN = benzonitrile; PhMe = toluene; TBA = tetra-*n*-butylammonium; TCE = 1,1,2,2-tetrachloroethane; THA = tetra-*n*-hexylammonium; THF = tetrahydrofuran. From Ref. 6e.

[a]Glassy carbon electrode. All others use Pt.

[b]Anodic peak potential

[c]Due to the presence of surface waves upon reoxidation, anodic peak potentials are reported.

[d] Controlled potential electrolysis used to generate C_{60}^- due to insolubility of C_{60} in MeCN.

[e]Scan rate > 5 V/s.

with a value of 450 ± 50 mV [7]. Redox potentials obtained under other solvent, supporting electrolyte, and temperature conditions are also presented in Table 1.

Two very important points about the cathodic behavior of C_{60} need to be mentioned. First, C_{60} anions appear to be stable on the voltammetric time scale, but when electrogenerated by controlled potential coulometry in solution, only the mono- through tetra-anions are stable [6b,6e]. Second, although neutral C_{60} may be insoluble in solvents such as dimethylformamide (DMF), acetonitrile, or tetrahydrofuran (THF), its anions dissolve readily. Therefore, these anions can be generated from a suspension of C_{60} [12].

Calculations of the HOMO (highest occupied molecular orbital) energy for C_{60} indicated that it was energetically low-lying and fivefold degenerate [2]. Furthermore, the ionization potential (IP) was calculated to have a high value, ~ 7.8 eV [13]. In later measurements in the gas phase a value of 7.6 eV was obtained [14]. Together, these two results suggested that the oxidation of C_{60} would be difficult. Indeed, initial studies on the anodic electrochemistry of C_{60} using various solvents and supporting electrolytes showed not only chemically irreversible behavior [10e,11,15,16] (see Table 2), but in some cases up to four electrons seemed to be transferred during the oxidation process [10e,16]. The first and only quasireversible ($\Delta E_{pp} \cong 80$ mV) oxidation of C_{60} was observed by CV and OSWV in 1993 (see Fig. 2). This one-electron oxidation wave at $E_{1/2} = +1.26$ V versus Fc/Fc^+ was obtained using 1,1,2,2-tetrachloroethane (TCE) under vacuum at room temperature [17]. At room temperature, the potential difference between the first oxidation

Table 2 Half-Wave Oxidation Potentials (in V vs/ Fc/Fc^+) of C_{60} Using Various Solvents, Supporting Electrolytes, and Temperatures

	Solvent	Supporting electrolyte	Temp (°C)	E_1^{ox}	E_2^{ox}	Reference
C_{60}	MeCN[a]	$TBABF_4$	RT?	+1.60[b]		15
	PhCN	$TBAPF_6$	RT	+1.30[b]		10e
	DCE	$TBAClO_4$	22	+1.28[b]		11
	DCM	$TBAClO_4$	22	+1.32[b]		11
	TCE	$TBAPF_6$	RT	+1.26		17
$C_{60}+C_{70}$	DCM	$TBAPF_6$	RT?	+1.65[c,d]	+1.75[c,b]	16

Note: See Table 1 for solvent abbreviations. From Ref. 6e.
[a]Film of C_{60} in MeCN.
[b]Chemically irreversible
[c]It was not reported which of these potentials corresponds to C_{60} and which one to C_{70}.
[d]Adsorption observed.

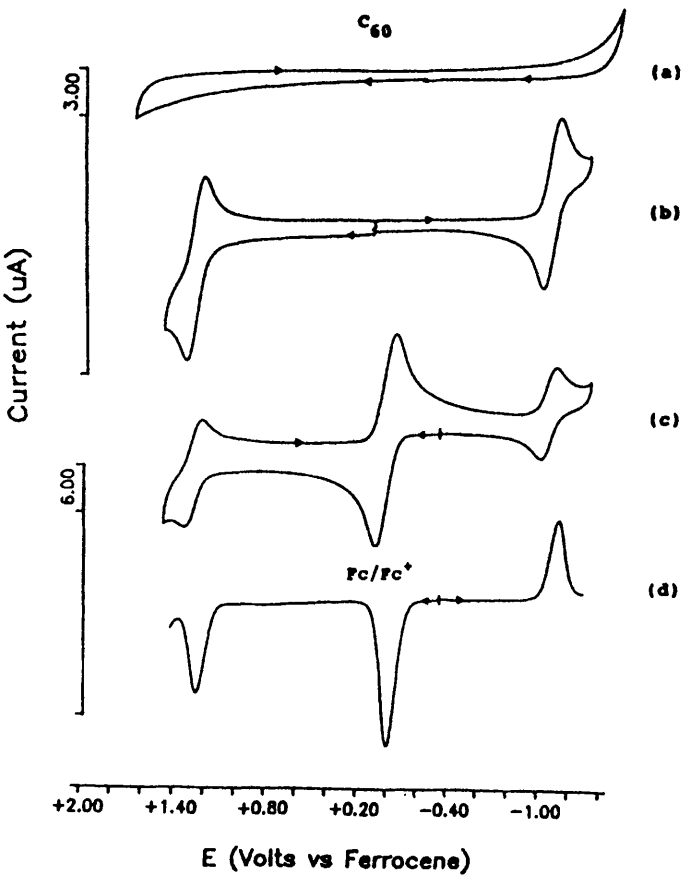

Figure 2. CV and OSWV scans showing oxidation and first reduction waves for C_{60} in TCE at room temperature. CVs were run at a scan rate of 100 mV/s. OSWVs were run at 60 mV/s. (a) CV of background solvent–electrolyte system. (b) CV of C_{60}, no ferrocene added. (c) Same as (b) after addition of ferrocene. (d) OSWV of the solution in (c). From Ref. 17.

and the first reduction of C_{60} which is a good measure of the HOMO–LUMO energy gap in solution, is 2.32 V.

Altogether, C_{60} displays a very rich electrochemistry, with eight oxidation states in solution, comprising six negative states, one neutral state, and one positive state.

III. REDUCTION AND OXIDATION OF C_{70}

Electrochemically, C_{70} behaves very similarly to C_{60}. Six reduction waves are observed in toluene/acetonitrile, but unlike C_{60}, all six waves can be detected at room temperature (see Fig. 3) [7]. Reduction potentials for C_{70} obtained under various conditions of solvent and temperature are presented in Table 3. In comparing the corresponding values shown in Tables 1 and 3 for the first and second reduction potentials of C_{60} and C_{70} in acetonitrile/toluene, one observes that they are nearly identical. However, from the trianion up to and including the hexanion, C_{70} becomes increasingly easier to reduce than C_{60}. A charge separation delocalization model has been evoked to explain this phenomenon [10c]. A noteworthy observation is the fact that the reduction potentials of C_{70} also appear to be solvent and/or temperature dependent, although no specific studies on the subject have been published.

Another similarity between C_{60} and C_{70} is their anodic electrochemical behavior. Of the solvents used thus far, the only one in which C_{70} undergoes a quasireversible oxidation process is in TCE [17]. Within the potential window of this solvent, two oxidation waves are observed by OSWV at +1.20 and +1.75 mV (see Fig. 4). The former is 60 mV more negative than the corresponding first oxidation potential of C_{60}. Thus C_{70} is easier to oxidize than C_{60}, a not surprising fact taking into account the lower ionization potential of C_{70} in the gas phase (7.3 eV) [13]. The second oxidation, which occurs at the limit of the

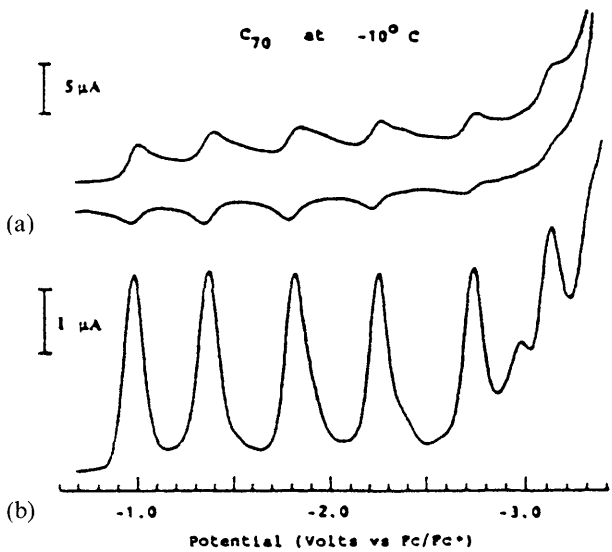

Figure 3. Reduction of C_{70} in acetonitrile/toluene using (a) cyclic voltammetry at 100 mV/s scan rate and (b) differential pulse voltammetry (50 mV pulse, 50 ms pulse width, 300 ms period, 25 mV/s scan rate). From Ref. 7.

Table 3 Half-Wave Reduction Potentials (in V vs. Fc/Fc^+) of C_{70} Using Various Solvents, Supporting Electrolytes, and Temperatures

Solvent	Supporting electrolyte	Temp. (°C)	E_1	E_2	E_3	E_4	E_5	E_6	Reference
Ph/Me/MeCN[a]	$TBAPF_6$	−10	−0.97	−1.34	−1.78	−2.21	−2.70	−3.70	7
DMA[b,c]	TBABr	−65	−0.45	−0.90	−1.34	−1.77	−2.33	−2.80	16
ODCB[d]	?	+25	−0.99	−1.44	−1.90				10b
THF	?	+25	−0.84	−1.41	−1.95				10b
PhCN	?	+25	−0.91	−1.32					10b
Ph/Me/DCM	$TBAPF_6$	RT?	−0.91	−1.28	−1.70				10c, 21
DCM	?	+25	−0.97	−1.35	−1.76				10b
	$TBAPF_6$	+25	−0.93	−1.31	−1.73	−2.09			22
TCE	$TBAPF_6$	+25	1.02						17

Note: See Table 1 for solvent abbreviations. From Ref. 6e.
[a]Glassy carbon electrode. All others use Pt.
[b]Cathodic peak potential.
[c] Vs Ag/AgCl.
[d]Scan rate = 25 mV/s.

solvent potential window, appears to be irreversible (see Table 4). The value of the HOMO–LUMO energy gap in solution for C_{70} is then 2.22 V at room temperature.

IV. REDOX PROPERTIES OF THE HIGHER FULLERENES

The higher fullerenes, C_{76}, C_{78}, C_{82}, and C_{84}, were expected to be more readily reduced and oxidized than C_{60} and C_{70} based on their estimated higher electron affinities and lower ionization potentials [13]. The experimental confirmation of these predictions, however, took longer than for C_{60} and C_{70} because the amount of higher fullerenes present in fullerene soot is very small, thus complicating the isolation and purification process [18,19]. It was not until these materials were obtained in microgram amounts that electrochemical studies were initiated. In addition, each of these fullerenes exists as two or more structural isomers with different symmetries in some cases [18]. If left as a mixture after their isolation from the soot, the presence of two or more isomers may result in the observation of multiple redox waves, a problem that in some cases has translated into uncertain assignments [20]. The half-wave reduction and oxidation potentials for these fullerenes obtained under different experimental conditions are presented in Tables 4 and 5, respectively. It is important to note that the loss of triply or nearly triply degenerate LUMOs, found in C_{60} and C_{70} [13], leads to potential separations between any two successive reductions that are not constant (see Table 4).

A. Electrochemistry of C_{76}

The electrochemical behavior of C_{76} has been easier to study than that of the other members of the higher fullerenes because it exists as a pair of chiral enantiomers with D_2 symmetry, and these are isolated as a 1:1 racemic mixture [23]. As shown in Table 4, up to six cathodic waves have been observed in a toluene/acetonitrile mixture at −15°C, although the sixth reduction is irreversible [24]. In dichloromethane (DCM) and benzoni-

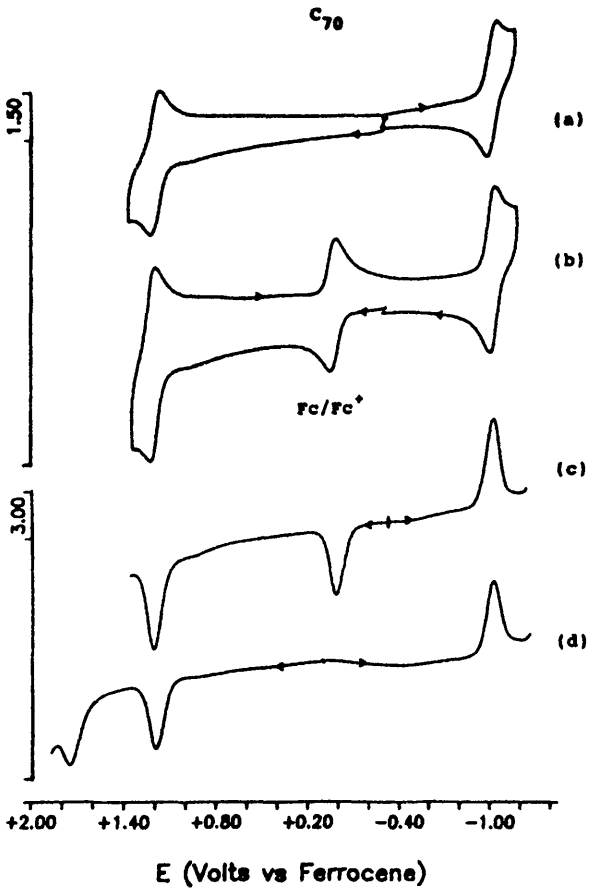

Figure 4. CV and OSWV scans showing oxidation and first reduction waves for C_{70} in TCE at room temperature. CVs were run at a scan rate of 100 mV/s. OSWVs were run at 60 mV/s. (a) CV of C_{70}, no ferrocene added. (b) Same as (a) after addition of ferrocene. (c) OSWV of the solution in (b). (d) OSWV of the solution in (a) without ferrocene added, scanned to more negative potential to show the second oxidation wave. From Ref. 17.

trile, four reversible waves have been observed [25], and in trichloroethane (TCE) only two. Confirming the higher estimated electron affinity of C_{76} [13], the monoanion of C_{76} in these solvents appears at a potential 100–200 mV more positive than C_{60}^{1-}. C_{76} is also easier to oxidize than C_{60} by 450 mV, with the first of two oxidations in TCE appearing at +0.81 V (see Table 5 and Fig. 5a) [26,27]. A single reversible oxidation is also observed in DCM, but various other solvents have been reported to produce chemically irreversible anodic behavior [24,25].

B. Electrochemistry of C_{78}

A 5:1 ratio mixture of the two most abundant constitutional isomers of C_{78}, C_{2v}-C_{78}, and D_3-C_{78}, have been separated from the other fullerenes. Selegue and coworkers reported the first study on the redox properties of the C_{2v} isomer in a toluene/acetonitrile mixture at −15°C. Five reversible and one irreversible reduction waves were

Table 4 Half-Wave Reduction Potentials (in V vs. Fc/Fc^+) of the Less Abundant Higher Fullerenes C_{76}, C_{78}, C_{82}, and C_{84} Using Various Solvents, Supporting Electrolytes, and Temperatures

	Solvent	Supporting electrolyte	Temp. (°C)	E_1	E_2	E_3	E_4	E_5	E_6	Reference
C_{76}	DCM	$TBABF_4$	RT	−0.79	−1.12	−1.57				25
		$TBAPF_6$	RT	−0.83	−1.15	−1.64	−2.01			22
	PhCN	$TBABF_4$	RT	−0.76[a]	−1.19[a]	−1.72[a]	−2.06[a]			25
		PPN^+Cl^-	RT?	−0.78	−1.16					27
	PhMe/MeCN	$TBAPF_6$	−15	−083	−1.17[b]	−1.68[b]	−2.10[b]	−2.61[b]	−3.04[b,c]	24
	TCE	$TBAPF_6$	RT	−0.83	−1.12					26
		PPN^+Cl^-	RT?	−0.91						27
C_{78}	PhCN	PPN^+Cl^-	RT?	−0.64	−1.06					27
	TCE	$TBAPF_6$	RT	−0.77	−1.08					26
		PPN^+Cl^-	RT?	−0.79	−1.13					27
C_{2v}-C_{78}	DCM	$TBAPF_6$	*RT*	−0.70	−1.04	−1.72	−2.07			22
	PhMe/MeCN	$TBAPF_6$	−15	−0.72[b]	−1.08[b]	−1.79[b]	−2.18[b]	−2.45[b]	−2.73[b]	24

D_3-C_{78}	DCM	$TBAPF_6$	RT	−0.64	−0.94	−1.70	−2.05			22
C_{82}	Pyridine	TBAP	RT?	−0.47	−0.80	−1.42	−1.84			33a
C_{84}[e]	ODCB	$TBAPF_6$	RT?	−1.00[d]	−1.29[d]	−1.60[d]	−1.96[d]	−2.21[d,f]		36
	PhCN[d]	$TEAPF_6$	RT?	−0.63	−0.95	−1.28	−1.58	−1.87		24,36
	PhMe/MeCN	$TBAPF_6$	+22	−0.67	−1.00	−1.34	−1.72	−1.99	−2.40[g]	20
	TCE	$TBAPF_6$	RT	−0.67	−0.96	−1.27				26
D_{2d}-C_{84}	Pyridine[h]	TBAP	+22	−0.52	−0.84	−1.20	−1.63[h]	−2.07[h]		20
	Pyridine	TBAP	RT?	−0.46	−0.77	−1.58	−1.98	−2.27[c]		37
D_2-C_{84}	Pyridine[b]	TBAP	+22	−0.61	−0.97	−1.30	−1.52[h]	−1.94[h]		20
	Pyridine	TBAP	RT?	−0.65	−0.98	−1.34	−1.75			37

Note. See Table 1 for solvent abbreviations. From Ref. 6e.

[a]Scan rate = 1 V/s.

[b]Scan rate = 2 V/s.

[c]May be irreversible.

[d]Reported value is ±40 mV due to adsorption and uncompensated resistance complications.

[e]Mixture of two major isomers, D_2- and D_{2d}-C_{84}

[f]Nature of this process is unknown because it was observed at the limit of the solvent potential window.

[g]Tentative assignment to the 6th reduction of C_{84}.

[h]The fourth and fifth reduction potentials are not assigned with certainty because of variation in the heights of the corresponding peaks (see Ref. 20).

Table 5 Half-Wave Oxidation Potentials (in V vs. Fc/Fc^+) of the Higher Fullerenes, C_{76}, C_{78}, and C_{84}, Using Various Solvents and Temperatures

	Solvent	Supporting electrolyte	Temp. (°C)	E_1^{ox}	E_2^{ox}	$< E_1^{ox} - E_1^{red}$	Reference
C_{76}	DCM	$TBAPF_6$	RT	+0.84	1.67		22
	TCE	$TBAPF_6$	RT	+0.81	+1.30[a]	1.64	26
C_{2v}-C_{78}	PhMe/MeCN	$TBAPF_6$	−15	+0.90[a]	1.62[b]		24
	TCE	$TBAPF_6$	RT	+0.95	+1.43	1.72	26
D_3-C_{78}	DCM	$TBAPF_6$	RT	+0.74	1.38		22
	TCE	$TBAPF_6$	RT	+0.70	+1.17	1.47	26
C_{84}	TCE	$TBAPF_6$	RT	+0.93	1.60		26

Note. See Table 1 for solvent abbreviations. From Ref. 6.
[a]Chemically irreversible.
[b]Calculated from data of Ref. 25.

observed by CV in addition to one irreversible oxidation step [24]. A second study performed with a mixture of the two isomers in TCE using OSWV [26] confirmed what has been predicted by theory [28]: comparable LUMO and different HOMO energies. Indeed, cathodic scans revealed only two one-electron reductions to form C_{78}^- and C_{78}^{2-} within the solvent potential window, indicating that in this solvent, the reductions of the two isomers essentially overlap. On the other hand, four oxidation waves were observed, consisting of two pairs of consecutive small and large waves with a current intensity ratio of 1:5. Thus, based on the current intensities, the waves were assigned to the D_3 and C_{2v} isomers, respectively (see Fig. 5b). Most recently, pure samples of the two isomers were obtained by the retro-Bingel reaction (C_{2v}) [29] and by high-performance liquid chromatography (HPLC) (D_3) [30]. CV studies of these samples at room temperature demonstrated that in dichloromethane the first and second reduction potentials of the two isomers are similar but not identical (see Table 4), with the D_3 isomer being the easiest to reduce by 60 and 100 mV, respectively [22]. The third and fourth reductions are essentially identical. In this solvent, however, only one reversible one-electron oxidation was observed for the D_3 isomer. Neither the two oxidations of the C_{2v} isomer nor the second oxidation of the D_3 isomer that had been observed in TCE could be observed in dichloromethane due to limitations in the solvent potential window. TCE seems to be a remarkable solvent for the observation of the anodic electrochemical behavior of fullerenes.

C. Electrochemistry of C_{82}

In general, electrochemical studies of C_{82} have been devoted to the study of its endohedral metallo complexes, in which metal atoms are trapped inside the fullerene cage. Part of the fascination with these molecules stems from two aspects of their electronic structures: (1) Unlike noble gas endofullerenes, metallofullerenes are formed from a stable ion-pair association between a fulleride anion of charge n^- and a cation of charge n^+, which cannot escape from the anionic cage nor react with other substances outside the

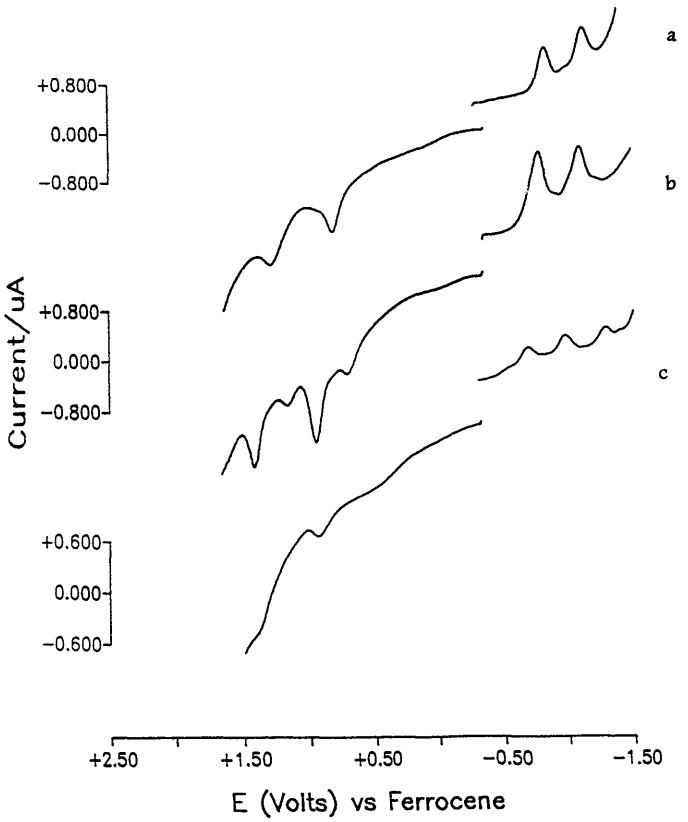

Figure 5. OSWV in TCE for (a) C_{76}, (b) C_{78}, and (c) C_{84} recorded at 60 mV/s. From Ref. 26.

cage [31]. (2) The trapped atom(s) may not necessarily sit at the center of the cage, in which case the symmetry of the cage may be altered [31]. Exploring the chemistry of these molecular rattles has been slowed down because their production is plagued by purification difficulties, low yield, and air sensitivity. Although other fullerenes have been detected acting as endohedral hosts, C_{82} encapsulating group III-B elements as well as members of the lanthanide series appears to be the most stable toward separation techniques [32].

Recently, Suzuki et al. reported a compilation of their four-year research in the electrochemistry of La@C_{82}, Ce@C_{82}, Gd@C_{82}, and Y@C_{82} [33]. Several conclusions were reached concerning these four metallofullerene complexes: (1) Unlike those of empty C_{60} and C_{70}, the reduction waves of these fullerolanthanides are not equally spaced, and they not always correspond to a one electron process (see Fig. 6); (2) the first reduction occurs $\sim$ 300 mV more positive than the empty C_{82} cage (see Table 6), indicating a better electron accepting ability; (3) of the two oxidation processes observed in all cases, the first one is reversible and slightly more positive than that of ferrocene, indicating that fullerolanthanides are also good electron donors; and (4) the separation between the first oxidation and the first reduction (HOMO-LUMO gap) is small (0.47–0.49 V), reflecting the possibility of an open shell electronic structure. The formal charges for these complexes are believed to be, in general $M^{3+}@C_{82}{}^{3-}$.

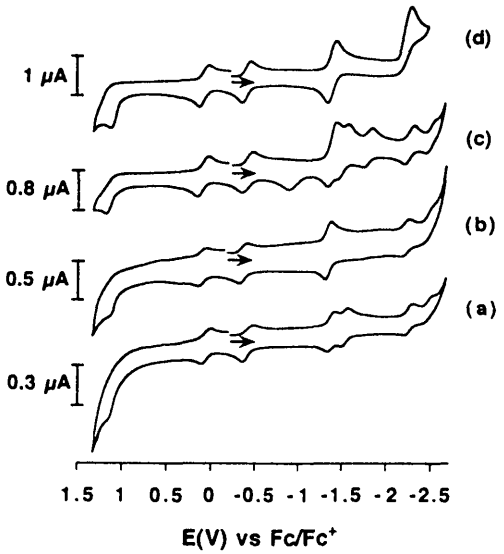

Figure 6. Cyclic voltammograms of (a) La–C_{82}, (b) Y–C_{82}, (c) Ce–C_{82}, and (d) Gd–C_{82} scanned at 20 mV/s in ODCB containing 0.1 M $TBAPF_6$. From Ref. 33.

A trimetallofullerene, $Sc_3@C_{82}$ has also been recently reported [34]. Its electrochemistry indicates that its MOs are very similar in energy to those of the monometallofullerenes in terms of energy. However, considering that more electrons are transferred to the cage by the trimer, occupancy of the energy levels is different. Therefore, its second oxidation and first reduction occur at potentials close to where the first oxidation and second reduction occur for monometallofullerenes. These considerations along with the fact that the neutral state is EPR silent have led the authors to suggest that $Sc_3^{4+}@C_{82}^{4-}$ represents the formal charges of the complex [34].

Table 6 Half-Wave Reduction and Oxidation Potentials (in V vs. Fc/Fc^+) of C_{82} and Some of Its Endohedral Complexes Obtained by CV

Compound	E_1^{ox}	E_2^{ox}	E_1^{red}	E_2^{red}	E_3^{ox}	E_4^{ox}	E_5^{ox}	E_6^{ox}	Reference
C_{82}		+0.72	−0.69	−1.04	−1.58	−1.94			33
La–C_{82}	+1.07[a,b]	+0.07	−0.42	−1.37	−1.53	−2.26	−2.46[b]		33
Ce–C_{82}	+1.08[a,b]	+0.08	−0.41	−1.41	−1.53	−1.79	−2.25	−2.50[b]	33
Gd–C_{82}	+1.08[a,b]	+0.09	−0.39	−1.38[c]		−2.22[a,b,c]			33
Y–C_82	+1.07[a,b]	+0.10	−0.37	−1.34[c]		−2.22	−2.47[b]		33
Sc_3–C_{82}[d,e]	−0.04	−0.32	−1.42	−1.67					34

Note. Conditions: 0.1 M $TBAPF_6$ in ODCB; working electrode, Pt disk. From Ref. 33.
[a]Irreversible.
[b]Values obtained by DPV (see Ref. 33).
[c]Two-electron process.
[d]Values obtained by OSWV.
[e]Conditions: 0.1 M $TBAClO_4$ in pyridine, glassy carbon working electrode.

D. Electrochemistry of C_{84}

Only the D_2 and D_{2d} isomers of C_{84} have been isolated as a 2:1 mixture (D_2:D_{2d}) from fullerene soot. None of the other 22 possible isomers [35] have been isolated, although the detection of a third isomer has been recently suggested [35d]. With one exception, all electrochemical studies done on C_{84} so far have involved the 2:1 mixture of D_2 and D_{2d} isomers, and as in the case for the other fullerenes, results have been solvent dependent (see Table 4) [20,24,26,36]. In all solvents studied with the exception of pyridine, there appears to be no difference in the reduction potential of the two isomers; i.e., no single reduction exhibits a two-component wave with the 2:1 current intensity ratio expected for the two separate isomers [24,25,36]. In pyridine, however, 10 redox waves are observed, of which the first six have been assigned to the first, second, and third reductions of each isomer with the aid of ESR spectroscopy (see also Table 4) [20]. The only known oxidation of C_{84} has been observed in TCE. The process occurs at $+0.93$ V versus Fc/Vc^+ (see Fig. 5c) [26].

Recently, the two isomers were separated by HPLC and their electrochemistry studied using OSWV. The current intensity ratio of the two corresponding voltammograms was used for the identification of the two isomers [37]. Two important differences between the two isomers emerged as a result of this study: (1) The assumed D_{2d} isomer is easier to reduce than the D_2 isomer by ~ 190 mV and (2) while the D_2 isomer exhibits a constant potential separation of ~ 350 mV between the four one-electron reduction waves observed, this is not the case for the D_{2d} isomer. The four waves observed for the latter are grouped in two sets of two equally spaced waves. The potential separation between the second and third waves is ~ 710 mV (see Table 4).

V. CONTROLLED POTENTIAL ELECTROLYSIS AS A SYNTHETIC TOOL: THE "SHUFFLE" AND THE RETRO-BINGEL REACTION

Coulometrically generated mono- to tetraanions of C_{60} are relatively stable species. This property has been used in the preparation of several derivatives of C_{60} [38–41] by mixing the dianion with the appropriate electrophile. In fact, it has already been established that formation of dialkyl derivatives of C_{60} occurs via an electron transfer mechanism followed by an S_N2 reaction [42].

Very recently, however, it was discovered that controlled potential electrolysis (CPE) of certain bis-methanofullerenes of the type shown in Fig. 7 resulted in a migration or "shuffling" of the adducts on the surface of the sphere to form other bis-adduct isomers [43]. For the *cis*-2 isomer, shuffling occurs after one-electron equivalent is added at the first reduction potential. For all other bis-adducts of C_{60} shown in Fig. 7 the process requires two electron-equivalents at the second reduction potential. This procedure is followed by reoxidation to the neutral species, chromatography to remove the electrolyte, and HPLC analysis. Interestingly, the product distribution is essentially the same in all cases, regardless of which isomer has undergone electrolysis (see Table 7). Four important observations have been made regarding these results. First, both the *e* and *trans* isomers are formed preferentially, a fact predicted by theoretical calculations [44] and attributed to the higher stability of these versus the *cis* isomers. Second, the *trans*-1 isomer, which is produced in a very small yield (0.8–2.0%) using other synthetic methods [45], is produced in $\sim 10\%$ yield using the coulometric method. If this yield is corrected for the statistical factor of four (there are four possible sites on C_{60} for the *trans*-2 isomer but only one site for the *trans*-1),

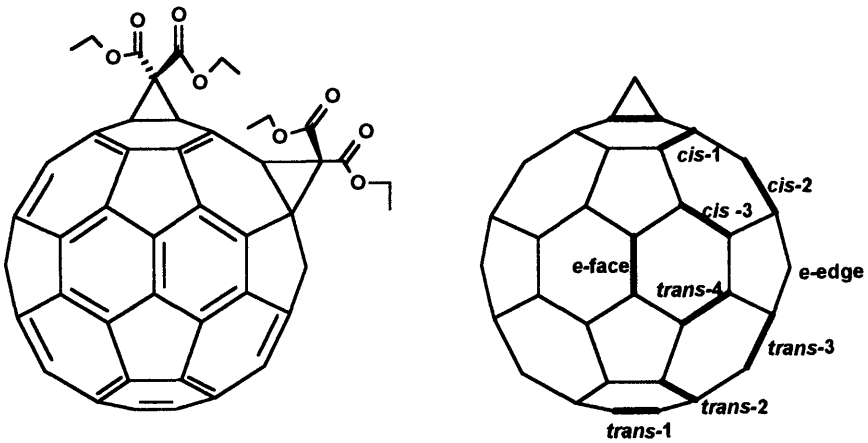

Figure 7. Representation of the C_{60} bismalonate adducts that were subjected to CPE at the second reduction potential. From Ref. 43.

it becomes 40% which is almost the same yield observed for the *trans*-2 isomer. Third, although a detailed mechanistic study has not been carried out yet, it is known, from crossover experiments using different addends that the shuffling process is intramolecular and not intermolecular. Fourth, CPE with two-electron equivalents also results in the removal of one or both addends, producing the mono-methanofullerene adduct as well as pure C_{60}. C_{60} is produced in very small amounts, while the mono adduct appears in 10–30% yield. This process of removing one or two of the addends is now known as the retro-Bingel reaction [46] because it is the reversal of the Bingel reaction [45b].

In order to understand the retro-Bingel reaction, it is important to note that after the two electrons have been added during the "shuffling" process of the bis adducts, a substantial amount of current remains. If, instead of reoxidizing back to the neutral state, electrolysis is allowed to proceed until the current reaches background levels, the total electron count is six electrons per molecule for the bis adducts. The *e* and *trans*-3 bis adducts have been converted in 75% yield into pure C_{60}. A mono-bis-malonate adduct also undergoes retro-Bingel at the second reduction potential, and it is also converted to C_{60} in 82% yield. The reaction appears to be very general for malonate adducts of C_{60}, C_{70}, C_{76}, C_{78}, and C_{84}. Although it may seem senseless to use this reaction to get back a

Table 7 Relative Distribution of C_{60} Bismalonate Bis Adducts After the Two-Electron Controlled Potential Electrolysis.

Starting material	*cis*(1-3)	*e*	*trans*-4	*trans*-3	*trans*-2	*trans*-1	Mono	Yield
cis-2	—	23,	5	8	52	12	29	49
cis-3	—	22	6	10	51	11	28	53
e (21)	—	26	9	12	44	9	10	44
trans-4	—	23	10	12	47	8	14	61
trans-3	—	23	9	12	46	10	23	43
trans-2	—	22	6	9	53	10	19	39

Note: From Ref. 6e.

pristine fullerene, successful separation of otherwise inseparable fullerene enantiomers has been achieved using this reaction. The process consists of attaching chiral addends to a mixture of enantiomers using the Bingel to form a diastereomeric mixture. When this mixture is subjected to CPE under retro-Bingel conditions followed by purification by HPLC, the pure enantiomers are isolated. So far, two enantiomers of C_{76} (^{f}A)-C_{76} and (^{f}C)-C_{76}, have been prepared [46], as well as a C_2-symmetric bis-methano adduct of C_{2v}-C_{78}, and pure C_{2v}-C_{78} [22]. Also, a successful separation of the D_2 and the D_{2d} isomers of C_{84} was achieved using this retro-Bingel protocol [47].

VI. CONCLUDING REMARKS

The contribution of discoveries made via electrochemical techniques to the understanding of fullerene chemistry continues at a very fast pace. Perhaps some of the unanswered mechanistic questions regarding the redox behavior of fullerenes will be answered soon. Unquestionably, the role of electrochemistry in the field of fullerenes continues to be strong. As new fullerene-derived materials are prepared, this role will become even stronger.

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Halogenated Organic Compounds

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I. INTRODUCTION

Electrochemical reduction of halogenated organic compounds continues to be a subject of intense investigation. This interest stems from desires (a) to characterize and understand the processes involved in the reductive cleavage of carbon–halogen bonds and (b) to utilize the electrolysis of halogenated organic compounds for practical syntheses. In previous editions of this volume [1–3] and in several reviews [4–7], a considerable body of knowledge has appeared concerning mechanistic and synthetic aspects of the reduction of carbon–halogen bonds. In the present chapter, there is a focus both on traditional material and on newer developments (especially those bearing on electrosynthesis) that involve direct reduction as well as indirect (catalytic or mediated) reduction of halogenated organic compounds.

II. MONOHALOGENATED ALKANES

It has become well established that, at inert cathodes, the electrochemical behavior of a simple alkyl monohalide (RX) can be characterized by means of the following mechanistic picture:

$$RX + e \rightleftharpoons [RX^{\cdot -}]$$
$$[RX^{\cdot -}] \longrightarrow R\cdot + X^-$$
$$R\cdot + e \longrightarrow R^-$$
$$2\,R\cdot \xrightarrow{\text{combination}} R_2$$
$$2\,R\cdot \xrightarrow{\text{disproportionation}} RH + R(-H)$$
$$R\cdot + SH \longrightarrow RH + S\cdot$$
$$R^- + SH \longrightarrow RH + S^-$$
$$R^- + RX \longrightarrow R_2 + X^-$$
$$R^- + HB \longrightarrow RH + B^-$$
$$RX + B^- \xrightarrow{E2} R(-H) + X^- + HB$$
$$RX + B^- \xrightarrow{S_N2} RB + X^-$$

Depending on the solvent, supporting electrolyte, electrode material, and potential, it is possible to electrogenerate either alkyl radicals or carbanions, which can lead to the formation of dimers (R_2), alkanes (RH), and olefins [R(–H)]. In addition, the solvent (SH) can act as a hydrogen atom donor or a proton donor. Also olefins can arise from the base-promoted dehydrohalogenation of RX, and other products (RB) can be formed via displacement of halide from RX by a base (B^-). When cathode materials such as

mercury, lead, and tin are employed, electrogenerated alkyl radicals can interact strongly with the metal to enhance the reduction of the alkyl monohalide and to afford organometallic compounds.

Tertiary alkyl halides are easier to reduce than secondary alkyl halides, which are, in turn, easier to reduce than primary alkyl halides. Ease of reduction of a carbon–halogen bond is governed by the identity of the halogen atom; (a) iodides are easier to reduce than bromides, (b) chlorides are so difficult to reduce that they often appear to undergo no direct reduction, and (c) no report of the direct reduction of an alkyl monofluoride has been published. Finally, the existence of the radical anion [$RX^{\cdot-}$], formed by addition of one electron to an alkyl monohalide, has never been demonstrated; Andrieux and coworkers [8] have discussed why such a species is not expected for simple alkyl monohalides, but why radical anions of aromatic halides are distinct intermediates in the electrochemical reduction of aromatic halides. Canadell and coworkers [9] have described the implications of theoretical calculations pertaining to the lifetime of the water-solvated radical anion of methyl chloride.

A. Reduction at Mercury Cathodes

1. Primary Alkyl Monohalides

Numerous investigations of the reduction of primary alkyl monohalides at mercury electrodes have been undertaken. In ethanol (EtOH) containing tetra-*n*-butyl-ammonium iodide (TBAI), reduction of iodoethane and 1-iodobutane affords diethylmercury and dibutylmercury, respectively, in essentially quantitative yields [10]. When 1-iododecane undergoes reduction at mercury in dimethylformamide (DMF) containing different tetraalkylammonium perchlorates, two irreversible cathodic waves are observed that correspond to successive formation of the decyl radical and the decyl carbanion [11]. For potentials at which decyl radicals are generated, an electrolysis of 1-iododecane leads to the formation of didecylmercury in at least 99% yield. However, for potentials at which decyl carbanions are formed, the principal products are decane and 1-decene, along with small quantities of 1-decanol, and telomers consisting of decyl and solvent-derived moieties [12]. Bilewicz and Osteryoung [13] found that the reductions of iodoethane, 1-iodobutane, and 1-iododecane at mercury in MeCN containing tetraalkylammonium salts are similar to those seen in DMF.

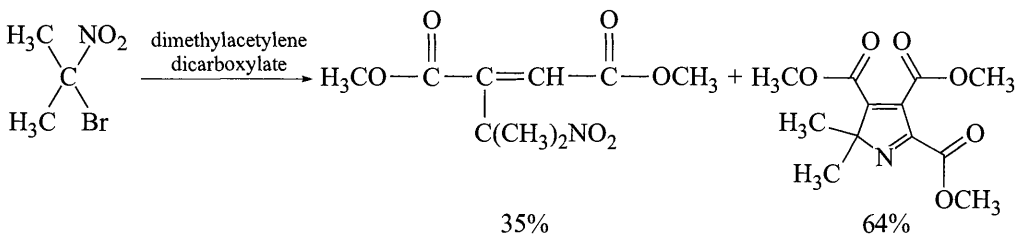
Primary alkyl monobromides typically undergo a one-step, two-electron reduction to the corresponding alkyl carbanions, which react to afford alkanes and alkenes. Electrolysis of 1-bromodecane in DMF containing a tetraalkylammonium salt gives products similar to those obtained from the reduction of 1-iododecane at very negative potentials [12]. However, Fry [14] reported that the reduction of 1-bromohexane at mercury in DMF containing TEABr yields hexane (70%), 1-hexene (12%), dihexylmercury (2%), and 1-hexanol (7%). At stainless steel in DMF containing tetra-*n*-butylammonium tetrafluoroborate ($TBABF_4$), 1-bromoheptane undergoes efficient reductive dimerization [15]. Wagenknecht and coworkers [16,17] investigated the reductions of bromoethane and 1-bromobutane at mercury in DMF containing TEABr and saturated with carbon dioxide. For the 1-bromobutane–carbon dioxide system, dibutylmercury, dibutyl oxalate, and butyl valerate are produced in comparable yields. For systems in which a dialkylmercury species (R_2Hg) is seen, the most satisfactory way to account for its formation is via the intermediacy of a short-lived adsorbed alkylmercury radical [$RHg^{\cdot}$(ads)]:

$$R^{\cdot} \rightarrow R^{\cdot}(ads)$$
$$R^{\cdot}(ads) + Hg \rightarrow RHg^{\cdot}(ads)$$
$$2\,RHg^{\cdot}(ads) \rightarrow R_2Hg + Hg$$

2. Secondary Alkyl Monohalides

Only one detailed report [18] about the reduction of secondary alkyl monohalides at mercury has appeared. In DMF containing tetraalkylammonium perchlorates, 2-iodooctane undergoes stepwise reduction, whereas 2-bromooctane exhibits just one stage of reduction. At a potential corresponding to the uptake of a single electron by 2-iodooctane, the electrogenerated *sec*-octyl radical (a) disproportionates to give octane, 1-octene, and 2-octene, (b) combines to form 7,8-dimethyltetradecane, and (c) interacts with mercury to yield di-*sec*-octylmercury. At a more negative potential, the *sec*-octyl carbanion arises from either 2-bromo- or 2-iodooctane; from both starting materials, the same products are obtained as before, except that the yield of octane is approximately doubled and the amounts of di-*sec*-octylmercury and 7,8-dimethyltetradecane are lower.

Montero and coworkers [19] have described the reduction of 2-bromo-2-nitropropane at mercury in dichloromethane containing $TBABF_4$ and dimethylacetylene dicarboxylate (a dipolarophile); two unexpected products were obtained:



3. Tertiary Alkyl Monohalides

Polarographic and voltammetric investigations [20–22] of the behavior of *tert*-butyl iodide and *tert*-butyl bromide have revealed that, depending on the solvent and supporting electrolyte, the iodide undergoes stepwise reduction and the bromide exhibits either a single two-electron reduction or a pair of one-electron reductions.

Cyclic voltammograms for the reduction of *tert*-butyl bromide at mercury in DMF containing various tetraalkylammonium perchlorates show two cathodic waves [23,24]. Macroelectrolyses at potentials corresponding to the first wave produce *tert*-butyl radicals, which form isobutane (40%) and isobutylene (40%) via disproportionation and which give 2,2,3,3-tetramethylbutane via radical combination. At more negative potentials, where *tert*-butyl carbanions are generated, isobutane and isobutylene are each formed in approximately 47% yield, via reactions that involve (a) protonation of the *tert*-butyl carbanion by a donor acid and (b) dehydrohalogenation of unreduced *tert*-butyl bromide by the conjugate base of the proton donor.

B. Reduction at Carbon Cathodes

An advantage of carbon electrodes over mercury electrodes for the reduction of alkyl monohalides is that dialkylmercury compounds cannot form. In addition, as Lambert

and Ingall [25] pointed out, it is possible with carbon cathodes to observe the direct reductive cleavage of the carbon–chlorine bond in compounds such as 1-chloropentane, 1-chlorohexane, 2-chlorobutane, and *tert*-butyl chloride in DMF containing TEAP.

Wagenknecht [17] found that the reduction of 1-bromobutane at graphite in carbon dioxide-saturated DMF containing TEABr is a two-electron process, and that the generated butyl carbanions lead to the formation of butane, 1-butene, octane, butyl valerate, butyl-*N*,*N*-dimethyloxamate, and dibutyl-2-methylmalonate. Earlier work by Kaabak and coworkers [26], dealing with the reduction of iodoethane and 1-bromobutane at graphite in DMF, revealed that alkanes, olefins, dimers, and solvent-derived species are produced.

In a study of the electrochemistry of alkyl monohalides at glassy carbon in DMF containing $TBABF_4$, Andrieux and coworkers [8,27] concluded that 1-bromobutane, 2-bromobutane, *tert*-butyl bromide, and 1-iodobutane undergo one-step, two-electron reductions, whereas 2-iodobutane and *tert*-butyl iodide exhibit a pair of one-electron reduction waves. Products derived from electrolyses of primary, secondary, and tertiary alkyl iodides and bromides at reticulated vitreous carbon cathodes have been determined in DMF containing tetraalkylammonium salts [28]. When 1-bromo- or 1-iododecane is electrolyzed, the principal products are decane and 1-decene, along with some 1-decanol, although eicosane has been obtained in 37% yield from 1-iododecane in the presence of TEAP. Electrolyses of 2-bromo- or 2-iodooctane afford mixtures of octane (30–35%), 1-octene (14–19%), 2-octene (9–19%), 2-octanol (1–2%), and 7,8-dimethyltetradecane (18–34%), and reduction of *tert*-butyl bromide gives isobutane (48%), isobutylene (42%), and 2,2,3,3-tetramethylbutane (8%).

Recent work [29], involving the use of reticulated vitreous carbon cathodes in DMF containing $TMABF_4$, has shown that the reduction of iodoethane is a two-electron process and that the products are ethane (55%), butane (32%), and ethylene (6%). In the same investigation [29], the electroreduction of 2-iodopropane was found to occur in two steps to give the 2-propyl radical and the 2-propyl carbanion, respectively; depending on the potential, propane, propylene, and 2,3-dimethylbutane are obtained in different yields.

In an investigation of the reduction of perfluoroalkyl monobromides and monoiodides at glassy carbon in nonaqueous solvents containing $TBABF_4$, Andrieux and coworkers [30] found that perfluoroalkyl radicals are better hydrogen-atom scavengers than simple alkyl radicals. Moreover, unlike simple alkyl radicals (and more like aryl radicals), perfluoroalkyl radicals do not couple with electrogenerated radical anions of aromatic compounds.

C. Reduction at Other Electrodes

Methyl, ethyl, propyl, and butyl halides are reduced at lead and tin cathodes to produce, respectively, the corresponding tetraalkyllead and tetraalkyltin compounds in excellent yield. Bismuth, gallium, indium, and thallium can be employed to prepare a variety of organometallic compounds. Feoktistov [2] and Hawley [4] have summarized many of these electrosyntheses.

Sock and coworkers [31] synthesized carboxylic acids by reducing alkyl bromides at platinum, gold, stainless steel, and graphite in the presence of carbon dioxide in either DMF or a THF–hexamethylphosphoramide (HMPA) mixture. Reduction of an alkyl monobromide at nickel in DMF containing TBABr and in the presence of an arylalkene and a sacrificial aluminum anode leads to an addition product [32].

D. Electrolyte Effects

Many workers [12,13,18,22,23,33] have noticed that carbon–halogen bonds become more difficult to cleave electrolytically as the size of the tetraalkylammonium cation of the supporting electrolyte increases. Fry and Krieger [22] determined the relative electron-transfer rates in dimethyl sulfoxide (DMSO) for reduction of both isobutyl bromide and *tert*-butyl bromide (as well as for bromo- and iodobenzene) as a function of the identity of the tetraalkylammonium cation comprising the supporting electrolyte. Trends in electrontransfer rates appear to depend on (a) the shifts in the location of the outer Helmholtz plane as different cations are employed and (b) the intrinsic changes in the electron-transfer process caused by the presence of different electrolytes. For electrosyntheses, it is important to be aware of the substantial shifts in the potentials needed to reduce carbon–halogen bonds when different supporting electrolytes are used.

Alkyl carbanions are potent bases, so they are protonated by almost any source of hydrogen ions, especially adventitious water in the solvent or supporting electrolyte. In the absence of water and other added proton donors, tetraalkylammonium cations can serve as proton donors toward alkyl carbanions; deprotonation of tetraalkylammonium ions leads, via the Hofmann elimination, to the corresponding trialkylamine and olefin. When tetramethylammonium salts are used as supporting electrolytes, there is evidence that proton transfer gives rise to trimethylammonium methylide [34,35].

III. POLYHALOGENATED ALKANES

A. *gem*-Dihaloalkanes, *gem*-Trihaloalkanes, and Carbon Tetrachloride

Stepwise electroreductive dehalogenation of 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane and 1,1-dichloro-2-hydroxy-2,2-bis(*p*-chlorophenyl)ethane takes place at mercury in water–EtOH media containing potassium nitrate [36]. Reduction of dichloromethane in the presence of alkenes has been employed to synthesize cyclopropanes [37,38]. Species containing the trichloromethyl moiety, such as 1,1,1,5-tetrachloropentane, 1,1,1-trichloro-5-cyanopentane, and 1,1,1,5-tetrachloro-3-pentene, can be converted into less chlorinated analogues in aqueous MeOH [39], and reduction of 1,1,1-trichloro-2-hydroxy-4-methyl-4-pentene gives 1,1-dichloro-4-methyl-2,4-pentadiene and 1,1-dichloro-2-hydroxy-4-methyl-4-pentene [40]. Reduction of trichloromethylphosphonate at mercury in DMF containing $TBABF_4$ and an alkyl halide yields a diethyl 1,1-dichloroalkylphosphonate [41]. Halofluoro compounds such as 1,1,1-trichloro-2,2,2-trifluoroethane, methyl chlorodifluoroacetate, trifluorobromomethane, and perfluoroiodobutane, when reduced at platinum in DMF containing TEAOTs, undergo reductive coupling with aldehydes [42]; electroreductive coupling of activated olefins and *gem*-polyhalo compounds has been carried out at stainless steel in DMF containing TBABr [43]. Semmelhack and Heinsohn [44] have selectively removed *gem*-polyhaloethoxy protecting groups from carboxylic acids.

Carbon tetrachloride undergoes stepwise reduction at mercury in DMF containing TEABr [45]. Several groups of workers [46–52] have electrogenerated the short-lived trichloromethyl anion, which can react with acrylonitrile, ethyl acrylate, diethyl fumarate, alkyl monohalides, and a variety of aldehydes and ketones. De Angelis and coworkers [53] have used dichlorocarbene, generated via reduction of carbon tetra-

chloride at lead in chloroform containing TEABr, to react with 2,3-dimethylindole to afford 3-chloro-2,4-dimethylquinoline and 3-(dichloromethyl)-2,3-dimethyl-3*H*-indole. Paratian and coworkers [54–56] have reduced bromotrifluoromethane at stainless steel in DMF containing TBABr in cells with sacrificial anodes of copper, cadmium, and zinc to prepare CF_3Cd, CF_3Zn, and CF_3Cu; reactions of CF_3Cu with aromatic, heteroaromatic, vinylic, benzylic, and allylic halides have been investigated. Reduction of carbonimidoyl dichlorides at mercury in DMF containing lithium perchlorate gives isocyanides in excellent yield [57]. Reduction of chlorodifluoromethyl enol ethers results in two-electron cleavage of the carbon–chlorine bond, and the resulting anion can react with trimethylchlorosilane to afford functionalized difluoromethyl allylsilanes [58].

B. Vicinal Dihaloalkanes and Trihaloalkanes

Typically, these compounds undergo a two-electron reduction with loss of two halide ions to give an olefin. Using a mercury cathode in DMF, Casanova and Rogers [59] demonstrated that 1,2-dibromo-2-phenylpropane is reduced to 2-phenylpropane, that *meso*-2,3-dibromobutane is reduced to *trans*-2-butene, and that *d,l*-2,3-dibromobutane is reduced to *cis*-2-butene. For the reduction of *d,l*-1,2-dibromo-1,2-diphenylethane at mercury in DMF, Lund and Holboth [60] discovered that the ratio of *cis*- to *trans*-stilbene depends on the identity and concentration of the supporting electrolyte. Other research dealing with the reduction of vicinal dibromides has been carried out by Závada and coworkers [61] and by Lund and coworkers [62]. Papers concerning the reduction of polyhalogenated ethanes (e.g., 1-bromo-2-chloro-1,1,2-trifluoroethane, 1,2-dibromo-1,1,2,2-tetrafluoroethane, and 1,1,2,2-tetrabromoethane) in EtOH and water–EtOH mixtures have been published by Feoktistov, Gol'din, and coworkers [63–67]. Rampazzo and coworkers [68] studied the reductions of $\alpha, \alpha, \alpha', \alpha'$-tetrabromo-*o*-xylene and 1,2-dibromobenzocyclobutene at mercury in DMF.

Casanova and Rogers [59] as well as Fry [69] postulate that the reduction of vicinal dihalides is a concerted process in which both carbon–halogen bonds are partially cleaved as a carbon–carbon double bond starts to form. Nonelectrochemical evidence [70] suggests that a vicinal dihalide undergoes one-electron reduction to a radical anion, which loses the first halide ion to form a neutral radical, after which the neutral radical accepts an electron to become a carbanion that eliminates the second halide ion to yield an olefin. From a study of the behavior of *meso*- and *d,l*-1,2-dibromo-1,2-diphenylethane, Fawell and coworkers [71,72] concluded that the reduction of vicinal dihalides is a stepwise process. Andrieux and coworkers [73] have examined the reductive elimination of vicinal dibromides at carbon in MeCN.

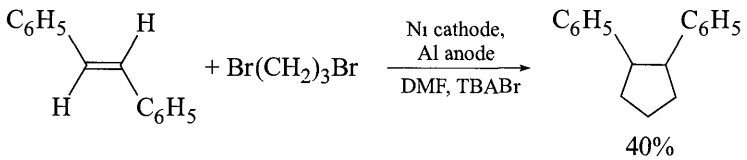
In an investigation of *meso*- and *d,l*-3,4-dibromohexane and of *meso*- and *d,l*-2,5-dimethyl-3,4-dibromohexane, Brown and coworkers [74] found that the *meso* compounds are easier to reduce than the *d,l* species. Moreover, for the reduction of 3,4-dibromohexane in DMF at less negative potentials, the *meso* isomer affords *trans*-hex-3-ene exclusively, whereas the *d,l* compound gives only *cis*-hex-3-ene; however, at more negative potentials, the stereoselectivity is lost, and the *trans–cis* product ratios are 50:50 for the *meso* isomer and 70:30 for the *d,l* isomer. Evans and coworkers [75,76] employed cyclic voltammetry to probe the temperature-dependent conformational equilibrium for a number of vicinal dibromides, and Lexa and coworkers [77] have discussed inner- and outer-sphere processes for the reduction of vicinal dibromides.

C. α, ω-Dihaloalkanes

Pioneering work by Rifi [78–80] centered on the reduction at mercury of a family of α, ω-dibromoalkanes in DMF containing TBAP. Cyclopropane was formed exclusively from 1,3-dibromopropane, and a mixture of cyclobutane (25%) and butane (75%) was produced from 1,4-dibromobutane; however, different results were obtained by Wiberg and Epling [81]. From electrolyses of 1,5-dibromopentane and 1,6-dibromohexane, only straight-chain alkanes were detected. Fry and Britton [82,83] investigated the behavior of *d,l* and *meso*-2,4-dibromopentane, and concluded, as did Wiberg and Epling, that the reduction of these compounds at mercury is a stepwise process involving intramolecular cyclization of a bromocarbanion intermediate.

A study by Casanova and Rogers [84] of the reduction of compounds ranging from 1,4-dibromobutane to 1,12-dibromododecane at mercury in DMF revealed that dialkylmercury species can be synthesized in high yield by means of controlled-potential electrolysis; however, constant-current electrolysis of the same starting materials produces a variety of acyclic and alicyclic hydrocarbons in low yield.

A number of other publications deal with the electrochemical behavior of α, ω-dibromoalkanes at mercury electrodes: polarographic studies [85,86]; electrolyses of 1,3-dibromopropane, 1,4-dibromobutane, and 1,5-dibromopentane [87,88]; reduction of 1,10-dibromo- and 1,10-diiododecane [89]; and electrosyntheses of phenylcyclopropane and cyclopropanol [90]. In the presence of an arylalkene, reduction of 1,3-dibromopropane or 1,4-dibromobutane at nickel in DMF containing TBABr and with a sacrificial aluminum anode yields the corresponding cyclopentane or cyclohexane adduct [32]:



40%

Recent papers concerning the reduction of α,ω-dihaloalkanes at carbon in DMF containing tetraalkylammonium salts have appeared. Electrolyses of 1,3-dihalopropanes at carbon afford cyclopropane in very high yields [91]. Reduction of 1,4-dihalobutanes [92] and 1,5-dihalopentanes [93] gives cyclobutane and cyclopentane in modest yields, respectively, along with various straight-chain compounds. For the reductions of 1,6-dihalohexanes [94], 1,8-dihalooctanes [95], and 1,10-dihalodecanes [95] at carbon electrodes, the products are alkanes, olefins, dienes, monohaloalkanes, and dimers. Lu and coworkers [37] have prepared derivatives of cyclopentane by reducing 1,3-dibromopropane in the presence of various alkenes.

IV. HALOGENATED ALKENES AND ALKYNES

A. Vinyl Halides

Reduction of a vinyl halide involves the uptake of one electron and the loss of a halide ion to give a vinyl radical

$$R_2C{=}CXR + e \rightarrow R_2C{=}\dot{C}R + X^-$$

which then undergoes further reduction and protonation:

$$R_2C{=}\dot{C}R + e + H^+ \rightarrow R_2C{=}CHR$$

In addition, the vinyl radical can rearrange, before accepting an electron and a proton, to afford either a *cis* or *trans* alkene as a final product. Among compounds that have been investigated are aryl-substituted vinyl bromides [96], *cis*- and *trans*-3-iodo-3-hexene [97], bromomaleate and bromofumarate [98], and aryl-substituted 3-chloroacrylonitriles [99]. Yoshida and coworkers [100] electrolyzed vinyl halides at platinum in DMF in the presence of trimethylchlorosilane to obtain silylation products.

Vicinal dibromoalkenes and diiodoalkenes undergo reduction, with loss of both halide ions, to yield alkynes that (depending on the presence of activating substituents) may be further reduced to olefins and saturated species; work by Rosenthal and coworkers [101] on the electrochemistry of diethyl dibromofumarate and diethyl dibromomaleate exemplifies this behavior. Unlike their dibromo and diiodo analogues, vicinal dichloroalkenes show more complicated electrochemistry; in some instances, the two carbon–chlorine bonds simply undergo successive two-electron, one-proton reductive cleavage [102], whereas in other cases the reduction leads to an alkyne [103].

B. Allyl Halides

Baizer and coworkers [46,104] examined the reduction of allyl bromide and allyl chloride; in DMSO containing tetraethylammonium perchlorate (TEAP), allyl bromide exhibits stepwise reduction to the radical and to the carbanion, whereas allyl chloride undergoes a single two-electron reduction [104]. However, in DMF containing tetraethylammonium tosylate or TEABr, each of these allyl halides is reduced in a one-step, two-electron process to the carbanion, which reacts with (a) a proton donor to give propene, (b) unreduced starting material to yield 1,5-hexadiene, (c) carbon dioxide to produce the carboxylate (which, in turn, can attack the allyl halide), and (d) other species, such as acrylonitrile and ethyl acrylate [46]. Reduction of allyl halides, 1-chloro-3-methyl-2-butene, and methyl-4-halo-2-butenoates at platinum in DMF containing diethyl fumarate gives the conjugate addition products [105], and reduction of 4-bromo- and 4-chloro-2-butene can be used to allylate acetone and benzaldehyde [106]. In DMF containing tetraalkylammonium salts, reductive coupling of methallyl chloride with ketones and aldehydes to afford alcohols occurs at carbon [107], and methallyl chloride undergoes electrodimerization at stainless steel [15].

According to Bard and Merz [108], in MeCN containing TBAP, allyl bromide and allyl iodide interact chemically with a mercury electrode to form allylmercury halides. These allylmercury halides undergo reduction to yield diallylmercury, which is itself electroactive. Allyl bromide and allyl iodide are reduced at platinum in MeCN in a two-electron process to give the allyl anion, and the allyl radical is not involved as an intermediate. Reduction of allyl halides at platinum in DMF containing TEAOTs and in the presence of trimethylchlorosilane results in silylated compounds [100].

Brillas and Costa [109] reported that 1,3-butadiene is an intermediate in the reduction of *trans*-1,4,-dibromo-2-butene and *trans*-1,4-dichloro-2-butene at mercury in DMF containing TEAP. Doupeux and Simonet [110,111] have described the electrochemical behavior of a number of polyhalogenated allyl halides in DMF.

C. Acetylenic Halides

Several investigations [112–115] have dealt with acetylenic halides that undergo reductive intramolecular cyclization. In DMF containing tetraalkylammonium perchlorates, elec-

trolysis of 6-bromo- or 6-iodo-1-phenyl-1-hexyne at mercury gives a potential-dependent product distribution [112]. At less negative potentials, the acetylenic halide is converted to a radical, which is adsorbed onto and interacts with mercury to give di(6-phenyl-5-hexyn-1-yl)mercury in a yield as high as 65%; alternatively, the radical can cyclize and abstract a hydrogen atom (probably from the solvent) to form benzylidenecyclopentane in modest yield (up to 24%). At more negative potentials, the starting material is reduced to the carbanion, which gains a proton from residual water or the supporting electrolyte cation to produce 1-phenyl-1-hexyne. In addition, 1-phenyl-5-hexen-1-yne is obtained via dehydrohalogenation of the starting material, and 1-phenyl-1-hexyn-6-ol arises from attack of hydroxide ion (from water) on the parent compound.

In DMF containing tetramethylammonium perchlorate (TMAP), a normal pulse polarogram for reduction of 1-iodo-5-decyne at mercury displays two waves, indicating stepwise formation of radical and carbanion intermediates, whereas reduction of 1-bromo-5-decyne gives a single wave, which corresponds to a net two-electron process [113]. Macroelectrolyses of both compounds at mercury afford products whose yields vary with potential. At less negative potentials, the electrogeneration of the 5-decyn-1-yl radical results in the formation of di(5-decyn-1-yl)mercury and pentylidenecyclopentane. At more negative potentials, the carbanion resulting from two-electron reduction of a 1-halo-5-decyne is protonated by residual water to yield 5-decyne. Hydroxide ion, resulting from deprotonation of water, can react with unreduced 1-halo-5-decyne to form 5-decyn-1-ol or 1-decen-5-yne, but formation of these two products is blocked by the deliberate addition of a proton donor.

When 1-halo-5-decynes are electrolyzed at carbon in DMF containing tetraalkylammonium perchlorates [114], the yield of pentylidenecyclopentane increases dramatically (up to 60%); two other major products are 5-decyne and 1-decen-5-yne. Reduction of 6-iodo-1-phenyl-1-hexyne at carbon in DMF containing TMAP affords benzylidenecyclopentane (36%) and 1-phenyl-1-hexyne (38%); however, in the presence of an added proton donor (1,1,1,3,3,3-hexafluoro-2-propanol), the yield of benzylidenecyclopentane climbs to approximately 60% [115].

V. BENZYL HALIDES AND RELATED COMPOUNDS

Reduction of benzyl iodide at mercury appears to proceed via an electroinitiated chain reaction with formation of benzylmercuric iodide [116,117]:

$$C_6H_5CH_2I + e \rightarrow [C_6H_5CH_2I^-] \rightarrow C_6H_5CH_2^{\cdot} + I^-$$

$$C_6H_5CH_2^{\cdot} + Hg \rightarrow C_6H_5CH_2Hg^{\cdot}$$

$$C_6H_5CH_2Hg^{\cdot} + C_6H_5CH_2I \rightarrow C_6H_5CH_2Hg^+ + C_6H_5CH_2^{\cdot} + I^-$$

$$C_6H_5CH_2Hg^+ + I^- \rightarrow C_6H_5CH_2HgI$$

Analogous processes may occur for benzyl bromide and benzyl chloride [118–120].

Electrolyses of benzyl bromide in MeCN [120] or DMF [46] and of benzyl chloride in aqueous EtOH [120] at mercury cathodes afford dibenzylmercury and toluene (and sometimes a small quantity of bibenzyl) in yields that depend on the potential. These products could arise via one-electron reduction of the benzylmercuric halide (or the benzylmercury cation) to give the benzylmercury radical, which undergoes either disproportionation or further reduction and protonation. Alternatively, the benzyl halide could be reduced to the benzyl radical, which can (a) accept another electron to yield the benzyl anion or (b)

combine with mercury to give the benzylmercury radical [121], each of which reacts as already described. Baizer and Chruma [46] suggest that the benzyl carbanion could arise via two-electron reduction of either benzylmercuric halide or benzyl halide; then attack of the carbanion on benzylmercuric halide would yield dibenzylmercury, and the reaction between the carbanion and benzyl halide would produce bibenzyl. Reduction of benzyl chloride at mercury in DMF containing tetraethylammonium halide and in the presence of carbon dioxide provides evidence for generation of the benzyl carbanion; benzyl phenylacetate [46] and phenylacetic acid [117] are obtained as electrolysis products. Benzyl chloride undergoes electrodimerization at a stainless-steel cathode in DMF containing $TBABF_4$ [15]. Chapter 21 offers further information about electrolytic reductive coupling reactions.

Reduction of *o*- and *p*-nitrobenzyl halides at mercury or platinum gives mainly the bibenzyl derivative, with nitrotoluene as a minor product [121–126]. However, *m*-nitrotoluene is the predominant product of the electrolysis of *m*-nitrobenzyl halides [123].

Koch and coworkers [127] investigated the reduction of benzyl halides at both platinum and carbon in MeCN containing TEAP. For the electrolysis of benzyl iodide at platinum, the products are toluene, bibenzyl, and hydrocinnamonitrile. Hydrocinnamonitrile arises from reaction of the electrogenerated benzyl anion with the solvent:

$$C_6H_5CH_2^- + CH_3CN \rightarrow C_6H_5CH_3 + {}^-CH_2CN$$
$${}^-CH_2CN + C_6H_5CH_2I \rightarrow C_6H_5CH_2CH_2CN + I^-$$

In the presence of carbon dioxide or diethyl malonate, some of the benzyl anion is converted, respectively, into benzyl phenylacetate or the diethyl ester of benzyl malonate.

Shono and coworkers [128] electrolyzed benzyl chloride or (1-chloroethyl)benzene at carbon in MeCN containing TEAOTs and in the presence of various acyl chlorides to prepare alkyl benzyl ketones. Electrolysis of benzyl chloride in the presence of various ketones and aldehydes can be used to synthesize alcohols [52].

For the reduction of 1-bromo-1-phenylethane at mercury in DMF containing $TEABF_4$, Yamasaki and coworkers [129] found that the product distribution depends on the potential. At less negative potentials, it appears that an organomercury radical is involved as an intermediate, and the products are *meso*-2,3-diphenylbutane (40%), *d,l*-2,3-diphenylbutane (40%), and phenylethane (18%). At more negative potentials, generation of an anionic intermediate via two-electron reduction of the carbon–bromine bond leads exclusively to phenylethane. Through the use of optically active 1-bromo-1-(deuterioethyl)benzene, some conclusions were reached about stereochemical inversion during the two-electron reduction and protonation process.

Using (1-bromo-2,2-dimethylpropyl)benzene, Fry and Powers [130] obtained more insight into the mechanism of formation of bibenzyl from the reduction of benzyl bromides. Electrolytic cleavage of the carbon–bromine bond gives a potential-dependent distribution of products. At less negative potentials, all products (*meso*- and *d,l*-2,2,5,5-tetramethyl-3,4-diphenylhexane, head-to-tail and tail-to-tail dimers, and neopentylbenzene) arise from a radical intermediate. At more negative potentials, two-electron reduction of the carbon–bromine bond gives a carbanion intermediate, which is protonated to yield neopentylbenzene; a small amount of α-phenylneopentanol is formed via dehydrohalogenation. A recent report by Fry and coworkers [131] describes steric effects on the reductive coupling of α-substituted benzyl bromides.

Other compounds that have been studied are benzhydryl halides [132,133] and α,α'-dibromoxylenes [134]. Trifluoromethylbenzene, chlorodifluoromethylbenzene, and

dichlorofluoromethylbenzene [135] can be electrolyzed at mercury in DMF containing TBAI to afford a series of species, each possessing one less halogen atom than its precursor. Trifluoromethyl arenes undergo reductive coupling with electrophiles such as carbon dioxide, dimethylformamide, and acetone [136]. Trichloromethylbenzene undergoes stepwise reduction with loss of chloride in DMF [45,137]; electrolysis at a potential corresponding to the first stage of reduction leads to 1,2-diphenyl-1,1,2,2-tetrachloroethane (63%), diphenylacetylene (25%), 1,2-dichloro-1,2-diphenylethene (7%), and dichloromethylbenzene (2%) [137]. However, reduction of trichloromethylbenzene in DMF containing $TBABF_4$ in the presence of acetic anhydride gives, besides the preceding products, 2-acetoxy-1-chloro-1-phenyl-1-propene and 1,2-diacetoxy-1-phenyl-1-propene [138]. Cathodic addition of trichloromethylbenzene to ketones gives α,β-unsaturated ketones [139]. Methyl esters of trifluoromethylbenzoic acid can be defluorinated by reduction at lead cathodes in MeOH [140,141]. Fry and Touster [142] have reduced a benzal halide at stainless steel in DMF containing trimethylchlorosilane to synthesize both the (α-halobenzyl)silane and the benzal disilane.

Amino acids can be synthesized via the coupling of Schiff bases with carbanions generated by reduction of benzyl halides [143,144]. Electrolysis of benzyl chloride at mercury in DMF containing TBABr, and in the presence of the Schiff base formed from benzylamine and benzyl pyruvate, affords α-methylphenylalanine in up to 86% yield (after hydrogenolysis over palladium–charcoal). An antihypertensive agent, α-methyl-β-(3,4-dihydroxyphenyl)alanine, has been prepared by reductive coupling of the aforementioned Schiff base with 3,4-methylenedioxybenzyl chloride.

VI. ALICYCLIC HALIDES

A. Monohalogenated Species

Early research dealt with the reduction of substituted and optically active 1-bromocyclopropanes and 1-iodocyclopropanes [145–147]. A principal concern was whether cleavage of the carbon–halogen bond at mercury and carbon cathodes leads to both radical and carbanion intermediates. Mann and Barnes [148] have discussed the mechanism of reduction of the carbon-halogen bond in these species. Hazard and coworkers [149] investigated how the identity of the supporting electrolyte cation affects the reduction of derivatives of 1-bromo-1-carboxy-2,2-diphenylcyclopropane; ammonium ion causes retention of configuration, whereas tetraalkylammonium salts lead to inversion. Other studies by the same group involve the effect of adsorbed alkaloids on the stereochemistry of reduction of 1-bromo-1-carboxy-2,2-diphenylcyclopropane [150] and the reduction of optically active derivatives of 2,2-dibromocyclopropane [151,152]. Monobromocycloalkanes, ranging from cyclobutyl bromide to cyclohexadecyl bromide, have been examined polarographically in DMF containing TEABr [20,153].

Polarographic data for 1-bromo- and 2-bromonorbornane [22,154–156], 1-bromobicyclo[2.2.2]octane [154,155], 1,7,7-trimethyl-3-halobicyclo[2.2.1]heptan-2-ones [157], and derivatives of 1-bromo- and 2-bromo-7-oxabicyclo[2.2.1]heptane [156] have been compiled. For electrolyses of 1-bromo- and 1-iodonorbornane at mercury in DMF, the dominant process is two-electron cleavage of the carbon–halogen bond to afford norbornane; only a small quantity of bis(1-norbornyl)mercury is obtained [158]. At a platinum cathode,

the reductions of 1-bromo-, 1-chloro-, and 1-iodonorbornane give mainly norbornane, along with a little 1,1′-binorbornyl [159].

B. Dihalogenated Species

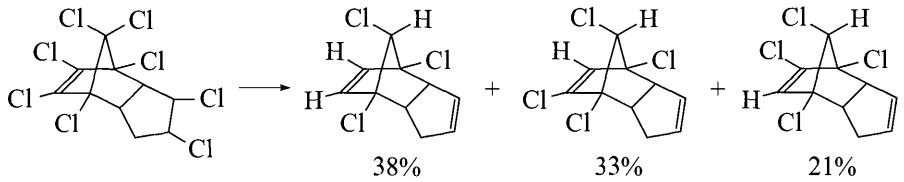
Fry and Reed [160] observed that electrochemical reduction of 2,2-dichloronorbornane, 2-*exo*-bromo-2-*endo*-chloronorbornane, and 2-*endo*-bromo-2-*exo*-chloronorbornane at mercury cathodes in DMF is a two-electron process, giving a mixture of nortricyclene and *endo*-2-chloronorbornane. Two papers [161,162], pertaining to the reduction of several 7,7-dihalobicyclo[4.1.0]heptanes, have revealed that formation of the less stable *endo*-7-halobicyclo[4.1.0]heptane is preferred over the *exo* isomer. According to Rifi [78,80], the electrolysis of 1-bromo-3-chlorocyclobutane at mercury in DMF containing lithium bromide yields bicyclo[1.1.0]butane, cyclobutane, and cyclobutene. A similar pattern of electroactivity prevails for 1,3-dibromo-1,3-dimethylcyclobutane. Hoffmann and Voss [163] found that 1,3-dibromocyclopentane and 1,3-dibromocyclohexane undergo reductive ring-closure reactions at a platinum cathode in DMF containing TPABr.

Low-temperature reduction of 1-bromo-4-chlorobicyclo[2.2.0]hexane at a mercury cathode in DMF containing a tetraethylammonium salt affords $\Delta^{1,4}$-bicyclo[2.2.0]hexane, which can be trapped with cyclopentadiene [164,165]. Rifi [80], as well as Wiberg and coworkers [166], electrolyzed 1,4-dibromobicyclo[2.2.2]octane in DMF containing a tetraalkylammonium salt; in the latter investigation, evidence was obtained that [2.2.2]propellane is formed transiently during the electrolysis. Rifi [80] reported that electrolysis of 1,5-dibromobicyclo[3.2.1]octane leads to the stable [3.2.1]propellane, and Leibzon and coworkers [167] found that reduction of 3,7-dibromo-3,7-dinitrobicyclo[3.3.1]nonane affords 3,7-dinitroadamantane in good yield (75–80%). Using glassy carbon in MeCN containing $TBABF_4$, Adcock and coworkers [168] have studied the reductions of 1,3-dihaloadamantanes, 1,4-dihalobicyclo[2.2.2]octanes, and 1,3-dihalobicyclo[1.1.1]pentanes.

For the reduction of 1,4-dihalonorbornanes at platinum in DMF containing TEABr, Wiberg and coworkers [159] found that the products are norbornane and 1,1′-binorbornyl, but there was no evidence for the formation of [2.2.1]propellane. However, when 1,4-dihalonorbornanes are electrolyzed at mercury in DMF [169,170], the major products are norbornane and bis(1-norbornyl)mercury, along with a small amount of 1,1′-binorbornyl, and it was concluded that [2.2.1]propellane is an intermediate.

C. Other Species

Semmelhack and coworkers [171] reduced 1,2-dimethyl-4,5,6,6-tetrachlorospiro[2.3]hexadiene at mercury in DMF containing lithium perchlorate and deuterium oxide to prepare 1,2-dimethyl-4,5,6-trichloro-6-deuteriospiro[2.3]hexadiene. A procedure for selective trimethylsilylation of tetrachlorocyclopropene to afford 1-(trimethylsilyl)trichlorocyclopropene has been described [172]. At mercury in aqueous EtOH containing TMACl, polyfluorocyclohexadienes can be reduced [173]. Strelow and coworkers [174] have reviewed the literature on the reduction of 1,1,3,3-tetrachlorodispirocyclobutanes to 1,3-dichlorodispirobicyclo[1.1.0]butanes. Chlordane, aldrin, and alodan (chlorinated insecticides) can be electrochemically dechlorinated at lead cathodes in MeOH containing TEABr [175]; for example, chlordane is converted into a mixture of three less chlorinated products:



Lindane (γ-hexachlorocyclohexane) undergoes stepwise dechlorination at a palladium-modified carbon-cloth cathode in MeOH containing TEABr [176].

VII. HALOGENATED AROMATIC COMPOUNDS

A. Monohalobenzenes

Electrochemical reduction of monohalobenzenes is generally believed to involve irreversible two-electron scission of the carbon–halogen bond followed by rapid protonation of the phenyl carbanion to give benzene. However, publications by Savéant and coworkers [8,177] have provided quantitative evidence that in nonaqueous media a more intricate mechanistic scheme for the reduction cleavage of these compounds must be considered. Accordingly, one can postulate a one-electron transfer to give a radical anion

$$C_6H_5X + e \rightleftharpoons C_6H_5X^{\cdot-}$$

which decomposes to yield the phenyl radical:

$$C_6H_5X^{\cdot-} \xrightarrow{k} C_6H_5^{\cdot} + X^-$$

A linear correlation exists between the logarithm of the rate constant k for scission of the electrogenerated radical anion and the standard potential for the C_6H_5X–$C_6H_5X^{\cdot-}$ couple; the more negative the standard potential, the larger is the rate constant [8]. Once formed, the phenyl radical can accept an electron,

$$C_6H_5^{\cdot} + e \rightarrow C_6H_5^-$$

or can react homogeneously with the initially generated radical anion,

$$C_6H_5^{\cdot} + C_6H_5X^{\cdot-} \rightarrow C_6H_5^- + C_6H_5X$$

and the resulting phenyl anion can be protonated by residual water in the solvent, by the supporting electrolyte, or by the solvent itself:

$$C_6H_5^- + H^+ \rightarrow C_6H_6$$

Other possible reactions include (a) abstraction of a hydrogen atom from the solvent by the phenyl radical, (b) homogeneous reduction of a solvent radical by the halobenzene radical anion, and (c) heterogeneous reduction of a solvent radical at the electrode surface.

Some examples of electrosyntheses based on the reduction of monohalobenzenes are now cited. Reduction of iodobenzene and bromobenzene at mercury in carbon dioxide-saturated DMF containing TEAP affords benzoic acid in up to 40% yield [178]. Bromobenzene, 3-methoxybromobenzene, 4-bromofluorobenzene, 4-(trifluoromethyl)-chlorobenzene, and 1,2,4-trichlorobenzene can be converted into aldehydes at a cadmium-coated stainless-steel cathode in DMF containing TBABr [179]. In the presence of trimethylchlorosilane, silylation products arise from the reduction of various aryl halides at platinum in DMF containing TEAOTs [100]. Reduction of *p*-iodoanisole at

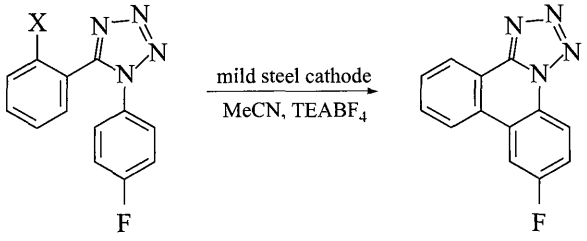
mercury in carbon dioxide-saturated DMF containing TMAP produces *p*-anisic acid, anisole, and bis(*p*-anisyl)mercury [180]. Electrolysis at a mercury cathode in diglyme containing a mixture of $TBABF_4$ and dimethylpyrrolidinium tetrafluoroborate has been used by Kariv-Miller and Vajtner [181] to convert fluorobenzene to benzene; the dimethylpyrrolidinium cation (DMP^+) acts catalytically by being reduced to an amalgam that reacts with fluorobenzene to produce the radical anion

$$DMP^+ + e + n\,Hg \rightarrow DMP(Hg)_n$$

$$C_6H_5F + DMP(Hg)_n \rightarrow C_6H_5F^- + DMP^+ + n\,Hg$$

which undergoes carbon–fluorine bond breakage, followed by further reduction and protonation to afford benzene. Chami and coworkers [182,183] demonstrated that electrolysis of substituted aryl halides in the presence of an olefin and a redox catalyst leads to arylated addition compounds; for example, the reduction of 4-chlorobenzonitrile at platinum in liquid ammonia containing 4-chlorostyrene and 4,4′-bipyridyl affords 1-(*p*-chlorophenyl)-2-(*p*-cyanophenyl)ethane in 64% yield, and electrolysis of 4-chlorobenzonitrile at mercury in DMF containing styrene and naphthonitrile gives 1-phenyl-2-(*p*-cyanophenyl)ethane in up to 80% yield.

Donnelly and coworkers [184,185] reported that the following intramolecular cyclization can be performed using a mild-steel cathode in MeCN containing $TEABF_4$:



80-90%

Reduction of an aryl halide at a cadmium-modified nickel cathode in DMF containing $TBABF_4$ leads to a formylation reaction between aryl carbanions and the solvent [186]. Two papers [187,188] have appeared in which reduction of aryl halides gives an aryl carbanion, which, by acting as a base to deprotonate a suitable nitrile, can cause coupling of the nitrile with esters, aldehydes, and ketones. Electrochemical trimethylsilylation of aryl halides can be effected at a stainless-steel or carbon-cloth cathode in THF–HMPA containing $TEABF_4$ and trimethylchlorosilane [189].

B. Polyhalobenzenes

Benzene bearing two different halogens can be reduced in a stepwise fashion. For example, electrolysis of *p*-fluoroiodobenzene yields fluorobenzene [190], and reduction of *p*-bromoiodobenzene gives bromobenzene in 98% yield [191]; of course, the monohalobenzenes can be further reduced. In DMSO containing TEABr, polychlorobenzenes can be selectively dechlorinated by electrolysis at mercury [192]. Studies have been made of the reductive dehalogenation of 1,3-difluorobenzene [181], the electrocarboxylation of dichlorobenzenes [193], the electrochemical behavior of the entire family of chlorinated benzenes [194], and the reductive coupling between 1,4-dichlorobenzene and 2,6-di-*tert*-butyl phenoxide [195]. Recently, during studies of the reduction of di-, tri-, and tetra-

halobenzenes at carbon in DMF containing TMAP [196], it was discovered that 1,2,4,5-tetrabromobenzene undergoes an electrolytically induced halogen dance, in which 1,3,5-tribromobenzene and 1,3-dibromobenzene are formed, along with 1,2,4-tribromobenzene and 1,4-dibromobenzene. For the electrolysis of *o*-dihalobenzenes, benzyne has been proposed as an intermediate [197–201].

A palladium-modified carbon-cloth cathode in MeOH containing TEABr has been used by Kulikov and coworkers [176] for the stepwise dechlorination of 1,2,3,5-tetrachlorobenzene and by Tsyganok and Otsuka [202] to carry out the dechlorination of 2,4-dichlorophenoxyacetic acid (a herbicide).

C. Halogenated Nitrobenzenes and Cyanobenzenes

Radical anions formed by addition of a single electron to a monohalobenzene are extremely short-lived; a halide ion is rapidly expelled and the resulting phenyl radical is quickly reduced. However, for a variety of mono- and polyhalogenated nitrobenzenes and cyanobenzenes, the electrogenerated radical anions are sufficiently stable that their EPR spectra can be recorded. In general, the stability of these radical anions is least for iodo compounds and greatest for fluoro species, and *ortho* halogens are expelled much more rapidly than *para* halogens, which are, in turn, lost faster than *meta* halogens. Hawley [4] has reviewed much of the available information about the electrochemical behavior of halogenated nitrobenzenes and cyanobenzenes. Andrieux and coworkers [203] have recently characterized the reduction of pentafluoronitrobenzene and pentachloronitrobenzene at glassy carbon in MeCN containing $TBABF_4$.

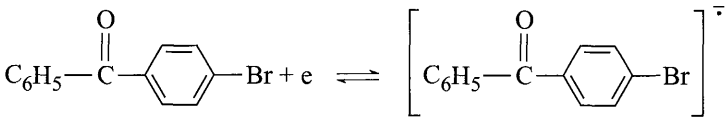
D. Halogenated Aryl Carbonyls

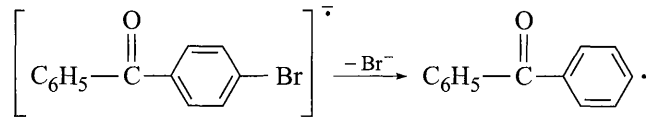
Product distributions have been determined for electrolyses of pentafluorobenzaldehyde, pentafluorobenzoic acid, and pentafluorobenzamide at mercury in aqueous media containing either sulfuric acid or $TEABF_4$ [204]. Reduction of the aldehyde gives pentafluorobenzyl alcohol and 2,3,5,6-tetrafluorobenzyl alcohol. Pentafluorobenzoic acid is initially converted to a mixture of 2,3,5,6-tetrafluorobenzoic acid (73%), pentafluorobenzyl alcohol (6%), and 2,3,5,6-tetrafluorobenzyl alcohol (20%); however, at a more negative potential, only the last two products are obtained in a 1 : 2 ratio. Pentafluorobenzaldehyde and 2,3,5,6-tetrafluorobenzaldehyde are easier to reduce than their benzoic acid analogues; therefore, the aldehydes cannot be isolated from electrolyses of the acids. In sulfuric acid, electrolysis of pentafluorobenzamide gives pentafluorobenzyl alcohol (58%) and 2,3,5,6-tetrafluorobenzyl alcohol. Using a lead cathode in sulfuric acid containing tetraalkylammonium salts, Sato and coworkers [205] selectively reduced pentafluorobenzoic acid to either 2,3,5,6-tetrafluorobenzyl alcohol or 2,3,5,6-tetrafluorobenzaldehyde.

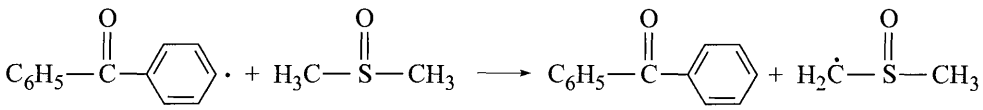
Fry and coworkers [191] observed that electrolysis of *m*-bromoacetophenone at mercury in DMF containing TEABr affords acetophenone, whereas reduction of *p*-bromo-γ-chlorobutyrophenone gives γ-chlorobutyrophenone.

According to M'Halla and coworkers [206], halogenated benzophenones behave in two different ways in nonaqueous solvents such as DMF, DMSO, and MeCN. For *m*-fluoro-, *p*-fluoro-, and *m*-chlorobenzophenone, a pair of electrons is apparently involved in the reduction, and benzophenone is produced quantitatively. However, for the electrolysis of *p*-chloro-, *m*-bromo-, and *p*-bromobenzophenone, fewer than two electrons per molecule are transferred, and benzophenone is obtained in less than 100% yield. For *p*-bro-

mobenzophenone in DMSO, the main reduction pathway is one-electron cleavage of the carbon–bromine bond, followed by hydrogen atom abstraction from the solvent:

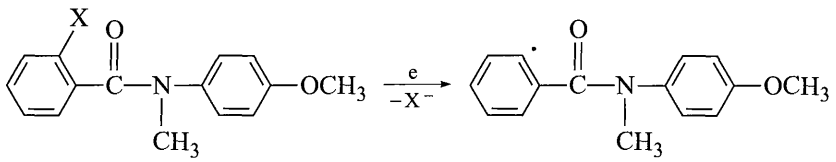






Then the solvent-derived radical can be reduced, or it can reoxidize the original radical anion of *p*-bromobenzophenone. In either event, the conjugate base of DMSO can attack the benzophenone radical to give substituted side products that cause both the yield of benzophenone to be well below 100% and the apparent coulometric *n* value to be lower than 2.

Reduction of 2-bromo- and 2-iodo-4′-methoxy-*N*-methylbenzanilide at mercury in DMF containing TPAP involves one-electron cleavage of the carbon–halogen bond to yield a radical intermediate [207,208]



which can undergo (a) further reduction and protonation to give 4′–methoxy-*N*-methylbenzanilide, (b) intramolecular cyclization to afford 2-methoxy-*N*-methylphenanthridinone, or (c) rearrangement followed by hydrogen atom abstraction to yield 4′-methoxy-*N*-methylbiphenyl-2-carboxamide.

E. Halogenated Biphenyls

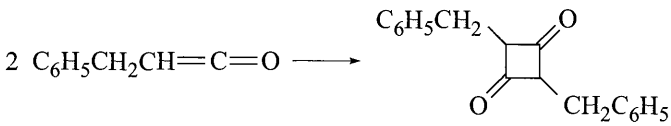
Farwell and coworkers [209,210] investigated the electrochemistry of mono- and polychlorobiphenyls at mercury in DMSO containing TEABr. These compounds exhibit sequential two-electron removal of chlorine, but there is a tendency (due to the varied pattern of chlorine substitution) for more than one product to be formed; sometimes two chlorines are expelled simultaneously. In another study, Maruyama and Murakami [211] reported that chlorinated biphenyls are reduced in DMF via one-electron cleavage of a carbon–chlorine bond to yield chloride and an aryl radical, which subsequently abstracts a hydrogen atom from the solvent. Rusling and Arena [212] probed the reduction of 4-bromo-, 4,4′-dibromo-, 3,4-dichloro-, and 2,2′,5,5′-tetrachlorobiphenyl at mercury in

DMF containing tetraalkylammonium iodides; their results are consistent with the sequence of events discussed earlier for the reduction of monohalobenzenes.

VIII. ACYL HALIDES

Barba and coworkers investigated the electrochemistry of benzoyl chloride [213], 1-naphthoyl chloride [213], 2-naphthoyl chloride [213], phthaloyl dichloride [214], cinnamoyl chloride [215], and 2- and 4-nitrobenzoyl chloride [216]. In dry acetone containing lithium perchlorate, the electrolysis of benzoyl chloride at mercury gives the acyl radical, which dimerizes to yield benzil [213]. Most probably, benzil then accepts one electron and is acylated by a molecule of benzoyl chloride, and the resulting intermediate is again reduced and acylated to give a 1 : 2 mixture of *cis*- and *trans*-stilbenediol dibenzoate. Similar reactions are seen for both 1-naphthoyl chloride and 2-naphthoyl chloride [213]. Cinnamoyl chloride [215] has been reported to accept one electron at a mercury cathode in acetone containing lithium perchlorate to form a radical

that abstracts a hydrogen atom to give an intermediate ketene, which dimerizes:



Reduction of benzoyl chloride and benzoyl fluoride at carbon and platinum cathodes in MeCN containing TEAP has been carried out by Cheek and Horine [217]. Macroelectrolysis of benzoyl chloride at carbon yields *cis*- and *trans*-stilbenediol dibenzoate, as reported earlier [213], but this product is reducible to diphenylacetylene at a more negative potential. Major electrolysis products derived from benzoyl fluoride are benzyl benzoate (15%) and diphenylacetylene (15%) along with stilbenol benzoate and other (polymeric) species of high molecular mass.

A study [218] of the effect of potential on the reduction of benzoyl chloride at mercury and carbon in MeCN containing tetraalkylammonium perchlorates revealed that *cis*- and *trans*-stilbenediol dibenzoate are formed exclusively at less negative potentials, whereas a mixture of benzaldehyde, benzyl benzoate, and *cis*- and *trans*-stilbenediol dibenzoate is obtained at more negative potentials. On the basis of deuterium labeling studies, acyl radicals and acyl anions were both postulated as intermediates. In the same work [218], reduction of heptanoyl chloride afforded mixtures of heptaldehyde and heptanoic anhydride, the latter product arising from the reaction between the acyl chloride and adventitious water to give heptanoic acid, which, in turn, interacts with more of the acyl chloride. Folest and coworkers [219] obtained symmetrical diketones by reducing aroyl and arylacetyl chlorides at nickel in MeCN containing $TBABF_4$.

Electrochemical reduction of glutaryl dichloride at mercury in MeCN containing TEAP [220] leads to 5-chlorovalerolactone and valerolactone, plus a significant amount of solid material believed to be a polymer such as $X[(CH_2)_3CHCl{-}O{-}C{-}O]_n(CH_2)_3X$, where X = CHO or CO_2H; in addition, glutaric anhydride is formed as a by-product.

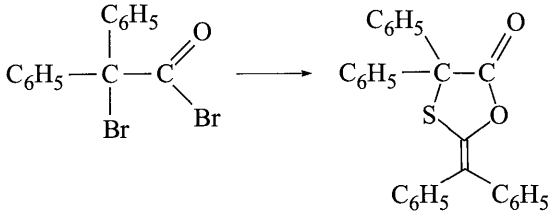
Trimethylacetyl chloride is reduced at carbon or mercury in MeCN containing either TMAP or TEAP to give trimethylacetaldehyde in yields up to 53%; trimethylacetic anhydride, the only other product, is formed via hydrolysis of the acyl chloride to trimethylacetic acid, which reacts with unreduced starting material [221]. Electrolysis of cyclohexanecarbonyl chloride at mercury in MeCN containing a tetraalkylammonium perchlorate leads to cyclohexanecarboxaldehyde (30–40%), along with tiny amounts of dicyclohexylketone and dicyclohexylethanedione (and two by-products, cyclohexanecarboxylic acid anhydride and cyclohexanecarboxylic acid) [222].

Acyl radicals and acyl anions are proposed intermediates in the reduction of phenylacetyl chloride and hydrocinnamoyl chloride at mercury in MeCN [223]. Among the products obtained from the reduction of phenylacetyl chloride are 1,4-diphenyl-2-butene-2,3-diol diphenylacetate, phenylacetaldehyde, toluene, 1,3-diphenylacetone, and 1,4-diphenyl-2,3-butanediol, as well as phenylacetic acid and phenylacetic acid anhydride. Analogous products arise from the reduction of hydrocinnamoyl chloride: 1,6-diphenyl-3-hexene-3,4-diol dihydrocinnamate, hydrocinnamaldehyde, ethyl benzene, 1,6-diphenyl-3,4-hexanediol, hydrocinnamic acid, and hydrocinnamic acid anhydride.

Upon being electrolyzed at carbon or mercury in MeCN containing TEAP, phthaloyl dichloride [224] is converted into 3-chlorophthalide, phthalide, and biphthalyl. However, this system is complicated by the fact that 3-chlorophthalide can itself be reduced (at a potential only slightly more negative than that needed for reduction of phthaloyl dichloride) to afford phthalide, biphthalyl, and dihydrobiphthalide.

Reduction of 2-furoyl chloride [225] at mercury in MeCN containing TEAP affords a variety of products, the most prominent of which is 1,2-di(2-furyl)ethene-1,2-diol di(2-furoate), along with small quantities of 2-furaldehyde, furil, furoin, hydrofuroin, 1,2-di(2-furyl)-2-hydroxy-3-cyanopropanone, and 3-(2-furyl)acrylonitrile. Electrolysis of 2,4,6-trimethylbenzoyl chloride [226] at carbon and mercury in MeCN containing TEAP gives mainly 2,4,6-trimethylbenzaldehyde and 3-(2,4,6-trimethylphenyl)acrylonitrile; however, traces of 2,4,6-trimethylbenzene, 2,4,6-trimethylbenzyl alcohol, 3-(2,4,6-trimethylphenyl)glutaronitrile, and 3-(2,4,6-trimethylphenyl)propionitrile are formed.

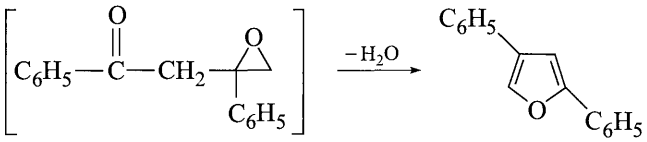
Quantitative conversion of 1-adamantanecarbonyl chloride to 1-adamantanecarboxaldehyde has been accomplished by reduction of the acyl halide at carbon and mercury in MeCN containing TEAP [227]. Lozano and Barba [228] reduced 2-chloro-2-phenylacetyl chloride at mercury in methylene chloride containing TEACl and obtained derivatives of pyran-2-one and pyran-4-one. In subsequent work [229,230], these authors investigated the reduction of 2-bromo-2,2-diphenylacetyl bromide at graphite in methylene chloride containing TEABr and in the presence of inorganic sulfur compounds; in the first study, a new sulfurated heterocyclic product was obtained:



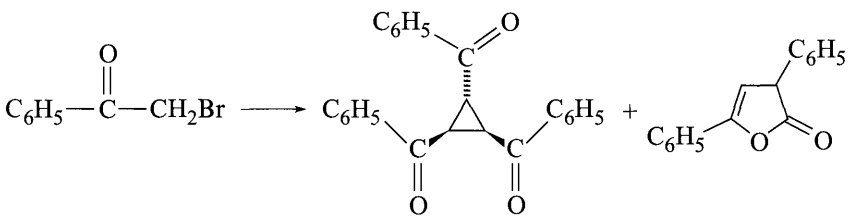
IX. PHENACYL HALIDES

Papers concerning the electrochemistry of phenacyl bromides have been published by Barba and coworkers [231–236]. Reduction of phenacyl bromide at mercury in DMF containing lithium perchlorate apparently involves two-electron cleavage of the carbon–bromine bond to form an anion

that reacts with excess starting material to give an intermediate that eliminates water to afford 2,4-diphenylfuran in 80% yield [231,232]:

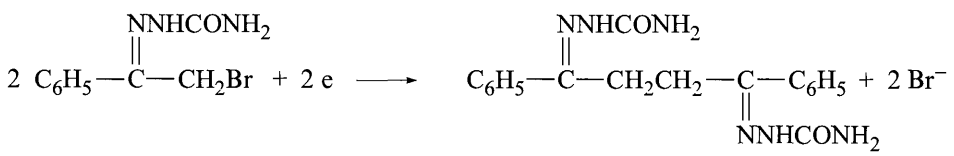


Other compounds that have been similarly synthesized are 2,4-bis(4-methoxyphenyl)furan, 2,4-bis(4-biphenylyl)furan, 2,4-bis(4-bromophenyl)furan, 2,4-bis(4-chlorophenyl)furan, and 2,4-bis(4-nitrophenyl)furan. When MeOH (a proton donor) is added to the system containing phenacyl bromide [232], the principal products are acetophenone (53%) and 2-bromo-1,3-diphenyl-3,4-epoxy-butan-1-one (37%). If, to DMF containing lithium perchlorate and ethyl bromoacetate, phenacyl bromide is slowly introduced and reduced at mercury, the distribution of products is different [233]:

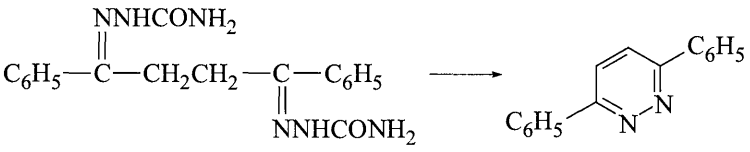


24% 44%

By protecting the carbonyl group of a phenacyl bromide through reaction with semicarbazide hydrochloride, by reducing the resultant semicarbazone at mercury in DMF containing lithium perchlorate to obtain a dimer, and by hydrolyzing the electrolytically formed dimer, one can synthesize a variety of 2,5-diarylfurans in excellent yield [234]. In addition, Barba and coworkers [235] demonstrated that reductive dimerization of the semicarbazone derivative of phenacyl bromide



can be followed by refluxing in DMF to form 3,6-diphenylpyridazine in 97% yield:



As pointed out by Barba and his colleagues [235], this method is suitable for the preparation of a variety of 3,6-diarylpyridazines.

In DMF containing lithium perchlorate, reduction of α-bromopropiophenone at mercury gives 1,4-diphenyl-2,3-dimethylbutan-1,4-dione in 65% yield [236]. However, electrolysis of α-bromopropiophenone in the presence of benzoyl chloride affords only 1,3-diphenyl-2-methylpropan-1,3-dione. Other studies involving reduction of phenacyl bromides include the electrosynthesis of 4-aryl-2-methylfurans [237] and the regioselective synthesis of enol carbonates [238]; semicarbazones of phenacyl bromide can be converted into 3,7-diaryl-2*H*-imidazo[2,1-*b*][1,3,4]oxadiazines [239]. Reduction of 1,2-dibenzoylchloroethane at mercury in DMF containing lithium perchlorate affords mixtures of phenyl tribenzoyl cyclopentanols and diphenyl dibenzoyl butanediones [240].

X. ALIPHATIC α-HALOCARBONYL COMPOUNDS

Polarographic studies of aliphatic α-haloaldehydes in water–dioxane containing lithium chloride [241,242] have shown that reduction of these compounds is influenced by the equilibrium involving the hydrated and unhydrated forms of the aldehyde. Each carbon–halogen bond is cleaved in a two-electron, one-proton process, and the final nonhalogenated aldehyde is reduced at a more negative potential [243].

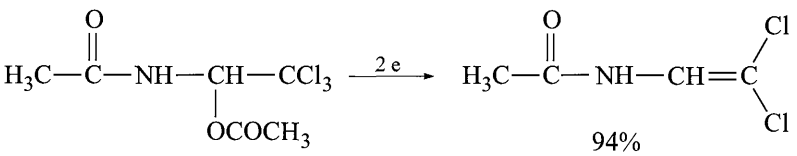
Dirlam and coworkers [244] reduced 2-bromo-3-pentanone at mercury in aqueous DMF containing lithium chloride; a 2 : 1 mixture of 3-pentanone and 1-hydroxy-3-pentanone was obtained. In the same study, electrolysis of α,α′-dibromoacetone in the presence of benzoate gave a mixture of products resulting from both reductive cleavage of a carbon–bromine bond and S_N2 displacement of bromide by benzoate. At mercury in an acetic acid–sodium acetate buffer, reduction of branched dibromo ketones, such as 2,4-dibromo-2,4-dimethyl-3-pentanone, affords α-acetoxyketones in excellent yield; less highly substituted species, such as 4,6-dibromo-5-nonanone, result in simple reductive cleavage of both carbon–bromine bonds [245]; further work pertaining to competition between reductive acetoxylation and double dehalogenation for these α,α′-dibromoketones has been reported [246,247].

Reduction of bis(α-bromocyclopropyl) ketone in an acetic acid–sodium acetate buffer can, depending on experimental conditions, yield a mixture of α-bromocyclopropyl cyclopropyl ketone (76%) and dicyclopropyl ketone (14%); in DMF containing acetic acid and sodium acetate, α-bromocyclopropyl cyclopropyl ketone is formed exclusively [248]. Fry and Scoggins [249] reported that the electrolysis of 2,4-dibromo-2-methylpentan-3-one gives 2,2-dimethylcyclopropanone as a transient intermediate, and Rampazzo and coworkers [250] studied the reduction of 2,4-dibromo-1,5-diphenyl-1,4-pentadien-3-one. Subsequently, van Tilborg and coworkers [251] demonstrated that the low-temperature reduction of alkylated α,α′-dihaloketones to cyclopropanones (isolated as hemiacetals or hemiacylals) can be accomplished with highly alkylated starting materials; for example, electrolysis of 2,4-dibromo-2,4-dimethylpentan-3-one in the presence of MeOH affords 1-methoxy-2,2,3,3-tetramethylcyclopropanol in 50–80% yield. Electrochemical cyclization

of 1,3-dihaloketones whose carbonyl moieties are protected as acetals, acylals, and aminals can produce the corresponding cyclopropanone derivatives; thus, reduction of 2,2-bis-(chloromethyl)-1,3-dioxolane gives the corresponding spirocyclopropane in 75% yield. Using mercury cathodes in DMF containing TEAP, Inesi and coworkers [252] reduced α,α'-dichloroketones in the presence of carboxylic acids, phenols, and diethyl malonate; depending on the substrate, it is possible to isolate Favorskii rearrangement products, dechlorinated ketones, and addition products; similarly, reduction of 1,1,3-tribromo- or 1,1,3-trichloro-3-methyl-2-pentanone in the presence of amines or phenols gives the corresponding α,β-unsaturated amides or esters [253].

Barba and coworkers [254] examined the behavior of α,α-dibromodibenzoylmethane at both platinum and mercury in DMF containing lithium perchlorate; for both electrode materials, the only product is α-bromodibenzoylmethane. In aqueous media, α-halocarboxylic acids as well as their esters undergo two-electron, one-proton reductive cleavage [255–257]. Baizer and Chruma [46] electrolyzed ethyl bromoacetate at mercury in slightly wet DMF containing TEAOTs to obtain mainly ethyl acetate and diethyl succinate, although small quantities of 1,2,3-tricarbethoxycyclopropane, 1,2,3-tricarbethoxypropane, and diethyl fumarate are formed. Reduction of ethyl trichloroacetate in the presence of acrylonitrile affords 1-carbethoxy-1-chloro-2-cyanocyclopropane and 1-carbethoxy-1,1,3-trichloro-3-cyanopropane.

Two recent reports [258,259] deal with the reduction of α-haloamides at mercury in DMF containing tetraethylammonium salts; *N*-benzyloxazolidine-2,4-dione (a biologically active compound) has been prepared by electrolysis of a solution containing α-chloro-*N*-benzylacetamide, carbon dioxide, and a probase (e.g., tetraethyl ethylenetetracarboxylate). Maran [260] studied the reduction of several α-haloamides at mercury in DMF containing TBAP; for example, the electrolysis of (*S*)-(–)-2-bromo-*N*-phenylpropanamide gives propananilide, 2-(dimethylamino)-5-methyl-3-phenyloxazolidin-4-one, and *cis*-1,4-diphenyl-3,6-dimethyl-2,5-dioxopiperazine. In other research, Casadei and coworkers [261] observed the following process at mercury in DMF containing tetraethylammonium salts:



Giomini and coworkers [262,263] have investigated the reduction of ethyl α, β-dibromopropanoate, ethyl α,γ-dibromobutyrate, and methyl α,δ-dibromovalerate at mercury in DMF containing TMAP or TEAP.

XI. HALOGENATED HETEROCYCLIC COMPOUNDS

Later in this volume, Chapter 18 presents a discussion of the electrochemical behavior of heterocyclic species. However, it is appropriate here to offer a short summary of the reduction of carbon–halogen bonds found in several classes of heterocyclic compounds. Many halogenated heterocyclic substances display behavior similar to that of aryl halides; the carbon–halogen bond is reductively cleaved in a process involving two electrons and a proton to give a hydrogenated product.

A. Heterocyclic Compounds with One Nitrogen Atom

Polarographic investigations of aqueous solutions of monohalogenated pyridines (such as 4-chloro-, 2-bromo-, and 3-iodopyridine), in either their unprotonated or protonated form, have revealed a two-electron cleavage of the carbon–halogen bond, followed by uptake of a proton to give pyridine [264–269]. In DMSO containing TPAP, reduction of 2-chloro-3-nitropyridine initially yields a stable radical anion [270], which at a more negative potential is dechlorinated to form the 3-nitropyridine radical anion. Andrieux and coworkers [177] have employed redox catalysis to examine the reduction of 2-bromo-, 3-bromo-, 2-chloro, and 3-chloropyridine at mercury in DMF containing TBAI. Polarographic reduction of 2,5-dibromo-, 2,3-dichloro-, and 2,6-dichloropyridine in EtOH–water has been carried out [271]. A recent paper describes the reduction of mono- and dihalopyridines at carbon cathodes in DMF containing TMAP [272].

Chambers and coworkers [273] investigated the reduction of some polyhalopyridines in DMF containing $TEABF_4$. Electrolysis of pentafluoropyridine at mercury affords perfluoro-4,4′-bipyridyl, whereas reduction of the same starting material in the presence of a proton donor (hydroquinone) gives 2,3,5,6-tetrafluoropyridine. However, electrolysis of pentachloropyridine in the absence of a proton donor results in the formatiaon of 2,3,5,6-tetrachloropyridine and bis(tetrachloropyridyl)mercury; apparently, the bulky *o*-chloro substituents inhibit dimerization of the intermediate radical anions. Finally, there is a patent concerning the large-scale electrolytic synthesis of 2,3,5-trichloropyridine from pentachloropyridine [274] as well as two patents that deal with the reduction of pentachloropyridine to 2,3,5,6-tetrachloropyridine [275,276].

Alwair and Grimshaw [277] reported that, in DMF containing TPAP, 6-chloroquinoline undergoes one-electron reduction to its radical anion, which fragments and then accepts a hydrogen atom from the solvent to form quinoline (which is reducible at a more negative potential). Fuchs and coworkers [278] studied chlorinated quinolines in DMF containing TBAI and discovered that, once a radical anion is generated, a carbon–halogen bond on the heterocyclic ring is cleaved faster than a carbon–chlorine bond on the fused benzene ring. Radical anions of chloroquinolines that are not rapidly dehalogenated react with added carbon dioxide to form carboxylated starting materials; unstable radical anions of chloroquinolines lose chloride to give neutral radicals that are further reduced before reacting with carbon dioxide.

According to Kyriacou and coworkers [279], reduction of 3,4,5,6-tetrachloro-2-picolinic acid at a silver electrode in an aqueous medium yields 3,4,6-trichloro-2-picolinic acid, which can be further reduced to 3,6-dichloro-2-picolinic acid.

B. Heterocyclic Compounds with Two Nitrogen Atoms

A survey [277] of the electrochemistry of 6-haloquinoxalines in DMF containing TPAP revealed that 6-chloroquinoxaline can be converted into a stable radical anion, whereas the bromo and iodo analogues accept one electron to yield radical anions, which undergo fragmentation and hydrogen atom abstraction to form quinoxaline.

In DMF, both 2-bromo- and 2-chlorophenazine are reversibly reduced to stable radical anions; however, the radical anion of 2-iodophenazine decomposes to yield iodide ion and phenazine [277].

Lund [280] observed that reduction of 4-chloroquinazoline in an alcoholic phosphate buffer results in the two-electron cleavage of the carbon–chlorine bond with formation of quinazoline in essentially quantitative yield.

C. Other Heterocyclic Species

Laviron [264] investigated the polarography of halogenated thiazoles, which are reduced by uptake of two electrons and one proton to afford thiazole, and Iversen [281] synthesized thiazole in 88% yield by reducing 2-bromothiazole at mercury in an acidic water–EtOH medium. Reduction of 2-bromothiazole at carbon in MeCN containing $TMABF_4$ involves both radical and carbanion intermediates, and thiazole is the sole product [282].

Polarographic studies have been undertaken of the reduction of brominated and iodinated thiophenes in aqueous and nonaqueous media [283–287]; the electrolytic cleavage of each carbon–halogen bond is a two-electron, one-proton process. Feldmann and Koberstein [288] have probed the three-step reduction of 2,3,5-tribromothiophene at mercury in MeOH, and Pletcher and Razaq [289] synthesized 3-bromothiophene via reduction of 2,3,5-tribromothiophene at lead, mercury, zinc, and graphite cathodes in dioxane–water containing sodium bromide. Gedye and coworkers [290] described the reduction of tetrabromothiophene, tetraiodothiophene, 2,3,4-tribromothiophene, and 3,4-dibromothiophene at mercury, copper, and lead electrodes in DMF containing TEABr. Electrosyntheses of (a) 3-bromo- or 3,4-dibromothiophene from tetrabromothiophene, (b) 3,4-dibromo-2-chlorothiophene from 2,3,4-tribromo-5-chlorothiophene, and (c) 3-bromo-4-chlorothiophene from 2,3,5-tribromo-4-chlorothiophene have been developed by Dapperheld and coworkers [291]. Recent work [292], concerning the reduction of mono- and dihalothiophenes at carbon in DMF, revealed that electrolyses of 2,3-dibromo-, 2,4-dibromo-, 2,5-dibromo-, and 2-bromo-5-chlorothiophene give rise to an electrolytically induced halogen dance. Justice and Hall [293] have synthesized 3-hydrobenzo[*b*]thiophene via the reduction of a substituted 3-chlorobenzo[*b*]thiophene.

Casadei and coworkers [294] studied the reduction of 3-halo-β-lactams and 3,3-dihalo-β-lactams. In DMF containing TEAP, *trans*-3-bromo- and *trans*-3-chloro-1,4-diphenylazetidin-2-one undergo two-step reduction; the first wave arises from cleavage of the carbon–halogen bond and the second wave is due to reduction of the β-lactam. Three stages of reduction are exhibited by 3,3-dichloro-1,4-diphenylazetidin-2-one, so that stepwise removal of the chlorines is possible. In the presence of carbon dioxide, a *trans*-3-halo-1,4-diphenylazetidin-2-one can be converted into *trans*-3-carboxy-1,4–diphenylazetidin-2-one; without carbon dioxide, the major product is the dehalogenated β-lactam, but a small amount of the ring-opened α,β-unsaturated amide is obtained.

XII. INDIRECT OR CATALYTIC REDUCTION OF THE CARBON–HALOGEN BOND

Direct electrolytic cleavage of the carbon–halogen bond is an intrinsically irreversible process. Thus, the potential needed to reduce a carbon–halogen bond heterogeneously at an electrode is often much more negative than the thermodynamically reversible potential. However, carbon–halogen bonds can be cleaved chemically with electron-transfer mediators (catalysts) that are electrogenerated at potentials more positive than those required for direct reduction of the carbon–halogen bond. In an early application of this concept, Lund and coworkers [295] catalytically reduced bromobenzene by the electrogenerated radical anion of chrysene. In nonaqueous media, chrysene (denoted here by Ar) is reduced reversibly at mercury to give the radical anion:

$$Ar + e \rightleftharpoons Ar^-$$

Bromobenzene cannot be reduced directly at the potential used to generate the radical anion of chrysene. However, the radical anion can react chemically and rapidly with bromobenzene in solution:

$$Ar^{\cdot -} + C_6H_5Br \rightarrow Ar + C_6H_5Br^{\cdot -}$$
$$C_6H_5Br^{\cdot -} \rightarrow C_6H_5^{\cdot} + Br^-$$
$$C_6H_5^{\cdot} + Ar^{\cdot -} \rightarrow C_6H_5^- + Ar$$
$$C_6H_5^- + H^+ \rightarrow C_6H_6$$

A. Electrogenerated Radical Anions as Mediators

Numerous studies [295–300] have shown that the rate of electron transfer between an electrogenerated radical anion (mediator) and a halogenated organic compound (substrate) *increases* as the difference between the standard potentials for reduction of the precursor of the mediator and for reduction of the substrate *decreases*.

In a study of the reaction between alkyl halides and the electrogenerated naphthalene radical anion, Sease and Reed [297] observed that only alkyl chlorides, such as 1-chlorohexane and 6-chloro-1-hexene, are catalytically reduced; 1-chlorohexane gives only *n*-hexane, whereas 6-chloro-1-hexene affords methylcyclopentane and 1-hexene. In an earlier paper [296], the reactions of 1-bromo- and 1-chlorobutane with the electrogenerated radical anions of *trans*-stilbene and anthracene in DMSO were examined. Britton and Fry [298] elucidated the kinetics of the electron-transfer reaction between 1-chlorooctane and the phenanthrene radical anion in DMF.

Another feature of reactions between alkyl halides and electrogenerated aromatic radical anions is that, once a single electron has been transferred to the alkyl halide to form an alkyl radical ($R^{\cdot}$), the radical can react with another radical anion to form an alkyl carbanion (R^-), which is then protonated to form RH, or the radical can bond with the radical anion to yield an alkylated aromatic hydrocarbon:

$$R^{\cdot} + Ar^{\cdot -} \rightarrow ArR^- \xrightarrow{H^+} ArRH$$

An example of the latter process is seen in a study of the electrolysis of stilbene in DMF containing TBAI and *tert*-butyl chloride [301]; the electrogenerated radical anion of stilbene initially converts *tert*-butyl chloride to the *tert*-butyl radical, which interacts with the stilbene radical anion to afford a 3:2 mixture of 3,3-dimethyl-1,2-diphenylbutane and 1-phenyl-2-(4′ = *tert*-butylphenyl)ethane.

Other studies of the reactions of alkyl halides with electrogenerated radical anions have involved reduction of diketones in the presence of methyl halides [302], reduction of nitrobenzene in the presence of alkyl halides [303], reductive coupling of 1,2- and 1,3-dihaloalkanes with anthracene [304], reductive coupling of phenylacetylene with alkyl halides [305], electron transfer between *meso*- or *d,l*-1,2-dichloro-1,2-diphenylethane and electrogenerated radical anions [306], and reductive coupling of *tert*-butyl bromide with azobenzene, quinoxaline, and anthracene [307]. Reactions between halogenated organic species and electrogenerated radical anions have been extended to include both unsubstituted and substituted benzyl chloride [308], vinyl bromides, 2-bromoindene, and 7,7-dichlorobicyclo[4.1.0]heptane [309], and bornyl, isobornyl, and *exo*- and *endo*-norbornyl bromides [310]. Chapter 29, which discusses electrogenerated reagents, provides more information on the preceding topics.

B. Transition-Metal Complexes as Mediators

Nédeléc and coworkers [311] recently reviewed the subject of organic electroreductive coupling reactions that utilize transition-metal complexes as catalysts. In an early report dealing with the catalytic reduction of alkyl halides by an electrogenerated transition-metal complex, Sofranko and coworkers [312] discovered that rhodium(I) coordinated to a pair of 1,2-bis(diphenylphosphino)ethane ligands undergoes reversible one-electron reduction at mercury to give the rhodium(0) species, which can catalytically reduce the carbon–halogen bond of bromo-, chloro-, and iodocyclohexane to give products dependent on both the substrate and the solvent.

Papers by Pletcher and coworkers [313–317] focused on the catalytic reduction of various bromoalkanes by nickel(I) complexes that are electrogenerated at platinum in MeCN from the corresponding nickel(II) species; ligands (L) coordinated to nickel(II) included Schiff bases and macrocyclic tetraamines. It was proposed that the nickel(II) complex, [Ni(II)L], is reversibly reduced, and that the resulting nickel(I) species, $[Ni(I)L]^-$, reacts with a bromoalkane to form an organonickel(III) intermediate, $[RNi(III)LBr]^-$. However, no evidence for the existence of the organonickel(III) intermediate has been obtained. Therefore, if the organonickel(III) species is formed at all, it must quickly (a) decompose to give an alkyl radical, (b) accept an electron to give an alkyl carbanion, or (c) react with unreduced bromoalkane before further reduction.

In contrast to the behavior of the foregoing nickel(I) complexes as catalysts, the catalytic reactions of alkyl halides with cobalt(I) species such as vitamin B_{12s}, cobaloximes(I), and cobalt(I) salen exhibit a significant difference. Cobalt(I) species, acting as potent nucleophiles in S_N2 reactions with alkyl halides, give stable alkylcobalt(III) intermediates. Lexa and coworkers [318] have discussed this mechanistic scheme for the catalytic reduction of 1-bromobutane by the electrogenerated cobalt(I) tetraphenylporphin complex, where TPP denotes the ligand. Reversible one-electron reduction of the parent cobalt(II) species

$$Co(II)TPP + e \rightleftharpoons [Co(I)TPP]^-$$

is followed by nucleophilic attack of the catalyst on 1-bromobutane:

$$[Co(I)TPP]^- + C_4H_9Br \rightarrow H_9C_4Co(III)TPP + Br^-$$

Then the cobalt(III) intermediate is subsequently reduced

$$H_9C_4Co(III)TPP + e \rightleftharpoons [H_9C_4Co(II)TPP]^-$$

and the resulting cobalt(II) species can decompose in two ways,

$$[H_9C_4Co(II)TPP]^- \rightarrow [Co(I)TPP]^- + {}^{\cdot}C_4H_9$$

$$[H_9C_4Co(II)TPP]^- \rightarrow Co(II)TPP + {}^-C_4H_9$$

to afford an alkyl radical or carbanion that leads to the final products.

In the following sections, examples of catalytic reductions of halogenated organic compounds by electrogenerated nickel, cobalt, and various other species are mentioned.

1. Nickel Complexes

Electrogenerated nickel(0) bipyridine complexes serve as catalysts for a number of syntheses: (a) formation of ketones from acyl halides and either alkyl or aryl halides [319], (b) production of β,γ-unsaturated esters via coupling of α-haloesters with aryl or vinyl halides [320], (c) coupling of α-chloroesters or α-chloronitriles with carbonyl

compounds [321], (d) formation of unsymmetrical biaryls from a mixture of two aryl halides [322], (e) reduction of alkyl halides or α,ω-dibromoalkanes to form dimers [323], (f) coupling of alkyl, benzyl, and aryl halides [324], (g) formation of α-arylated ketones via coupling of α-chloroketones with aryl halides [325], (h) cross-coupling of aryl halides and ethyl chloroacetate [326], (i) coupling of aryl halides and activated olefins [327], (j) cross-coupling between aryl halides and activated alkyl halides [328], (k) formation of ketones via coupling of organic halides with carbon monoxide [329], (l) production of ketones via reduction of a mixture of a benzyl or alkyl halide with a metal carbonyl [330], and (m) preparation of symmetrical ketones from alkyl, benzyl, and aryl halides [331].

Nickel(0) triphenylphosphine species have been used to convert allyl halides to 1,5-hexadiene [332], for the reductive coupling of ethylene with aryl halides to give 1,1-diarylethanes [333], and for the coupling of aryl halides and alkenes to prepare substituted olefins [334]. In addition, 1,2-bis[(di-2-propylphosphino)benzene]nickel(0) has been used for the reductive coupling of aryl halides [335], and 1,2-bis[(diphenylphosphino)ethane]-nickel(0) has been employed to synthesize biphenyl from bromobenzene [336] and to prepare benzoic acid from bromobenzene in the presence of carbon dioxide [337].

Electrogenerated nickel(I) salen has been used as a catalyst for the reductive intramolecular cyclizations of 6-bromo- and 6-iodo-1-phenyl-1-hexyne [338], the reduction of several α,ω-dihaloalkanes [339], the reductive coupling of 2-bromo- and 2-iodoethanol to prepare 1,4-butanediol [340], the conversion of cyclohexanecarbonyl chloride to a tetramer [341], and the reduction of benzal chloride [342].

Various electrogenerated nickel(I) tetraazamacrocycles with ligands such as cyclam, tetramethylcyclam, and hexamethylcyclam serve as catalysts for the reduction of allyl *o*-halophenyl ethers [343] and the reductive intramolecular cyclization of *o*-haloaryl compounds possessing unsaturated side chains [344,345]. Espenson and coworkers have used such nickel(I) catalysts to reduce alkyl and benzyl halides [346–349], α,ω-dihaloalkanes [350,351], 1-bromo-4-cyanobutane [352], and other halogenated compounds [353]. Using this same class of nickel(I) catalysts, Ozaki and coworkers have carried out a number of interesting electrosyntheses: (a) intramolecular cyclization of 2-bromoalkyl- and 3-bromoalkyl-2-cyclohexen-1-ones [354], (b) radical cyclization of halogenated ethers [355], (c) intermolecular addition of alkyl radicals to activated olefins [356], (d) intramolecular cyclization of *n*-allylic and *n*-propargylic α-bromoamides and of *o*-bromoacryloylanilides to give five-membered lactams [357], (e) cyclization of vinyl and aryl halides [358], (f) cyclization of α-bromo- and α-iodoamides [359], (g) cyclization of acetylenic halides to prepare functionalized (methylene)cyclopentanes [360], (h) stereoselective addition of *n*-, *sec*-, and *tert*-butyl radicals to α-methylenebutyrolactones [361], and (i) reduction of 2-bromo- and 2-iodo-1,6-dienes to give bicyclo[3.1.0]-, 3-azabicyclo[3.1.0]-, and 3-oxabicyclo[3.1.0]hexane derivatives [362]. Gómez and coworkers [363] converted nickel and palladium tetraazamacrocyclic complexes to their corresponding zero-valent states to reduce unsaturated *o*-haloaryl and *o*-halobenzyl ethers; the nickel(0) complex caused intramolecular cyclization, whereas the palladium(0) complex caused cleavage of the carbon–oxygen bond of the ethers.

Stolzenberg and coworkers have used electrogenerated nickel(I) tetrapyrrole complexes for the catalytic reduction of dichloromethane and methyl iodide [364], alkyl halides [365–367], and aryl halides [367], and Lexa and coworkers [368] have discussed the catalytic reduction of *trans*-1,2-dibromocyclohexane to cyclohexene by electrogenerated nickel(I), cobalt(I), and iron(I) porphyrin complexes.

2. Cobalt Complexes

Allyl halides have been reduced with electrogenerated tris(bipyridine)cobalt(I) to afford 1,5-hexadiene [369,370]. Some of the earliest work with cobalt(I) salen involved its use for the catalytic reduction of bromoethane [371], bromobenzene [371], and *tert*-butyl bromide and chloride [372]. More recently, Fry and coworkers examined the cobalt(I) salen-catalyzed reductions of benzal chloride [373–375] and of benzotrichloride [376], and the catalytic reductions of 1-bromobutane [377,378], 1-iodobutane [378], 1,2-dibromobutane [378], benzyl and 4-(trifluoromethyl)benzyl chlorides [379], iodoethane [380], diphenyl disulfide [381], 1,8-diiodooctane [382], and 3-chloro-2,4-pentanedione [383] have been investigated.

Rusling and coworkers have carried out extensive studies of the use of electrogenerated cobalt(I) complexes (including cobalt(I) salen, vitamin B_{12s}, and cobalt(I) phthalocyanine) as catalysts both in homogeneous phase and in bicontinuous microemulsions [384] for the reductions of 1,2-dibromoethane and 1,2-dibromobutane [385], the debromination of alkyl vicinal dibromides [386], the dechlorination of DDT [387], the reductions of 1-bromobutane, 1-bromododecane, and *trans*-1,2-dibromocyclohexane [388,389], and the reduction of benzyl bromide [390].

Other uses of cobalt(I) catalysts include the reductive intramolecular cyclization of bromocyclohexenones to form bicyclic ketones [391] and the radical cyclization of bromoacetals [392,393]. Kräutler and coworkers [394] found that 1,4-dibromobutane interacts with electrogenerated cob(I)alamin to afford a tetramethylene-1,4-di$=Co_{\beta}$-cobalamin species. In a recent study of the reactions of cobalt(I) tetraphenyl porphyrin with benzyl chloride or 1-chlorobutane, Zheng and coworkers [395] reported that alkyl radicals are transferred from the cobalt center to a nitrogen of a pyrrole ring, leading to formation of an *N*-alkyl cobalt porphyrin complex.

3. Other Catalysts

Several papers have appeared that describe the use of electrogenerated samarium(II) for the catalytic reduction of organic halides at a nickel cathode in DMF containing $TBABF_4$ [396], for the reductive coupling of 3-chloropropanoate with ketones to yield γ-butyrolactones [397], and for the reductive coupling of allyl chloride with ketones [398]. Hall and coworkers [399] electrogenerated tris(acetylacetonato)iron(II) for the reductive coupling and disproportionation of 1-bromooctane, and Wade and Castro [400] investigated the reactions of iron(II) porphyrin with vicinal dihalides as well as alkyl, allyl, benzyl, and propargyl halides. Catalytic dehalogenation of ethylene dibromide and trichloroacetic acid has been accomplished with iron(II) myoglobin in biomembrane-like surfactant films on pyrolytic graphite electrodes [401].

Vanhoye and coworkers [402] synthesized aldehydes by using the electrogenerated radical anion of iron pentacarbonyl to reduce iodoethane and benzyl bromide in the presence of carbon monoxide. Esters can be prepared catalytically from alkyl halides and alcohols in the presence of iron pentacarbonyl [403]. Yoshida and coworkers reduced mixtures of organic halides and iron pentacarbonyl and then introduced an electrophile to obtain carbonyl compounds [404] and converted alkyl halides into aldehydes by using iron pentacarbonyl as a catalyst [405,406]. Finally, a review by Torii [407] provides references to additional papers that deal with catalytic processes involving complexes of nickel, cobalt, iron, palladium, rhodium, platinum, chromium, molybdenum, tungsten, manganese, rhenium, tin, lead, zinc, mercury, and titanium.

C. Reduction of Carbon–Halogen Bonds at Chemically Modified Electrodes

Some papers have appeared that deal with the use of electrodes whose surfaces are modified with materials suitable for the catalytic reduction of halogenated organic compounds. Kerr and coworkers [408] employed a platinum electrode coated with poly-*p*-nitrostyrene for the catalytic reduction of 1,2-dibromo-1,2-diphenylethane. Catalytic reduction of 1,2-dibromo-1,2-diphenylethane, 1,2-dibromophenylethane, and 1,2-dibromopropane has been achieved with an electrode coated with covalently immobilized cobalt(II) or copper(II) tetraphenylporphyrin [409]. Carbon electrodes modified with *meso*-tetra(*p*-aminophenyl)porphyrinatoiron(III) can be used for the catalytic reduction of benzyl bromide, triphenylmethyl bromide, and hexachloroethane when the surface-bound porphyrin is in the Fe(I) state [410]. Metal phthalocyanine-containing films on pyrolytic graphite have been utilized for the catalytic reduction of *trans*-1,2-dibromocyclohexane and trichloroacetic acid [411], and copper and nickel phthalocyanines adsorbed onto carbon promote the catalytic reduction of 1,2-dibromobutane, *trans*-1,2-dibromocyclohexane, and trichloroacetic acid in bicontinuous microemulsions [412]. When carbon electrodes coated with anodically polymerized films of nickel(II) salen are cathodically polarized to generate nickel(I) sites, it is possible to carry out the catalytic reduction of iodoethane and 2-iodopropane [29] and the reductive intramolecular cyclizations of 1,3-dibromopropane and of 1,4-dibromo- and 1,4-diiodobutane [413]. A volume edited by Murray [414] contains a valuable set of review chapters by experts in the field of chemically modified electrodes.

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Cathodic Reduction of Nitro and Related Compounds

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I. INTRODUCTION

The electrolytic reduction of nitro compounds has played an important role in the development of organic electrochemistry in the "classic" period about 1900 [1]. It was the investigation of the stepwise reduction of nitrobenzene that led Haber [2] to the idea that the deciding factor in determining the product was the potential of the working electrode, and he was also the first to apply the principle to organic electrolysis.

In this chapter there will be discussed the reduction of aliphatic and aromatic as well as *N*-nitro compounds and the further reduction of the products obtained, such as nitroso, azoxy, azo compounds, and hydroxylamines. The electrochemistry of these compounds has been treated in reviews [3].

II. ALIPHATIC NITRO COMPOUNDS AND DERIVATIVES

A. Nitroalkanes

1. Primary and Secondary Nitroalkanes

Primary and secondary nitroalkanes are reducible in acid and neutral solutions, whereas the formation of the anion of the *aci* form in alkaline solution generally prevents their reduction in this medium. Electrolysis of nitroalkanes in acid solution at low temperature yields as main product the corresponding alkylhydroxylamine [4–7], which is further reducible only in a rather narrow pH region, around pH 7. The electrolytic reduction of nitroalkanes in hydrochloric acid is probably the method of choice for the preparation of alkylhydroxylamines; evaporation of the catholyte after reduction yields the alkylhydroxylamine hydrochloride in a rather pure form [6]. In Table 1 the yields of alkylhydroxylamines and amines from the reduction of some nitroalkanes are given.

A small amount of alkylamine and of a carbonyl compound is formed during the reduction. The hydroxylamine is not reduced to amine under these conditions. Reduction of *N*-methylhydroxylamine [8] has been attempted at −1.15 V (SCE) in hydrochloric acid at 20–30°C for 16 h. Hydrogen was evolved, but no methylamine was detected. Equation (1) has been suggested to explain the side products obtained [7,8]:

$$\underset{\text{(I)}}{RR'CHNO_2} \xrightarrow[2e+2H^+]{H^+} \underset{\text{(II)}}{[RR'CHNO]H^+} \xrightarrow{2e+2H^+} \underset{\text{(III)}}{RR'\overset{+}{C}HNH_2OH}$$

$$\downarrow$$

$$\underset{\text{(IV)}}{[RR'C{=}NOH]H^+} \xrightarrow{4e+4H^+} RR'\overset{+}{C}HNH_3 \qquad (1)$$

$$\downarrow H_2O$$

$$RR'CO + H_3\overset{+}{N}OH$$

Table 1 Results from Electrolytic Reduction of Nitroalkanes at 20°C

R	Amount of RNO_2 (g)	Analysis of catholyte			Current yield (%)	% Isolated RNNOH
		% RNNOH	% RNH_2	% RNO_2		
Me	28.2	89	3.6	1.2	92.6	77
Et	31.1	82	9.9	0.8	92.9	59
1-Pr	40.1	83	5.9	1.2	91.6	62
2-Pr	39.7	86	4.6	0.8	90.5	81

Source: From Ref. 6.

It has been recommended that one reduce nitromethane to methylhydroxylamine in dilute hydrochloric acid at constant current in a divided filter press cell with a nickel, stainless steel, or Monel 400 cathode; unreacted nitromethane was distilled off and the water removed at 30 mm Hg at $t < 50°C$ to avoid decomposition [9].

The tautomerization of the nitroso derivative (II) to the oxime (IV) competes with the further reduction, and any parameter that retards the competing chemical reaction raises the yield of the alkylhydroxylamine (III). An increase in temperature would be expected to favor the tautomerization reaction compared to the further reduction, and reduction at a low temperature would thus be essential for the preparation of alkylhydroxylamines.

Accordingly, it has been found that α-hydroxynitroalkanes at 65–86°C are reduced to the amino alcohols [10], whereas at 0–35°C the hydroxylamino alcohol is the product [11].

α-Nitrobenzylic compounds may be converted into the corresponding oximes on reduction in protic medium; the simultaneously formed hydroxylamine may be oxidized to the oxime by iodine. The yields are best if an electron-attracting group is substituted in the ring or at the benzylic carbon; the substituent stabilizes the intermediate benzyldihydroxylamine [12].

The electrochemical reduction of suitable nitro compounds in aqueous methanolic hydrochloric acid has been used for the preparation of β-hydroxylaminoalkylphosphoryl compounds [$HONHCH_2CHR\text{-}P(O)R^1R^2$ [13].

In aqueous alkaline solution of low ionic strength the transformation of a nitroalkane into the irreducible anion is sufficiently slow to allow cyclic voltammetry of the nitroalkane. It has been shown [14] that the reduction occurs in two steps, the first one leading to the radical ion.

In nitroalkanes substituted α to the nitro group with an irreducible electron-attracting group, the α-hydrogen dissociates more easily, and the rearrangement (II)→(IV) proceeds at a higher rate; a relatively high proportion of amine must thus be expected. Thus, whereas a single carboxylic ester or sulfamido group α to the nitro group [15–17] sometimes (but not always) makes the α-hydrogen too labile for the electrolytic preparation of the hydroxylamine, the presence of two carboxylic ester groups always does. It has thus been impossible to prepare 2-hydroxylaminomalonic ester by reduction of the nitro compound. The reduction of 2-nitro-2-alkylmalonic esters, however, produces the expected 2-alkyl-2-hydroxylaminomalonic ester on reduction [18]; here the tautomerization to the oxime is excluded as no α-hydrogen atoms are available.

Ethyl nitroacetate is a relatively strong acid ($pK_A(H_2O) = 5.75$, pK_A (DMSO) = 9.2); it may be deprotonated by $O_2^{-\cdot}$ formed on reduction of dioxygen in air-saturated MeCN. The anion is useful in several kinds of synthesis. Direct reduction of ethyl nitroacetate produces some anion, but also some cleavage with formation of nitrile [19].

Electrolysis of pure nitromethane with an Ni cathode and a sacrificial Mg anode produces the anion of nitromethane, which may be useful in many addition reactions. If nitromethane in MeCN is reduced, the yield of addition products is low [20].

Protonation of the anion of the *aci* form, the nitronate anion, takes place at the highest rate on the oxygen; the *aci* form is unstable and either tautomerizes to the nitroalkane or is hydrolyzed to a carbonyl compound and N_2O. The reduction of an *aci* nitro compound, prepared from the anion, is thus generally difficult to study, but its polarographic behavior can be investigated during the reduction of α-halonitroalkanes.

9-Nitrofluorene anion, however, may be acidified to the relatively stable *aci* form, which in acid solution is reduced to 9-aminofluorene; in dimethyl formamide (DMF), CV

shows the reduction to fluorenone oxime and further reduction through the imine to 9-aminofluorene [21].

Anodic oxidation of the nitroalkane anion to a radical may lead to dimerization [22], addition to unsaturated systems [23], or substitution in aromatic compounds [24]; these reaactions are treated in Chapter 22.

2. Tertiary Nitroalkanes

These compounds differ from the primary and secondary nitroalkanes in that the intermediate nitroso derivative cannot rearrange into an oxime and this side reaction is avoided. The yield of alkylhydroxylamine is thus high. A small amount of amine (< 3%) is, however, usually found [8], but it is not yet clear how this is formed.

The nitroso intermediate can in this case be detected directly in the reduction mixture by its bluish green color and its polarographic wave; the nitroso compound is, as most other nitroso derivatives, more easily reducible than the corresponding nitro compound.

In nonaqueous aprotic solvents, such as dimethoxyethane [25] or acetonitrile [26,27], the reduction product from tertiary nitroalkanes is the radical anion. Cyclic voltammetric data of 2-nitro-2-methylpropane showed that the electrochemical rate constant was rather low and depended on the size of the supporting electrolyte cation; the electrochemical transfer coefficient α was found to be potential dependent [28]. The nitro-*t*-butyl radical anion is rather unstable (half-life of 0.66s) and decomposes into nitrite ion and *t*-butyl radical. Continued electrolysis results in the formatrion of di-*t*-alkyl nitroxide radical [25,27].

$$R_3CNO_2 \xrightarrow{e^-} R_3CNO_2^{\cdot -} \longrightarrow R_3C^{\cdot} + NO_2^- \qquad (2)$$

$$R_3C^{\cdot} + R_3CNO_2^{\cdot -} \longrightarrow (R_3C_2)_2NO_2^- \xrightarrow{+H^+} (R_3C)_2\dot{N}O + {}^{\cdot}OH$$

In acid solution the primary step is probably also formation of a radical anion, but in this medium the latter is protonated and further reduced more rapidly than the decomposition of the radical anion; in more acidic solution a preprotonation may take place.

3. α-β-Unsaturated Nitro Compounds

The reduction of an α,β-unsaturated nitro compound [29], such as β-nitrostyrene (V), occurs in two steps. The first reduction of (V) is a four-electron reaction that yields phenylacetaldoxime (VI); the reaction has been formulated as a reduction of the nitro group followed by a rearrangement of the unsaturated hydroxylamine (VII), but might also be regarded as a 1,4-reduction of the intermediate unsaturated nitroso compound. There is no conclusive evidence for either route, but the former has been chosen here, as the protonation of the heteroatom would be expected to be faster than protonation of the carbon atom:

$$\underset{\text{(V)}}{C_6H_5CH{=}CHNO_2} \xrightarrow[-H_3O]{4e^- + 4H^+} \underset{\text{(VII)}}{C_6H_5CH{=}CHNHOH} \longrightarrow \underset{\text{(VI)}}{C_6H_5CH_2CH{=}NOH} \qquad (3)$$

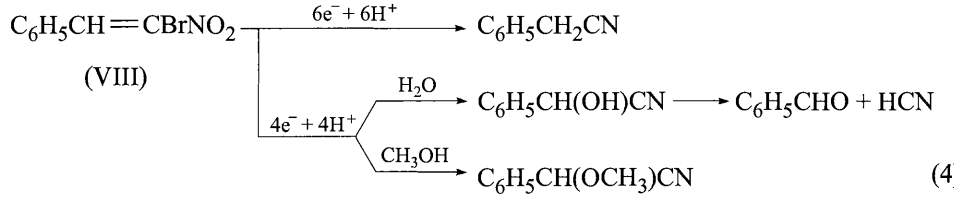
Reduction in acid solution of nitroalkenes prepared from carbonyl compounds and nitroalkanes has been employed for the synthesis of oximes and carbonyl compounds [30–32] with a longer carbon chain.

The reduction of derivatives of α-nitroacrylic acid to amino acids follows a similar route; the amine seems for α-nitro carboxylic acids to be formed partly through the oxime and partly, at a more negative potential, through another intermediate [33].

Reduction of 1-nitro-1-alkenes in DMF in the presence of $TiCl_4$ affords nitriles in good yield; this is a method to transform aldehydes to one-carbon elongated nitriles through reaction with nitromethane [34].

4. α-Substituted α, β-Unsaturated Nitroalkanes

β-Bromo-β-nitrostyrene (VIII) [35] gives a six-electron polarographic wave at about the same potentials as β-nitrostyrene (V), but the wave of VIII is not followed by a second wave as is the wave of V. Reduction of VIII in 0.6 N H_2SO_4 containing dioxane at E −0.4 V yielded benzyl cyanide and some benzaldehyde; if the reduction was performed in aqueous methanol, some $C_6H_5CH(OCH_3)CN$ was formed. Polarographic data for the nitrile oxide, $C_6H_5CH_2CNO$ [36,37], show that this compound is not an intermediate in the reduction:



(4)

The reduction mechanism is not fully elucidated [38].

A similar reduction route is found for the reduction of β,β-dinitrostyrene.

5. α-Substituted Nitroalkanes

Substituents at the α-carbon atom of nitroalkanes may influence their electrode reactions considerably. The influence of electronegative groups on the rate of the nitroso to oxime transformation was mentioned. If an electronegative group is a good leaving group, it may be reductively removed; substituents of this type are halogens and nitro groups. When a nitro group is reductively lost as a nitrite ion, a further reaction between nitrous acid and a suitable substrate must always be considered a side reaction.

6. Polynitroalkanes

2,2-Dinitropropane is in alkaline solution reduced in a two-electron reaction [39–42] to 2-nitropropane anion; in slightly acid solution the nitronic acid is reduced to acetone oxime. 1,1-Dinitroethane behaves differently, and a wave height corresponding to n=5–6 is found in acid solution. The following explanation has been suggested [38]:

$$CH_3CH(NO_2)_2 \xrightarrow{2e^-} CH_3CH{=}NO_2^- + NO_2^- \xrightarrow{2H^+} CH_3CH{=}NO_2H + HNO_2 \longrightarrow$$

$$CH_3C(NO_2){=}NOH \xrightarrow{4e^- + 4H^+} CH_3C(NHOH){=}NOH \qquad (5)$$

(IX) (X)

Radical anions of geminal nitro compounds in DMF cleave rapidly to nitrite and a radical which initiate a free radical chain in which a *vic*-dinitro compound is formed [43]. Radical anions of other α-substituted nitroalkanes may cleave either the nitro group or the other substituent; 1-cyano-1-nitrocyclohexane thus splits off nitrite whereas 1-nitrocyclohexyl p-tolyl sulfone loses p-tolylsulfinate [44].

The ethyl nitrolic acid (IX) has been shown [45] to be electrolytically reducible to *N*-hydroxyacetamidoxime (X), which can be oxidized anodically to ethyl nitrosolic acid. In alkaline solution ethyl nitrolic acid (IX) forms an azo derivative (XI) [46] in low yield according to:

$$CH_3C(NOH)NO_2 \xrightarrow{4e^- + 4H^+} \tfrac{1}{2}CH_3C(NOH)N{=}NC(NOH)CH_3 \qquad (6)$$

(IX) (XI)

Tetranitromethane [47,48] is reduced polarographically to trinitromethane; this is, in turn reduced at pH 6 to the rather unstable dihydroxyguanidine [41], which in alkaline solution is rearranged and further reduced to hydroxyguanidine.

7. Pseudonitroles

In pseudonitroles, such as 2-nitro-2-nitrosopropane [42], the first reduction in acid solution is a two-electron reaction that results in the loss of the nitro group as a nitrite ion. Protonation of the primarily formed anion on oxygen forms an oxime:

$$(CH_3)_2C(NO)NO_2 \xrightarrow{2e^-} NO_2^- + [(CH_3)_2CNO]^- \xrightarrow{H^+} (CH_3)_2C{=}NOH \qquad (7)$$

8. Halogenated Nitroalkanes

The halogen atom in α-halogenated nitroalkanes is generally removed at a less negative potential than that necessary for the reduction of the nitro group [42,49]; thus, controlled potential reduction of 2-chloro-2-nitropropane (pH 0.25; E -0.6V, t = 10°C) gave acetone in 98% yield [42], formed by hydrolysis of the nitrolic acid.

1-Bromo-1-nitroethane (XII) shows three polarographic waves in acid solution. The half-wave potential of the first wave is pH independent, and the third wave corresponds to a reduction of acetaldoxime [42]. A reduction at a potential corresponding to the second polarographic wave yielded 60% acetaldoxime and 30% acetaldehyde:

$$\text{First Wave}: \quad CH_3CHBrNO_2 \xrightarrow{2e^-} CH_3CH{=}NO_2^- + Br^- \xrightarrow[H^+]{\text{slow}} CH_3CH_2NO_2 \qquad (8)$$

(XII)

$$CH_3CH{=}NO_2^- \xrightarrow{H^+,\ \text{fast}} CH_3CH{=}NO_2H$$

(XIII)

Second Wave: $CH_3CH{=}NO_2H \xrightarrow{2e^- + 2H^+} CH_3CH{=}NOH + H_2O$ (9)

Third Wave: $CH_3CH{=}NOH \xrightarrow[4e^- + 4H^+]{H^+} CH_3CH_2\overset{+}{N}H_3 + H_2O$ (10)

The second wave thus indicates the electrolytic behavior of a nitrolic acid (XIII).

A similar reduction route is found for dihalogenated nitroalkanes such as 1,1-dichloro-1-nitroethane [42]. This compound shows two polarographic two-electron waves. The second wave does not correspond to the reduction of 1-chloro-1-nitroethane, which is the isolated product from a controlled potential reduction (E −0.2V, pH 1) at the potential of the first wave, but rather to a reduction of a chloronitrolic acid, $CH_3CCl{=}NO_2H$. Accordingly, a reduction at the plateau of the second wave (E −1.0V, pH 0.2, t = 5°C) produced chloroacetaldoxime, which was further characterized by its transformation into acetonitriloxide at pH 6.

In aprotic medium reduction of α-halogenated nitroalkanes may yield dimers: 2-chloro-2-nitropropane thus yields 2,3-dimethyl-2,3-dinitrobutane [50] in good yield. The reaction has been suggested to be a two-electron reduction to the anion, which in a nucleophilic reaction attacks the substrate.

The reduction of trichloronitromethane may give methylamine [51] or methylhydroxylamine [52], but by working with a cooled tin cathode in 35% sulfuric acid at t < 5°C it was possible to obtain dichloroformoxime [53] as a product. By employing a suitable extraction procedure the yield of this compound could be raised [54].

A polarographic investigation of trichloronitromethane [42] shows a stepwise removal of chlorine under these conditions before the reduction of the nitro group occurs. Whether the difference in reduction path reflects the difference in the electrode material, electrode potential, or medium is not known.

Fluorotrinitromethane is in the first step reduced to fluorodinitromethane, which in turn is reduced to fluoronitromethane [55,56]; on reduction at the first step [57], chlorotrinitromethane is mainly reduced to chlorodinitromethane, whereas the main product from bromotrinitromethane is trinitromethane.

9. Nitrohydrazones

The phenylhydrazone of nitroacetaldehyde (XIV) [58] gives at all pH values a single polarographic wave with a height corresponding to n = 2.9–3.5 Electrolysis of the compound in 0.05N sulfuric acid (E −0.9V) consumed 3.7 F/mol, and the hydrazooxime (XV) was detected as product by its anodic wave, which is caused by a two-electron oxidation to the azooxime (XVI):

$$\underset{\text{(XIV)}}{CH_3C(NO_2){=}NNHC_6H_5} \xrightarrow[-H_2O]{2e^- + 2H^+} \underset{\text{(XVI)}}{[CH_3C(NOH)N{=}NC_6H_5]} \quad (11)$$

$$2e^- + 2H^+ \left\downarrow \right. \quad \left. \uparrow \right\rfloor -2e^- - 2H^+$$

$$\underset{\text{(XV)}}{CH_3C(NOH)NNHC_6H_5}$$

In *N*-nitro hydrazones the nitro group is first reduced to a hydroxylamine before the hydrazone is reduced [59].

The corresponding hydrazooxime, obtained by reduction of the nitrohydrazone $O_2NC_6H_4NHN{=}C(NO_2)C_6H_5$ from benzaldehyde and *o*- or *p*-nitrophenylhydrazine, is further reducible [60a] to the amidrazone; this is in analogy with the finding that benzamidoxime is reducible to benzamidine [60b].

10. β-Substituted Nitro Compounds

The polarographic behavior of β-hydroxynitroalkanes is sometimes complicated in acid solution by the dehydration to the more easily reducible nitroalkene [61,62]. Nitroalkenes are also obtained from α,β-dibromonitroalkanes on reduction [35]. Reduction in DMF of acylated β-hydroxynitroalkanes produces alkenes [63]; vicinal dinitroalkanes are reduced similarly [64].

Reduction of α-nitro-β-hydroxybutyric acid to D,L-threonine [65] and similar reactions [33,66] have been investigated for the preparation of amino acids. The reduction to amine passes predominantly through the hydroxylamino derivative and only to a smaller degree through the oxime.

2,3-Dinitroalkenes-2 like 2,3-dinitrobutene-2 show [67] a two-electron polarographic wave at all pH values. In acid solution it is followed by another wave. A preparative reduction also indicates n = 2 and a mixture of 2-nitro-2-butene and diacetylmonoxime is the product in acid solution, whereas the former is the major product at higher pH. At pH 6 the reaction is

$$\begin{array}{l} CH_3{-}\underset{\displaystyle NO_2}{\underset{|}{C}}{=}\underset{\displaystyle NO_2}{\underset{|}{C}}{-}CH_3 \xrightarrow{2e^- + H^+} CH_3{-}\underset{\displaystyle NO_2^-}{\underset{\|}{C}}{-}\underset{\displaystyle NO_2H}{\underset{\|}{C}}{-}CH_3 \longrightarrow \\ \\ CH_3\underset{\displaystyle NO_2^-}{\underset{\|}{C}}{-}CH(NO_2)CH_3 \longrightarrow CH_3C(NO_2){=}CHCH_3 + NO_2^- \end{array} \qquad (12)$$

In β-carbonylnitroalkanes the nitro group is more easily reducible than the carbonyl group [68,69], whereas in 2-bromo-2-nitroacetophenone [68] the bromine is most easily reduced. A pH < 5, 2-nitroacetophenone shows a kinetic polarographic wave followed by another wave; the sum of the waves corresponds to n = 4. The kinetic wave is unusual in that its height grows with pH. The explanation is that the more easily reducible species is the enolate, which is favored by a higher pH; at low pH the nitro ketone is reduced as in:

$$C_6H_5COCH_2NO_2 \rightleftharpoons C_6H_5C(OH){=}CHNO_2 \xrightarrow[-H_2O]{4e^- + 4H^+} [C_6H_5COCH_2NHOH] \qquad (13)$$

The product from the electrolysis has not been identified; possibly a condensation of a primarily formed ketoalkylhydroxylamine to a pyrazine derivative takes place.

The polarographic behavior of some β-nitrooximes has been investigated [69,70] but the reduction is not fully elucidated. Reduction of *trans*-chloro-(2-nitrocyclohexyl)mercury yields cyclohexene in a two-electron reduction [63].

B. Nitroso Compounds

Aliphatic primary and secondary nitroso compounds are not stable but tautomerize to oximes. In nitrosocyclohexane the special steric conditions favor a dimerization rather than a tautomerization. The dimer is reduced polarographically in a six-electron reaction to *N*,*N*′-dicyclohexylhydrazine [71]. Aliphatic *t*-nitro compounds are dimers in the solid state, but dissociates in solution to a degree depending on the solvent; the monomer is easier reducible than the dimer [72]. Only the monomer reacts as a spin trap; the rate constant for the dissociation in MeCN is $1.5 \times 10^{-3} s^{-1}$ [72a].

Tertiary nitroso compounds are stable and are generally reduced similarly to the corresponding nitro compound, but somewhat more easily. The reduction of mono- and dihalogenated nitrosoalkanes also goes analogously to that of the corresponding nitroalkanes; thus 2-chloro-2-nitrosopropane [42] gives acetoxime on reduction (pH3, E – 0.5V) in 98% yield:

$$(CH_3)_2CClNO \xrightarrow{2e^-} [(CH_3)_2CNO^- + Cl^- \xrightarrow{H^+} (CH_3)_2C{=}NOH \tag{14}$$

and 1,1-dichloro-1-nitrosoethane produces chloroacetaldoxime in 76% yield on electrolytic reduction.

Oximes are tautomeric with nitroso compounds. Oximes are generally reduced to amines in a reaction in which the N–O bond is cleaved before the hydrogenation of the C=N double bond occurs. In acid solution the reaction is as in Eq. 15 [60]:

$$RR'C{=}NOH \overset{H^+}{\rightleftharpoons} [RR'C{=}NOH]H^+ \xrightarrow[-H_2O]{2e^- + 2H^+} RR'C{=}\overset{+}{N}H_2 \xrightarrow{2e^- + 2H^+} RR'CH\overset{+}{N}H_3 \tag{15}$$

The reduction of oximes is discussed Chapter 11.

C. Alkylhydroxylamines

Aliphatic hydroxylamines are not easily reduced electrolytically. The polarographic wave of such compounds is not well defined and is visible only in a narrow pH region, around pH 7. In acid solution the wave is masked by hydrogen evolution, and the hydroxylamines are catalytically active in that reaction. It has been suggested [73] that a branching in the reaction takes place after the uptake of the first electron, which leads either to a further reduction of the radical or to hydrogen evolution:

$$RNHOH + H^+ \rightleftharpoons R\overset{+}{N}H_2OH \xrightarrow{e^-} R\dot{N}H_2OH$$

$$R\dot{N}H_2OH \begin{cases} \xrightarrow{e^-} RNH_2 + OH^- \\ \xrightarrow{H^+ + e^-} RNHOH + H_2 \end{cases} \tag{16}$$

In acid solution the catalytic reaction is fast and only traces (if any) of amine are formed on reduction. Possibly by lowering the cathode potential and allowing a copious evolution of hydrogen, more amine could be obtained [74]. Alkylhydroxylamines are, however, reducible [75] to amines by electrolytically generated Ti^{3+} or Fe^{2+}.

Alkylhydroxylamines give a well-defined anodic wave in alkaline solution [6,76]. Anodic oxidation of hexafluorodimethylhydroxylamine to the stable free radical, hexafluorodimethyl nitroxide, is a convenient way of preparing this radical [77]. Dialkylhydroxylamines may be oxidized to nitrones by electrogenerated "I^+" in methanol using constant current [78]; paired synthesis can be used [79].

D. Azoxy and Azo Compounds and Hydrazines

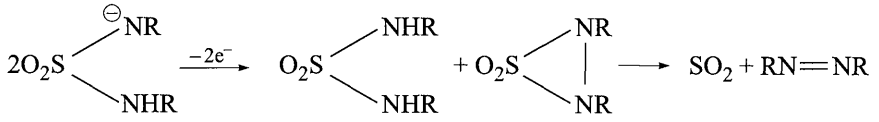
Aliphatic azoxy compounds may be prepared from nitroalkanes by electrolytic reduction to alkylhydroxylamines as described earlier followed by anodic oxidation in alkaline solution. Azoxymethane and azoxycyclopropane have been prepared by this method [80].

Another method is the reduction of aliphatic azodioxy compounds [81], obtained by addition of nitrosyl chloride to alkenes, to azoxy compounds.

Reduction of aliphatic azoxy compounds gives the symmetrical hydrazines in good yield. This makes it possible to prepare such hydrazines from nitroalkanes in a three-step synthesis by reversing the current twice but without isolating the intermediates [80].

$$\begin{array}{l} RNO_2 \xrightarrow[-H_2O]{4e^- + 4H^+} RNHOH \xrightarrow{-2e^- - 2H^+} [RNO] \xrightarrow[-H_2O]{RNHOH} \\ \qquad\qquad\qquad\

Anodic oxidation of the anions of *N,N'*-dialkylsulfamides in methanol at carbon or platinum anodes yields azoalkanes according to [84]:



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XVII

A phosphorus analog of aliphatic azo compounds, bis[tris-(trimethylsilyl)methyl]diphosphene, $(Me_3Si)_3C{-}P{=}P{-}CSiMe_3$, shows a rapid reversible one-electron reduction to its radical anion at a mercury-coated platinum electrode in DME, MeCN [85], or THF [86]. The arseneous analog is reduced similarly [86] at a potential about 0.5V less negative; the anion radical is less stable than that of the phosphorus compound.

Aliphatic diazo compounds are discussed in Chapter 11.

E. Nitric Acid Esters

Such esters are reduced polarographically in a pH-independent two-electron wave to nitrite ion and alcohol [87]:

$$R{-}O{-}NO_2 \xrightarrow{2e^-} RO^- + NO_2^- \xrightarrow{H^+} ROH \qquad (20)$$

In DMF, CV of benzyl nitrate gives an irreversible peak followed by a peak of one of the products, benzaldehyde, the other products being benzyl alcohol and nitrite. The primarily formed anion radical loses nitrite, and the benzyloxy radical abstracts a hydrogen atom, presumably from the substrate or another benzyloxy radical [88].

III. AROMATIC NITRO COMPOUNDS AND DERIVATIVES

Numerous investigations [1] have been made on the reduction of aromatic nitro compounds and a number of different reaction products have been obtained. This is caused more by differences in the chemical follow-up reactions rather than by the electrochemical steps.

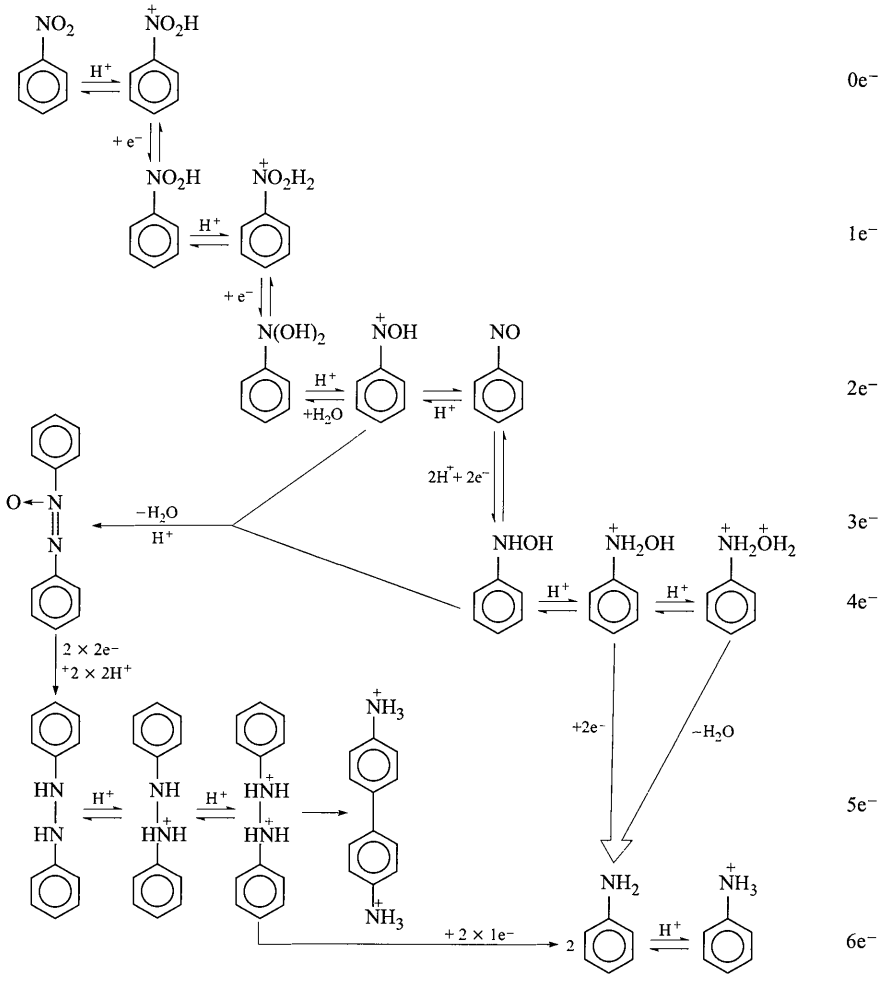
The transfer of the first electron to a nitrobenzene in an aprotic solvent produces a radical anion. In the radical anion of an aliphatic nitro compound the charge on the nitro group is virtually unity, whereas in the radical anions from nitrocyclopropanes [89], nitroolefins [89,90], and nitrobenzenes [91–93], a certain delocalization of the charge occurs according to electron spin resonance (ESR) measurements. The degree of localization in the aromatic ring can be varied, particularly by twisting the nitro group out of the plane of the ring by introducing suitable substituents.

A. Mononitrobenzenes

Nitrobenzene is reduced in aqueous medium at mercury and gold at low pH in two waves, and at high pH in one wave [94]. In CV in neutral buffer is found a four-electron reduction peak to phenylhydroxylamine, which on the anodic sweep is oxidized to nitrosobenzene; on the second cathodic sweep the reduction of nitrosobenzene is observed. The response at

glassy carbon is qualitatively similar, with a shift in the potentials, and at platinum no peak was observed before the discharge of protons [95]. The two-electron reduction to a dihydroxylamine has been described by a nine-membered square scheme [96] showing electron and proton transfers and cleavage/formation of bonds.

In the presence of a neutral or cationic surfactant or a higher concentration of alcohol the first wave in polarography is a four-electron wave and the second one a two-electron reduction [94,97]. In the absence of surfactants the first wave corresponds to $4 < n < 5$, but the sum of the first and second wave remains constant. This has been interpreted as resulting from two competitive reduction routes, one of them being a four-electron reduction to phenylhydroxylamine and further reduction to aniline at a more negative potential, and the other one going through a coupling occurring at the surface of the electrode between a protonated nitrosobenzene and phenylhydroxylamine to azoxybenzene and further reduction of this compound. The polarographic reduction of nitrobenzene has been represented by Scheme 1 [94].



Scheme 1

CV of 4-nitropyridine shows a similar pattern [96]. The current consists of two parts, a surface redox current and a diffusion controlled current; the latter is dominant at slow sweep rate whereas the former becomes important at fast sweep rates. The reduction path is illustrated by a bicubic reaction diagram.

CV of nitrobenzene in the presence of sodium dodecylsulfate or high concentrations of DMF gives a one-electron peak followed by a three-electron peak, whereas in the presence of cationic or neutral surfactants a four-electron wave is found at the hanging mercury electrode. [97].

There has been some discussion about the detailed mechanism of the reduction of aromatic nitro compounds. In acid solution the slow step in the four-electron reduction has been found [96,98] to be the uptake of the second electron, the reduction of $ArNO_2H^{\cdot}$ to the dihydroxylamine, $ArN(OH)_2$. According to some authors, $ArNO_2H^{\cdot}$ [96,98,99] is formed on protonation of the radical anion, but there are also strong proponents for its formation by electron transfer to a preprotonated nitro compound [100,101]. In water the pK_A of the protonated radical anion, $ArNO_2H^{\cdot}$, for most aromatic nitro compounds, is between 2 and 4 [102].

The rate of the dehydration of the irreducible dihydroxylamine to the nitroso compound depends on the electron-attracting properties of the aryl group; thus the aryldihydroxylamine can be detected experimentally when Ar is an electron attracting group as protonated pyridyl or *p*-nitrophenyl [103]. The electron-attracting group helps to stabilize the hydrated form just as in the case of hydrated aldehydes.

At catalytic active electrodes, such as Devarda copper, Raney nickel or copper preoxidized to $Cu(OH)_2$, nitrobenzene can be reduced to aniline in good material and current yield [104].

In preparative reductions, higher concentrations of organic solvents and/or substrate are present and the surface reaction, the coupling, would not be expected to play a prominent role in acid solution. A reduction at a potential of the first wave would thus result in the formation of a species, here represented by $[C_6H_5\overset{+}{N}H_2OH]$ (XVIII) at the electrode surface, and the diversity of products obtained can be explained by the reactivity of XVIII. The different reaction paths open to XVIII and the products resulting from these processes are discussed later.

In acidic solution in the presence of an arenesulfinic acid, the nitrosoarene adds the sulfinic acid in preference to water [105]; the addition product is stable toward further reduction and oxidation and the arenesulfinic acid may thus be used as a protecting group during the reduction of a nitro compound and during an oxidation of a hydroxylamine to a nitroso compound, thus avoiding the formation of azoxycompounds. The protecting group may be removed by alkaline hydrolysis.

In aprotic solvents, such as DMF [106] and ammonia [107], nitrobenzene is reduced reversibly to the radical anion and at a more negative potential to the dianion; in the absence of electrophiles the dianion is stable, but if impurities are present, the second wave becomes irreversible. In some cases the radical anion of a nitroarene may dimerize; 9-nitroanthracene radical anion dimerizes thus to the dianion of 9,9′-dinitro-9,9′,10,10′-tetrahydro-9,9′-biantryl [108]. Radical anions of nitroarenes may be used as electron transfer reagents (Chapter 29).

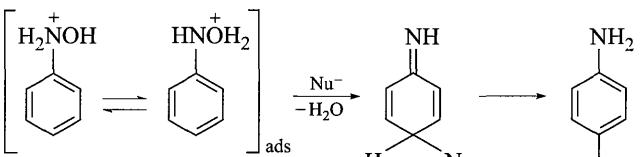
1. Desorption

When the electrode potential is such that a further reduction is excluded and no catalyst is present to promote a dehydration reaction, the phenylhydroxylamine is obtained by

desorption of the four-electron reduction product. The medium of choice should have pH 3–9 and not contain strong nucleophiles; a mixture of ammonia and ammonium chloride [109] or an acetate buffer [110] is often suitable. The electrode material is of minor importance as long as the cathode potential is controlled in some way; the pH must not be too low as rearrangements occur or too high as azoxybenzene then is formed. The temperature must be kept low.

2. Substitution

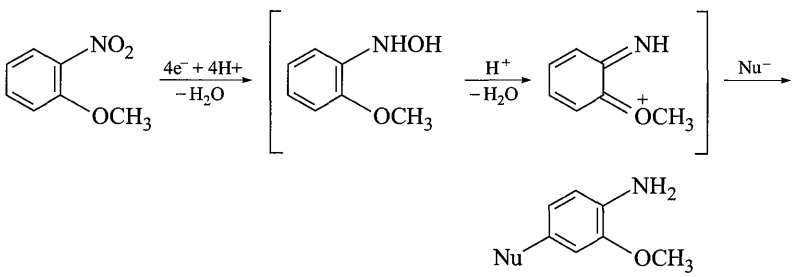
In strongly acid solution, different substitution reactions may occur; the reduction product XVIII, protonated on nitrogen and/or oxygen, has a tendency to lose water, and this loss may be assisted by the attack of a nucleophile on the aromatic ring. Whether the loss of water occurs before the attack by the nucleophile or in a concerted reaction is not known yet. Any species that can act as a nucleophile in the strongly acidic solution may be employed for this kind of cathodic substitution reaction. The reaction may be represented by Eq. (21):



(XVIII) (21)

It is well known that phenylhydroxylamine is similarly rearranged in acid solution, but the rate is somewhat slower than that occurring during the electrolytic reduction. This finding has been expressed here by representing the four-electron reduction product as adsorbed phenylhydroxylamine.

In the reduction of nitrobenzene in 4N hydrochloric acid, a mixture of *p*- and *o*-chloraniline and *p*-aminophenol in the proportion 3:1:1 is found [111,112]; in sulfuric acid the hydrogen sulfate ion is too weak a nucleophile to compete with the water as nucleophile and the resulting product is *p*-aminophenol. Substituents capable of delocalizing the positive charge left by the loss of water from the protonated reduction product (in the position *ortho* to the hydroxylamine group) greatly facilitate the attack *para* to the hydroxylamino group. The methoxy group is excellent in this respect and *o*-nitroanisole is easily substituted cathodically:



(22)

The electrolytic preparation of *p*-aminophenol was first studied by Gattermann [113]. A wide variety of conditions for the reaction has been described in different patents [114] and the reaction is still under study [115–117]. The reaction is usually run in a fairly strong sulfuric acid at an elevated temperature; if ethanolic sulfuric acid is used, *p*-phene-

tidine is the product [118]. The electrochemical preparation of *p*-aminophenol ought to be competitive with the chemical reaction.

A complication for the preparation of *p*-aminophenol (XIX) from phenylhydroxylamine, regardless of how the latter is prepared, is that XIX may act as a nucleophile in competition with water with the formation of 4,4′-diaminodiphenyloxide (XX) [119]; the yield of XX increases with increasing concentrations of XIX. XX is carcinogenic and must be removed carefully from pharmaceutical preparations of XIX to *N*-acetyl-4-aminophenol, paracetamol.

When a substituent is *para* to the hydroxylamino group, an *ipso* substitution may take place; this may result in a loss of the substituent or a rearrangement.

A loss of substituent is found when X=−Cl [120] or −OCH_3 [121,122] and has also been reported to occur during the reduction of *p*-nitrobenzoic acid in strong sulfuric acid [123].

p-Nitrotoluenes may form different products. In 25% sulfuric acid at 90°C, *p*-nitrotoluene is reduced with four electrons and the product is 2,5-dihydroxytoluene [120]. A similar reaction was found in the reduction of 2-methyl-5-nitrobenzoic acid.

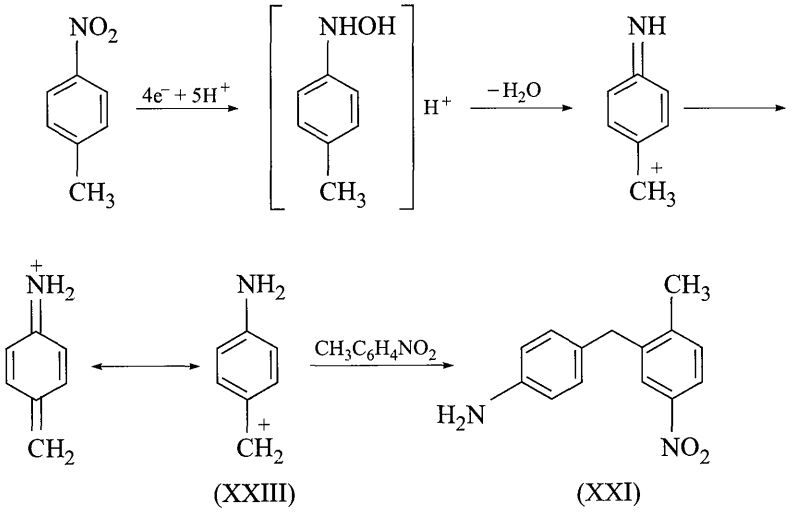
p-Methylthionitrobenzene is reduced to the hydroxylamine, which may react in the usual ways; besides those already discussed a rearrangement of the *p*-methylthiophenylhydroxylamine to *p*-aminophenylmethylsulfoxide [124,125] may take place (yield 35–40%):

$$CH_3SC_6H_4NHOH \xrightarrow{[H^+]} CH_3SOC_6H_4NH_2 \qquad (23)$$

3. Side-Chain Reactions

p-Alkyl nitroarenes may on reduction lose a proton from the side chain either during the acid-catalyzed rearrangement of the arylhydroxylamine or from the parent compound, from which an electrogenerated base (EGB) may abstract one of the relatively acidic protons α to the nitroaryl.

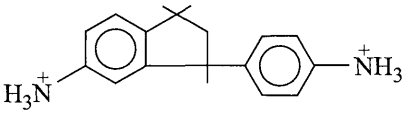
In concentrated sulfuric acid *p*-nitrotoluene is reported to give 4-amino-2′-methyl-5′-nitrodiphenylmethane (XXI) [113,126], which has been verified [127]. Gattermann and Koppert [126] suggested that the primarily formed *p*-tolylhydroxylamine rearranged into *p*-aminobenzyl alcohol (XXII), which then attacked unreduced *p*-nitrotoluene. It seems more likely that the intermediate is a carbocation (XXIII), which on addition of water would form XXII, and on addition to *p*-nitrotoluene would give XXI:



(XXIII) (XXI) (24)

The electrophilic reqgent (XXIII) may attack any aromatic compound present [127]; when this is too reactive, it may, however, be attacked by the solvent rather than by XXIII.

An analogous reaction occurs during the reduction of 4-nitroisopropylbenzene in sulfuric acid, which in a four-electron reduction forms 5-amino-3-(4-aminophenyl)-1,1,3-trimethylindan (XXIV); the initially formed phenylhydroxylamine loses water to the equivalent of *p*-amino-α-methylstyrene, which dimerizes to the indan derivative [127].



(XXIV)

The reduction of *o*- and *p*-nitrotoluene and *p*-ethylnitrobenzene in DMF in the presence of dioxygen to *o*- and *p*-nitrobenzoic acid and *p*-nitroacetophenone plus 1-(*p*-nitrophenyl)ethanol, respectively, has been suggested [128] to proceed via a proton or hydrogen atom abstraction from the side chain followed by reaction of this species with superoxide ion and/or dioxygen to the isolated products.

A similar EGB-induced reaction may take place during the reduction of *o*-nitrotoluene in DMF in the presence of paraformaldehyde to 2-(2-nitrophenyl)ethanol and 2-(2-nitrophenyl)propane-1,3-diol [129].

4. Condensation Reactions

Phenylhydroxylamine may act as a nucleophile toward any electrophilic center present. As it is the unprotonated phenylhydroxylamine that acts as a nucleophile, a lowering of pH will diminish the concentration of the nucleophile; a higher acidity may, however, make the electrophilic center more reactive, so the overall effect of a change in pH is a function of the properties of both centers.

Nitrosobenzene may act as an electrophilic center, and in alkaline solution phenylhydroxylamine reacts with it with formation of azoxybenzene [130–132]. The reaaction may go through an initial, homogeneous one-electron transfer followed by a radical coupling [132]. This reaction occurs generally during the reduction of simple nitrobenzenes in alkaline solution and makes azo and hydrazobenzenes as well as benzidines easily available. Azoxybenzenes may, however, also be formed in acid solution [94,104,121]:

$$2C_6H_5NO_2 \xrightarrow[-2H_2O]{6e^- + 6H^+} [C_6H_5NO + C_6H_5NHOH] \longrightarrow C_6H_5\overset{+}{N}(O^-)=NC_6H_5 + H_2O \tag{25}$$

The preparation of azoxy compounds is possible under a variety of conditions, and a number of patents [133] have been issued covering these processes. The yields are generally fair to good (40–90%); substituents *ortho* to the nitro group retard the formation of azoxybenzenes. A rotating cathode has been employed for this reaction [134,135].

An intramolecular azoxy coupling has been used for the preparation of heterocyclic compounds; this aspect is treated in Chapter 18.

Carbonyl groups react readily with phenylhydroxylamine, and this reaction, in which nitrones are formed, may be used to trap the intermediate phenylhydroxylamine [136]. The reaction may take place intramolecularly with the formation of a heterocyclic

N-oxide or hydroxamic acid (Chapter 18). The condensation of nitrosobenzene with benzenesulfinic acid [105] was mentioned.

A special kind of condensation reaction occurs as a side reaction during the reduction of *o*-nitroaniline [120,137]: A phenazine derivative is formed. In the reaction (Chapter 18), a double Michael addition of *o*-phenylenediamine to the intermediate *o*-quinonediimine takes place; other nucleophiles might under suitable conditions attack the diimine.

Reduction of aromatic nitro compounds in aprotic medium in the presence of acetic anhydride [138] or alkyl halides [139] leads in high yield to *O*,*N*-diacylated or dialkylated arylhydroxylamines, respectively.

5. Reduction and Oxidation

In acid solution the protonated phenylhydroxylamine is further reducible at a potential somewhat more negative than that required for the reduction of the nitro compound. Sometimes addition of salts, such as Sn^{2+} or Ti^{4+} [140], facilitates the reduction; this may be regarded as an indirect reduction and is treated in Chapter 29.

If an amino or hydroxyl group is situated *ortho* or *para* to the nitro group, the intermediate phenylhydroxylamine very rapidly loses water to form the easily reducible quinone mono- or diimine. This loss of water takes place fastest in acid and alkaline solution and somewhat more slowly at pH 5, which is evident from the polarographic behavior of *p*- and *o*-nitrophenol [141]. At pH 5 the loss of water is so slow that the four-electron product diffuses away from the electrode before it has lost the water. Reduction of *o*-nitrophenol in DMF containing acetic anhydride gives the diacetylated *o*-hydroxylaminophenol [138]. As mentioned, alkoxy groups *para* to the nitro group may be lost by substitution and *p*-aminophenol is the product. A similar reaction may occur in the ortho series [141a,b] and in the hydroxypyridine series [141c]. Some heterocyclic nitro compounds behave similarly [100c]. The reduction of *p*-nitrophenol to *p*-aminophenol has been reinvestigated [142,143].

A *para* alkyl substituent may function in the same manner as a hydroxyl group in promoting loss of water from the phenylhydroxylamine and stabilizing the quinonoid intermediate. 5-Nitroacenaphthene is thus in acid solution reduced to 5-aminoacenaphthene in a six-electron reduction [144].

6. Substituted Nitro Compounds

In compounds with two reactive centers, the outcome of a reduction depends on the mutual interaction between the electroactive groups. If the interaction is weak one of the groups will just modify the reaction of the other electroactive group, whereas a strong interaction may give a qualitatively different outcome of the electrode reaction for one or both of the groups. Nitro, azo and azoxy groups are reduced at about the same potential.

Reduction of a substituted nitrobenzene follows generally one of the reaction paths described, as the nitro group usually is the more easily reducible group. Nitrobenzyl halides [145,146], however, are reduced in the side chain rather than in the nitro group, and dinitrobibenzyl and nitrotoluene are prominent products (see Chapter 8).

The reduction of 4-nitrobenzoic acid through 4-hydroxylaminobenzoic acid (XXVI) to 4-aminobenzoic acid under industrial conditions [149] has been investigated in 3M H_2SO_4; it was found that especially the reduction of XXVI was accelerated by raising the temperature to 60°C.

The nitro group in 4-nitrobenzoyl chloride is in dry acetone reduced at a less negative potential than the acid chloride; the radical anion is attacked by the acid chloride, which

also attacks other nucleophilic intermediates. Among the products is the mixed anhydride of 4-nitrobezoic acid and 4-(4-nitrobenzoylamino)benzoic acid; the anhydride precipitates during the reduction [148].

The use of the 4-nitrobenzyloxycarbonyl group as protecting group is discussed in Chapter 23.

Phenylhydroxylamines may be reoxidized anodically to the nitroso compound; this may be used in ring-closure reactions (Chapter 18) [149]. If the reduction of the nitro compound and the reoxidation of the phenylhydroxylamine is done in a cell with two closely spaced porous electrodes, a condensation to azoxybenzene may be avoided [149].

An unusual loss of an aromatic nitro group as nitrite is observed during the reduction of 1,2,4,5-tetrafluoro-3,5-dinitrobenzene in DMF containing a proton donor [150].

Mononitro derivatives of aromatic heterocyclic compounds and condensed aromatic systems behave as described for benzene derivatives. As in the benzene series, any prediction of the most likely reaction route for a given compound must be based upon considerations of the reactivity of the compound and its reduction products in the different types of reactions possible under a given set of parameters.

B. Dinitrobenzenes

Dinitrobenzenes are in principle reduced like the mononitrobenzenes and the same chemical follow-up reactions may occur, but generally not all of the possible reduction products are observed. In substituted dinitrobenzenes also the question arises as to which of the two nitro groups is reduced first.

1. *o*-Dinitrobenzenes

In dilute mineral acid solution *o*-dinitrobenzenes may be reduced to an *o*-nitrophenylhydroxylamine or further to the *o*-phenylenediamine [151,152]. The first step in the reduction of 1-X-2,3-dinitrobenzenes leads to 1-X-2-nitro-3-hydroxylaminobenzene (X = H, COOH, Br, CH_3, OC_2H_5), whereas 1-X-3,4-dinitrobenzenes in the first reduction form either 1-X-3-nitro-4-hydroxylaminobenzenes (X = COOH) or 1-X-3-hydroxylamino-4-nitrobenenes (X = Cl, CH_3, OCH_3) [152].

The differences in cathode potential between the first and second reduction is 0.2–0.3 V; a selective reduction thus requires good control of the cathode potential and a suitable cell design.

The hydroxylamino group may react further. A Gatterman reaction has, however, been observed only in the reduction of 2,3-dinitrotoluene. When a carboxyl group is neighbor to the hydroxylamino group, an isoxazolone may be formed; this reaction has been used as an indication of which nitro group is most easily reduced in dinitrobenzoic acids [152].

Reduction of *o*-dinitrobenzene in alkaline solution at the potential of the first polarographic wave (−0.7V) also yields *o*-nitrophenylhydroxylamine [151]. In slightly acid solution, some phenazine derivatives may be formed [137].

2. *m*-Dinitrobenzenes

Reduction in acid solution at room temperature generally may yield a nitrophenylhydroxylamine, a phenylene dihydroxylamine, or a phenylenediamine [122,151,153]. In alkaline solution it was found difficult [151] to effect a selective reduction of one of the nitro groups.

For unsymmetrically substituted *m*-dinitrobenzenes (1-X-2,4-dinitrobenzenes) the first reduction occurs either at the 2-nitro group (X = Cl, Br, I) or at the 4-nitro group (X = COOH, CH_3, C_2H_5) [122]. These differences may be caused by inductive effects and by steric inhibition of coplanarity with the benzene ring of the nitro group or of other substituents. In 2,4-dinitrochlorobenzene the inductive effect from the chlorine on the 2-nitro group probably is responsible for its easier reduction; in the first four-electron reduction 2-hydroxylamino-4-nitrochlorobenzene is formed; in the second four-electron step, 2,4-dihydroxylaminochlorobenzene; and in the last four-electron reduction, 2,4-diaminochlorobenzene.

Whereas a dinitroanisole, like 3,5-dinitroanisole, is reduced similarly, the 2,4- and 2,6-dinitroanisoles may or may not lose the alkoxy group, depending on the potential [122].

In DMSO, *m*-dinitrobenzene is reduced to *m*-nitrophenylhydroxylamine in the presence of a proton donor, whereas the radical anion, which is reduced further in a second step, is obtained in the absence of protons [154].

3. *p*-Dinitrobenzenes

Substituted *p*-dinitrobenzenes may in acid solution be reduced selectively to a nitrophenylhydroxylamine [151,155,156]; further reduction leads to the *p*-phenylenediamine; *p,p'*-dinitroazoxybenzene has been shown to be an intermediate [94]. 1-X-2,5-Dinitrobenzenes are reduced first in the 2-nitro group when X = COOH, $CONH_2$, or Br, whereas the 5-nitro group is first attacked when X = CH_3 or OCH_3 [156].

In alkaline solution the polarographic reduction shows [151,155] a two-electron wave (E −0.35V) followed by a ten-electron wave (E −1.6V). The two-electron reduction product $(O_2NC_6H_4NO_2)^{2-}$ is not stable and undergoes secondary chemical reactions; one of the reactions is probably a disproportionation to dinitrobenzene and nitrophenylhydroxylamine. Other intermediates, such as nitrosoaniline, have been suggested [155], but their presence has not been proved.

In DMF, 1,4-dinitrobenzene shows in CV two one-electron redox systems; the dianion formed in the second reduction is reasonably stable [157].

4. Dinitronaphthalenes

Several dinitronaphthalenes have been investigated polarographically [158,159]. The first wave is usually a four-electron reduction. The 1,2- and 1,4-dinitronaphthalenes behave like *o* and *p*-dinitrobenzenes, whereas 2,3-dinitronaphthalene does not exhibit a conjugation effect similar to that of *o*-dinitrobenzene. Nitro groups in α-positions are reduced in preference to those in β-positions.

The synthesis of 1,8-diaminonaphthalene by electrolysis of a suspension of 1,8-dinitronaphthalene in sulfuric acid containing a titanium salt gives a yield and purity similar to the synthesis by catalytic hydrogenation [160]. Technical and economic comparisons show that for large productions (several hundred tons per year) the catalytic hydrogenation is advantageous, whereas for smaller productions (several tons per year) the flexibility of electrolysis has some economic advantages.

Other dinitro compounds with nitro groups in different rings or one in a side chain may form heterocyclic compounds on reduction; such reactions are treated in Chapter 18.

C. Nitroso Compounds

Nitroso compounds are reduced like the nitro compounds, but at a less negative potential [161]; nitrosobenzene can thus not be isolated directly from a reduction of nitrobenzene. The presence of nitrosobenzene as an intermediate in the reduction of nitrobenzene can be shown by trapping it with a suitable nucleophile; for activated nitro compounds the hydrated nitroso compound may have sufficient stability to be detected [103,104]. The reaction with phenylhydroxylamine to form azoxybenzene has been discussed; Haber [2] used hydroxylamine and coupled the resulting diazo compound with β-naphthol. Other nucleophiles might be used to trap the nitroso compound and produce products that might have synthetic value. Some applications for the preparation of heterocyclic compounds are discussed in Chapter 18.

A detailed investigation of the reduction of nitrosobenzene betwen pH 0.4 and 13 indicated that, similarly to the reduction of nitrobenzenes, a rapid surface reaction of adsorbed compound took place simultaneously with the diffusion controlled reduction [162].

An investigation of nitrosobenzene in alkaline solution is complicated by the reaction of nitrosobenzene with hydroxyl ions [163,164]. There is a relatively fast, reversible addition of hydroxyl ion to the nitroso group. Besides that, there is in aqueous solutions at pH > 13 in the absence of dioxygen a relatively slow reaction giving mainly a mixture of azoxybenzene and 4-hydroxynitrosobenzene (p-quinone monoxime) in a reaction suggested as involving a hydride ion transfer from the initially formed 4-hydroxycyclohexadiene oxime anion to nitrosobenzene; hydride ion transfer to nitrosobenzene probably also occurs in alcoholic solutions when an alkoxide is present. In the presence of dioxygen, some nitrobenzene is formed.

In nonaqueous medium (MeCN and DMF) a similar reaction from EGB occurs during an exhaustive reduction; azoxybenzene was isolated in about 75% and several products resulting from an attack of EGB on nitrosobenzene, possibly on the aromatic ring, were indicated by TLC [165]. During a spectroelectrochemical investigation of the reduction of nitrosobenzene in acetonitrile, nitrosodiphenylhydroxylamine was detected [166]; an absorption band at 320 nm, which was assigned to the radical anion of nitrosobenzene, was also detected during the reduction. It was concluded that 4-nitrosodiphenylhydroxylamine was formed by an attack of nitrosobenzene radical anion on nitrosobenzene, whereas azoxybenzene was formed through a dimerization of nitrosobenzene radical anion.

The electrochemical reduction of nitrosobenzene in THF in the presence of fluorene or indene gives a mixture of an anil, a nitrone, and azoxybenzene and requires only a catalytic amount of electricity. The hydrocarbons act as proton donors and the anion thus formed add to nitrosobenzene [167]. The pK_A of the radical anion in water has been measured by pulse radiolysis to 11.7 [168].

Nitrosobenzenes may function as spin traps; the main advantage of nitrosobenzenes as compared to nitrones is that the radical is added to the nitrogen rather than to the carbon as in the nitrones; this gives more direct information on the structure of the trapped radical; the main disadvantage is the rather narrow potential window available [169,170].

The presence of a nitroso intermediate in nonaqueous solution may also be deduced from results of cyclic voltammetry. Trifluoromethylnitrobenzenes [171] show two polarographic steps in DMF; the first one is due to a diffusion-controlled one-electron transfer producing a stable radical anion; the second one is a two-electron ECE process resulting in

a substituted nitrosobenzene radical anion [172]. Addition of hydroquinone as a proton donor enhances the formation of the nitroso intermediate [171].

In cyclic voltammetry measurements of DMF solutions of nitroso-, azoxy-, and azobenzene using the hanging mercury drop electrode, it was found that besides the usual peaks of redox processes an additional, new system of peaks was observed. Its properties were nearly identical for all three substrates. The most probable interpretation seems to be to attribute this additional system of peaks to a reaction between adsorbed azobenzene dianion and mercury; at graphite such additional peaks were not observed [173]:

$$C_{12}H_{10}N_2^{2-}, 2M^+ + Hg - 2e^- \rightleftharpoons (C_{12}H_{10}N_2^{2-}, Hg^{2+}) + 2M^+ \quad (26)$$

By reducing a nitrobenzene in acid solution in a flow cell in which it is reduced to phenylhydroxylamine during passage, through a porous cathode and immediately after oxidized in a porous anode, it is possible to obtain nitrosobenzenes in good yield [174,175].

D. Phenylhydroxylamines

Polarographic data show that below pH 1 the doubly protonated phenylhydroxylamine is the species reduced at the dropping mercury electrode (DME); between pH 5 and 7 the monoprotonated molecule is reduced. The unprotonated molecule is not reducible [176]. Phenylhydroxylamine is for the main part reduced to aniline, but according to the polarographic data a certain degree of dimerization of an intermediate radical takes place. As discussed, phenylhydroxylamines may react chemically in several ways.

E. Azoxybenzenes

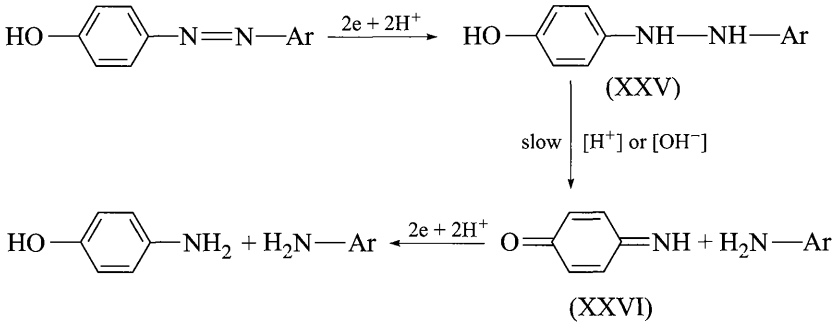
Azoxybenzenes are reduced in a four-electron reduction to hydrazobenzenes and are generally in protic solvents more difficult to reduce than the azobenzenes; in this respect the system azoxybenzene–azobenzene is similar to that of nitrobenzene–nitrosobenzene. The analogy can be extended: Further reduction of azobenzene yields hydrazobenzene, which can be reoxidized to azobenzene and which easily rearranges in acid solution; analogously, phenylhydroxylamine can be reoxidized to nitrosobenzene and can be rearranged to *p*-aminophenol or similar products in acid solution.

The reduction of azoxybenzene to hydrazobenzene is of preparative interest [132,134], due to the easy conversion of hydrazobenzenes to benzidines and similar compounds. Several patents [177] describe the conversion of nitrobenzene to azoxybenzene and further to hydrazobenzene; environmental considerations are in favor of the electrochemical reduction compared with the metal powder reductions, and the method stands a good chance to be competitive in the future.

F. Azobenzenes

Azobenzenes may be prepared by oxidation of hydrazobenzenes; this may be made in an undivided cell by reduction of the nitro compound with constant current [178]. Additionally, azobenzenes may be obtained in low to fair yield by anodic oxidation of aromatic amines at a rotating platinum screen cylinder anode in aqueous DMF [179].

The reduction of azobenzenes may follow two routes, either a reversible two-electron reduction or a four-electron reaction with cleavage of the nitrogen–nitrogen bond. The latter reaction is the predominant one for *p*-hydroxy- and *p*-aminoazobenzenes [180–182]. In this cas the reaction may be formulated as:



(27)

The cleavage of the nitrogen–nitrogen bond of XXV may be catalyzed by both acids and bases [183,184]; when Ar = C_6H_5, the acid catalysis is fast enough to ensure a four-electron polarographic wave, whereas a two-electron wave is observed in alkaline solution [180]. Under preparative conditions and at elevated temperatures (50–90°C) the reduction consumes 4F/mol [185]. Possibly XXV is able to reduce XXVI in solution to *p*-aminophenol thereby being oxidized to *p*-hydroxyazobenzene. If Ar is strongly electron withdrawing, the rate of cleavage in alkaline solution is enhanced and the height of the polarographic wave approaches that of n = 4 [183,184].

A similar disproportionation of the initially formed hydrazine is found during the reduction of azobenzene-4,4′-disulfonamide to 4-aminobenzenesulfonamide [186].

The system azobenzene–hydrazobenzene is one of the rather few organic redox couples that behave reversibly or very nearly so at the dropping mercury electrode [187]. In nonaqueous solvents, like DMF, azobenzenes are reduced in two, one-electron steps: The first one produces the radical anion, whereas the second one yields a hydrazobenzene dianion. This dianion is easily protonated; it has a tendency to decompose into arylhydrazine [188].

The stability of the radical anions of the azo compound makes them useful as electron transfer reagents, either in solution or bonded to an electrode surface. These aspects are treated in Chapter 29. The preparation of heterocyclic compounds by reduction of azo compounds in the presence of electrophiles is discussed in Chapter 18.

The hydrazobenzene dianion is a strong base, the monoanion less so. The reduction of azobenzene and substituted azobenzenes has been used for an electrolytic generation of a base in DMF, which has been employed in some base-catalyzed reactions. This aspect is discussed in Chapter 30.

The azo group is more easily reducible than most other functional groups and is reduced close to that of a nitro group. In aqueous alkaline media 2-nitroazobenzenes are reduced to 2-arylbenzotriazole-*N*-oxides [189,190] (and further at more negative potentials, Chapter 18), and 2-nitrohydrazobenzene has been reported to be the first intermediate [190]. In DMF [191], 1,3-dihydroxy-2-phenylbenzotriazole is formed from 2-nitroazobenzene and 2-nitrosoazobenzene has been suggested to be an intermediate.

2,2′,4,4′,6,6′-Hexanitroazobenzene is in MeCN reduced in two reversible one-electron steps; in the presence of a proton donor the hexanitrohydrazobenzene is formed [192].

G. Hydrazobenzenes

Hydrazobenzene is not polarographically reducible at pH > 4, and in acid solution polarographic curves are difficult to obtain due to the fast rearrangement to benzidine. Polarographic curves of azo and azoxybenzene show at pH < 4 a second reduction (n = 2) corresponding to the formation of aniline. From the pH dependence of the half-wave potentials and a logarithmic analysis of the curves it is proposed that only the diprotonated hydrazobenzene cations undergo reduction, whereas the monoprotonated cation exhibits a catalytic effect on the hydrogen evolution reaction [193].

H. Diazonium Salts

Aryldiazonium salts are reducible at a mercury cathode. Polarograms in acid solution show a pH-independent one-electron wave followed by a larger pH-dependent wave [194,195]. Reduction on the plateau of the first wave [196] showed n = 1 and only arylmercury salts were isolated, indicating the initial formation of a radical.

During a preparative reduction at a potential of the second wave, care must be taken to avoid the reaction between the diazonium salt and the product, phenylhydrazine. By using a flow cell with a small volume–cathode area ratio and low temperatures, the loss by this side reaction was diminished [197]. In the reduction of *p*-methoxyphenyldiazonium chloride to *p*-methoxyphenylhydrazine in dilute hydrochloric acid an amalgamated lead electrode was found to give the best yield [198]. Generally, the best yields of arylhydrazine are obtained from diazonium salts having electron-donating substituents in the aryl group and using low substrate concentrations [199].

Reduction of PhN_2^+ at Cu, Fe, or Ti electrodes in the presence of alkenes gave phenylated products; at a Pt electrode no addition products were formed [200].

IV. *N*-NITRAMINES, NITROSAMINES, AND AZIDES

A. *N*-Nitramines

Protonated *N*-nitramines are reduced in a single six-electron reaction to the unsymmetric hydrazine [201–205] together with some amine [205].

$$RR'N{-}NO_2 \xrightarrow{6e + 6H^+} RR'NNH_2 + 2H_2O \tag{28}$$

In alkaline solution most *N*-nitro derivatives of primary amines form an irreducible anion $[R{-}\overset{-}{N}{-}NO_2]^-$, with nitraminopyridines as exceptions [205], whereas nitramines of secondary amines are reduced in two steps. [202]. The first reduction consumes 2F/mol and produces an *N*-nitrosamine. It is noteworthy that *N*-nitrosamines in alkaline solution are more difficult to reduce than the corresponding *N*-nitramines; it seems to be the only class of nitro compounds in which the nitro group is more easily reducible than the nitroso group.

Reduction of nitroguanidine in a 2M ammonium sulfate solution at a mercury cathode at −1.0V yields nitrosoguanidine, which precipitates; addition of nickel ions increases the yield [206].

Reduction of 1-nitropyrazol in acid medium results in a cleavage of the N–N bond and formation of nitrous acid; at pH > 4 a competitive reduction to the nitrosamine occurs [100a].

B. *N*-Nitrosamines

N-Nitrosamines are reducible in both acid and alkaline solutions. Polarographic data show [207–209] that the protonated compound is reduced in a four-electron reaction, whereas the unprotonated nitrosamine consumes only 2F/mol. Controlled potential reduction has proved [207] the following reactions:

$$\text{Acid solution: } RR'NNO \xrightarrow[4e^- + 4H^+]{H^+} RR'\overset{+}{N}NH_3 + H_2O \tag{29}$$

$$\text{Alkaline solution: } RR'NNO \xrightarrow{2e^- + 2H^+} RR'NH + \tfrac{1}{2}N_2O + \tfrac{1}{2}H_2O \tag{30}$$

The electrochemical reduction of *N*-nitrosamines in acid solution is a convenient and general synthetic route to dialkylated, unsymmetrical hydrazines [210]. Quite a few nitrosamines were reduced to hydrazines in the classic period, but later investigations [211,212] also indicate a continued interest in the reaction.

The nitrosation of secondary amines is reversible in acid solution, so *N*-nitrosamines may be hydrolized at low pH. Such hydrolysis is especially important for diaryl nitrosamines but also significant for aryl akyl nitrosamines. The NO^+ liberated in the hydrolysis may react with the reduction product from the *N*-nitrosamine, the unsymmetrical hydrazine, with formation of amine and N_2O [213,214]:

$$RR'NNH_2 + NO^+ \longrightarrow RR'NH + N_2O + H^+ \tag{31}$$

Anodic oxidation of *N*-nitrosamines [215] in acetonitrile in the presence of oxygen results in *N*-nitramines and some β-ketonitrosamines.

C. *N*-Nitrosamides

N-nitrosamides behave in acid solution like *N*-nitrosamines; they are reduced to acylated hydrazines. In this way alkylhydrazines may be prepared from primary amines by the following reactions [216].

$$RNH_2 \xrightarrow[-HCl]{CH_3COCl} RNHCOCH_3 \xrightarrow[-H_2O]{HNO_2} RN(NO)COCH_3 \xrightarrow{4e^- + 4H^+}$$
$$RN(NH_2)COCH_3 \xrightarrow{H_2O} RNHNH_2 \tag{32}$$

Similarly, nitro and nitroso derivatives of urea and guanidine have been reduced to semicarbazides and aminoguanidines in acid solution [204,217–219]. In aprotic media (DMF) the primarily formed anion radical of *N*-nitrosourea gives rise to a self-protonation step; the deprotonated substrate cleaves easily into several products [220].

D. Azides

Azides may in protic solvents be reduced in two different ways, n = 2 in both cases. The usual reaction is a cleavage to amine and dinitrogen [221, 222]. Phenyl and benzyl azide are thus reduced according to:

$$R-\overset{-}{N}-\overset{+}{N}\equiv N + 2e + 2H^+ \longrightarrow R-NH_2 + N_2 \tag{33}$$

Azide groups at activated methylene groups may be reductively lost with formation of azide ion and a methyl group [221]. Phenacylazide and 4-azidomethylpyridine are thus reduced to acetophenone and 4-methylpyridine, respectively:

$$R-CH_2N_3 + 2e + H^+ \longrightarrow R-CH_3 + N_3^- \tag{34}$$

This cleavage reaction has been exploited in the electrosynthesis of N-substituted imidazole-2-thiones [227].

The reduction of p-nitrophenyl azide in acetonitrile yields the radical anion, which loses dinitrogen to the nitrene radical anion. This radical anion dimerizes to the dianion of 4,4′-dinitroazobenzene. In DMF, the nitrene radical anion forms a coupling product with DMF, either in an addition/radical fragmentation reaction or by abstracting a hydrogen atom from DMF followed by a coupling between the nitrene radical anion and the radical $Me_2NOC^{\cdot}$ [223], analogous to the reaction of this radical with anthraquinone radical anion [224].

In aprotic media, α-azidostyrenes have been reduced in the presence of acetic anhydride to mono- and diacetylated enamines and further reduced compounds [225]. α-Azidocinnamic esters may under similar conditions be reduced to *N*,*N*-diacetylated α-aminocinnamic ester or, by careful addition of a proton donor, to α-aminocinnamic ester [226]:

$$C_6H_5CH=C(N_3)-COOCH_3 \xrightarrow[-N_2]{2e + 2[H^+]} C_6H_5CH=C(NH_2)COOCH_3 \tag{35}$$

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10
Carbonyl Compounds

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I. REACTION MECHANISMS

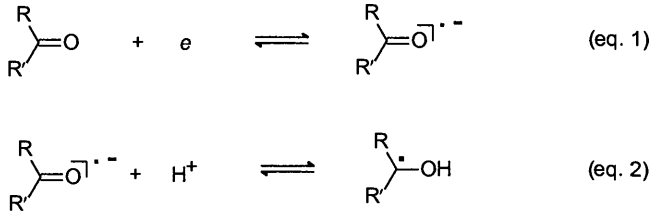
The carbonyl group is an electrophore and all compounds containing it in the free form are electroreducible. For some aliphatic aldehydes including formaldehyde and glyoxylic acid [1], as well as many heterocyclic aldehydes [2], the carbonyl group is masked as the *gem*-diol, while for others like glucose it is masked as the cyclic hemiacetal. In any of these masked forms, the carbonyl group becomes nonreducible. Reduction is then kinetically controlled by the formation of a trace of the free carbonyl group. Carbonyl derivatives (Chapter 11) in which the C=O bond is replaced by a C=N bond are more easily reducible than the parent compound.

Addition of an electron to the LUMO of the carbonyl group to form a radical anion is the first step in the reduction process. Radical anions can be characterized in aprotic solvents by electron spin resonance (esr) spectroscopy. Those derived from unconjugated carbonyl compounds are highly reactive and can only be detected in a matrix at low temperatures [3]. Decay is rapid because the excess carbonyl compound acts as a proton donor toward the basic oxygen center in the radical anion. Aromatic carbonyl compounds give less reactive radical anions in which the free electron is delocalized over the whole

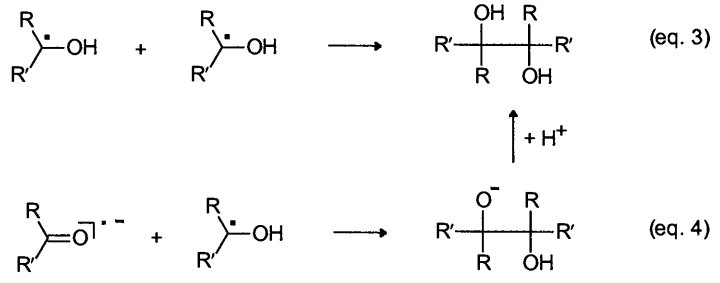
conjugated π-system. These intermediates can be generated [4] by electrochemical reduction in dimethylformamide within the cavity of the esr spectrometer.

Electrochemical modulated infrared (ir) spectroscopy has been used to obtain in situ spectra of the radical anion of benzophenone [5]. There is a red shift of the vibrational modes of the benzene rings and considerable loosening of the carbonyl bond. Carbonyl compound radical anions are protonated on the oxygen center. The conjugate acids of alkanones and alkanals have pK_a values [6] in the range 11–12, while those from conjugated aromatic carbonyl compounds [7] are in the range 8–10.

Preparative scale reduction of carbonyl compounds involves a cascade of electron and proton additions within which there are competing reaction pathways. In the absence of any other reactive functional group, these pathways lead to a mixture of alcohol and pinacol (the hydrodimer). The radical intermediates will also add to unsaturated functions, and these reactions are discussed in a later section. Intermediates from dialkyl carbonyl compounds are so reactive that it has proved impossible to obtain information on the rates of competing stages. Reactions of alkyl-aryl carbonyl compounds are amenable to physicochemical study, and the general reaction scheme derived from this work is assumed to apply to all carbonyl compounds. Early work involved the use of polarographic techniques [8,9], and the results have been extended using linear sweep voltammetry, which has allowed the extraction of rate data for the fast homogeneous chemical reactions involved in the pinacol formation step [10].



In general, the first electrochemical step [Eq. (1)] is the reversible transfer of an electron from the electrode to the carbonyl compound, and this is followed by reversible protonation [Eq. (2)] of the radical anion. It has been proposed [2] that, in the acidic solution, preprotonation of the carbonyl lone pair occurs followed by electron addition to the protonated form. In thermodynamic terms, either sequence of steps leads to the same



overall free energy change. Formation of the glycol next proceeds either by reaction of two radicals [Eq. (3)] or from reaction between a radical and a radical anion [Eq. (4)]. Which of these processes predominates depends on the pH of the solution. Reaction between two radical anions is relatively slow and can be discounted in protic solvents. The graph of

(eq. 5)

faradays consumed versus pH for reduction of aromatic carbonyl compounds shows a bell shape indicating a 1F process in acidic or basic solution and approaching a 2F process around pH 8.5 [8]. This arises from the competition between the bimolecular radical processes and further reduction of the protonated radical anion generating the alcohol after another protonation step [Eq. (5)].

The electrode material may react with radical intermediates, particularly in strongly acid solutions. Extensive corrosion of lead cathodes to give lead containing organic compounds has been noted in the presence of aldehydes and ketones [11–13]. Mercury compounds also form at a mercury cathode [14]. Organometallic intermediates are involved in the electrochemical Clemmensen reaction discussed later for the conversion of the carbonyl group to methylene. The conversion of aromatic ketones or methylene can also be achieved by catalytic hydrogenation using hydrogen, generated electrochemically, at cathodes of platinum or palladium [15].

II. REDUCTION PRODUCTS

A. Aliphatic Carbonyl Compounds to Alcohols and Pinacols

The principal product from reduction of unconjugated aldehydes and ketones in buffers over the pH range 1–14 is the corresponding alcohol. Some representative examples are given in Table 1 (and later in Table 3). Competing reactions to give pinacol are only important during the electrochemical reduction of aldehydes and of acetone in acid solution. In general for aldehydes, the yield of pinacol increases with the length of the hydrocarbon chain attached to the carbonyl group [16]. An electrolyte of pH 2–5 with a tin cathode gives the best yields of pinacol.

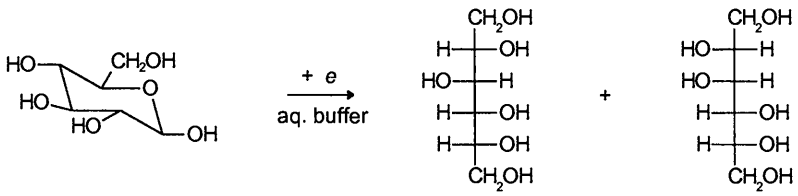
The electrochemical reduction of formaldehyde to the corresponding pinacol, dihydroxyethane, has been closely examined as a possible technical scale process. Yields are very dependent on the choice of reaction conditions. Best results are obtained with a graphite cathode and sodium formate as electrolyte at 57°C [20]. The reduction of acetone to pinacol has also been examined from a technical point of view. Moderate yields of pinacol are obtained at a lead cathode in acid solution together with isopropanol and propane. The propane arises by hydrolysis of lead alkyl intermediates and under some conditions tetraisopropyllead is formed [21]. A pilot plant scale production of acetone

Table 1 Alcohols from the Reduction of Aliphatic Carbonyl Compounds in Protic Solvents.

Substrate	Conditions: Solvent–Electrolyte–Cathode	Yield (%)	Ref.
Acetone	Water–H_2SO_4–Hg	100	[17]
Butan-2-one	Water–NaOAc–Pb	poor	[18]
3-Methylpentan-4-ol-2-one	Water–$NaHCO_3 + CO_2$–Hg	66	[19]
2-Methylhept-2-en-6-one	EtOH–H_2SO_4–Pb	45	[12]
Menthol	EtOH–H_2SO_4–Pb	82	[12]
Camphor	EtOH–H_2SO_4–Pb	45	[17]
Glucose	Water–various buffers–Hg	81	[23]

pinacol in 52% yield has been achieved using graphite cathodes and with propan-2-ol as the main by-product [22].

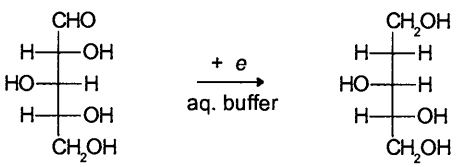
Sugars with a potential aldehyde function can be reduced electrochemically at electrodes of mercury or amalgamated lead [23]. The rate of this process is controlled by the rate for the conversion of the cyclic to the open-chain form of the sugar. A technical-scale plant [24] for the conversion of glucose to either sorbitol or mannitol was operated in the past, but this method has largely been ousted by other processes. Glucose is converted to



I II

sorbitol (I), without change in sterochemistry, in neutral or weakly alkaline solutions but strongly alkaline solutions catalyze the epimerization of glucose after which reduction also affords mannitol (II). A by-product from reduction of glucose is the pinacol-type dimer [25]. Several attempts have been made to revive the electrochemical production of sorbitol. The reaction can be carried out in an undivided cell with a lead cathode and a porous hydrogen diffusion anode [26]. Overall, protons consumed at the cathode are replaced by the anodic oxidation of hydrogen. A completely different approach to the conversion of glucose to sorbitol has used electrocatalytic hydrogenation at a Raney nickel cathode [27]. This electrocatalytic hydrogenation process has also been combined in the same cell with an anode reaction of the oxidation of glucose to gluconic acid using bromine generated from calcium bromide electrolyte at a graphite anode [28].

The pentose sugars, ribose and xylose also yield the pentitols on reduction under similar conditions [29]. In these cases a by-product is the 2-deoxypolyol formed by reductive elimination of the hydroxyl group adjacent to the carbonyl function. This reaction predominates during the reduction of D-xylose in solution at pH 9 at amalgamated lead when 2-deoxy-D-xylitol (III) is formed in 62% yield [30].



III

The majority of aliphatic ketones give the secondary alcohol on reduction at electrodes of carbon, mercury, lead, or platinum. The usual choice of electrolyte has been dilute sulfuric acid, acetate buffer, or a neutral salt solution, which will become alkaline during the course of reaction that consumes protons. Relatively few studies have been recorded of the isomer ratio obtained by reduction of open chain ketones with a prochiral center adjacent to the carbonyl function [32,33]. Results are collected in Table 2, and one aromatic carbonyl compound is included here for convenience. In general, the *erythro*-alcohol is favored and in an excess over that present in the equilibrium mixture [32,33]. These results are explained in terms of adsorption of intermediates at the electrode surface. For many of the examples in Table 2, the total yield of alcohol is low and this result is not generally typical of aliphatic carbonyl compounds, as can be seen from Table 3.

Table 2 Secondary Alcohols from the Reduction of Open-Chain Ketones

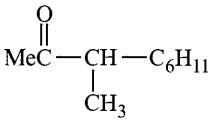
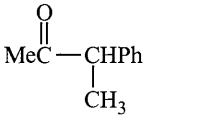
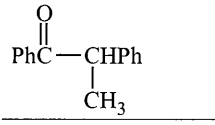
Substrate	Conditions: Solvent–Electrolyte–Cathode	Yield (%)	Isomer Ratio, *erythro:threo*	Ref.
	MeOH–borate buffer–Hg	3	60:40	[33]
	MeOH–NaOH–Hg	3	65:35	
	MeOH–H_2SO_4–Hg	7	52:48	
	MeOH–borate buffer–Hg	17	42:58	[33]
	MeOH–NaOH–Hg	20	44:56	
	MeOH–H_2SO_4–Hg	7	43:57	
	MeOH–borate buffer–Hg	86	74:26	[33]
	MeOH–NaOH–Hg	91	80:20	
	MeOH–H_2SO_4–Hg	10	64:34	
	EtOH–veronal buffer pH 8–Hg		Mostly *erythro*	[32]

Table 3 Stereochemistry of Alcohols from Reduction of Cyclohexanones and Cyclopentanones

Substrate	Conditions: Solvent–Electrolyte–Cathode	Total yield (%)	Ratio, *trans:cis*	Ref.
3-Methylcyclohexanone	PrOH–Et_4NTos–C	58	22:78	[35]
	MeOH–dil. H_2SO_4–C	48	52:48	[35]
4-Methylcyclohexanone	Pr^iOH–Et_4NTos–C	60	78:22	[35]
	MeOH–dil.H_2SO_4–C	45	38:62	[35]
4-*tert*-Butylcyclohexanone	Pr^iOH–Et_4NTos–C	56	85:15	[35]
	MeOH–dil. H_2SO_4–C	55	48:52	[35]
	MeOH–HOAc–LiCl–Hg	100	60:40	[36]
	HMPT–EtOH–LiCl–Pt	87	95:5	[31]
3,3,5-Trimethylcyclohexanone	Pr^iOH–Et_4NTos–C	55	26:74	[35]
	MeOH–dil. H_2SO_4–C	50	40:60	[35]
	HMPT–EtOH–LiCl–Pt	65	9:91	[31]
2-Methylcyclopentanone	Pr^iOH–Et_4NTos–C	54	58:42	[35]
	MeOH–dil. H_2SO_4–C	40	42:58	[35]
2-Isopropylcyclopentanone	Pr^iOH–Et_4NTos–C	54	58:42	[35]
	MeOH–dil. H_2SO_4–C	40	42:58	[34]
Androstan-17β-ol-3-one	EtOH–Bu_4NCl, Bu_4NOH–Hg	100	3β-17β-diol	[34]
Etiocholan-17β-ol-3-one	EtOH–Bu_4NCl, Bu_4NOH–Hg	95	3α-17β-diol	[34]
			endo:exo	
Norcamphor	Pr^iOH–Et_4NTos–C	60	16:84	[35]
	MeOH–dil. H_2SO_4–C	30	98:2	[35]
Camphor	Pr^iOH–Et_4NTos–C	55	76:24	[35]
	HMPT–EtOH–LiCl–Pt		84:16	[31]

The *axial*:*equatorial* isomer ratio for the cyclohexanols obtained from reduction of cyclohexanones has been examined in some detail and the data are collected in Table 3. The catholytes used can be grouped into three types: (a) acidic, (b) alkaline, and (c) initially neutral but unbuffered. The last group will become strongly alkaline as the reaction proceeds because protons are consumed at the cathode. Product ratios from reduction in isopropanol with tetraethylammonium tosylate as electrolyte, and also in hexamethylphosphoramide with lithium chloride as electrolyte, approach the equilibrium value for the stereoisomeric alcohols. Reduction of ketosteroids in alkaline solution gives good yields of the equatorial alcohol [34]. The literature contains examples of 3-, 11-, 12-, and 17-ketosteroids including an etiocholan-3-one with a *cis*-A/B ring junction. In acid solutions, it is proposed that protonation of carbanion intermediates occurs very close to the electrode surface where steric effects give rise to a preferential control of the protonation step [35,36]. In alkaline solution it is proposed that protonation occurs in bulk solution giving the equilibrium isomer distribution.

Both 2-cyanocyclohexanone and 2-cyanocyclopentanone give good yields of the *cis*-alcohol by reduction at a mercury cathode in aqueous alcohol at pH 8 [37]. Reduction of 2-carbethoxy-substituted cyclopentanone and cyclohexanone under the same conditions favors the *cis*-alcohol at −6°C, but at 80°C the thermodynamically favored *trans*-isomer predominates [38].

The isomer distribution from reduction of cyclohexanones becomes strongly biased in favour of the axial-hydroxyl component on addition to the electrolyte of cations with a high surface charge density (see Table 4). The most effective ion tried is zinc(II). This high selectivity is explained in terms of ion pairing between key carbanion intermediates and the aqueous metal ion [36]. The metal ion is larger than a hydroxyl group and so prefers an equatorial position. The carbanionic center is then protonated from the side coordinated with the metal ion to give an axial alcohol. Preference for an axial alcohol is less marked in the reduction of *trans*-decalones, steroid ketones have not been examined under these conditions.

B. Radical Addition to Alkene Bonds and Aromatic Rings

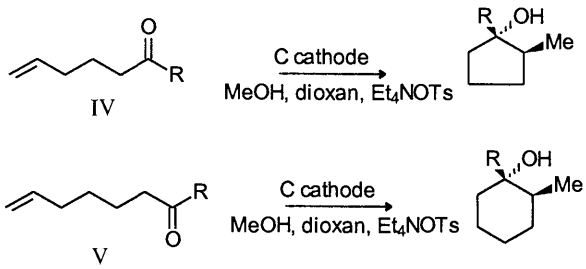
The trapping by alkene bonds of radicals obtained in the reduction of aliphatic carbonyl compounds has proved to be a versatile route for the formation of carbon–carbon bonds. Reactions are carried out in protic solvents where the reactive species is the σ-radical formed by protonation of the carbonyl radical anion. The competing reaction is reduction of the carbonyl group to the alcohol.

Table 4 Influence of Metal Ions on the Isomer Distribution from Reduction of Cyclohexanones in Dry Ethanol Using a Divided Cell and Mercury Cathode at Constant Current (62.5 mA cm^{-2})

	Ratio axial:equatorial alcohol formed in		
Substrate	0.1M LiCl	0.1M $MgCL_2$	0.1M $Zn(ClO_4)_2$
4-*t*-Butylcyclohexanone	42:54	98:2	98:2
3,3,5-Trimethylcyclohexanone	20:80	54:46	78:22
trans-Decal-2-one	42:58	—	58:42

Note. Data from Ref. 36. Traces of hydrocarbon are also formed.

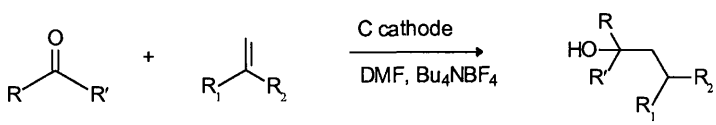
The intramolecular cyclization process is illustrated here with two examples using substrates IV and V. Reactions are best carried out in a mixed solvent of methanol–dioxan with carbon electrodes in an undivided cell. Bond formation always takes place on the



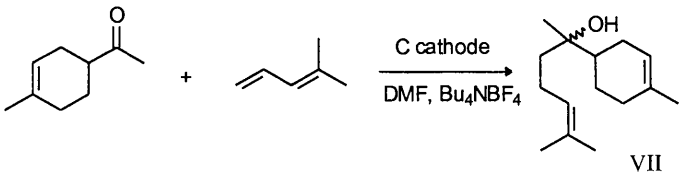
more substituted carbon atom of the alkene group closer to the carbonyl function and is restricted to the formation of either a five- or a six-membered ring. A high degree of stereoselectivity is observed, giving the product with a *cis*-arrangement of two adjacent alkyl groups on the newly formed ring [39,40]. This stereoselectivity has been explained on the hypothesis that the energetically preferred transition state will have adjacent bulky groups in pseudo-equatorial positions [41].

Reduction of V, R = Me, in dimethylformamide at mercury leads to conversion of the ketone function to secondary alcohol with essentially no cyclization process observed. However, in the presence of a mediator the course of reaction changes. Addition of *N*,*N*-dimethylpyrrolidinium fluoroborate causes formation of the cyclized tertiary alcohol. The pyrrolidinium salt is reduced at −2.7V (vs. SCE) at mercury to yield a complex DMP(Hg_5) which is thought to act as a single-electron-transfer mediator [42]. Cyclization also occurs in dimethylformamide at a mercury cathode using a homogeneous redox catalyst such as phenanthrene or 2-methoxybiphenol with a redox potential in the range −2.4 to −2.7 (vs. SCE) [43]. Because during these reactions one electron is delivered to the carbonyl compound in solution by the reduced mediator, cyclization of the reduced carbonyl compound can occur before a second electron donor is encountered.

Intermolecular reaction between acetone and an alkene was first carried out only in low yields using acetone as the solvent and either *p*-toluenesulfonic acid or sulfuric acid as electrolyte [44–46]. Conjugated alkenes reduced at less negative potentials than acetone

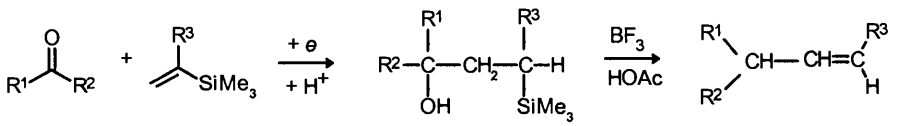


do not react. Better yields have been achieved more recently in reactions between aliphatic ketones and terminal olefins of the type VI. Dimethylformamide is found to be the best solvent with carbonized polyacrylonitrile fiber as cathode material in a divided cell under constant current conditions [47]. The reaction has been used, for example, as one stage in the synthesis of the bisabolol skeleton VII and this process illustrates the greater reactivity of a terminal olefin center in the diene [47]. In general, nonterminal alkenes do not react at all, while disubstituted terminal alkenes give substantially decreased yields of coupled product.



VII

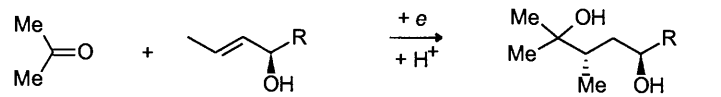
Silicon substituents are known to stabilize both radical and carbanion centers. Thus, better and more consistent yields are obtained from intermolecular coupling reactions using trimethylsilyl substituted alkenes such as VII as substrates for reaction with carbonyl



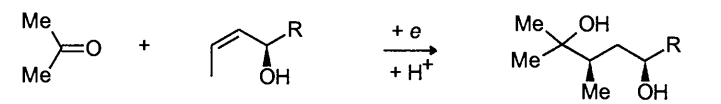
VIII

compounds [48]. The products so formed are useful in synthesis because conversion to an alkene occurs on treatment with boron trifluoride in acetic acid [49].

Allylic alcohols are especially active in this coupling process [50]. Even nonterminal alkenes such as IX are activated toward coupling by the adjacent hydroxyl function. A chiral allylalcohol center will also play an important role in promoting coupling with a



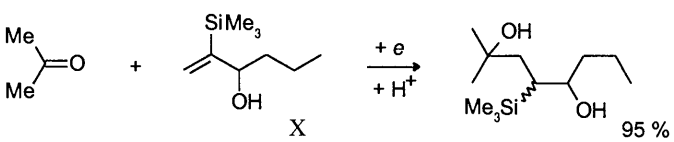
trans-(R)-IX Yield 60 %, > 85 % *d.e.*



cis-(R)-IX Yield 70 %, > 85 % *d.e.*

high degree of disastereoselectivity as illustrated by the reaction of the *cis* and *trans* isomers of IX. The transition state for these reactions is considered to be stabilized by hydrogen bonding between the ketone radical anion and the allyl hydroxyl group. Stereoselectivity in the product arises from the transition state having minimum interaction between substituents on the developing carbon–carbon bond.

Cathodic coupling reactions of ketones to trimethylsilyl substituted allyl alcohols X

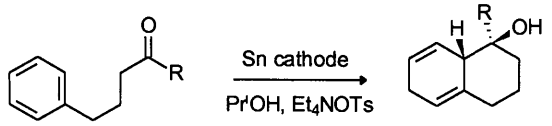


X

are very effective and give up to 95% of diol product [51]. Excellent yields are also obtained in the coupling of ketones with alkenes bearing the ethoxydimethylsilyl group. The primary products of these reactions can be chemically oxidized to the corresponding 1,3-diols [52].

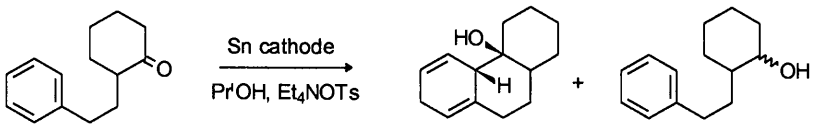
The intramolecular reductive coupling of carbonyl groups to a benzene ring has also been achieved. The best conditions for this process are at a tin cathode with isopropanol as

solvent and tetraethylammonium tosylate as supporting electrolyte [53,54]. Reaction is performed at constant current in a divided cell. Examples of this method are given with the substrates XI and XII. The reaction is limited to the formation of six-membered rings, and



XI

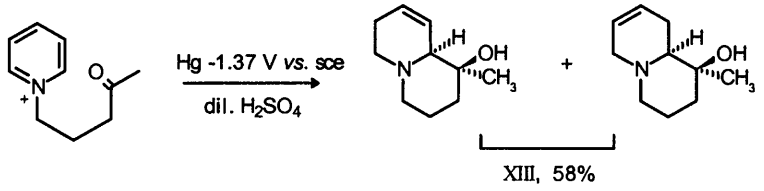
R = Me, yield 70%
R = Et, yield = 55%



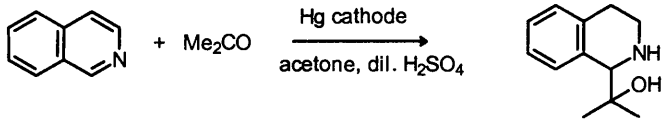
XII 45% 37%

in structure XI the R group must be methyl of ethyl. Reaction failed with R as isopropyl or phenyl. In all cases examined, the reaction has yielded a single stereoisomer of the product, and the stereochemistry of the product derived from XI is based on a ^{1}H-NMR spectral comparison with a sample of the tetrahydroderivative prepared by a different route [55]. Deuterium labeling experiments show that the radical formed after cyclization onto the benzene ring abstracts a hydrogen atom from the solvent to yield the final product. The main side product from these reactions is the secondary alcohol formed by reduction of the carbonyl group.

Radical addition to the pyridine ring is a facile process, and coupling of radical intermediates from reduction of ketones to pyridines in sulfuric acid solution has been



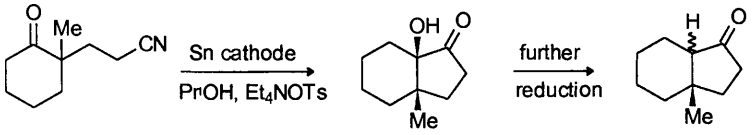
XIII, 58%



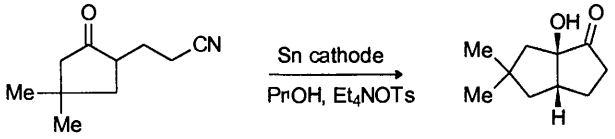
XIV, 78%

achieved in both intermolecular [46] and intramolecular reactions [56]. Dihydropyridines are formed initially and reduced further under the reaction conditions to the tetrahydropyridine XIII level. The stereochemistry of these tetrahydropyridines is based on an x-ray crystal structure. Isoquinoline reacts with acetone to give 1-substituted tetrahydroisoquinoline XIV by further reduction of the initially formed dihydroisoquinoline [57].

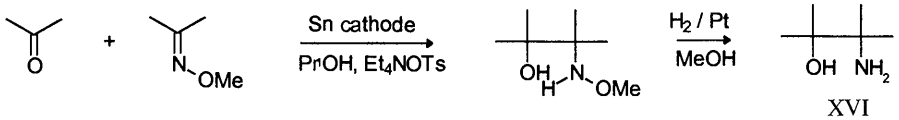
Intramolecular coupling between the aliphatic carbonyl group and a nitrile function can be achieved by reduction at a tin cathode in isopropanol. This reaction allows the formation of five- or six-membered rings only and in good yields. It has been extensively employed as a stage in the construction of condensed ring sesquiterpenes. The use of other cathode materials, cadmium, lead, or zinc, and of dimethylformamide as solvent resulted



XV



in decreased yields of coupled product [59]. The isolated products are α-hydroxyketones, e.g, XV, formed by the loss of ammonia. The hydroxyl group in these compounds is cleaved during prolonged reduction. Intermolecular coupling between cyclohexanones and acetonitrile can be achieved in low yield by reduction of the ketone at a tin cathode in a mixture of acetonitrile and isopropanol as solvent. In these reactions, isopropanol acts as a proton source [58]. Reduction of aliphatic ketones in acetonitrile in the absence of any other proton source generates strong bases, which catalyze unwanted side reactions of the carbonyl group.



XVI

Intermolecular coupling between ketones and *O*-methyl oximes, hydrazones, and nitrones occurs during reduction at a tin cathode in isopropanol [59]. The reaction with O-methyloximes is a convenient synthesis of 2-aminoalcohols XVI. It is not clear in these reactions which of the functions, C=N or C=O, is reduced first to generate the species active toward the coupling reaction.

C. Carbonyl Group to Methylene

Aliphatic ketones show an anomalous polarographic wave in acid solution with a humped maximum just prior to the hydrogen discharge process. This wave is thought to be due to the formation of an insoluble film of mercury compounds on the electrode [60]. The isolation of organomercury and organolead compounds during the reduction of carbonyl compounds in acid solution was previously noted. These organometallic compounds are hydrolyzed by acid, and this overall mechanism accounts for the frequently observed reduction of carbonyl to methylene in acid solution. A systematic examination of the competitive formation of propan-2-ol, pinacol, and propane during reduction of acetone in aqueous sulfuric acid has been made at various cathode materials. Cathodes of cadmium and zinc gave the highest yields of propane [61]. Two alternative reduction courses for 4-ketopentanoic acid have also been noted. Reduction at a lead cathode in aqueous alcohol sulfuric acid afforded pentanoic acid in 80% yield, but 4-hydroxypentanoic acid resulted from reaction in aqueous sodium hydroxide [62]. A series of related ketoacids have been converted to the alkanoic acid by reduction at a mercury cathode in sulfuric acid medium [63].

In general, cadmium [64] or amalgamated zinc [65] is the most effective cathode material for the conversion of a carbonyl group to methylene [66]. However, reactions

at cathodes of lead or mercury continue to be published. Reduction of ketosteroids in dioxane–aqueous sulfuric acid at a lead cathode in a divided cell is a convenient route for the conversion of the carbonyl group to methylene [67]. Menthone has been reduced to the hydrocarbon under relatively mild conditions at a mercury cathode with an electrolyte of either magnesium or zinc perchlorate in ethanol [68]. The more general applicability of this procedure has not, however, been tested. Data from the reduction of other cyclohexanones to the axial alcohol (Table 4) suggest that in general a competition between reduction to the alcohol and formation of the methylene compound will be found in the presence of magnesium or zinc ions.

III. AROMATIC ALDEHYDES AND KETONES

A. Aromatic Carbonyl Compounds to Alcohols and Pinacols

Many early papers indicate that the reduction of aromatic carbonyl compounds at a nickel or lead cathode in alkaline solution gives the pinacol as principal product. Mercury has been used as cathode material in more recent work. Some results are collected in Table 5. Formation of the primary or secondary mono-alcohol by reduction of the carbonyl function is in general a minor competing process. It only becomes important under special preparative conditions. When dilute sulfuric acid is used as the electrolyte under constant current conditions, the mono-alcohol is produced in significant quantities from the benzaldehyde at 14°C but at 35°C or higher the pinacol predominates [69]. Reduction of aromatic carbonyl compounds in an aqueous sodium bicarbonate–carbon dioxide buffer gives mainly the mono-alcohol at a mercury cathode [70]. Reduction of benzophenones in alkaline solution gives only the benzhydrol. The pinacol is formed first, but under alkaline conditions this intermediate undergoes carbon–carbon bond cleavage to form the benzhydrol and benzophenone. Thus on the time scale of a preparative reaction no pinacol can be isolated.

Table 5 Pinacols from the Reduction of Aromatic Carbonyl Compounds in Protic Solvents

Substrate	Conditions: Solvent–Electrolyte–Cathode	Yield of pinacols (%)	Ref.
Benzaldehyde	EtOH–KOH–Ni		[71]
4-Methylbenzaldehyde	EtOH–KOH–Ni	100	[69]
4-Isopropylbenzaldehyde	EtOH–KOH–Ni		[71]
4-Methoxybenzaldehyde	EtOH–KOH–Ni	100	[71]
4-Chlorobenzaldehyde	EtOH–KOH–Cu		[72]
Salicylaldehyde	EtOH–KOH–Ni	70	[71]
2,4-Dimethylbenzaldehyde	EtOH–KOH–Ni	60	[69]
3,5-Dimethylbenzaldehyde	EtOH–KOH–Ni	95	[69]
Vanillin	EtOH–KOH–Ni	45	[71]
Piperonal	EtOH–KOH–Ni	100	[71]
Furfural	Water–phosphate pH 9–Cd		[73]
Acetophenone	EtOH–KOAC–Hg	86	[74]
4-Hydroxyacetophenone	Water–NaOH–Pb		[75]
Benzophenone	EtOH–H_2SO_4–Pb		[76]
4-Methylbenzophenone	EtOH–H_2SO_4–Pb	87	[77]

Preparative-scale conversion of aromatic carbonyl compounds to pinacols is best carried out in aqueous alkaline solution. The pinacol is isolated as a mixture of stereoisomers. Reduction in acetonitrile or dimethylformamide can under some circumstances, discussed below, favor formation of the (±) pinacol. Data for the (±):*meso* ratio for pinacols from acetophenone and propiophenone are collected in Table 6.

Any investigation on the stereochemistry of electrode reactions is important for the elucidation of reaction mechanism. This point is discussed in a collective manner in Chapter 27. Sharp difference for values of the (±):*meso* isomer ratio for pinacols from reduction of aryl alkyl ketones in acid or in alkaline solutions indicates different dimerization mechanisms in the two media. At low pH values, dimerization involves the combination of two neutral radicals since the same (±):*meso* ratio is found from the photochemical reaction of the carbonyl compound in methanol [81]. The latter reaction certainly involves neutral radicals. In alkaline solution, a large proportion of radical anion is present in the solution along with a small fraction of its protonated form, and dimerization occurs in a fast reaction between the radical anion and the neutral radical. The radical anion has a significant charge density on the oxygen atom and hydrogen bonding between this center and the hydroxyl group of the approaching neutral radical becomes important, leading to a preference in favor of the (±)-pinacol for the dimerization process in alkaline solution. Radical anion, radical anion reaction is slower, relative to the radical anion, neutral radical reaction, because of Coulombic repulsive forces [10]. In the case of benzaldehyde, the (±):*meso* isomer ratio does not change significantly with pH. This is because the hydroxylbenzyl radical is less sterically hindered than the corresponding radical from either of the two ketones. Consequently, the dimerization step has lower activation energy and can occur on collision, before hydrogen bonding forces are able to orientate the two species within the encounter complex.

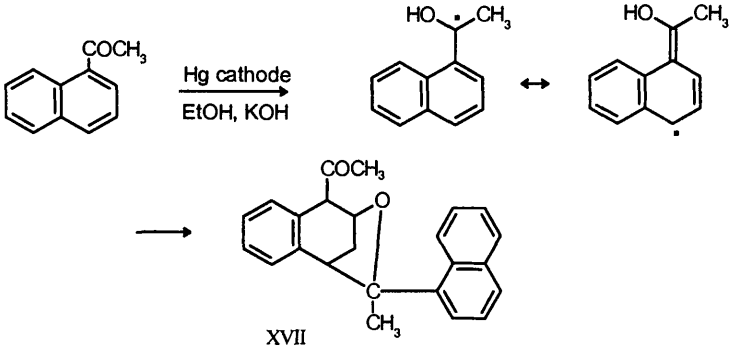
Reduction in dry aprotic solvents allows the formation of ion pairs between the radical anion and a countercation. Where the cation can interact simultaneously with two radical species, dimerization favors the (±)-product because there are fewer steric interactions, in the corresponding transition state, between groups attached to the reacting radicals. Solvent and supporting electrolyte combinations that give a high yield of (±)-pinacol are acetonitrile with tetraethylammonium bromide [82], dimethylformamide with sodium perchlorate [83], and dimethylformamide with europium(III) chloride. Europium(II) is formed in the last

Table 6 Isomer Ratio for Pinacols Formed by Controlled Potential Reduction in Aqueous Alcohol Medium

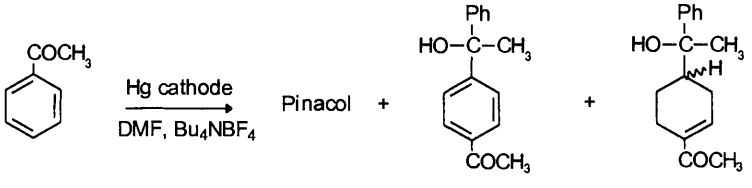
Substrate	Conditions	Pinacols, (±):*meso* ratio	Ref.
PhCHO	Acidic	1:12	[74]
	Basic	1.19 ± 0.06	[74]
p-HOC_6H_4CHO	Acidic	0.93	[78]
	Basic	0.51 ± 0.05	[78]
$PhCOCH_3$	Acidic	1.12 ± 0.20	[79]
	Basic	2.88 ± 0.22	[79]
p-$MeOC_6H_4COCH_3$	Acidic	1.24	[80]
	Basic	3.03	[80]
$PhCOCH_2CH_3$	Acidic	1.40 ± 0.01	[74]
	Basic	2.86 ± 0.22	[74]

system, and dimerization occurs with the involvement of this ion and the ketone in a complex [84]. Good yields with very high diastereomeric excess are also obtained by reduction in dimethylformamide in an undivided cell with sacrificial magnesium anode [85]. The anode provides magnesium ions, which take part in ion pairing.

Radical intermediates in the reductive dimerization of aromatic carbonyl compounds are stabilized by overlap with the benzene ring π-cloud. Examples have been noted of dimerization occurring through substitution onto the benzene ring of one reacting radical. This is the major reaction course for the reduction of 1-acetylnaphthalene, yielding XVII in alkaline solution by a radical-ion, radical coupling mechanism [86]. Small amounts of related reaction products, XVIII and two diastereoisomers of XIX, can be detected in the reduction of acetophenone, and the yield of these compounds is increased by the reduction of acetophenone encapsulated in a cyclodextrin [87]. 2-Aminoacetophenone undergoes carbonyl-to-ring coupling to the extent of 36% during reduction in alkaline solution [88].



XVII



XVIII XIX

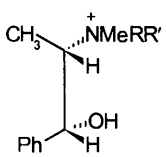
no additive	94.8	0.7	4.5%
with α-cyclodextrin	40.0	4.9	55.4%

Efforts have been made to achieve the reduction of aryl ketones to monoalcohols coupled to asymmetric induction at the electrochemically generated chiral center. Optically active compounds, which form a surface excess at the mercury–water interface, can generate a chiral surface layer. Asymmetric induction is to be expected during the protonation of carbanions generated by the two-electron reduction of phenyl alkyl ketones within this surface layer. Reduction of acetophenone using a chiral conducting salt derived from (−)-ephedrine XXa gives 1-phenylethanol with low optical yield. Substantial amounts of pinacol are also formed and the (±) pinacol shows no asymmetric induction [90–93]. Values for the enantiomeric excess from reduction of acetophenone and related compounds are collected in Table 7. Experiments with ephedrine XXa in buffered aqueous alcohol show that the protonated form of this alkaloid is responsible for generating an

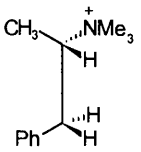
Table 7 Chiral Secondary Alcohols Isolated from Reduction of Ketones at a Mercury Cathode in Aqueous Methanol Containing an Asymmetric Electrolyte

Substrate PhCOR R=	Enantiomeric excess (e.e) of alcohol in presence of anion			
	XXa	XXb	XXI	XXc
	e.e (%)	e.e (%)	e.e (%)	e.e (%)
CH_3	4.2 R	8.4 S	2.0 S	18 S
CH_2CH_3	1.8 R	7.2 S	2.3 S	
$CH(CH_3)_2$	2.7 S	5.8 S	1.9 S	

Note. Data from Refs 91 and 89.



XX**a**: R = R′ = H; XX**b**: R = R′ = Me
XX**c**: R = Me, R′ = $(CH_2)_3CN$



XXI

enantiomeric excess of the (*R*)-1-phenylethanol. In strongly alkaline solution where the free base is present, an excess of (*S*)-1-phenylethanol results [93]. The greatest enantiomeric excess has been obtained in the presence of quaternary ammonium salts containing the nitrile function [92,94]. A maximum enantiomeric excess of 18% was achieved in the reduction of acetophenone to 1-phenylethanol.

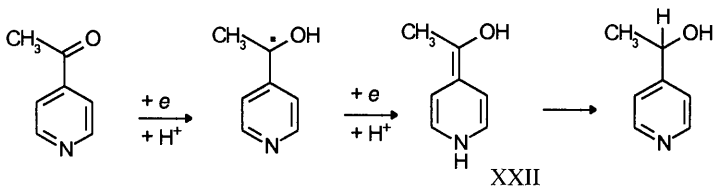
Reduction of acetophenone in acetonitrile containing (*S*)-trimethyl-1-phenylethylammonium salts shows no optical induction in the 1-phenylethanol formed, but the (±)-pinacol is obtained with up to 26% excess of one enantiomer [95]. These results further confirm the importance of some counterions in orienting radical-ion and radical species during the dimerization step to form the pinacols.

A second approach to asymmetric induction during a reduction process at a mercury cathode uses a low concentration of alkaloid in an aqueous alcohol acetate buffer. Induction results because a layer of alkaloid is strongly absorbed on the electrode surface where a proton can be transferred to a carbanion intermediate in an asymmetric environment. Asymmetric induction under these conditions was first observed [96] during the conversion of 4-methylcoumarin to 4-methyl-3,4-dihydrocoumarin. Up to 16% asymmetric induction has been achieved in 1-phenylethanol recovered from reduction of acetophenone in a buffer of pH 4.8 in the presence of quinidine. Pinacol formed simultaneously showed no optical activity. However, quinidine itself is reduced at the potential employed so that the actual catalyst for the asymmetric induction process is not defined [91,97]. A variety of chiral alkaloids (see Table 8) have been screened in the reduction of 2- and 4-acetylpyridine [98]. The added alkaloid gives rise to both asymmetric induction and an increased yield of secondary alcohol at the expense of the pinacols relative to reactions where no alkaloid is present. Reduction of 3-acetylpyridine gave no optically active alcohol under any conditions employed. The high enantiomeric excess found during the reduction of 4-acetylpyridine is thought to be due to first formation of the enol XXII, which tautomerizes in the presence of the chiral alkaloid. Reduction of 2-acetylpyridine can give an equivalent enol, but this route is not open to 3-acetylpyridine.

Table 8 Enantiomeric Excess for Pyridinylethanols from Reduction of 2- and 4-Acetylpyridine at Mercury in the Presence of an Alkaloid (5×10^{-4}M) in Aqueous Acetate Buffer (pH 4.5)–Ethanol (1:1) at 0°C

	Enantiomeric Excess of Pyridinylethanol from	
Alkaloid	2-Acetylpyridine	4-Acetylpyridine
Strychnine	47.5% of (*R*)-(+)	40% of (*R*)-(+)
Brucine	27% of (*R*)-(+)	18% of (*R*)-(+)
Quinine	(±)-Form only	(±)-Form only
Yohimbine	5% of (*R*)-(+)	4% of (*R*)-(+)
Sparteine	2% of *R*-(+)	(±)-Form only
Ephedrine XXa	(±)-Form only	(±)-Form only

Note. Data from Ref. 98.



XXII

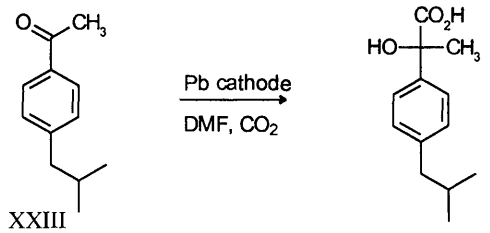
Asymmetric reduction has also been achieved during the reaction of phenylglycollic acid in aqueous alcohol buffers in the presence of strychnine. Mandelic acid was obtained with a 13–20% enantiomeric excess of the (*R*)-isomer [99]. This result compares well with the maximum value of 20% excess (*R*)-isomer found from reduction of (−)-menthyl phenylglycollate in aqueous buffers where the (−)-menthyl ester is the only chiral reagent present [100].

Attempts to achieve optical induction during the reduction of aromatic ketones to the secondary alcohol with the help of a single layer of chiral catalyst covalently attached to a graphite cathode have been much less successful. Reduction of 4-acetylpyridine at a graphite surface coated with (S)-phenylalanine methyl ester afforded an enantiomeric excess of the (S)-pyridinylethanol. In other experiments, ethyl glyoxylate afforded ethyl (−)-mandelate with 9.7% enantiomeric excess [101]. Results using such modified surfaces have, however, proved highly irreproducible [102].

B. Carboxylation of Aromatic Carbonyl Radical Anions

Early workers [103] detected benzilic acid formed during the reduction of benzophenone in dimethylformamide in the presence of carbon dioxide. The carbon dioxide radical anion system is known to have $E^\circ = -2.2$V (vs. SCE) [104] and will thus not be formed in preference to the ketone radical anion. Reaction occurs through trapping of aromatic carbonyl radical anions by carbon dioxide, and this has been developed into a convenient synthesis of aryllactic acids. The modern technological process uses constant current conditions. On a small scale, a divided cell with mercury cathode has been used to obtain benzilic acids from substituted benzophenones and carbon dioxide in 70–90% yields [105] and to convert 4-isopropylacetophenone to the corresponding phenyllactic acid in 85% yield [106]. On a technical scale, these reactions are best carried out in an undivided cell using a lead cathode and a sacrificial aluminum anode with dimethylformamide as solvent

and a moderate pressure of carbon dioxide [107]. The product precipitates as an aluminum(III) chelate and is protected from further reaction. Acidification of this chelate affords the aryllactic acid. Using this technique, benzaldehyde can be converted to mandelic acid in 40% yield [108]. Yields of over 90% have been obtained from the reactions of 4-isobutylacetophenone XXIII and 1-acetyl-6-methoxynaphthalene in an undivided cell under constant current conditions [109]. Tetrabutylammonium bromide proved the best electrolyte to use in dimethylformamide at 35°C. The ketone was slowly added to the reaction mixture, and carbon dioxide was introduced at a pressure of 5 atm.



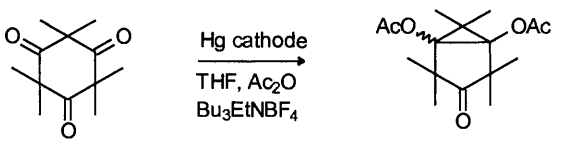
XXIII

IV. DICARBONYL COMPOUNDS

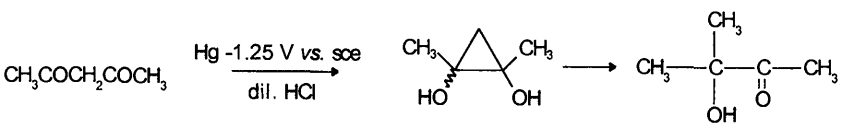
A. Formation of Cyclic 1,2-Diols

Exploration of the reduction of dicarbonyl compounds has centered on attempts to achieve intramolecular coupling of radical intermediates to give a cyclic 1,2-diol. A mechanistic study of the production of cyclopropanediols, during the reduction of 1,3-dibenzoylpropane in acetonitrile, has been made [110]. It is suggested that the rate-determining cyclization step is the addition of the radical anion from one ketone function onto the second carbonyl group in the same molecule.

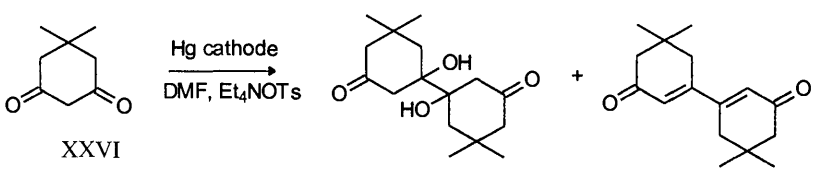
Some aliphatic 1,3-diones can be reduced to the cyclopropanediol, but this route is generally not satisfactory for the preparation of larger ring compounds from aliphatic



XXIV



XXV



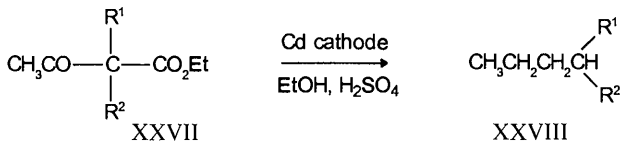
XXVI

ketones. *gem*-Dialkyl substitution as in substrate XXIV favors cyclopropane ring formation [111]. Acetylacetone is reduced in aqueous hydrochloric acid [112] to the cyclopropanediol, and this undergoes ring opening catalyzed by protons to form the skeletal rearranged product XXV. Reduction of XXVI affords the dimeric pinacol and its dehydration product [113]. Attempts to prepare the strained bicyclobutane system by reduction of cyclobutane-1,3-diones have proved unsuccessful [114].

Reduction of α,ω-dibenzoylalkanes at a mercury cathode has been investigated in both aqueous sodium hydroxide [115] and in acetonitrile containing tetraethylammonium tetrafluoroborate [110]. Good yields of the 1,2-diphenylcycloalkan-1,2-diol are obtained only when a ring size of five or six members is the result. Attempts to extend the process to formation of seven-membered rings lead only to oligomeric materials. Reduction of 1,8-dibenzoylnaphthalene gives mainly the *cis*-acenaphthenediol in acid solution together with some ketone formed by pinacol rearrangement of the initial product. In alkaline solution, this diketone gives mainly *trans*-acenaphthenediol together with a bis-secondary alcohol [115,116]. It has been proposed that carbon-carbon bond formation can occur by nucleophilic addition of a carbanion from two-electron reduction of one carbonyl group onto the adjacent carbonyl group [116].

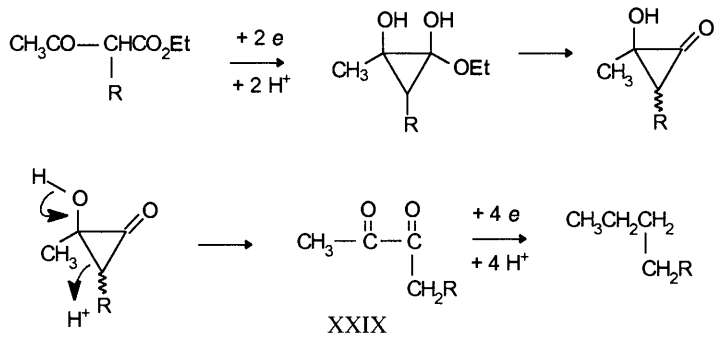
B. The Tafel Rearrangement—Reduction of β-Ketoesters

Reduction of β-ketoesters in aqueous alcohol sulfuric acid leads to removal of both functional groups combined with a carbon skeletal rearrangement and the isolation of a hydrocarbon containing the same number of carbon atoms as the original β-ketoacid. Conversions of the type XXVII into XXVIII occur in 30–60% yields [117–119]. The reaction was recognized in 1912 as a skeletal rearrangement [119] and is termed the Tafel rearrangement. Confirmatory evidence for the structures of a number of reaction products has been given [120,121].



XXVII XXVIII

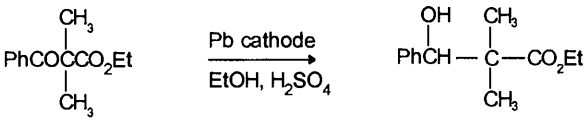
The Tafel rearrangement only occurs under acid conditions. A satisfactory reaction mechanism was established in 1976 [122]. In acid medium it is proposed that reduction of carbonyl groups is followed by reaction of intermediates to form a hydroxycyclopropanone. Acid-catalyzed ring opening then yields a α-diketone XXIX. This last intermediate is



XXIX

reduced in stages to the hydrocarbon. Lead and mercury have been used as cathode materials, but the best material has been found to be cadmium [119], probably because this metal promotes the electrochemical conversion of a carbonyl group to methylene. Evidence for the overall reaction pathway comes from the isolation of two monoketones, derived by partial deoxygenation of the α-diketone XXIX, together with secondary alcohols from reduction of these monoketones. In separate experiments it was shown that the α-diketone is reduced electrochemically to the hydrocarbon. β-Ketoesters derived from alicyclic ketones do not undergo the Tafel rearrangement, probably because of the difficulty of forming the cyclopropane intermediate [122,123].

An unconjugated carbonyl function is necessary for rearrangement. Ethyl benzoylacetate and the related ketoester XXX do not undergo the Tafel rearrangement. For these two substrates, reduction in acid solution converts the carbonyl group to secondary alcohol [124,125]. Reduction of ethyl benzoylacetate in dimethylformamide gives a pinacol, which subsequently undergoes a Diekmann reaction due to the presence of electrogenerated base [126].

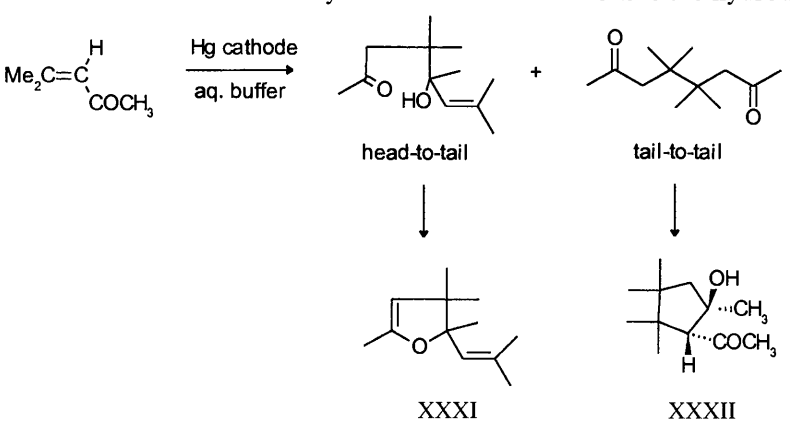


XXX

C. Alcohols From Reduction of α,β-Unsaturated Carbonyl Compounds

The radical anion formed by electron attachment, and the radical formed by protonation of this intermediate on the oxygen center, are delocalized species. Both species show radical character on the carbonyl carbon atom, which is the head group, as well as on the β-carbon atom, which is the tail group. Radical coupling can occur head-to-head, head-to-tail, or tail-to-tail so the hydrodimer mixture from reduction of α,β-unsaturated carbonyl compounds is often complex. Further, each of these hydrodimers may exist as stereoisomers. In general, a hindered β-position favors the formation of glycol by head-to-head coupling and the hydroxyketone by head-to-tail coupling. Tail-to-tail coupling to give a diketone is considered in another chapter along with other related hydrodimerization process.

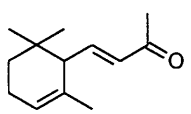
One of the most continuously studied of these reactions is the hydrodimerization of



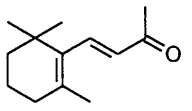
XXXI XXXII

mesityl oxide. Early workers [127–129] were able to isolate many of the products in a pure state, and the structures of these were confirmed in 1955 [130]. Reduction of mesityl oxide at mercury in an acetate buffer leads to a mixture of head-to-tail and tail-to-tail hydrodimers. The initial reaction products undergo further chemical reactions so that XXXI and XXXII are isolated [131]. These same products result from the reduction of mesityloxide by magnesium or zinc in acetic acid. From some reactions, a small yield of the head-to-head glycol has been isolated [132–134]. Methyl vinyl ketone has a relatively unhindered tail position and affords 75% of the diketone hydrodimer with only 10% of the pinacol at a mercury cathode [135].

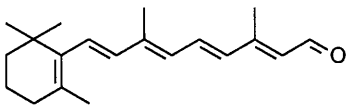
The two methyl ketones, α- and β-ionone, as well as the aldehyde retinal, have a



α-ionone



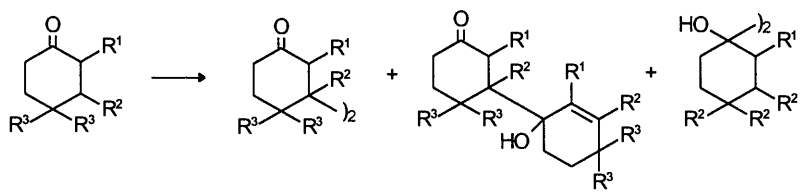
β-ionone



retinal

sterically hindered tail position relative to the head position. Reduction of the α- and β-ionones affords a mixture of (±)- and *meso*-pinacols in yields up to 70% either in dimethylformamide containing tetrabutylammonium iodide or in aqueous acetonitrile with an acetate buffer as supporting electrolyte [136]. Retinal is unstable in the presence of proton donors such as water and acetic acid, and reduction in aqueous media leads to complex mixtures of products. Retinal pinacol is obtained in 50% yields from reduction in acetonitrile containing some diethyl malonate, which can act as a proton donor [137].

Cyclohexenone is reduced either by sodium amalgam [138] or electrochemically in acetonitrile containing tetrabutylammonium fluoroborate [139] and affords mainly the tail-to-tail diketonic hydrodimer. Some 10–26% of the head-to-tail hydrodimer has been detected in the mixture of products from reduction at a mercury cathode in aqueous ethanol under both acidic and basic conditions [140]. Substituents on the 3- and 4-positions, as in XXXIII, cause formation of some head-to-tail XXXV and head-to-head hydrodimers XXXVI (see Table 9). The product ratios depended on the concentration of water in acetonitrile used as solvent. Other work discussed later indicates that the presence of metal ions that can coordinate with alkoxy groups also changes these product ratios.



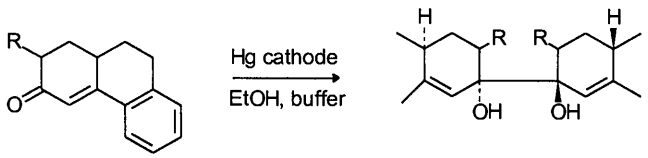
XXXIII XXXIV XXXV XXXVI

Table 9 Products from Reduction of Cyclohexenones at a Mercury Cathode in Acetonitrile Containing Water with Bu_4NBF_4 as Supporting Electrolyte

Substrate XXXIII	Water (%)	Product yields (%)		
		XXXIV	XXXV	XXXVI
$R^1 = R^2 = R^3 = H$	0	97		
	5	97		
$R^1 = R^2H, R^3 = Me$	0	52	11	16
	5	28	4	67
$R^1 = R^3 = Me, R^2 = H$	0	10	40	50
	5		10	90
$R^1 = H, R^2 = R^3 = Me$	0	10	60	30
	5		45	50

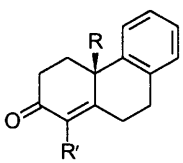
Note. Data from Ref. 141.

Cholesterone, progesterone, and other eneones in the cholestane series have a highly sterically hindered tail position and afford only head-to-head pinacols at a mercury cathode in ethanolic buffers at both pH5 and pH12.5 [142–144]. The stereochemistry of the pinacols formed from some cyclohexenones similar of structure to the steroids has been studied in some detail [145,146]. Dimerization of radicals derived from XXXVII is highly enantioselective. It occurs by reaction between radicals from the same enantiomeric configuration to give only one of the possible racemic pinacols XXXVIII. Where an angular methyl substituent is present as in XXXIX, the dimerization is less enantioselective. It is



(±)-XXXVII
R = H or Me

(±)-XXXVIII



(±)-XXXIX, R = H or Me

assumed that the radical derived by protonation of the anion radical is adsorbed on the mercury electrode surface through both the π-system and the hydroxyl group. Desorption then occurs from the benzene ring end of the radical. There must be greater steric hindrance to the approach of two enantiomeric radicals than is the case for two radicals having the same stereochemistry. Good yields of pinacol result from these processes.

The presence of chromium(III) or tin(II) ions in the electrolyte considerably increases the yields of coupled products from the reduction of α,β-unsaturated carbonyl

compounds. These ions coordinate with radical-ion intermediates through the oxygen center, increasing the radical nature of the intermediate. Reduction of the highly conjugated enones β-ionone, β-ionylidene acetaldehyde, and retinal in dimethylformamide containing sodium perchlorate and chromium(III) ions gives the pinacols in good yields [147]. The transition metal ions are reduced to the chromium(II) state under the conditions employed. Reduction of α- and β-ionone in aqueous methanolic sulfuric acid at a platinum cathode in an undivided cell with either metallic tin or a tin(II) salt present gives pinacols in 60–70% yields [148]. Literature on the reduction of enones by dissolving metals indicates that zinc dust–acetic acid reduction favors production of pinacol relative to reduction by sodium amalgam [135], indicating the participation of zinc(II) ions in the dimerization step.

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11

Reduction of Azomethine Compounds

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I. Introduction
II. Derivatives of Ammonia
  A. Imines and Schiff bases
  B. Immonium salts
  C. Azomethine derivatives of acids
III. Derivatives of Hydrazine
  A. Azines
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IV. Derivatives of Hydroxylamine
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V. Diazoalkanes
References

I. INTRODUCTION

In this chapter the reduction of compounds with a carbon–nitrogen double bond is discussed; besides the classic carbonyl derivatives, such as Schiff bases, hydrazones, and oximes, diazoalkanes are also treated.

The reduction of azomethine compounds depends on their structure and the experimental conditions, but most of the reactions can be described by relatively few schemes. In acidic solutions, compounds of the type $RR'C{=}N{-}Y$ are reduced with saturation of the double bond if Y is carbon, but if Y is a heteroatom (oxygen or nitrogen), the reduction follows Eqs. (1) through (3) [1]:

$$RR'C{=}N{-}Y + H^+ \rightleftharpoons (RR'C{=}N{-}Y)H^+ \tag{1}$$

$$(RR'C{=}N{-}Y)H^+ + 2e^- + 2H^+ \longrightarrow RR'C{=}\overset{+}{N}H_2 + HY \tag{2}$$

$$RRC{=}\overset{+}{N}H_2 + 2e^- + 2H^+ \longrightarrow RR'CH{-}\overset{+}{N}H_3 \quad (3)$$

In alkaline solution many of the azomethine compounds are not reducible but if the azomethine group is conjugated with suitable groups, the carbon–nitrogen double bond may be reduced.

In aprotic media, such as DMF or MeCN, cleavage of the N–Y bond is the usual reaction, but in some cases the double bond is saturated. For derivatives of aldehydes a special reaction may proceed when Y is a good leaving group; a nitrile is formed as a result of an elimination of HY, possibly induced by an electrogenerated base.

Formally, compounds of the type RR′C=N–Y resemble vinylic compounds RR′C=CR″Y, where Y is a leaving group. It has been suggested [2] on the basis of a rather low reorganization energy λ connected with the electron transfer to vinyl halides that the first electron was added to the π^*-orbital of the π-electron system rather than to the σ^* orbital of the C–Y single bond.

The linear connection [3] between the reduction potential of N,N-dimethylhydrazones and their rate of cleavage [vide infra] supports the analogy with the reduction of vinylic halides. The analogy is further substantiated by the fact that vinyl halides of the type RCH=CR″Y form acetylenic compounds RC≡CR″ by a base-induced elimination on reduction in aprotic medium [2], analogously to the formation of nitriles from RCH=NY under similar conditions [4].

From the analogy with vinyl compounds, two factors are expected to be of prime importance for the reduction of an azomethine compound; the electron affinity of the π-electron system and the leaving group ability of Y^-; the latter is usually inversely proportional to the acidity of HY. Protonation of RR′C=NY would facilitate the reduction of the compound both by enhancing the electron affinity of the system and by increasing the leaving group ability substantially by changing the leaving group from Y^- to the much weaker base HY.

A review on the electrochemistry of azomethine compounds gives leading references up to early 1968 [5]; the reduction of oximes [6] and hydrazones has been reviewed more recently [7,8]. In this chapter the azomethine compounds are treated in four sections according to whether they are derivatives of ammonia, hydrazine, hydroxylamine, or a diazoalkane.

Electrochemical oxidation of azomethine compounds is discussed in Chapter 15.

II. DERIVATIVES OF AMMONIA

A. Imines and Schiff Bases

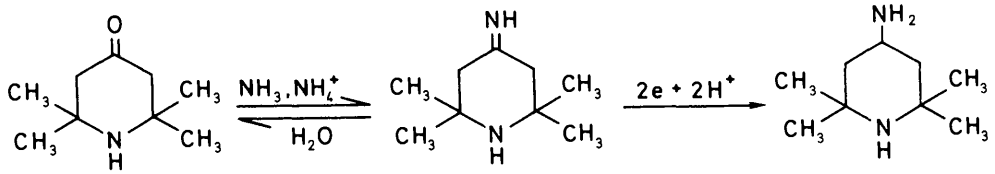
1. Protic Medium

The azomethine group is generally more easily reducible than the carbonyl group from which it is derived. Imines and Schiff bases of aldehydes and ketones are reducible in a pH region that depends on their structure; imines from simple, aliphatic ketones are reducible only in alkaline solution. The compounds are easily hydrolyzed, and in most cases the equilibrium [Eq. (4)] lies far to the left

$$>C{=}O + HNRR' \rightleftharpoons >C(OH)NRR' \overset{H^+}{\rightleftharpoons} >C{=}\overset{+}{N}RR' + H_2O \quad (4)$$

The easy hydrolysis of the imine interferes with its polarographic or preparative reduction in aqueous solution. Polarographically inactive unconjugated ketones may,

however, be determined polarographically in solutions with a large excess of ammonia [1,9,10]. Preparative reduction of such imines may also be made by reducing a solution of the ketone in the presence of a large excess of ammonia or amine, if the potential is held at the reduction potential of the imine. Using this method, cyclohexanone was reduced in the presence of an excess methylamine to methylcyclohexylamine [1] and 2,2,6,6-tetramethyl-4-oxopiperidine (I) reduced to 4-amino-2,2,6,6-tetramethylpiperidine (II) in a solution of ammonia and ammonium chloride as in Eq. (5) [11]. When high concentrations of I are used, some of the product (II) condenses with I to a reducible azomethine compound, and varying amounts of secondary amine, $(C_9H_{18}N)_2NH$, are formed.



(I) (II)

(5)

The reaction is rather general for ketones with ammonia, primary, and even secondary amines [10]; amino acids [12,13] have thus been prepared from α-ketoacids by reductive amination.

In a paired electrolysis, amines have been *N*-alkylated in alcoholic solution. At the Pt(Pt) anode the alcohol was oxidized to an aldehyde that condensed with the amine to an imine; the imine was reduced at the cathode to a secondary amine. Benzylamine was thus electrolyzed to benzylethylamine in 96% yield (65% current yield) in ethanol containing 10 vol% of water [14].

Although only a few imines are stable in aqueous solution, reduction in cold 50% sulfuric acid at a lead cathode may give the amine [15,16]. In this connection it can be mentioned that 2,4-dihydroxybenzophenone oxime on reduction on the first wave in acid solution gives an imine stable enough to be isolated [17]. Schiff bases of some other benzophenone derivatives are stable in acid solution; their reduction is a straightforward saturation of the azomethine group [18,19].

Some Schiff bases of aromatic aldehydes and ketones give two, one-electron waves in aqueous acidic solution; at higher pH the waves merge to one, two-electron wave in much the same manner as carbonyl compounds [1,20]. The product of the first one-electron reduction is a radical that may either dimerize or be reduced further at a more negative potential. The yield of dimer depends on a number of factors, including proton availability, supporting electrolyte, cathode material, and concentration of Schiff base [21]. If the reduction is performed using a chiral supporting electrolyte, some chiral induction is observed in the secondary amine, but not in the dimer [22]; such reactions are discussed in Chapter 25, where the stereochemistry of the reduction of some Schiff bases is also discussed [23].

2. Aprotic Medium

In MeCN, most Schiff bases give a single two-electron wave; the radical anions of imines are more basic than the corresponding ketyl anions and are able to abstract a proton from the medium [24]. Aliphatic ketimines behave similarly in dimethylformamide (DMF) [23], whereas some aldehyde anils give two peaks in cyclic voltammetry (CV), depending on the

sweep rate; the mechanism of the two-electron reduction of Schiff bases probably involves a solution electron transfer from the radical anion to the protonated radical anion [24,25]. In DMF, the radical anions from fluorenone imine and anil are stable on the time scale of CV; the dianions have half-lives of less than1 ms and abstract a proton to give the anion of the fluorenyl amine [26].

Mixed couplings with Schiff bases have been described; reduction of benzylidene aniline in the presence of acrylonitrile gave a mixture containing 1,5-diphenyl-2-pyrrolidone [27] and other products. Reductive coupling reactions are discussed in Chapter 21.

In nonaqueous solution azomethine compounds are usually stable, and several types have been reductively coupled with alkyl halides or carbon dioxide. Benzophenone anil (III) gives thus on reduction in DMF–TBAI in the presence of methyl chloride a mixture of N- and C-methylated and N,C-dimethylated products [28]:

$$\underset{\text{(III)}}{Ph_2C{=}NPh} \xrightarrow[CH_3Cl]{2e} \underset{57\%}{Ph_2CH{-}N(CH_3)Ph} + \underset{20\%}{Ph_2C(CH_3){-}NHPh} + \underset{23\%}{Ph_2C(CH_3){-}N(CH_3)Ph} \quad (6)$$

Benzil dianil is under similar conditions reduced to a mixture of *cis* (12%) and *trans* (88%) 1,2-di-(*N*-methylanilino)-1,2-diphenylethane; interestingly enough, *cis* compound seems to be the thermodynamically stable isomer [29]; the structure was proved by x-ray analysis [30]. In these couplings the reduced azomethine compound reacts with the alkyl halide in a nucleophilic displacement reaction.

Sterically hindered halides may be used in some cases; thus, reduction of benzylidenephenethylamine in the presence of 2-bromonorbornane in DMF–TBAI gives *N*-(norborn-2-ylbenzyl)phenethylamine (33%), *N*-benzyl-*N*-norborn-2-ylphenethylamine (26%), and some *N*-benzylphenethylamine [31].

Another type of mechanism operates in the synthesis of amino acids by electroreductive coupling of alkyl halides with Schiff bases in DMF; in these reactions the alkyl halide chosen is reduced at less negative potentials than the azomethine derivative of an α-ketoester, and the coupling is proposed to be a nucleophilic addition of an alkyl anion [Eq. (7)] to the azomethine compound, [Eq. (8)]; the benzyl group is afterward reductively removed [32,33]:

$$RX \overset{e}{\rightleftharpoons} R^{\cdot} + X^{-} \overset{e}{\rightleftharpoons} R^{-} + X^{-} \quad (7)$$

$$PhCH_2N{=}C(R')OOR'' \xrightarrow[(2)\,H^+]{(1)\,R^-} PhCH_2NHCR(R')COOR'' \quad (8)$$

Amino acids may also be prepared from azomethine compounds by reducing them in the presence of carbon dioxide [34–38]. Thus reduction of benzylidene aniline (IV) in molten tetraethylammonium *p*-toluenesulfonate saturated with carbon dioxide at 140°C gave *N*-phenyl-phenylglycine (60% yield) [34], [Eq. (9)]. In DMF a similar yield was obtained together with small amounts of a dimer and some phenylbenzylamine [38].

$$C_6H_5CH{=}NC_6H_5 \xrightarrow[CO_2]{2e+H^+} C_6H_5CH(NHC_6H_5)COO^- \quad (9)$$

(IV)

B. Immonium Salts

Immonium salts have been used as model compounds for the study of the dimerization reaction in aprotic media, partly because no protons are involved in the reaction. It was shown that the electrodimerization process for immonium cations was purely radical [39,40].

Radicals from reduction of derivatives of benzophenone immonium salts are rather stable under aprotic conditions, whereas less conjugated radicals dimerize at the central carbon with rates depending on the conjugation [41].

From an electrochemical reduction of some cyclic immonium salts of the type *N*-cyclohexylidenepyrrolidinium fluoborate in aprotic media, the enamine and the saturated tertiary amine were the major products [42]. It was suggested that the reaction was a one-electron transfer followed by a rate-determining radical–radical disporportionation involving hydrogen atom transfer.

C. Azomethine Derivatives of Acids

Imidic esters are easily hydrolyzed in aqueous solution, but some are stable enough for a polarographic investigation in a cold solution. Reduction at a lead cathode in cold 1 M sulfuric acid of ethyl benzimidate gave benzylamine in 76% yield [43]. The reduction can probably be described by:

$$RC(OR'){=}\overset{+}{N}H_2 \xrightarrow{2e+2H^+} RCH(OR')\overset{+}{N}H_3 \xrightarrow{-R'OH}$$

$$RCH{=}\overset{+}{N}H_2 \xrightarrow{2e+2H^+} RCH_2\overset{+}{N}H_3 \quad (10)$$

In DMF, methyl benzimidiate shows a reversible reduction to the radical anion at about −2.3 V (SCE) [11].

S-Methylisothiobenzanilide is polarographically reducible in two steps; the product from the first two-electron reduction could by hydrolyzed to benzaldehyde, so the reduction route is probably analogous to Eq. (10) [5].

Amidines of aliphatic acids are generally not reducible in buffered solution. Some amidines derived from aromatic acids are reducible at very negative potentials and only in a narrow pH interval from slightly acid to alkaline solution. The reduction is similar to that of imidic esters [Eq. (10)], and yields the amine [44].

Aromatic isothiocyanates have been investigated polarographically; in acid solution, a four-electron wave or two poorly separated two-electron waves are found, whereas a single two-electron wave occurs in alkaline solution [45,46]. Controlled potential reduction of phenylisothiocyanate (V) in alkaline solution yielded thioformanilide (VI), as in Eq. (11) [45]. VI in acid solution is reduced at the second wave of V.

$$C_6H_5N{=}C{=}S \xrightarrow{2e+[2H^+]} C_6H_5NHCH{=}S \quad (11)$$

(V) (VI)

III. DERIVATIVES OF HYDRAZINE

A. Azines

1. Protic Medium

Benzalazine is in slightly acid solution reduced to benzylamine in a six-electron reduction, whereas it forms benzaldehyde benzylhydrazone in a two-electron reaction in alkaline solution [1]. Benzaldehyde benzylhydrazone is reduced in acid solution to benzylamine in a four-electron reaction at potentials slightly less negative than those of benzalazine, so it is not quite clear whether benzaldehyde benzylhydrazone is an intermediate in acidic solution or whether there is initially a cleavage of the central nitrogen–nitrogen bond.

It has been suggested [47] that 2-benzoylpyridine azine is reduced via the azo and hydrazine derivatives, rather than through the route suggested previously for benzalazine [1]. It would be rather exceptional if a hydrazine were reducible at the same potential as the azine.

Unsymmetrical azines of an aromatic and an aliphatic carbonyl compound, such as benzophenone cyclohexanone azine, are reduced in slightly acidic solution with cleavage of the nitrogen–nitrogen bond and saturation of the aromatic azomethine group [Eq. (12)], whereas the aliphatic imine is then hydrolyzed [Eq. (13)] [48]; unsymmetrical cyclic azines, such as 5-*H*-2,3-benzodiazepines, are reduced similarly, usually with ring contraction.

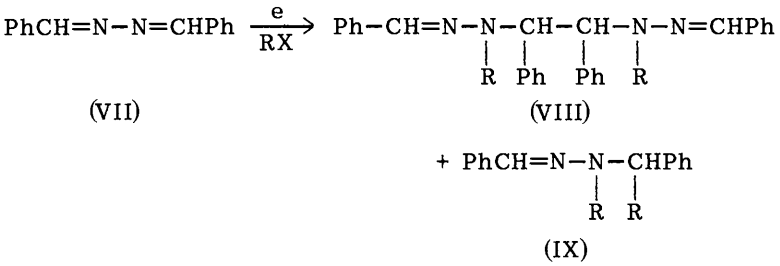
$$Ph_2C{=}N{-}N{=}CRR' + 4e + 5H^+ \longrightarrow Ph_2\overset{+}{C}HNH_3 + RR'C{=}NH \tag{12}$$

$$RR'C{=}NH + H_2O \longrightarrow RR'C{=}O + NH_3 \tag{13}$$

Electrochemical reduction of 2,2,6,6-tetramethyl-4-oxopiperidine (I) azine or a mixture of I and hydrazine at a lead cathode in neutral medium gave a nearly quantitative yield of 4-amino-2,2,6,6-tetramethylpiperidine II [49].

2. Aprotic Medium

In DMF, benzalazine (VII) shows two, one-electron steps in CV. Preparative reduction of VII in the presence of an alkylating agent yields alkylated bis-hydrazines (VIII) or the dialkylated hydrazone (IX) [51], as in Eq. (14). An assignment of the stereochemistry of the bis-hydrazones, obtained by reduction of VII followed by protonation, could be achieved by cyclization with aldehydes to imidazolidines.



(VII) (VIII) (IX) (14)

Aromatic azines may be reduced in aprotic media in the presence of carbon dioxide to amino acids; thus ArCR=N–N=CRAr can be reduced (R=H) in MeCN saturated with CO_2 at −1.7 to −2.0 V (SCE) to *N*-arylideneamino-2-arylglycines or at −2.1 to −2.2 V to *N*-unsubstituted arylglycines [50].

In some cases the radical anions of azines in DMF are stable enough to allow their electron spin resonance (esr) spectra to be obtained. The radical anion of fluorenone azine is thus stable for months in DMF [52,53]. In the absence of a proton donor, the radical anion is reduced to the dianion, which is stable on the time scale of CV. In the presence of a relatively strong proton donor, such as hexafluoro-2-propanol, fluorenone fluorenylhydrazine is obtained [53]; this is analogous to the reduction of benzalazine in aqueous alkaline solution [1].

B. Hydrazones

1. Protic Medium

The electrochemistry of hydrazones, azines, and other derivatives of hydrazine is complicated by the possibility of tautomerization. The following forms must be considered [54,55]:

$$\underset{\text{(X)}}{RCH_2{-}CH_2{-}N{=}NR'} \rightleftharpoons \underset{\text{(XI)}}{RCH_2CH{=}NNHR''} \rightleftharpoons \underset{\text{(XII)}}{RCH{=}CHNHNHR'}$$

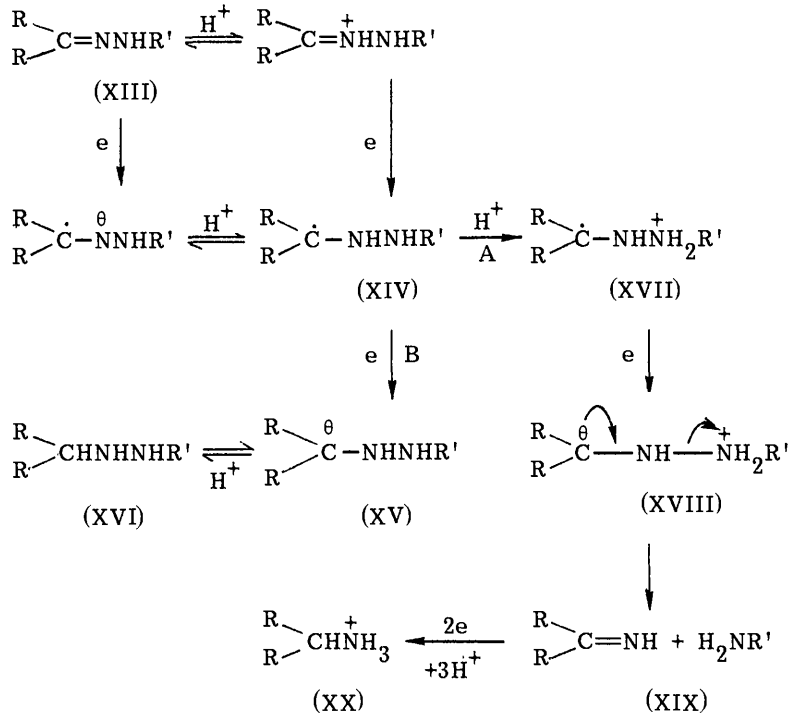
The hydrazone (XI) is the predominant form, and in acid and neutral solution no indication of either the azo- (X) or the ene-hydrazine form (XII) has been found. In alkaline solution, however, studies with tritium [56] have shown exchange both of the aldehyde hydrogen and of hydrogen atoms at the α-carbon, indicating the presence of both the forms (X and XII). The equilibrium constant in 0.1 M ethanolic KOH for the equilibrium benzyl phenyldiazene $\rightleftharpoons$ benzaldehyde phenylhydrazone is about 10^8, but for monoalkylhydrazones of aliphatic carbonyl compounds a higher proportion of the azo form is found. Acetaldehyde propylhydrazone is thus in *t*-butanol containing 0.02 M potassium *t*-butylate at 100°C in equilibrium with 3.7% of the azo form [57].

The different tautomeric forms may be reduced at different potentials, and the removal from the equilibrium of one of the forms by reduction leads to a continuous formation of the easiest reducible tautomer in an attempt to restore the equilibrium. The rate of the formation of the reducible tautomer is thus of importance for the electrode reaction, and electrochemical techniques that may be slow compared with the (usually unknown) rate of tautomerization are therefore of limited value in determining the position of the tautomeric equilibria.

The *o*- and *p*-phenylazophenols in alkaline solution and azo groups conjugated with certain heterocyclic nuclei may in some respects be treated as hydrazones; these are, however, discussed in Chapter 9 under azo compounds.

Phenylhydrazones of aromatic carbonyl compounds are generally reducible in acid solution in a four-electron reduction, which leads to the formation of aniline and another amine; in alkaline solutions only α, β-unsaturated phenylhydrazones are reducible, and the reduction leads in a two-electron reaction to a saturated phenylhydrazone [1]. Scheme 1 shows the reduction route in aqueous solution that has been suggested [1,58].

Polarographic evidence suggests that in acid solution a protonation occurs before the electron transfer; this is supported by the polarographic reduction of some quaternized hydrzones [59]. An argument in favor of this reaction sequence (Scheme 1) is that the hydrazine (XVI) is not reducible under the conditions used for the reduction of the phenylhydrazone. Another argument is that the imine (XIX) is reduced at about the same potential or more easily than the phenylhydrazone.



Schemes 1

After the uptake of a proton and an electron, the radical (XIV) thus formed may accept either a proton (route A) or an electron (route B). In route A the protonated radical (XVII) accepts an electron, which results in a cleavage of the nitrogen-nitrogen bond with aniline as leaving group. The imine thus formed (XIX) is protonated and reduces further. In route B the protonation in alkaline solution is relatively slow and the radical is reduced to the carbanion (XV); the leaving group would be the very basic anion of aniline, so protonation to the hydrazine may be the favored reaction rather than the cleavage of the N–N bond. (In the scheme, H^+ stands for any proton source).

Phenylhydrazones of aliphatic ketones are not reducible in aqueous solution; however, trimethylhydrazonium salts of such ketones are reducible in neutral and alkaline media [11]:

$$C_6H_5CH_2C(CH_3)=NN(\overset{+}{C}H_3)_3 + 4e + 3H^+ \longrightarrow C_6H_5CH_2CH(NH_2)CH_3 + (CH_3)_3N \quad (15)$$

2. Aprotic Medium

In aprotic medium, hydrazones of aromatic carbonyl compounds of the type ArRC=N–$NR^-R'R''$ where R,R′ and R″ are carbon substituents are reduced to the radical anion, which may cleave to an amine anion and an imine radical; the reduction is analogous to the reduction of vinyl halides of the type ArR=CR′X. For R′ and R″ equal to methyl the rate of cleavage is a linear function of the reversible reduction potential of the hydrazone [3]. When R is hydrogen and R′ and R″ are carbon substituents, the base generated in the reduction (EGB) may induce an elimination of an amine with formation of a nitrile [3], when the leaving amine anion is a good leaving group; an analogous elimination to an

acetylenic compound is found during the reduction of vinyl halides ArCH=CR′X. When R′ is hydrogen the hydrazone may be sufficiently acidic to protonate the radical anion ("father/son reaction"); this is especially found when R″ is an electron-attracting group such as benzoyl. For phenylhydrazones, bases generated during the further reduction of the cleavage products may deprotonate the parent.

Phenylhydrazones of aromatic aldehydes have been investigated polarographically in DMF [60]; they show two waves, the first being a one-electron wave. Reduction at the limiting current of the first wave of the phenylhydrazones of benzoin and salicylaldehyde showed aniline as a product.

Fluorenone fluorenylhydrazone may be reduced in two ways in DMF, depending on the availability of protons. If the anion radical is not protonated by either an added proton donor or starting material, decomposition occurs by carbon–nitrogen bond cleavage to give fluorene and fluorenone hydrazone. In the presence of a proton donor, reduction with cleavage of the nitrogen–nitrogen bond occurs; the final produce is 9-aminofluorene [53].

Reduction of 1-arylidenetrimethylhydrazinium salts in DMF yields a benzonitrile derivative. The reaction was proposed to proceed via an electron uptake and a cleavage of the N–N bond followed by a loss of a hydrogen atom, thus forming a benzonitrile derivative [61]. Alternative formulations may be those discussed for the formation of benzonitrile from benzaldehyde oxime [vide infra] involving an electrogenerated base [62]. In this connection it is of interest that the dimethylhydrazone of nitrobenzaldehyde undergoes base-induced cleavage to the nitrile at potentials of the second wave or by an electrochemically generted base, the anion of 4-nitro-*N*-methylimidazole [63]; other benzaldehyde hydrazones behave similarly [63].

Several substituted phenylhydrazones and other hydrazones have been investigated [64–67]; nitro groups are generlly reduced before the hydrazone, but at a suitable potential the phenylhydrazone part of the molecule is reduced according to the general scheme.

C. Acylated Hydrazones

1. Protic Medium

Acylated hydrazones of aromatic carbonyl compounds are reducible in acid solution following the usual scheme; anisylidene benzohydrazide was thus at pH 4.25 reduced to 4-methoxybenzylamine and benzamide [68]:

$$CH_3OC_6H_4CH{=}NNHCOC_6H_5 \xrightarrow[\text{pH } 4.25]{4e+5H^+} CH_3OC_6H_4CH_2\overset{+}{N}H_3 + H_2NCOC_6H_5 \qquad (16)$$

In alkaline medium benzylidene benzohydrazide is reduced in a two-electron reaction to *N*-benzoyl-*N*-benzylhydrazine:

$$C_6H_5CH{=}NNHCOC_6H_5 \xrightarrow[\text{pH } 12]{2e+2H^+} C_6H_5CH_2NHNHCOC_6H_5 \qquad (17)$$

The reduction of nicotinoyl- and isonicotinoylhydrazones of several carbonyl compounds has been investigated. The reaction involves the expected reduction of the hydrazone and also the reduction of the amide to an alcohol [69].

The reaction schemes (16) and (17) usually seem to be followed in protic solvents; for example, benzhydrylidene hydrazides of disubstituted glycolic acids [70] and bis-benzyli-

dene succinic hydrazide derivatives [71] have been reported to be reduced according to Eqs. (16) and (17).

Several polarographic investigations of Girard hydrazones and of semi- and thiosemicarbazones have been made [1, 72–80], but relatively few controlled potential reductions have been reported [1, 76–80]. From these, it appears that in acid solution a four-electron reduction is found and that the first step is hydrogeneolysis of the nitrogen–nitrogen bond; in some cases a catalytic hydrogen evolution is found [80]. In strongly acid solution there is often a tendency found to a stepwise reduction. Thus, benzaldehyde thiosemicarbazone [76] gives at pH 0 two waves at −0.66 and −0.73 V (SCE); when alcohol is present, the separation of the waves is poor or not visible at all. In alkaline solution some of the compounds are reducible, and then a two-electron reduction is found that results in a saturation of the carbon–nitrogen double bond to the hydrazine. At intermediate pH values both reduction paths may be followed simultaneously and the relative importance of the two routes depends on many factors, such as pH, buffer concentration, temperature, and solvent. Thus, benzaldehyde and benzophenone semicarbazone [1], *p*-acetamidobenzaldehyde thiosemicarbazone [76], *p*-acetamidobenzaldehyde *S*-methylthiosemicarbazone [77], and cyclopentanone and benzophenone Girard hydrazone [77] all yielded the expected amine at low pH; at high pH values, benzophenone Girard-D hydrazine [77] and benzaldehyde semicarbazone [79] were reduced in high yield to the acylated hydrazine; and at medium pH, several of the compounds gave mixtures of the amine and the hydrazine [1,76,77].

Benzaldehyde thiobenzoylhydrazone (XXI) is reduced in acid solution according to the general reduction scheme in which the initial step is the hydrogenolysis of the nitrogen–nitrogen bond. At pH < 2 three polarographic waves are found [59], and on the basis of controlled potential reductions the following steps were suggested:

1. Wave: $C_6H_5CH{=}NNHCSC_6H_5 \xrightarrow[2e+2H^+]{H^+} C_6H_5CH=\overset{+}{N}H_2 + H_2NCSC_6H_5$

(XXI) (18)

2. Wave: $C_6H_5CH=\overset{+}{N}H_2 \xrightarrow{2e+2H^+} C_6H_5CH_2\overset{+}{N}H_3$ (19)

3. Wave: $C_6H_5CSNH_2 \xrightarrow[2e+2H^+]{H^+} C_6H_5CH(SH)\overset{+}{N}H_3$ (20)

followed by hydrolysis and reduction of benzaldimine and benzaldehyde.

In alkaline solution, a two-electron reduction is found that results primarily in a saturation of the carbon–nitrogen double bond; the reducible species is probably the azomethine compound $C_6H_5CH{=}N{-}C(S^-)C_6H_5$.

The reduction of cyclic acylated hydrazones like pyridazinones [59] and phthalazinones [81] is discussed in Chapter 18.

The anodic oxidation of hydrazones and semicarbazones to heterocyclic compounds is discussed in Chapter 18.

2. Aprotic Medium

In DMF, benzaldehyde benzoylhydrazone (XXII) is reduced to a mixture of the anion of XXII (from XXII by deprotonation by EGB), benzamide and benzaldehyde, the latter formed from benzylideneimine. The cleavage of the N–N bond occurs after the uptake of

one electron. No traces of *N*-benzyl-*N'*-benzoylhydrazine could be found by high-performance liquid chromatography (hplc) or nuclear magnetic resonance (nmr) [82], although this compound has previously been suggested to be an intermediate [60].

Tosylhydrazones behave as weak acids on reduction in DMF at a platinum electrode; the first peak of fluorenone tosylhydrazone (XXIII) is due to reduction of a proton with formation of the tosylhydrazone anion (XXIV) [83]:

$$\underset{\text{(XXIII)}}{\text{Fl=NNHTs}} + e \rightleftharpoons \text{Fl=NNHTs}^- \longrightarrow \tfrac{1}{2}H_2 + \underset{\text{(XXIV)}}{\text{Fl=N}\bar{\text{N}}\text{Ts}} \qquad (21)$$

A similar formation of bases and hydrogen has also been described for both carbon and nitrogen acids [84].

Compound XXIV is reduced at a more negative potential in a reaction reversible on the time scale of CV, but the dianion radical reacts further on the coulometric time scale. The product distribution is dependent on the pK_A of the added proton donors. The following scheme is suggested [83]:

$$\text{Fl=N}\bar{\text{N}}\text{Ts} + e \rightleftharpoons \text{Fl=NNTs}^{2-} \xrightarrow[\text{slow}]{[H^+]} \text{Fl}^{\cdot}\text{–NH}\bar{\text{N}}\text{Ts} \qquad (22)$$

$$\text{Fl–NHN}\bar{\bar{\text{N}}}\text{Ts} \longrightarrow \text{Fl=NH} + \text{TsN}^{\bar{\cdot}} \qquad (23)$$

$$\text{Fl=NH} + 2e + H^+ \longrightarrow \text{FlNH}_2^- \qquad (24)$$

The nitrene anion radical $TsN^{\bar{\cdot}}$ is proposed to be an intermediate; it may either abstract a hydrogen atom or be protonated and further reduced, depending on the proton donor.

IV. DERIVATIVES OF HYDROXYLAMINE

A. Oximes

1. Protic Medium

Among the azomethine derivatives of hydroxylamine, the ordinary oximes are the most important, and many polarographic and electrolytic investigations of oximes have been made [1,85,86]. Most oximes are reducible in acid solution, and only few in alkaline solution; polarographic data prove that it is the protonated oxime that is the reducible species in acid and neutral solutions. Classic reductions in sulfuric acid at lead cathodes or controlled potential reductions in acid solution at mercury cathodes yield the amine in a four-electron reduction. As the hydroxylamine corresponding to the oxime is not reducible under the conditions employed, it has been suggested [1] that the reduction proceeds as in:

$$\text{RR'C=NOH} \overset{H^+}{\rightleftharpoons} (\text{RR'C=NOH})H^+ \xrightarrow{2e+2H^+} (\text{RR'C=}\overset{+}{\text{N}}\text{H}_2) + H_2O$$

$$\xrightarrow{2e+2H^+} \text{RR'CH}\overset{+}{\text{N}}\text{H}_3 \qquad (25)$$

As the site of the protonation at the species to which the transfer of electrons occurs is not known, both a protonation at N and at O may be considered.

The reduction at a lead cathode of 2,2,6,6-tetramethyl-4-hydroxyiminopiperidine as such or prepared in situ is an excellent method for the preparation of II [49].

Cyclic, α, β-unsaturated oximes, such as testosteronepropionate oxime, are reduced in two, two-electron steps in acid solution. The first reduction yields the imine, which is hydrolyzed to the unsaturated ketone. Reduction at the potential of the second wave yields the unsaturated amine [1].

The postulated intermediate, the imine, can in most cases not be isolated or detected by classic polarography. The reduction of 2,4-dihydroxybenzophenone oxime occurs [87], however, in two steps, and reduction at the potential of the first wave produced the imine, which in this case was sufficiently stable to permit its isolation.

If the reaction path shown is as general as the available evidence suggests, attempts to reduce protonated oximes electrolytically to hydroxylamines are not likely to succeed. Some unprotonated oximes, such as benzaldoxime and benzophenone oxime, are reducible in not too strongly alkaline solution; the oxime anion is not reducible. An investigation of the reduction of benzaldoxime in alkaline solution [79] showed that some benzylhydroxylamine is formed under these conditions.

Monoximes of α-diketones are reduced to α-aminoketones through an intermediate enaminol [88]; dioximes of α-diketones are reduced to the diamines through diimines and endiamines.

Polarographically there is a difference between the *syn*- and the *anti*-oxime in unbuffered solutions having tetraalkylammonium ions as supporting electrolyte [89]. *syn*-Benzaldoxime and other *syn*-oximes give two waves in this medium; the first wave at -1.84 V (SCE) of *syn*-benzaldoxime is kinetically controlled, whereas the second one at -2.2 V (SCE) is diffusion controlled. *anti*-Benzaldoxime gives only one wave [at -1.84 V (SCE)], which is diffusion controlled. It has been suggested [89] that the two waves of the *syn* form reflect the tautomeric equilibrium $>C{=}NOH \rightleftharpoons >C{=}\overset{+}{N}HO^-$.

In some cases stereoselective electrochemical reduction of oximes has been found [90–92]; this is discussed in Chapter 26.

Aldoximes may be transformed into nitriles via nitrile oxides, obtained by indirect anodic oxidation of the aldoxime in methanol, followed by cathodic reduction of the nitrile oxide [92].

2. Aprotic Medium

Electrochemical reduction of aromatic oximes in DMF containing phenol as proton donor results in amines analogous to the reduction in aqueous acidic solvent [61].

The reduction of oximes in aprotic medium is complicted by reactions with electrogenerated bases, EGB. The benzaldehyde oximes (Z and E) give in CV a small peak followed by the reduction of benzonitrile, and preparative reduction gave with a low n value benzonitrile [3] and some benzaldehyde in a chain reaction induced by EGB. The chain might involve a direct attack on the oxime, which, however, would be expected to give the more difficultly reducible anion, and as the *O*-methyl derivative in CV behaved as the parent oxime, the following reaction scheme involving an initial cleavage of the N–O bond [Eq. (27)] and attack by base on the radical with formation of the radical anion of benzonitrile [Eq. (28)] was suggested [62]. The radical anion in turn reduces the incoming oxime [Eq. (29)].

$$PhCH{=}NOH + e^- \longrightarrow PhCH{=}NOH^- \tag{26}$$

$$PhCH{=}NOH^- \longrightarrow PhCH{=}N^{\cdot} + OH^- \tag{27}$$

$$PhCH{=}N^{\cdot} + OH^{-} \longrightarrow PhCN^{-} + H_2O \tag{28}$$

$$PhCN^{-} + PhCH{=}NOH \longrightarrow PhCN + PhCH{=}NOH^{-} \tag{29}$$

Ketoximes are deprotonated by EGB to the oxime anion, which requires a more negative potential for its reduction. Fluorenone oxime gave for $n = 1$ unchanged oxime, fluorenone (hydrolysis of fluorenone imine), fluorenone imine, and some *O*-butylfluorenone oxime, presumably formed by attach of the oxime anion on $TBABF_4$ [62].

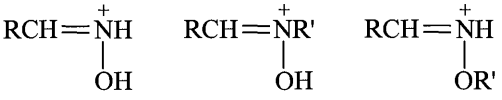
Oxidation of ketoximes in wet acetonitrile gives the corresponding ketones, whereas oxidationof benzaldoximes besides benzaldehyde forms benzoic acid and some 1,2,4-oxadiazoles [93].

B. Alkylated and Acylated Oximes

Oximes may be alkylated at nitrogen or oxygen; both types are electrolytically reducible [1,94,95] in their protonated form. The nitrones are generally also reducible in alkaline solution, whereas the *O*-methyl ethers of oximes are not reducible in ordinary media containing alkali metal ions. In solutions containing quaternary ammonium *p*-toluenesulfonates, some *O*-alkylated oximes give a polarographic wave.

N-Alkyl-substituted oximes both of aliphatic and aromatic aldehydes are reduced in a single four-electron wave in slightly acid or alkaline solution [1,94,95]. *N*-Phenylbenzaldoxime is reduced in two or more steps; the first two-electron reduction results in the formation of benzalaniline, which in acid solution is reduced in two, one-electron reactions [94].

The reduction of the *O*-methyl oximes [94] is probably analogous to the reduction of the oximes in that the nitrogen–oxygen bond is cleaved before the saturation of the carbon–nitrogen double bond. The similarity in the reduction in acid solution of the oxime and its alkylated derivatives is understandable when the close resemblance between the electroactive forms is considered:



Nitrones have been used to indicate the presence of short-lived radicals, as the addition of a radical to a nitrone forms a radical which is stable enough for an esr-investigation [96]. Reduction of a nitrone as *N*-*t*-butylphenylnitrone in DMF yields the Schiff base, which is further reduced. In the presence of a proton donor the protonated radical anion from the Schiff base may add to the nitrone to a stable radical, so it is recommended not to have a proton donor present when using nitrones for investigation of the formation of radicals during a reduction.

N-Acylated hydroxylamines may exist in several tautomeric forms; the protonated hydroxamic acid may be reducible. Protonation of a hydroxamic acid takes place mainly on oxygen to $R{-}C(OH){=}\overset{+}{N}HOH$ [97]. Aromatic hydroxamic acids with electron-attracting groups, such as *p*-cyanobenzhydroxamic acid or isonicotinic hydroxamic acid, are reducible to the amides [98].

C. Amide Oximes

Aromatic amide oximes are reduced in acid solution similarly to other reducible derivatives of hydroxylamine [1,99]; the first step is a reductive loss of oxygen. The reduction of benzamide oxime thus yields benzamidine [1]:

$$PhC(NH_2)=NOH \overset{+H}{\rightleftharpoons} PhC(NH_2)=\overset{+}{N}HOH \xrightarrow[2H^+]{2e} PhC(NH_2)=\overset{+}{N}H_2 + H_2O \qquad (30)$$

V. DIAZOALKANES

A special group of azomethine derivatives is diazoalkanes, $RR'C=\overset{+}{N}=\overset{-}{N}:$. They have been investigated in some detail electrochemically after it was shown that dissociative electron attachment to diazoalkanes was a convenient way of preparing carbene anion radicals in the gas phase.

Reduction of diazoalkanes, such as 9-diazofluorene [100] or diazophenylmethane [101,102], in DMF or MeCN gives a high yield of the corresponding azine and sometimes the ketone and other compounds as minor products, as in eq. (31). The proposal that a carbene anion radical was a detectable intermediate in the reaction was later proved unlikely [103,104].

$$2RR'CN_2 \overset{e}{\rightarrow} RR'C=N-N=CRR' + N_2 \qquad (31)$$

The reaction is a chain reaction with a dimerization of the diazoalkane radical anion as the first chemical step; the structure of the two kinds of intermediate dimerized dianions detected by CV is not settled [105].

A carbonyl group neighbouring the diazo group changes the reaction route, as the carbene anion radical formed in the unimolecular decomposition of the radical anion of the diazo compound has a longer lifetime than those obtained from diazoalkanes. The reduction of diethyl diazomalonate in DMF or MeCN in the presence of a proton donor, such as hexafluoro-2-propanol, guanidinium perchlorate, or benzoic acid, has been suggested [106] to follow Eqs. (32) through (35) with formation of diethyl malonate, n = 2.

$$(EtOOC)_2C=N_2 + e \rightleftharpoons (EtOOC)_2C=N_2^{\cdot-}$$

(XXV) (32)

$$(XXV) \longrightarrow N_2 + (EtOOC)_2C^{\cdot-} \qquad (33)$$

$$(EtO_2C)_2C^{\cdot-} + HA \longrightarrow (EtO_2C)_2CH^{\cdot} + A^- \qquad (34)$$

$$(EtO_2C)_2CH^{\cdot} + (XXV) \longrightarrow (EtO_2C)_2CH^- \xrightarrow[-A^-]{HA} (EtO_2C)_2CH_2 \qquad (35)$$

The diazocompounds, such as azibenzil [107], 2,3,4,5-tetraphenyldiazocyclopentadiene [108], diazodimedone [109], and diethyl diazomalonate [106], whose anion radicals decompose to relatively stable carbene anion radicals, are all derived from compounds with relatively low pK_A values (from 13 to 18 in DMSO). It thus seem essential for the lifetime of the carbene radical anion that the negative charge can be accommodated in the structure [110].

In aqueous solution diazoacetophenone has been investigated by polarography and coulometric reduction; between pH 6 and 8 three waves were found with n = 6, 2, and 2. The following reactions were proposed [111]:

$$C_6H_5COCH=\overset{+}{N}=\overset{-}{N} + 7H^+ + 6e \longrightarrow C_6H_5COCH_2NH_2 + \overset{+}{N}H_4 \quad (36)$$

$$C_6H_5COCH_2NH_2 + 3H^+ + 2e \longrightarrow C_6H_5COCH_3 + \overset{+}{N}H_4 \quad (37)$$

$$C_6H_5COCH_3 + 2H^+ + 2e \longrightarrow C_6H_5CHOHCH_3 \quad (38)$$

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12
Carboxylic Acids and Derivatives

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I. Introduction
II. Cathodic reduction of carboxylic acids
III. Cathodic reduction of esters, lactones, anhydrides, and acyl halides
IV. Cathodic reduction of amides, lactams, imides, and hydrazides
V. Cathodic reduction of nitriles
References

I. INTRODUCTION

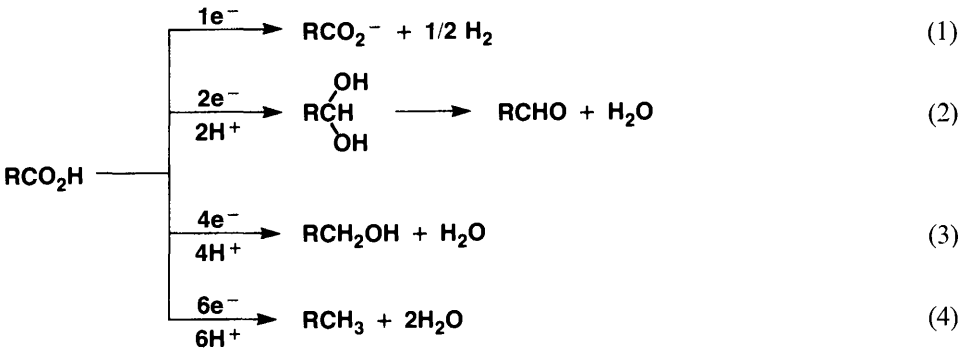
This chapter is concerned with the cathodic reduction of carboxylic acids and their derivatives, that is, esters, amides, anhydrides, acyl halides, hydrazides, nitriles, and corresponding thio derivatives. Cyclic derivatives of substituted carboxylic and polycarboxylic acids, such as lactones, lactams, imides, and anhydrides, are also included. Only those transformations in which the functional group itself is involved are discussed. Reductive coupling of carboxylic acids and derivatives is covered in Chapter 22, and there is some overlap with reduction of heterocycles in Chapter 18.

Cathodic conversions of the carboxyl group and its derivatives have been long known, and tabulations and discussions of these reactions can be found in several places [1–5]. Most of the earlier work on these processes involved constant-current reduction with careful selection and control of solvent, temperature, pH, and electrode material. More recently, mechanistic studies of these processes have been made using modern electroanalytical techniques, but our knowledge in this area remains far from complete.

†Deceased.

II. CATHODIC REDUCTION OF CARBOXYLIC ACIDS

The cathodic reduction of a carboxyl group can give the carboxylate anion, the aldehyde, the alcohol, or the hydrocarbon in one-, two-, four-, or six-electron reductions, respectively, shown in Eqs. (1) through (4):



(1)

(2)

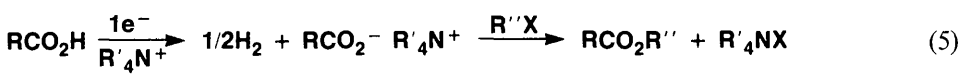
(3)

(4)

Successful utilization of the reactions (2) through (4) is dependent on being able to avoid the proton reduction reaction (1).

It is generally difficult to stop the reduction at the aldehyde stage since aldehydes are usually reduced at less negative potentials than the corresponding acids. Certain "tricks" discussed later, however, often allow one to isolate the aldehyde form.

Aliphatic and aromatic acids that are not strongly activated by electron withdrawing groups and do not contain more easily reducible groups give well-developed polarographic waves in aqueous [6] or nonaqueous [7,8] solvents, but this is usually due to reduction of protons to hydrogen. As an example, the hydrogen wave from acetic acid in acetonitrile–0.1 M tetraethylammonium perchlorate appears at −2 V (SCE) and in aqueous medium in the intermediate pH region at −1.76 V (SCE). Controlled potential electrolysis (CPE) of acetic acid in acetonitrile at −2.3 V (SCE) demonstrates that the electrode process is actually the reduction of protons. No second wave is found in the accessible potential region of these media, indicating that $RCOO^-$ the species left after reduction of the proton, is very difficult to reduce. Using this reaction, esters may be prepared under quite mild conditions [9]:



(5)

Unless activated, therefore, it is unlikely that carboxylic acids will be easily reduced in slightly acidic or alkaline solution or in nonaqueous media. In strongly acidic medium the situation may be different since protonation of the carboxyl group may lead to the formation of a species capable of accepting electrons into the carbon–oxygen bonds.

For reduction of dicarboxylic acids in acetone solution, polarographic half-wave potentials and limiting currents are dependent on concentration in a way that suggests that at low concentration the acids are sufficiently dissociated for reduction of solvated protons to predominate, whereas at higher concentrations the more difficult reduction of undissociated acid is observed [10].

Acids containing certain activating groups can be reduced without interference from hydrogen evolution. 1-Ethyl-4-carboxypyridinium ion (I, as the bromide) is such a case, having the very strong electron-withdrawing quaternary ammonium ion as part of the

aromatic ring [11]. The carboxyl group is the most easily reducible group at pH values below 7. The half-wave potential of I moves toward more negative potentials with increasing pH in such a way that the $E_{1/2}$–pH curve can be approximated by three lines: the first (pH 0.5–1.5) with a slope of 0.029 V/pH, the second (pH 2–7) with a slope of 0.068 V/pH, and the third (pH 8–13) with a slope of 0.007 V/pH. The total variation in $E_{1/2}$ is between −0.74 V in strongly acidic and −1.22 V in alkaline solution. Hydrogen evolution takes place at yet more negative potentials. From this pH dependence it was concluded that from pH 8 to 13 the reducible species contains the carboxyl group as the carboxylate ion and below 7 exists in its undissociated form. Since the pK of the acid is 1.75, the carboxyl group must be formed in a recombination reaction at the electrode surface in the pH region 2–7, as indicated by the slope of the $E_{1/2}$–pH line in this interval [12].

Controlled potential electrolysis of I in slightly acidic buffers at −1.0 V (SCE) gives the corresponding aldehyde in good yield, provided that the reaction is stopped at 2 F/mol (prolonged reaction times led to a further slow reduction of the aldehyde, suggesting a small equilibrium concentration of free aldehyde and a slow rate of conversion of the hydrated form to free aldehyde). The best yields of aldehyde are obtained in the pH region 2–5. At alkaline pH no aldehyde can be detected, possibly because the heterocyclic ring system becomes the more easily reducible group of the molecule. The corresponding *N*-methyl derivative has been shown to be reduced to the dianion radical in strongly basic ethanolic solution [13]. Aldehyde formation is also negligible at pH < 0.

In contrast, reductions of *N*-methylpyridine 2- and 3-carboxylic acids in acidic solution led only to the corresponding alcohols [14], although the difference may have been that reductions of the latter were performed until all carboxylate was consumed, whereas in the earlier work electrolysis was stopped after 2 F/mol was passed. An extensive evaluation of *N*-methylpyridine 3-carboxylic acid by polarography and cyclic voltammetry over a wide pH range gave evidence for dimer formation in both acidic and basic solution, although no product isolation was attempted [15].

Aldehydes are usually more easily reduced than carboxylic acids, but as in the previous case the aldehyde may exist in aqueous solution predominantly as the hydrate [Eq. (2)]. The hydrates are reduced at more negative potentials than carboxylic acids. Several other systems have been found to behave similarly [16,17]: pyridine-2- and -4-carboxylic acid, imidazole-2-carboxylic acid, and thiazole-2-carboxylic acid. In the last case the yield is low due to competing reduction of the ring. Yields of aldehyde are better at low temperatures due to the slowing of the dehydration reaction. In neutral or basic solution there is electroanalytical evidence for dimerization in the reduction of pyridine-4-carboxylic acid [18].

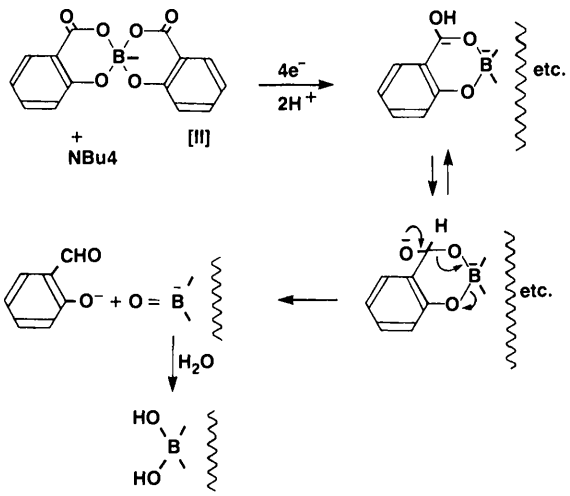
In summary, it seems [16] that the following requirements must be fulfilled for the reduction of a carboxyl group to an aldehyde function to take place: (1) The carboxyl group must be activated by an electron-withdrawing group; (2) the carboxyl group must be the most easily reducible group in the molecule (which automatically excludes the nitro group and a number of nitrogen-containing heteroaromatic groups as activating groups); and (3) the aldehyde formed must be protected against further reduction by formation of a nonreducible derivative, such as a hydrate or hemiacetal. The last criterion is probably the most important and stringent. It is important to note that aldehydes are not direct cathodic reduction products but that the hydrated form is first produced. Subsequent dehydration leads to the electroactive aldehyde.

In many cases, dehydration to the aldehyde occurs at a rate slow enough to allow the hydrated form to escape from the electrode surface. Dehydration in the bulk allows other schemes for protecting the aldehyde.

Other acids that fulfil these requirements and can be reduced cathodically to aldehydes are oxalic acid to glyoxylic acid (a reaction studied in great detail including process development [19]), and lactic acid [3]. Phthalic acid, also an activated acid, cannot be reduced to an aldehyde in neutral or weakly acidic electrolytes at a lead cathode but instead is converted into phthalide [20].

Reduction of phthalic acid in acidic solution (e.g., 5% aqueous H_2SO_4) results in aromatic ring reduction, giving 1,2-dihydrophthalic acid [21–26], a reaction believed to have been practiced commercially [27].

Hydration is not the only way in which an aldehyde intermediate may be protected against reduction; the aldehyde may be converted in situ into a borate complex of the hydrate [28–31] or into a bisulfite addition complex [32,33]. There is compelling evidence that borate complexes, such as II in Eq. (6), in the case of salicylic acid reduction, are intermediates. The salt (II) has been isolated and characterized [31], and in the presence of proton donors it undergoes four-electron reduction; a plausible mechanism is suggested:



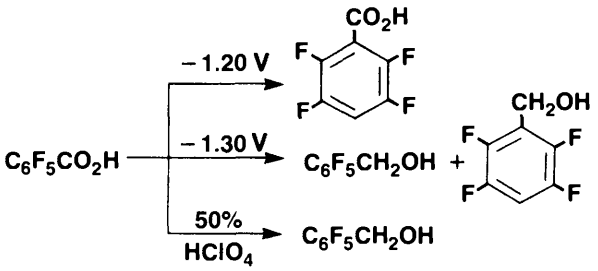
(6)

The reduction of salicylic acid to salicylaldehyde is believed to have been practiced commercially in India and the USSR [27]. Two-phase systems may also be used so that the aldehyde is rapidly removed from aqueous solution by extraction into an organic phase [28–30]. It was shown that correct choice of buffer and a two-phase system allows reductions of aromatic acids to aldehydes in acceptable yield (> 50%); in addition, the likelihood of such success is greater with the lower pK_a value of the acid and lower $E_{1/2}$ value for reduction of the corresponding methyl ester [30].

Four-electron reductions of aromatic carboxylic acids occur when reactions are carried out in strongly acidic solutions at lead or mercury cathodes, giving excellent yields of the corresponding benzyl alcohols [23,34–36]. The reaction is easily performed on a large scale. For example, the adaptation of a filter press cell for continuous reduction of benzoic acid has been described [37].

A procedure for the cathodic reduction of anthranilic acid to the corresponding alcohol is described in *Organic Synthesis* [36]. Because the carboxylic acid group is so difficult to reduce, the method cannot normally be used for acid substituted with easily reducible functions or groups. For instance, pentafluorobenzoic acid loses fluorine by cathodic cleavage at mercury, in 20% sulfuric acid, at −1.20 V (SCE); 2,3,5,6-tetrafluorobenzoic acid is obtained in 75% yield [38]. However, at potentials more negative than

−1.30 V, reduction of the carboxylic acid group becomes significant and a mixture of the pentafluoro- and tetrafluorobenzyl alcohols is produced [Eq. (7)]. In very strongly acidic medium (50% $HClO_4$) only pentalfuorobenzyl alcohol is produced.



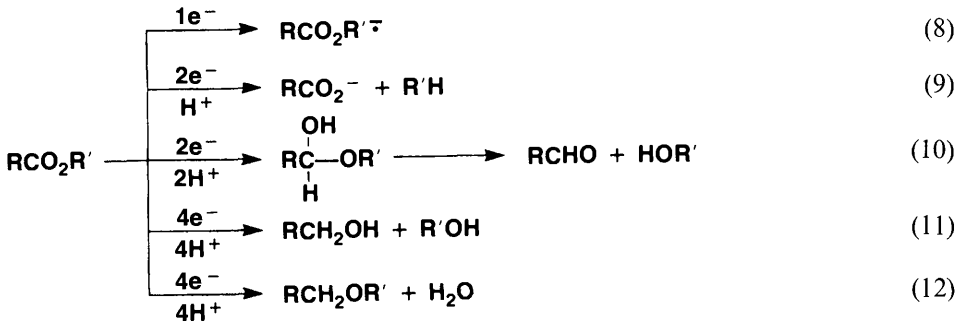
(7)

Aliphatic carboxylic acids are reducible to the alcohol in low yield in strongly acidic electrolytes. Thus, phenylacetic acid is reduced to 2-phenylethanol in 25–50% yield at a lead cathode in 50% sulfuric acid–ethanol [39] and butyric acid to butanol in 80% sulfuric acid in 6.5% yield [40]. The latter conversion can also be performed in 17% yield in 7% aqueous sodium hydroxide, despite the fact that the carboxylate form of the acid, which is reducible only with difficulty, predominates in bulk solution, suggesting an electrocatalytic reduction involving specific interaction of the substrate and electrode surface.

The six-electron reductions of carboxylic acids to methyl groups are known, such as the reduction of pyridine-2- and 4-carboxylic acids to the picolines in strongly acidic medium [41].

III. CATHODIC REDUCTION OF ESTERS, LACTONES, ANHYDRIDES, AND ACYL HALIDES

Nonactivated esters are reduced with difficulty unless strongly acidic solutions are used. Unsaturated esters, such as α,β-unsaturated and aromatic esters, are reduced relatively easily because of the activating effect of the strongly electron-withdrawing ester group for reduction of the attached unsaturated function. In these cases, the products of reduction may include those of hydrodimerization and the hydrogenation of the unsaturated function (e.g., aromatic ring) as well as those of reduction of the ester function. The possibilities are summarized in Eqs. (8)–(12), and subsequent discussion focuses on reduction of the ester function.



(8)
(9)
(10)
(11)
(12)

The electrochemical reduction of ethyl 2-picolinate at a lead cathode in sulfuric acid leads to all three products, the two-electron produce (aldehyde), the four-electron product

(alcohol), and the six-electron product (picoline). Conditions have been optimized for preparation of 2-hydroxymethylpyridine [42].

The first step in the cathodic reduction of an ester in acidic medium leads to an aldehyde, presumably via the hemiacetal [Eq. (10)]. The aldehyde, if not stabilized in the form of an electroinactive addition compound, is the reduced in a second step to form the corresponding carbinol [43] (or sometimes also the pinacol [44]). However, a competing pathway for ester reduction in strongly acidic medium is the formation of ethers [Eq. (12)], sometimes in good yields [23,34,45,46].

Aliphatic esters may be reduced to the corresponding alcohol [Eq. (11)], provided a magnesium cathode is used [47]. Interestingly, reduction of aliphatic esters at a magnesium cathode in aprotic solvents [48,49] leads to coupling resulting in the diketone:

$$2RCO_2R' \xrightarrow[\text{Cathode}]{\text{Mg}} RC(=O)-CR(=O) + 2\,R'O^- \tag{13}$$

Vicinal diesters may be reduced to the corresponding acetylene by reductive elimination of the two ester groups as in Eq. (14) [50].

$$Ph-\underset{\displaystyle OAc}{\overset{\displaystyle OAc}{C}}=\underset{\displaystyle OAc}{\overset{\displaystyle OAc}{C}}-Ph \xrightarrow[\text{DMF}]{\text{Dry}} PhC{\equiv}CPh + 2\,AcO^- \tag{14}$$

Voltammetric data for ester reductions are available for several aromatic esters [51–54], and in particular cyclic voltammetry shows clearly that in the absence of proton donors reversible formation of anion radical occurs [51]. In dimethylformamide (DMF) solution the peak potential for reduction of methyl benzoate is −2.29 V (versus SCE); for comparison dimethyl terephthalate reduces at −1.68 V and phthalic anhydride at −1.25 V [4]. Half-wave potentials for reduction of aromatic carboxylate esters in an unbuffered solution of pH 7.2 are linearly correlated with σ values [51]; electron-withdrawing substituents in the ring or alkoxy group shift $E_{1/2}$ toward less negative potentials. Generally, esters seem to be more easily reducible than the parent carboxylic acids. Anion radicals of methyl, ethyl, and isopropyl benzoate have been detected by electron paramagnetic resonance (epr) spectroscopy upon cathodic reduction of these esters in acetonitrile–tetrapropylammonium perchlorate [52]. The anion radicals of several anhydrides, including phthalic anhydride, have similarly been studied [55].

Benzoate esters are reduced under aprotic conditions initially, as mentioned earlier, to the corresponding anion radical. The anion radicals are not stable for long periods of time, however, and generally cleave, giving benzoate and the alkyl radical as in Eq. (15) [56–58].

$$ArCO_2R \xrightarrow{1e^-} ArCO_2R^{\cdot -} \longrightarrow ArCO_2^- + R\cdot \tag{15}$$

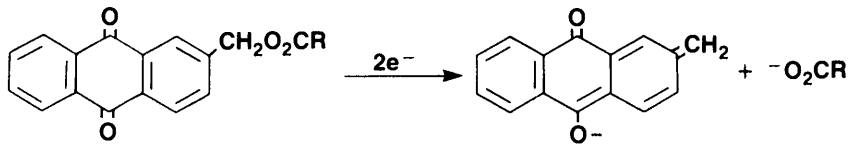
The rate of cleavage of the anion radical to benzoate and free radical is higher as the stability of the free radical increases. Thus, the anion radical of *tert*-butyl benzoate cleaves according to Eq. (15) much faster than the corresponding anion radical of methyl benzoate. The free radical thus formed may undergo a variety of reactions, including substitution onto the aromatic ring of the starting ester [58]. A large number of aromatic dicarboxylic esters and thio esters have been reduced to the corresponding anion radicals, many of which are sufficiently stable to allow one to obtain epr spectra [58a].

It has also been reported that reduction of benzoate esters in dry acetonitrile leads to solvent interaction resulting in benzoylacetonitrile in good yield as in Eq. (16) [59]:

$$ArCO_2R \xrightarrow[\text{Reduction}]{\text{Electro}-} ArCOCH_2CN \qquad (16)$$

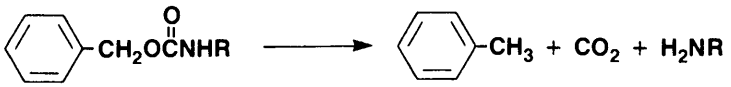
In a reaction similar to that shown above for aliphatic esters [Eq. (13)], it has been reported that aromatic esters may also be reduced to the corresponding diketone provided the reduction is carried out using a cadmium cathode and magnesium anode [60]. Earlier work demonstrated that phenyl benzoate anion radical cleaves to form phenolate in good yield and presumably benzoyl radical, which leads to dibenzoyl [16]. Nitro-substituted phenyl benzoates are similarly cleaved on reduction to give phenolate [62,63].

The cathodic reduction of esters has been used for a variety of deprotection reactions. For example, 2-methylene-9,10-anthraquinone esters have been reduced in DMF to free the corresponding carboxylate as in Eq. (17) [64]:



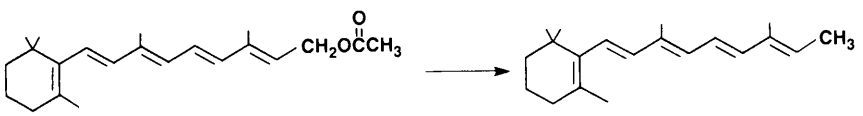
(17)

The *p*-nitrobenzyl ester of cephalosporin has been cleaved cathodically to yield cephalosporin [65]. The widely used benzyloxycarbonyl protecting group for amines is cathodically removed, giving free amine, CO_2, and toluene [66]:



(18)

The reduction of certain esters results in formation of carboxylate and the reduced form of the alcohol precursor fragment [67–70]. For example, the cathodic cleavage at mercury of vitamin A acetate gives axerophthene in good yield [71]:

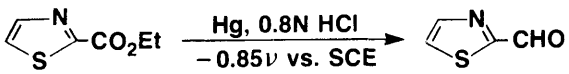


(19)

Mixed esters of oxalate containing one benzylic substituent are reduced in good yield using in situ trans-esterification to the corresponding hydrocarbon and oxalate half-ester [72]. Esters of vicinal diols (including cyclic carbonate esters) [73] and β-halo esters [74] are often reduced to the corresponding olefin [72,75].

Nonactivated esters are reduced only slowly if at all in strongly acidic medium at a lead cathode [45], whereas alkyl benzoates are reduced to a mixture of benzyl alcohol and alkyl benzyl ether [45,46], and alkyl 4-imidazolecarboxylates similarly are reduced to a mixture of the corresponding alcohol and ether [76]. Phenyl and benzyl benzoate give predominantly esters [23,34], as do also ethyl *o*-chloro- and *m*-bromobenzoate [46].

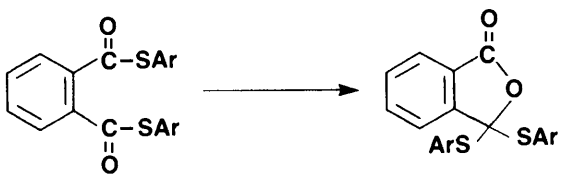
For activated esters, the problem of halting reduction at the aldehyde stage is similar to that faced in the reduction of carboxylic acids; the aldehyde must be converted in situ into an electroinactive form. In one case, that of reduction of ethyl 2-thiazolecarboxylate [17], the strongly hydrated aldehyde may be obtained in about 70% yield:



(20)

Presumably for similar reasons, cathodic reduction of diethyl terephthalate and diethyl furan- and thiophene-2,5-dicarboxylate [51–53] in a buffered ethanolic solution of "pH 4.2" affords the aldehyde ester under controlled potential electrolysis (CPE) conditions (in the interval between −1.50 and −1.65 V). Diethyloxalate [77] is reduced at a mercury cathode in acidic medium to give the ethyl hemiacetal of ethyl glyoxylate (38–50% yield). In contrast, diethyl and monoethyl phthalate gave phthalide under similar conditions [21,78].

An interesting $S_{RN}1$ reaction occurs on cathodically induced rearrangement of *S*, *S*-diphenylbenzene-1,2-dicarbothiolate, forming 3,3-bis(phenylthio) phthalide [79]:



(21)

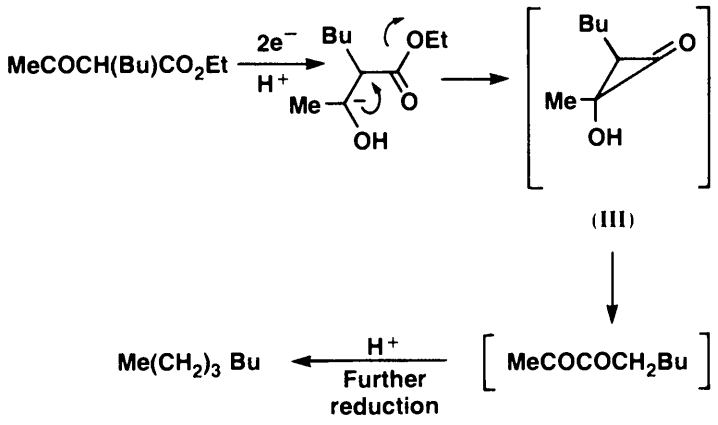
Although not officially a transformation involving carboxylate, the anion formed by two electron reduction of 1-methyl-4-(methoxycarbonyl)pyridinium iodide has been extensively used as an electron transfer agent in the study of aliphatic nucleophilic substitution reactions [80].

In aprotic conditions, diethyl oxalate is reduced reversibly, and its relatively stable anion radical has been well characterized by epr spectroscopy [81,82]. Not all oxalate esters give reversible reduction; the anion radicals of several (e.g., dibenzyl oxalate) undergo rapid fragmentation [72,83].

Ethenetetracarboxylate esters may be reduced to the anion radical or stable dianion states depending on the cathode potential. Both have been used extensively as electrogenerated bases [84]. Interestingly, ethanetetracarboxylate esters do not give stable anion radicals but cleave to give the corresponding malonate anions [85].

Methyl 2-naphthoate is reduced [86] in the presence of boric acid in methanolic solution at a mercury cathode to form 2-naphthalenemethanol in 19% yield, a mixture of diastereomeric pinacols from further reduction of the intermediate aldehyde in 19% yield, and a mixture of methyl 1,2- and 1,4-dihydro-2-naphthoates in 42% yield. Methyl 1-naphthoate under the same conditions [87] gives methyl-1,4-dihydro-1-naphthoate (43%), a 4,4′-dimer of the 1,4-dihydro derivative (20%), di-1-naphthylglyoxal (5%), and 1-naphthalenemethanol (5%). Because mercury cathodes are used with sodium salt electrolytes, it is possible that electrogenerated sodium amalgam is the reducing agent.

2-Alkyl-substituted acetoacetic esters undergo an interesting rearrangement reaction (the Tafel rearrangement) upon reduction at a lead cathode in an acidic medium [Eq. (22)], with complete reduction of the functional groups [88–93]. The cathodic reduction of β-diketones gives analogous rearrangements, and because these are known to involve cyclopropanediol intermediates [94], it is tempting to suggest that the intermediate (III) is involved in the Tafel rearrangement. In partial support of Eq. (22), there is evidence, although not by isolation, that 2,3-octanedione is one of the many by-products of the Tafel rearrangement of ethyl 2-butylacetoacetate [93].

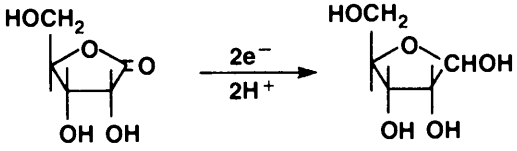


(22)

Both aliphatic and aromatic esters may be converted to amides by electrochemical reduction of the ester in the presence of an amine in a divided cell as in Eq. (23) [95]. This reaction is not formally a reduction, but the reaction does not occur without passage of current. The mechanism is likely formation of an anion radical with abstracts a proton from ammonia to form amide ion. The amide ion subsequently displaces alkoxide in a chain reaction to form carboxamide.

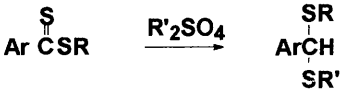
$$R'COOR'' + RNH_2 \rightarrow R'CONHR \tag{23}$$

Lactones are in principle reducible to hydroxyaldehydes, and when applied to lactones of sugar acids the method works well because cyclic acetal or ketal formation stabilizes the carbonyl function and prevents overreduction [3,96–100]. In particular, D-ribose may be prepared from the cathodic reduction of D-ribono-γ-lactone as in Eq. (24); the optimum conditions for this reaction include careful buffering of the electrolyte [97–100].



(24)

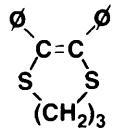
Thiol esters of aromatic acids, ArC(O)SR, are cathodically reduced, with fission of the S–CO bond generating the arylcarbonyl radical and thiolate as in Eq. (25) [101]. The thiol may be obtained in good yield [102]—for example, L-cysteine in 83% yield from *S*-benzoyl-L-cysteine at a mercury cathode in DMF–water–tetramethylammonium chloride. The electroreduction of aryl thioesters [containing -C(O)SR, -C(S)OR, and -C(S)SR functions] has been studied, and some interesting products have been formed [103–105], as in Eqs. (26) through (29). Trithiocarbonates are reduced to the tetraalkyltetrathioethylenes [106].



(25)

$$4\text{ØCSSR} \xrightarrow{6e^-} \text{ØC}\equiv\text{CØ} + 2\text{ØCS}_2^- + 4\text{RS}^- \tag{26}$$

$$2\,\text{Ø}\,\text{CS}_2\text{Me} + \text{MeSO}_3(\text{CH}_2)_3\text{O}_3\text{SMe} \xrightarrow{4e^-} \tag{27}$$



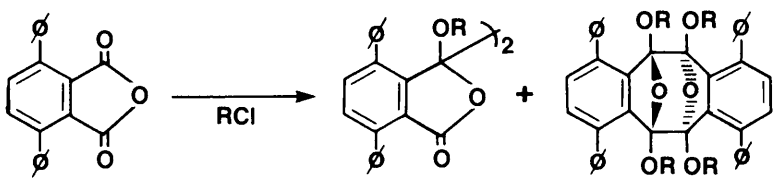
$$\text{ØCS}_2\,\text{CH}_2\,\text{CH}_2\,\text{S}_2\,\text{CØ} \tag{28}$$

$$\xrightarrow{2e^-,\ 2\text{MeI}}$$

$$\text{ArCSSR} + 2e + \text{R}_2'\text{SO}_4 \rightarrow \text{ArCH(SR)SR}' \tag{29}$$

Anhydrides have received very little attention as substrates for cathodic reduction. Polarography of cyclic anhydrides [107] in acetonitrile and DMF displayed two, one-electron waves for the most easily reduced anhydrides (pyromellitic, dibromopyromellitic, and tetrachlorophthalic anhydride). For 10 mono- and dianhydrides of aromatic carboxylic acids, the $E_{1/2}$ values for reduction in acetonitrile have been measured and listed [108].

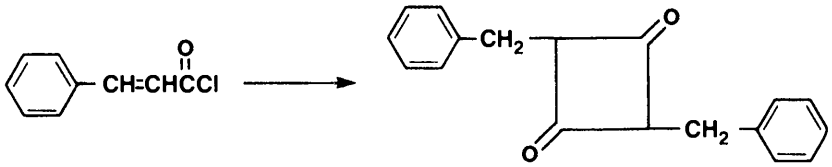
Controlled potential electrolyses of phthalic and pyromellitic anhydrides at the potential of the first wave gave highly colored, oxygen-sensitive solutions, which later were shown to give well-resolved esr spectra of the corresponding radical ions [55]. Phthalic anhydride has been reduced to phthalide on a preparative scale [109], but the reaction conditions employed (ethanol–water–ammonium carbonate) indicate that monoethyl phthalate must have been the actual substrate. An interesting reduction of 3,6-diphenylphthalic anhydride in the presence of trimethylsilyl chloride gives two types of dimeric species [110]:



(30)

R = Me_3Si

There have been a few reports describing electroreduction of acyl halides. Benzoyl chloride when reduced ($E_p = -1.82$ V versus Ag/0.1 M $AgNO_3$) in aprotic media gives good yields (85%) of stilbenediol dibenzoate [111,112]. This seems to be a general reaction for a variety of acyl chlorides [113]. The reduction of cinnamoyl chloride leads to 2,4-dibenzyl-1,3-cyclobutadione [114]:

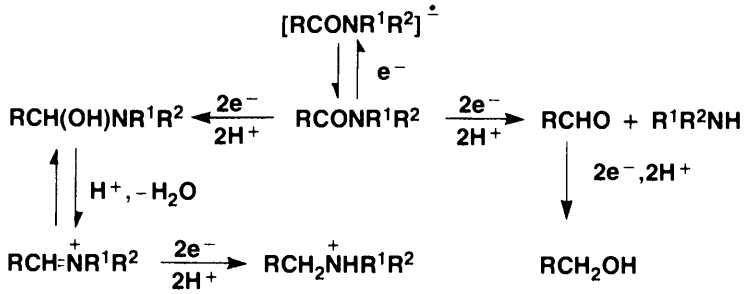


(31)

An interesting coupling of acyl halide with Michael acceptors involves an organometallic intermediate and photochemical step as well as an electroreduction. The electrochemical reduction, however, is used to reduce the intermediate cobalt oxidation state [115].

IV. CATHODIC REDUCTION OF AMIDES, LACTAMS, IMIDES, AND HYDRAZIDES

The carbonyl group of amides, lactams, and imides is reducible at lead and mercury cathodes in strongly acidic media, usually to the corresponding methylene compound. In media of lesser acidity cathodic cleavage may occur, and depending on the structure of the starting material and the detailed reaction conditions, the products outlined in Eq. (32) are accessible by cathodic reduction.

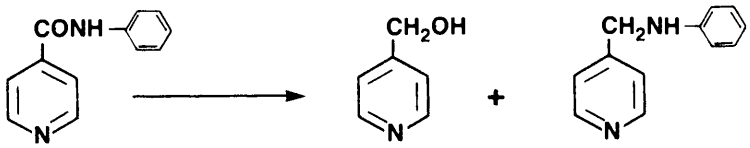


(32)

Voltammetric and epr spectroscopic studies using aprotic conditions show that several amides give reversible one-electron reduction to relatively stable anion radicals, for example, for *N*, *N*-dimethylbenzamide [4], *N*-alkylphthalimides [56,116-118], and oxamides [119]. In a similar fashion, the electrogeneration of anion radicals from sulfur analogs [containing the $RC(S)NR^1R^2$,$RR'NC(S)CC(S)NR^2R^3$, and $ArC(S)CONR^1R^2$ functions] has been thoroughly investigated [120–122].

The polarography of pyridine-4-carboxamide and some of its derivatives [123,124], as well as carboxamides of other heterocyclic systems [16,17,125], has been carefully studied in aqueous medium over the whole pH range. Pyridine-4-carboxamide (IV) displays a polarographic wave with $E_{1/2}$ ranging from about −0.6 V at pH 0 to −1.3 V at pH 13, with the change being related to the extent of protonation. Controlled potential electrolysis of IV in 0.8 M hydrochloric acid at −0.80 V (SCE) gave a good yield of pyridine-4-aldehyde, whereas at pH 4.5, 4-pyridine methanol was formed.

Substitution of hydrogen by phenyl in the amide group changes the product composition considerably; electrolysis of *N*-phenyl-4-phenyl-4-pyridine carboxamide in 1 M hydrochloric acid at −0.75 V gives a mixture of 4-pyridinemethanol and 4-anilinomethylpyridine:



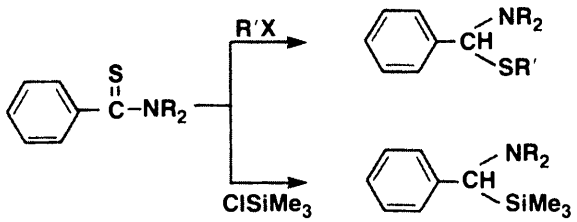
(33)

Pyridine-4-thiocarboxamide is reduced in two, two-electron steps in acidic medium; at the potential of the second wave, reduction gives 4-aminomethylpyridine. The product of reduction at the first wave is believed to be the aminothiol [126]. These three cases show that the preparative outcome of an amide reduction is strongly dependent on the substituents at the amide group and that the changes manifest themselves in the chemical step [Eq. (32)]. For the amides of aromatic carboxylic acids, the reduction potential may be gleaned from a comprehensive compilation [127].

A large number of preparative applications of amide group reductions have been compiled and discussed by other authors [1–5]. Generally, these reactions are performed at lead cathodes in aqueous sulfuric acid or ethanolic aqueous sulfuric acid and result in good yields of the corresponding aminomethyl compounds. Since the media employed are so strongly acidic, it is probable that the electroactive species is the protonated amide in these cases. Simple aliphatic amides of the general formula $RCONH_2$ have not been studied; however, a number of *N*,*N*-diphenyl-substituted aliphatic amides have been successfully reduced. Benzamides give good yields of benzylamines, *N*,*N*-disubstitution favoring amine formation also in these cases. Thioamides can be used as substrates with similar results.

In alkaline solution, *N*-substituted benzamides undergo cathodic cleavage to form benzyl alcohol and an amine [127,128]. In acidic solution *N*-substituted 2-pyridinecarboxamides are reduced to the corresponding aldehyde and alcohol unless severe steric crowding is present, which results in the corresponding methylene amine being formed [129].

The reduction of thiobenzamides in anhydrous CH_3CN leads to fair yields of β-dialkylaminocinnamonitriles via a complex mechanism involving electrogenerated cyanomethyl anions [59]. However, thiobenzamides when reduced in the presence of such alkylating agents as alkyl halides or dimethyl sulfate give excellent yields of the corresponding α-aminothioethers [Eq. (34)]. Use of chlorotrimethylsilane as the alkylating agent, however, results in loss of sulfur to form a C–Si bond [130]:

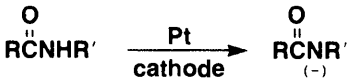


(34)

(35)

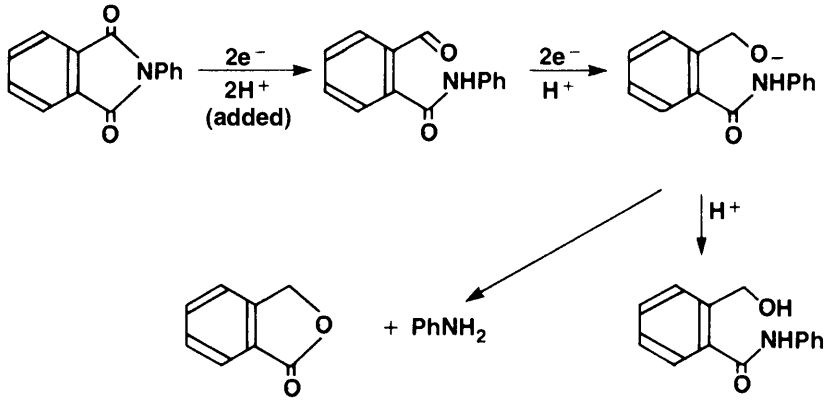
In amine solvents, the reduction of amides by electrogenerated solvated electrons gives the corresponding alcohol product in the absence of proton donor [131]. If a proton donor, such as ethanol, is added, good yields of aldehyde may be formed.

Amides containing at least one hydrogen on the nitrogen are sufficiently acidic in aprotic media to evolve H_2 on reduction at a Pt cathode, resulting in the corresponding amide anion [Eq. (36)], which has been used as an electrogenerated base [132]. This reaction in the presence of alkylating agents leads to *N*-alkylation of the amide [132,133]. The reaction also occurs for carbamates.



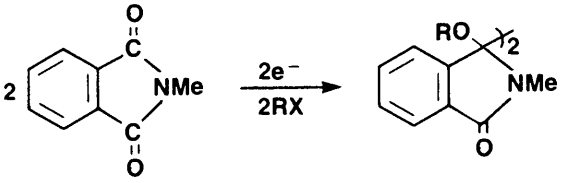
(36)

Phthalimide and substituted phthalimides are relatively easily reduced $E_{\frac{1}{2}}$ in DMF ~ -1.4 V (versus SCE)]. In alkaline or aprotic solution, two, one-electron reduction steps are observed in voltammetric experiments [134–137]; anion radical formation at the first wave has been confirmed by esr spectroscopy [55,135,136]. Considerable attention has been given to the detailed mechanism of reduction of phthalimide derivatives [134–137]:



(37)

Reduction of *N*-methylphthalimide in the presence of dimethyl sulfate or trimethylsilyl chloride led to a dimeric product [138]:

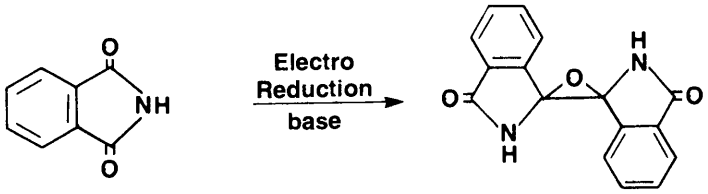


(38)

The electroreduction of *N*-phenylphthalimide in the presence of trimethylsilyl chloride formed a bis-silylether [138]:

(39)

O-Acetyl-2-hydroxymethylbenzanilide is formed as a result of reduction [136] of *N*-phenylphthalimide in DMF in the presence of acetic anhydride. In alkaline solution phthalimide is reduced to a dimer epoxide [139]:



(40)

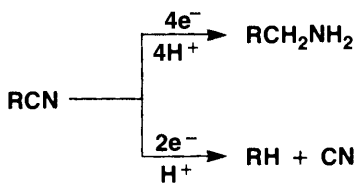
In macroscale electrolyses, lactams or fully saturated cyclic amines are obtained in good yields from imides in strongly acidic electrolytes [1–5]; for example, *N*-methylsuccinimide is reduced in good yield to *N*-methylpyrrolidone at a lead cathode in sulfuric acid solution [140].

The reduction of acyl hydrazines has been investigated very little. Polarography of 4-pyridine carboxylic acid hydrazide in acid and neutral solution shows that it is reduced in two, two-electrons steps [141]. The result of controlled potential electrolysis is cleavage of the N–N bond to form 4-pyridine-carboxamide, which then undergoes reduction to the aldehyde in the second step. Other hydrazides of heterocyclic carboxylic acids behave analogously.

The *N*,*N*-diphenylhydrazone of benzoyl chloride has been reduced to form benzonitrile and diphenylamide [142].

V. CATHODIC REDUCTION OF NITRILES

Both aliphatic and aromatic nitriles are reduced in acidic solution to give amines [Eq. (41)], whereas in neutral or alkaline medium cleavage of the C–CN bond takes place [Eq. (42)]:



(41)

(42)

Reactions (41) and (42) have been studied polarographically [143]. In acid solution, aromatic nitriles of the type *p*-$RCOC_6H_4CN$ (R = H or CH_3) undergo a four-electron reduction at −0.70 V (SCE) with formation of the corresponding benzylamine. The protonated nitrile is the electroactive species. In neutral medium, nitriles of the type XC_6H_4CN (X = *p*-COO^-, *p*-SO_2NH_2, and *m*-SO_2NH_2) give two-electron reduction with formation of cyanide ion and C_6H_5X. This duality in mechanism has been thoroughly studied in the case of 2- and 4-cyanopyridine [144,145], and it was shown that both pH and electrode material play an important role in determining the mechanism.

The electrochemical cleavage of nitriles can also be performed in anhydrous amine media [146], making possible C–CN bond cleavage in aliphatic nitriles, such as cycloheptanecarbonitrile and heptanecarbonitrile. This reaction was interpreted as due to reductive cleavage by solvated electrons. This reaction has also been accomplished with electrogenerated solvated electrons [147].

A number of aromatic nitriles including benzonitrile have been reduced electrochemically in DMF–tetrapropylammonium perchlorate to give solutions of relatively stable anion radicals whose epr spectra have been recorded [148]. These anion radicals are capable of transferring and electron to more difficulty reducible species such as carbon dioxide [149]:

(43)

The anion radical of benzonitrile in dry DMF slowly loses cyanide to form phenyl radical, which is reduced to phenyl anion, which abstracts a proton from the electrolyte

[150]. Phthalonitrile, which gives two, one-electron waves on polarography in this medium, undergoes decyanation on CPE at the potential of the second wave. There is evidence that the anion radicals of 1,3-dicyanobenzene and 1,3,5-tricyanobenzene may dimerize and lose cyanide to form biphenyl derivatives [151].

The preparative use of nitrile reduction has been primarily for the synthesis of amines [1,2,152–157]. This is done in acidic medium and gives fair to good yields. Electrocatalytic hydrogenation of nitriles is also sometimes efficient [158]; in these cases, nickel or palladium black, deposited on the cathode, promotes reduction by electrolytically generated hydrogen atoms.

Imino ether hydrochlorides can be reduced to amines in good yields at lead cathodes in aqueous sulfuric acid [159]. Cathodic reduction of nitriles in ethanolic sulfuric acid should be a useful procedure, therefore, with the first step in situ formation of an imino ether salt.

Acetonitrile has been reduced at a tin cathode to give low yields of tetramethyltin [160].

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13
Anodic Oxidation of Hydrocarbons

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I. INTRODUCTION

For many years electrochemical studies of hydrocarbon oxidation was confined to preparative studies of aromatic and alkyl aromatic hydrocarbons in water-containing electrolytes under constant-current conditions [1–3]. Usually, complex mixtures are obtained. The use of nonaqueous solvents led to significant advances in the study of the anodic behavior of hydrocarbons. A pioneering study [4] of the voltammetry of aromatic hydrocarbons in MeCN–$NaClO_4$ at a vibrating Pt electrode was followed by a large number of electrochemical investigations in nonaqueous solvents. Concurrent preparative studies, although not always very helpful in clarifying the nature of the initial electrochemical

step, have nevertheless been of great help in finding out about the nature of the chemical reactions following electron transfer. Altogether these studies have provided an excellent insight into the products that may be obtained by electrochemical oxidation of hydrocarbons and also the mechanisms by which they are formed.

The purpose of the present chapter is to summarize the electrochemical oxidation of hydrocarbons with special reference to the electrode processes involved. The reader may also find material of interest in Chapters 22 (Electrolytic oxidative coupling), 24 (Anodic substitution and addition), and 32 (Conducting polymers).

II. GENERAL MECHANISTIC CONSIDERATIONS

The exchange of an electron between an electrode and a molecule in solution is usually referred to as a direct process, which for the oxidation of most organic substrates results in the formation of the corresponding radical cations. For hydrocarbons, direct oxidation is typically observed for unsaturated compounds, including aromatics, and involves the removal of an electron from a bonding π-orbital. Radical cations are also the primary intermediates in the oxidation of many hydrocarbons by high valent metal ions [5]. The general properties and reactions of radical cations (and dications) in solution have been described in several reviews and monographs [6–11].

In contrast to the direct process, an indirect process is one in which a foreign molecule or ion serves to shuttle electrons between the electrode and the substrate molecules. An indirect oxidation process may also involve the transfer of a hydrogen atom from a suitable substrate to a radical generated electrochemically. Indirect processes are typically observed for saturated aliphatic hydrocarbons and substrates that are more difficult to oxidize than the solvent-supporting electrolyte system.

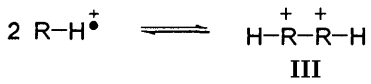
A. Direct Anodic Oxidation

The radical cations initially formed during the direct oxidation of hydrocarbons [Eq. (1)] are highly reactive species, and their formation is usually followed by a fast reaction in solution. This involves typically a nucleophile (Nu^- or NuH) or a base (B), resulting in the formation of either an addition product, **I**, or an elimination product, **II**, as illustrated by Eqs. (2) and (3). Reaction (2) may be observed for almost any radical cation when a suitable nucleophile is present, whereas reaction (3) is typically observed for alkyl-substituted aromatic hydrocarbons having at least one hydrogen atom in an α position. Other common follow-up reactions are dimerization [Eq. (4)] and the coupling of a radical cation and a molecule of substrate [Eq. (5)]. The neutral molecule in Eq. (5) may also be a hydrocarbon different from R–H:

$$R\text{–}H \rightleftharpoons R\text{–}H^{+\bullet} + e^- \qquad (1)$$

$$R\text{–}H^{+\bullet} + Nu^- \text{ (or NuH)} \rightleftharpoons \underset{\mathbf{I}}{\bullet R(H)Nu} \text{ (or } \underset{\mathbf{I'}}{\bullet R(H)NuH^+}\text{)} \qquad (2)$$

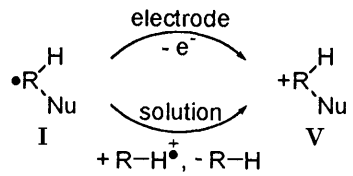
$$R\text{–}H^{+\bullet} + B \rightleftharpoons \underset{\mathbf{II}}{R^\bullet} + BH^+ \qquad (3)$$



(4)

(5)

Radicals such as **I**, **II**, and **IV** are as a rule more easily oxidized than R–H [12–15], making possible the transfer of a second electron, at the electrode or in solution, where in the latter case $R-H^+$ serves as the oxidant:



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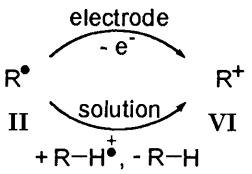

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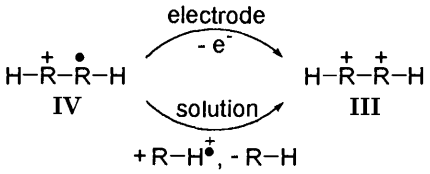
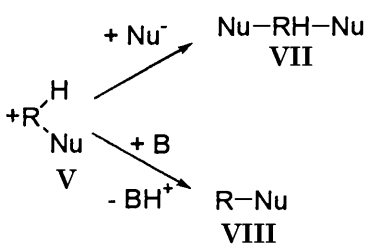


(8)

Whether this second electron transfer takes place at the electrode (ECE mechanism) or in solution (DISP mechanism) is a question of how close to the electrode the radicals are formed. This again is related to the rate of the chemical reactions, Eq. (2), (3), or (5), by which they are formed. The distinction between these types of electron transfer is important when voltammetric curves are used for kinetics and mechanism analysis. This problem is discussed in more detail in Chapters 1 and 2.

The cations **III**, **V**, and **VI** are finally converted to neutral products by reaction with a nucleophile or base as shown in Eqs. (9)–(13).



Addition (9)

Substitution (addition–elimination) (10)

$$R^+ + Nu^- \longrightarrow R\text{–}Nu \qquad \text{Substitution (elimination–addition)} \qquad (11)$$

VI IX

$$H\text{–}\overset{+}{R}\text{–}\overset{+}{R}\text{–}H \xrightarrow{+\,2\,Nu^-} Nu\text{–}RH\text{–}RH\text{–}Nu \qquad \text{Dimerization–addition} \qquad (12)$$

III X

$$H\text{–}\overset{+}{R}\text{–}\overset{+}{R}\text{–}H \xrightarrow[-\,2\,BH^+]{+\,2\,B} R\text{–}R \qquad \text{Dimerization–elimination} \qquad (13)$$

III XI

In rare cases the reaction mechanism involves the disproportionation of the radical cations [Eq. (14)], resulting in the formation of the dication, **XII**, which rapidly reacts further to products.

$$R\text{–}H^{+\bullet} + R\text{–}H^{+\bullet} \overset{K_{dispr}}{\rightleftharpoons} R\text{–}H^{2+} + R\text{–}H \qquad (14)$$

XII

This mechanism does not constitute a major reaction pathway for the anodic oxidation of alternant aromatic hydrocarbons (AAH) or alkyl-substituted AAH under common experimental conditions [12,16–19], but has been found to be operative, for example, for tetraarylethylenes [20–23]. The difference in the reaction pattern of AAH and tetraarylethylenes is related to the rotational freedom around the central C–C bond experienced by the radical cations of the latter [24]. This results in a small or even negative difference between the standard potentials for the first and second one-electron transfer, E_1° and E_2°, and, accordingly, the value of K_{dispr} [Eq. (15)] may take relatively large values.

$$\ln K_{dispr} = (E_1^\circ - E_2^\circ)nF/(RT) \qquad (15)$$

Dications of AAH are only formed—for example, during cyclic voltammetry—when the radical cations are stable on the time scale of the experiment or under conditions that allow controlled potential electrolysis (CPE) to be carried out at the potential of the second voltammetric oxidation wave.

B. Indirect Anodic Oxidation

Indirect oxidation mechanisms have been proposed in some cases, such as for the oxidation of aliphatic hydrocarbons [25], for which voltammetric studies do not give unambiguous information about the nature of the electroactive species. Often, they are assumed to involve the oxidation of the anion of the supporting electrolyte to form an inorganic radical [Eq. (16)], which subsequently either attacks a C–H bond in the organic substrate [Eq. (17)] or oxidizes the substrate in an electron transfer process [Eq. (18)]:

$$X^- \rightleftharpoons X^\bullet + e^- \qquad (16)$$

$$X^\bullet + R - H \longrightarrow HX + R^\bullet \qquad (17)$$

$$X^\bullet + R - H \longrightarrow X^- + R - \overset{+}{H}^\bullet \qquad (18)$$

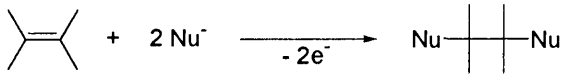
It is sometimes difficult to distinguish this type of mechanism from the direct one. The combination of reactions (16) and (18) is an example of a so-called mediated electrolysis in

which a mediator redox system, here the $X^-/X^\cdot$ system, serves to shuttle electrons between the electrode and the substrate. In other cases the mediator system is of the $M^{n+}/M^{(n+1)+}$ type, where $M^{n+1)+}$ is a high-valent metal ion such as Ce^{4+} [26,27], Co^{3+} [27], or Mn^{3+} [27,28] (see also Ref. 5).

III. COMMON REACTION TYPES AND PREPARATIVE ASPECTS

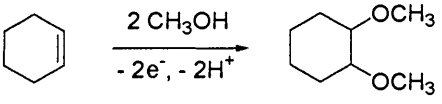
The anodic oxidation of hydrocarbons is a convenient method for the preparation of a number of useful products, which in many cases can be prepared only with difficulty by other methods. Examples are given next together with a short discussion of some preparative aspects. More comprehensive treatments are available [29–31].

A. Addition Reactions



(19)

(See also Chapter 24.) The oxidative addition [Eqs. (1), (2), (6), and (9)] of nucleophilic reagents to an isolated double bond or a larger π-system is a synthetically useful reaction. The stoichiometry of the overall reaction is given by Eq. (19). Usually the addition is of the 1,2- or the 1,4-type as illustrated by the 1,2-addition of MeOH to cyclohexene [Eq. (20)] [32] and acenaphthylene [Eq. (21)] [33] and the 1,4-additions of MeOH to cyclopentadiene [Eq. (22)] [34] and of AcOH to anthracenes [Eq. (23)] [35–37]. As a rule, mixtures of *cis*- and *trans*-isomers are obtained.



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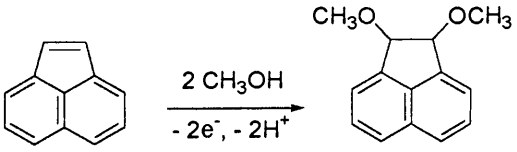

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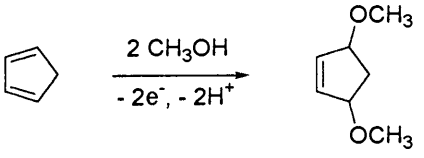

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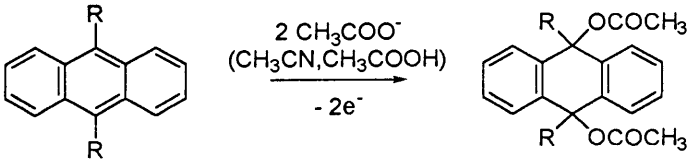
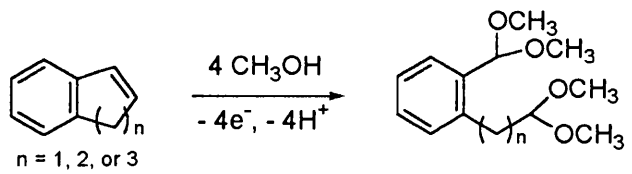


(R = H, CH_3) (23)

The 1,2- and 1,4-addition reactions have been observed also for alkyl-substituted aromatics, but the yields are often low, in particular for benzene derivatives, owing to competing side-chain substitution reactions. Examples include the addition of MeOH to methyl-substituted benzenes [38–42], naphthalenes [43], and anthracenes [43,44]. In a similar fashion, the anodic oxidation of 1,3-dienes in MeOH [45,46] results in mixtures of 1,2- and 1,4-addition products accompanied by substitution products and methoxy-containing dimers and trimers [46]. Styrenes are oxidized in MeOH to the 1,2-addition product together with products formed by dimerization–addition [47,48]. Oxidation of allenes results in most cases in complicated product mixtures resulting from single and double addition reactions [49–52].

In addition to MeOH and AcOH nucleophiles such as pyridine [4,53–58], azide ion [59], chloride ion [60], and cyanide ion [61], as well as the anions of 1,3-dicarbonyl compounds and aliphatic nitro compounds [59], and even Grignard reagents [59], have been employed.

The 1,2-addition process results in a product with a π-system that expands over a carbon skeleton that is two carbons less than that of the starting material and in the case of 1,4-additions the resulting π-system is even separated into two smaller systems. Simple alkenes result in products that are fully saturated. For these reasons the addition product is usually more difficult to oxidize than the starting material and, accordingly, does not suffer further oxidation at the potential necessary for the oxidation of the substrate. This feature is a major reason for the success of anodic addition processes in synthetic organic electrochemistry. However, occasionally it happens that the addition product is further oxidized, resulting eventually in cleavage of the former double bond. This has been observed, for example, during the oxidation of 1-phenylcycloalkenes [Eq. (24)] [62] and vinylarenes [63] in MeOH.

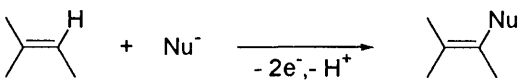


(24)

B. Substitution Reactions

(See also Chapter 24.)

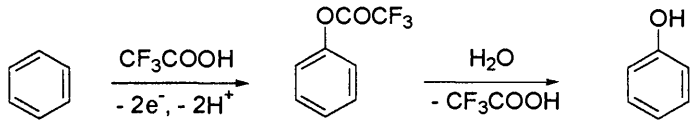
1. Nuclear Substitution



(25)

When the ring carbon at which the nucleophilic attack takes place carries a hydrogen atom, the intermediate carbocation, **V**, may deprotonate resulting in nuclear substitution [Eqs. (1), (2), (6), and (10)]. The overall reaction, Eq. (25), includes reestablishment of the double bond. When Nu is electron withdrawing the product is less easy to oxidize than the starting material and is for that reason not further converted. In such cases the yields of the substituted products are usually good. Examples are trifluoroacetoxylation, which

after hydrolysis leads to phenolic products [Eq. (26)] [64,65], and acetamidations via a nitrilium ion intermediate [Eq. (27)] [66].



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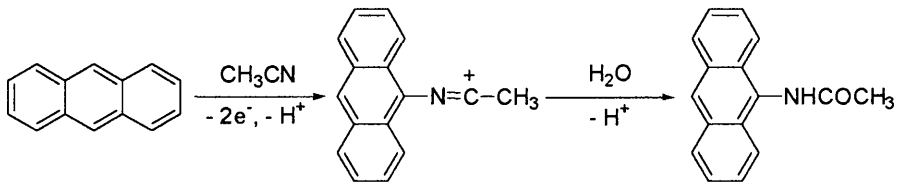
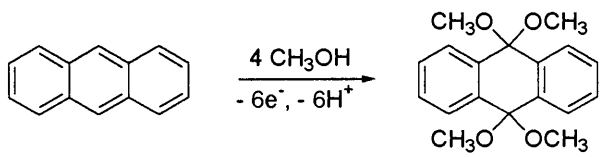


(27)

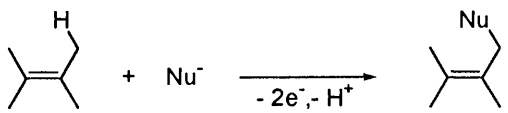
In addition, deactivating nitro and halogen substituents have been introduced by anodic oxidation (see Chapter 24.)

When Nu is electron donating the product is as a rule more easily oxidized than the starting material, resulting in further oxidation under the reaction conditions and, frequently, complex reaction mixtures. The anodic methoxylation of naphthalene, which results in 1-methoxy-, 1,2-dimethoxy-, and 1,4-dimethoxynaphthalene, approximately in a 1 : 2 : 1 ratio, serves as an illustration of this problem [67]. However, in other cases, a single major product is obtained after a sequence of reactions, such as the oxidation of mesitylene in MeCN-diluted H_2SO_4 to 2,4,6-trimethyl-4-hydroxycyclohexa-2,5-dien-1-one in a substitution–elimination reaction [68] or the oxidation of anthracene in MeOH to 9,9,10,10-tetramethoxy-9,10-dihydroanthracene in a substitution–addition reaction [Eq. (28)] [69].



(28)

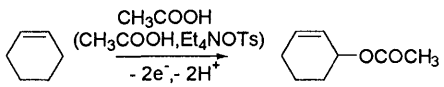
2. Substitution at α-Carbon Atoms



(29)

An important case is the oxidation of alkenes or alkyl arenes containing at least one hydrogen in an α-position [70–77]. The reaction sequence that leads to α-substitution [Eq. (29)] for alkylbenzenes and -naphthalenes most likely includes Eqs. (1), (3), (7), and (11), whereas for alkylanthracenes there is evidence that substitution may take place as an addition–elimination process (see Sec. IV for details). Typical examples are the oxidation of cyclohexene to 3-acetylcyclohexene in AcOH [Eq. (30)] [76], the oxidation of 1,3,5-cycloheptatriene to 7-methoxy-1,3,5-cycloheptatriene in MeOH [74], and the two-

step oxidation of *p-tert*-butyltoluene to *p-tert*-butylbenzaldehyde dimethyl acetal in MeOH [Eq. (31)] [75].



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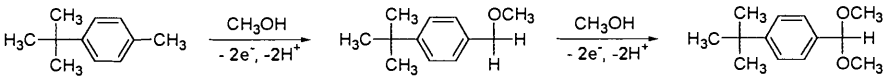
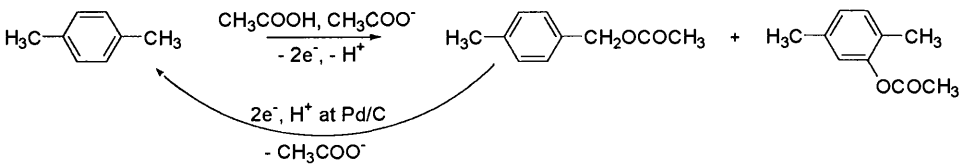


(31)

In moist MeCN, electrolysis of alkylaromatics at the first oxidation potential gives moderate to high yields of the corresponding *N*-benzylacetamides, which are themselves relatively easily oxidized. In some cases the corresponding bibenzyls were also isolated [78,79]. The oxidation of hexamethylbenzene at the potential of the second voltammetric wave results in side-chain bisacetamidation at the 1,3-positions [80].

α-Substitution in alkyl arenes is often accompanied by nuclear substitution. In an elegant study of the acetoxylation of alkylbenzenes, good yields of the nuclear substitution product were obtained by taking advantage of the fact that the α-substituted product selectively could be reduced back to the starting material by using a Pd/C cathode in an undivided cell, here illustrated for *p*-xylene [Eq. (32)] [71].

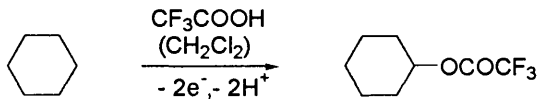


(32)

3. Substitution in Saturated Aliphatic Hydrocarbons

$$R - H + Nu^- \xrightarrow[-2e^-,\,-H^+]{} R - Nu \tag{33}$$

The anodic oxidation of saturated aliphatic hydrocarbons takes place at potentials close to those for the decomposition of most solvent-supporting electrolyte systems [81], and for that reason detailed kinetic and mechanistic studies are in most cases difficult or impossible. Thus, it is generally not known whether the reaction proceeds in a direct fashion involving removal of an electron from a σ-type bond resulting in a highly energetic radical cation or in an indirect fashion via hydrogen abstraction [Eq. (17)]. In any case, it is not a surprise that the oxidation of a long-chain aliphatic hydrocarbon is nonselective. However, anodic substitution is a convenient method for the functionalization of saturated aliphatic hydrocarbons possessing a high degree of symmetry, which reduces the number of possible products considerably, sometimes to the extent that a single major product may be obtained. Examples include the oxidation of cyclohexane and other cyclic and bicyclic hydrocarbons in $CH_2Cl_2/CF_3COOH/(CF_3CO)_2O$ or $CH_2Cl_2/\ CF_3COOH$ to the corresponding trifluoroacetates [Eq. (34)] [82,83] and the oxidation of adamantane in MeCN, which leads to the corresponding acetamide [Eq. (35)] [84]



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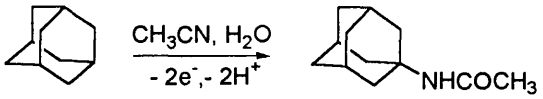
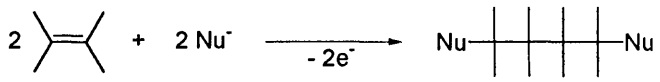


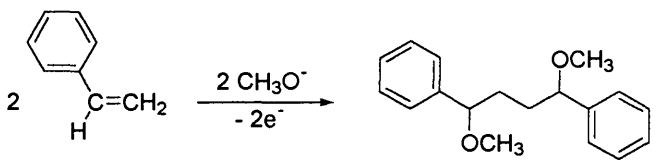
(35)

C. Dimerization–Addition Reactions



(36)

(See also Chapter 22.) Dimerization followed by addition [Eqs. (1), (4), (12), or (1), (5), (8), and (12)], resulting in overall Eq. (36), is a useful reaction [59,85,86] taking place in the anodic oxidation of suitable substituted alkenes, such as arylalkenes and butadiene, in an electrolyte usually consisting of MeOH/NaOMe or MeOH/NaI. The reaction is favored by the use of a carbon anode [59]. Styrene, for instance, may be oxidized in this way to 1,4-diphenyl-1,4-dimethoxybutane [Eq. (37)] [85].



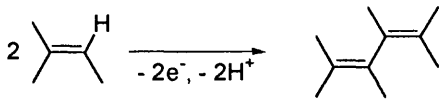
(37)

This reaction may also be carried out in an intramolecular fashion by oxidation of bis-styrylalkanes, giving rise to cyclized products [87].

D. Dimerization–Elimination Reactions

(See also Chapter 22.)

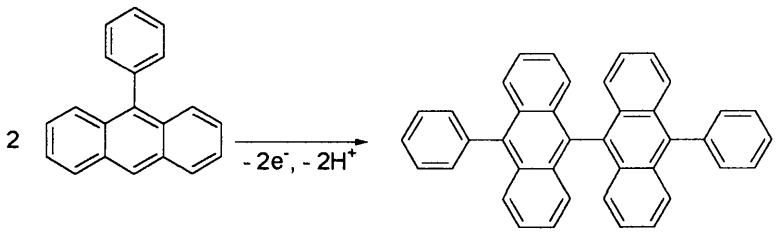
1. Nuclear Dimerization



(38)

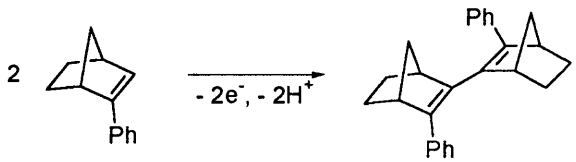
Nuclear dimerization [Eq. (38)], apparently may proceed by either of two mechanisms, Eqs. (1), (4), and (13) or Eqs. (1), (5), (8), and (13), dependent on the nature of the substrate and the reaction conditions. Similarly to what is being observed for nuclear substitution with electron-donating substituents, the products of nuclear dimerization are as a rule more easy to oxidize, which results in further oxidation at the potential needed to oxidize the starting material. However, under conditions of low nucleophilicity the radical cation of the dimer may survive as long as the concentrations are kept at the millimolar level, and the dimer may then be obtained after back reduction to the neutral stage. The failure to conduct reactions of this type at higher concentrations is most likely

caused by formation of the highly reactive dimer dication by disproportionation, Eq. (14). In some cases the dimers, which as a rule are less soluble than the substrates, precipitate and in this way avoid further oxidation. This has been observed, for instance, during the dimerization of 9-phenylanthracene to the 10,10′-dimer in MeCN [88] or MeCN-CF_3COOH [Eq. (39)] [89].

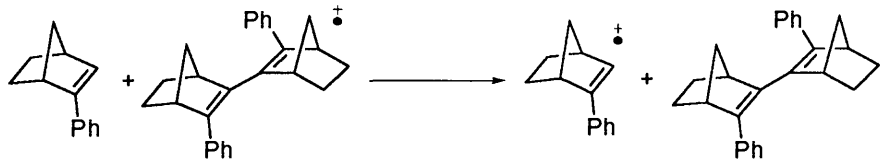


(39)

An interesting example is the anodic dimerization of 2-phenylnorbornene [Eq. (40)] [90]. The experimental results indicate that the dimer radical cation in this case oxidizes the substrate to the corresponding radical cation in solution via Eq. (41), so fast that follow-up reactions leading to the degradation of the dimer are avoided.

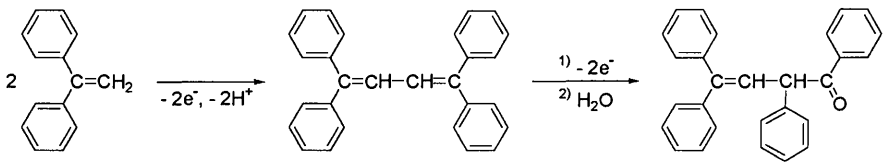


(40)



(41)

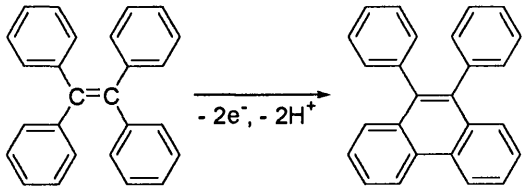
Under conditions that are not strictly nonaqueous, the oxidized dimer may be trapped by water, as was observed during the oxidation of 1,1-diphenylethylene catalyzed by the radical cation of dibenzo-1,4-dioxin [91]. The dimer dication upon reaction with water undergoes a 1,2-phenyl shift, resulting finally in 1,2,4,4-tetraphenyl-3-buten-1-one [Eq. (42)], reminiscent of the 1,2-shifts observed during anodic oxidation of 1-phenyl- and 1,4-diphenylnaphthalene in acidic dimethylformamide (DMF) [92].



(42)

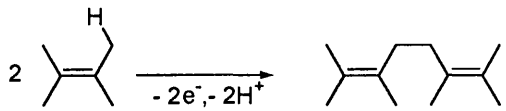
Oxidation of arenes under nonaqueous conditions often results in polymerization [93], which has been observed for most of the simple arenes, such as benzene [94–97], naphthalene [98], pyrene [99], biphenyl [96], triphenylene [99], fluoranthene [99], and fluorene [99–101]. (See Chapter 32 for details.) Polymerization is often accompanied by severe electrode passivation [100].

An intramolecular reaction has been observed for the oxidation of tetraphenylethylene [Eq. (43)] in MeCN-Et_4NClO_4 [102] and in CH_2Cl_2-CF_3COOH [20,23].



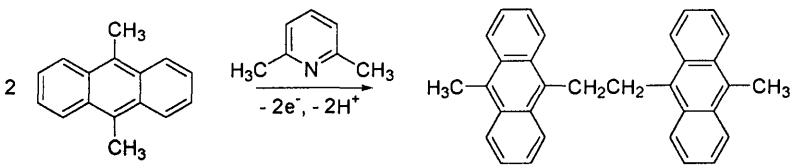
(43)

2. Dimerization at α-Carbon Atoms



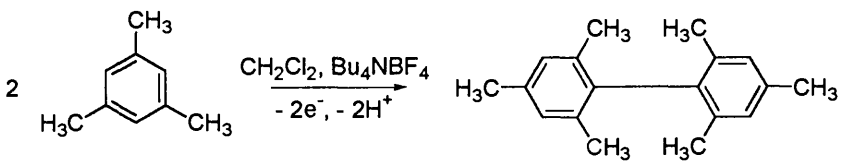
(44)

Dimers linked through the α-carbon [Eq. (44)] may be observed when dimerization of the radical, **II**, competes favorably with further oxidation [Eq. (7)]. For instance, oxidation of 9,10-dimethylanthracene in the presence of the hindered base, 2,6-lutidine, results in the symmetrical dimer [Eq. (45)] [103].



(45)

However, the outcome of the oxidation of alkyl-substituted arenes is not easy to predict owing to the competition between nuclear dimerization and dimerization through an α-carbon. For instance, a major product from oxidation of mesitylene in CH_2Cl_2 is bimesityl [Eq. (46)], and from durene in CH_2Cl_2-CF_3SO_3H, the heptamethyldiphenylmethane [Eq. (47)] [104,105]; no diphenylmethane is formed from mesitylene nor biphenyl from durene.



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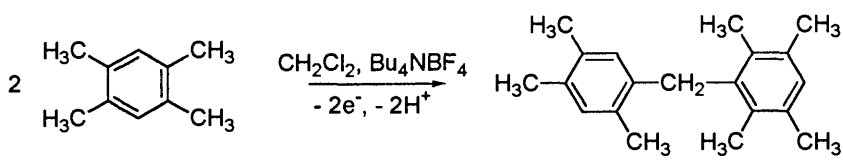


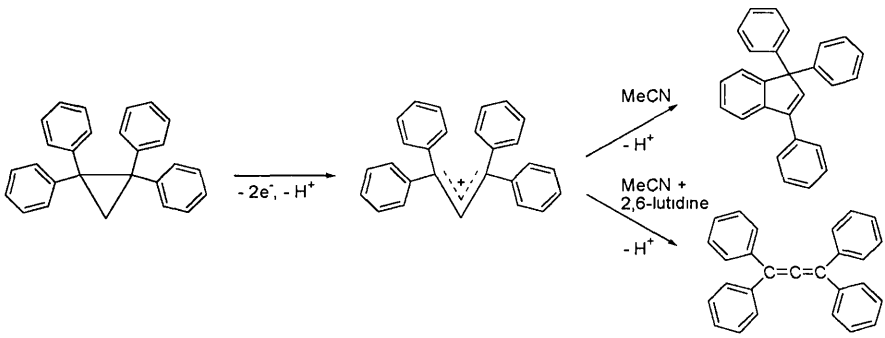
(47)

Related to these reactions is the formation of mixed biaryls, for example, during the anodic oxidation of naphthalene in the presence of alkylbenzenes [106].

E. Cleavages

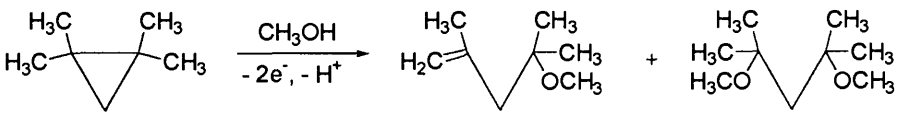
The relief of steric strain plays a central role in the anodic oxidative ring opening of cyclopropanes. For instance, 1,1,2,2-tetraphenylcyclopropane is converted via the

1,1,3,3-tetraphenylpropenyl cation to 1,3,3-triphenylindene or tetraphenylallene, depending on the basicity of the solvent system [107,108]:



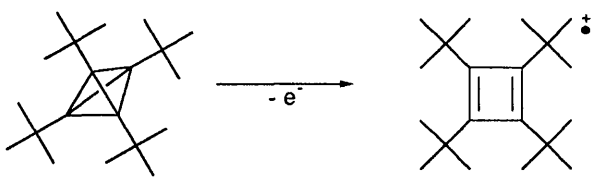
(48)

Similarly, the oxidation of 1-cyclopropylnaphthalene in MeOH gives 1-(1,3-dimethoxypropyl)naphthalene and other ring-opened products [109], and oxidation of cyclopropylbenzene gives 1,3-dimethoxypropylbenzene [110]. Related to these reactions are the oxidation of 1,1,2,2-tetramethylcyclopropane in MeOH, as in Eq. (49) [111], and of polycyclic cyclopropanes in AcOH/triethylamine to ring-opened products [112].



(49)

Relief of steric strain is also an important factor in the oxidation of tetra-*tert*-butyltetrahedrane to the radical cation of tetra-*tert*-butylcyclobutadiene [113]:



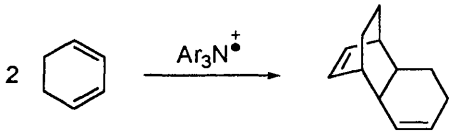
(50)

Cleavage of a C–C bond is observed also during the electrochemical oxidation of (−)-α-pinene [114].

F. Chain Reactions

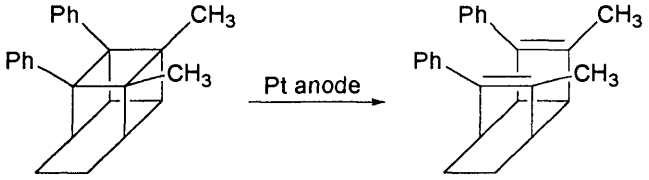
The radical cation-catalyzed cycloadditions of the Diels–Alder type are well known and have been the subject of a number of studies to which reader is referred for details [115–118].

The prototype cyclodimerization of 1,3-cyclohexadiene catalyzed by tris(4-bromophenyl)aminium ion ($Ar_3N^{+\cdot}$) proceeds smoothly in CH_2Cl_2 at room temperature or below to a 70% yield of the Diels–Alder dimer [Eq. (51)] [116]. The direct anodic oxidation of 1,3-cyclohexadiene results in formation of the Diels–Alder product only in low yield, with the major product being a polymer linked through the 1,4-positions [119].



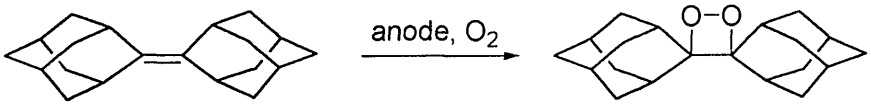
(51)

A chain reaction is involved also in the anodically stimulated [2 + 2] cycloreversion [120]:



(52)

Another type of chain reaction is sometimes observed when electrochemical oxidation of unsaturated hydrocarbons is carried out in the presence of atmospheric oxygen, which may result in the formation of dioxetanes exemplified by the oxidation of biadamantylidene [Eq. (53)] and related compounds [121–123]. Similar behavior has been observed for other alkenes [124].



(53)

G. Indirect Oxidations

The situation in which the supporting electrolyte and/or the solvent is oxidized at a lower potential than the organic substrate is frequently encountered. Anodic methoxylation and cyanation are two typical cases for which homolytic processes involving methoxy and cyano radicals, respectively, have been invoked [125,126]. However, it can be shown that in cyanation [127–129] and at least some cases of methoxylation [130], one must work at an anode potential around or higher than the half-wave potential of the organic substrate in order to get any substitution product. Similar mechanism problems are apparent for the side-chain acetoxylation of alkylaromatic compounds in AcOH–Me_4NNO_3 [131,132].

Organic electron transfer reactions are often accompanied by large activation energies (overpotentials), and in such cases it is sometimes advantageous to include a mediator in the solvent-supporting electrolyte system. Examples include the oxidation of naphthalene to naphthoquinone by electrochemically generated Ce^{4+} [26], anthracene to anthraquinone in a slurry containing both a surfactant and a redox mediator, Mn^{3+} [28], and of toluenes to benzaldehydes by electrochemically generated Ce^{4+}, Co^{3+}, or Mn^{3+} [27].

IV. VOLTAMMETRY AND STUDIES OF KINETICS AND MECHANISMS

The major voltammetric methods employed for studies of the anodic oxidation of aromatic hydrocarbons are linear sweep voltammetry (LSV), cyclic voltammetry (CV), and derivative cyclic voltammetry (DCV). Second harmonic ac (SHAC) voltammetry and

voltammetry at rotating disc electrodes (RDE) are now used less frequently. (See Chapter 2 for a discussion of the application of electroanalytical techniques.)

In LSV or CV the experimental data are usually presented as anodic peak potentials (E_p) or half-peak potentials ($E_{p/2}$). The latter quantity, which for a one-electron process at 298 K is related to E_p through Eq. (54), may more easily be measured to a high degree of precision owing to the steepness of the voltammetric wave in the potential region corresponding to $E_{p/2}$.

$$E_p - E_{p/2} = 56.5\,\text{mV} \tag{54}$$

Voltammetry at RDEs results in S-shaped current–voltage curves similar to those obtained by polarography. The experimental data are given as half-wave potentials, $E_{1/2}$, which are related to E_p:

$$E_p - E_{1/2} = 28.5\,\text{mV} \tag{55}$$

The gathering of fundamental information concerning the initial electron transfer, such as standard potentials, E°, or rather formal potentials, $E^{\circ\prime}$, for radical cation formation, was earlier greatly hindered by the occurrence of rapid reactions of the intermediates. (See Chapter 1 for a discussion of the difference between formal potentials and standard potentials.) Reaction with impurities in the solvent, or even the solvent itself, and/or rapid proton loss are common reasons for not observing reversible formation of radical cations; the consequent irreversibility is in CV associated with a shift in E_p, in the negative direction, from that for reversible oxidation. Considerable progress has been made in countering these difficulties.

The use of acidic solutions greatly slows down proton loss [12,133], the rigorous drying of solvents precludes rapid hydroxylation of cationic species [18,134–136], and the use of nonnucleophilic solvents, such as liquid SO_2 [137–140], 1,1,1,3,3,3-hexafluoropropan-2-ol [141], or $CF_3COOH/(CF_3CO)_2O$, alone [18,142] or mixed with CH_2Cl_2 [12,135,143–146], also permits the formation of several persistent radical cations and dications. For 9,9′-bianthryl even the tetracation has been observed in liquid SO_2 [138].

The application of phase-selective SHAC voltammetry to organic systems has proved to be fruitful [147,148]. This method is capable of measuring $E^{\circ\prime}$ even when the radical cation undergoes a moderately rapid reaction. Another approach for obtaining $E^{\circ\prime}$, for the formation of reactive radical cations is the application of CV with voltage sweep rates in the $kV \cdot s^{-1}$ range [149–155].

Finally, the stability of radical cations and other reactive intermediates is, of course, enhanced at low temperatures [12,156–159]. This is an additional reason why follow-up reactions are effectively suppressed in liquid SO_2. Another aspect of low-temperature conditions is the possibility of preparing stable salts of highly reactive radical cations as demonstrated by the formation of a solid with the composition $(ArH)_2PF_6$ by oxidation of ArH in CH_2Cl_2 between −30°C and −70°C with Bu_4NPF_6 as supporting electrolyte [160–162].

A. Aromatic Hydrocarbons

A much-used approach to the study of the primary electrochemical step of aromatic hydrocarbons involves the use of model compounds whose corresponding radical cations (and in some cases dications) are relatively stable. Substituted anthracenes, particularly 9,10-diphenylanthracene (9,10-DPA), have featured largely in such work [12,53–58,135,137,151,163–168]. For instance, on slow-sweep CV in MeCN, purified without

critical regard to dryness, 9,10-DPA is reversibly oxidized to the radical cation at $E_p = 1.22$ V versus SCE, followed by irreversible oxidation to the dication at ~ 1.6 V.

Anthracenes without substituents in the 9,10-positions as well as most benzenes and naphthalenes give rise to irreversible oxidation in, for example, MeCN and CH_2Cl_2 during CV at moderate voltage sweep rates.

Voltammetric data for a number of representative aromatic hydrocarbons are summarized in Table 1, and it is seen that the ease of oxidation, as expected, increases when the π-system becomes more extended. A more comprehensive collection of such information is available elsewhere [141,152,153,169,170].

It has long been realized that excellent correlations exist between $E_{1/2}$ or E_p and molecular orbital parameters [172,178–181]. Correlations between voltammetric data and experimental observables such as ionization potentials (IP) [172,178,182,183], charge-transfer transition energies [172], and positions of p-bands in ultraviolet (UV) absorption spectra of the hydrocarbons [4,172] have been reported as well. The basis and limitations of such correlations have been examined critically [147,175,184]. For alkyl aromatic hydrocarbons (AAHs), the slope, a, of the correlation line [Eq. (56)], where E° is the standard potential for the reversible one-electron oxidation, is close to unity and has been used to suggest that in MeCN the solvation energies of the hydrocarbon radical cations are constant throughout the series [175].

$$E^\circ = a \cdot \mathrm{IP} + b \tag{56}$$

It was further concluded that the solvation energies of such species are nearly equal and of the order of -2 eV.

Phase-selective SHAC voltammetry has been used to evaluate the temperature dependence of $E^{\circ\prime}$ for a number of aromatic hydrocarbons [148] and hence the entropy changes associated with the formation of the radical cations:

$$dE^{\circ\prime}/dT = \Delta S/F \tag{57}$$

The values of $-\Delta S_{273.2}$ were observed to be in the range 5–20 e.u. and were attributed to reflect mainly differences in solvation. A slight increase in $-\Delta S_{273.2}$ was observed with increasing concentration of the supporting electrolyte and in going through the solvent series: PC < DMF < MeCN.

Convincing evidence has been put forward that the reaction pathway in the oxidative addition of two molecules of a pyridine derivative to 9,10-DPA [Eq. (31)] [53–58] includes Eqs. (1), (2), (6), and (9). By studying the number of electrons transferred (n_{obs}) in the oxidation of 9,10-DPA in the presence of different nucleophiles at the rotating disk electrode as a function of the rotation rate ω, it has been possible to show [53] that the strength of the nucleophile strongly affects the dependence of n_{obs} on ω. Approximate pseudo-first-order rate constants for the rate determining attack by the nucleophile on 9,10-DPA$^+$ could be obtained by fitting the experimental data for n_{obs} versus ω to the working curve calculated for the ECE mechanism. The results demonstrated that the rates follow the order of nucleophilicity of the pyridines. (This conclusion is not affected by the fact that the working curves were calculated for an ECE mechanism instead of the DISP mechanism that is actually followed.)

The rate law for the reaction between 9,10-DPA$^{+\cdot}$ and pyridine (PYR) at the millimolar concentration level is given by Eq. (58). The value of k_{58} has been determined by spectroelectrochemical methods [54–56] and by homogeneous kinetics [55–57] and was found to be in the range $2 \times 10^4\ M^{-1}\,s^{-1}$ to $4 \times 10^4\ M^{-1}\,s^{-1}$ in MeCN at room temperature. However, at much lower concentrations (0.01 mM), stopped-flow experiments

Table 1 Oxidation Potentials of Aromatic Hydrocarbons and Substituted Aromatic Hydrocarbons

Compound	$E_{1/2}$ (V)		E_p (V) or $E_{p/2}$ (V)	
	vs. SCE[a]	vs. Ag/Ag^+	vs. SCE	vs. Ag/Ag^+
Benzene			2.62[b]	
Toluene		1.98[c]; 1.93[d]		1.93[e]
p-Xylene		1.56[c]		1.64[e]
Mesitylene	1.90	1.55[c]		1.69[e]; 1.72[f]
1,2,3,4-Tetramethylbenzene			1.77[g]	
Durene	1.62	1.29[c]	1.75[g]	1.41[e]; 1.70[h]
Pentamethylbenzene	1.62	1.28[c]	1.69[g]	1.33[e]; 1.63[h]
Hexamethylbenzene	1.52	1.16[c]	1.58[g]	1.20[e]; 1.50[h]
Naphthalene	1.72	1.34[c]; 1.31[d]	1.87[a]	
Anthracene	1.20[f]	0.84[i]	1.31[j]; 1.40[k,l]	1.13[m]
9,10-Diphenylanthracene		0.86[l]	1.20[j]; 1.27[l]	
Biphenyl	1.91[f]	1.48[c]		
Fluorene	1.65	1.32[n]; 1.25[c]		
Perylene	1.0		1.09[a]	

[a] AcOH–NaOAc [171].
[b] MeCN–Bu_4NClO_4 [152].
[c] MeCN–$NaClO_4$ [4].
[d] MeCN–$NaClO_4$ [172].
[e] CF_3COOH–$(CF_3CO)_2O$–Bu_4NClO_4 [153].
[f] MeCN–Bu_4NBF_4 [173].
[g] Values of E° in MeCN–Bu_4NBF_4 [155].
[h] MeCN–Bu4$NClO_4$ [153].
[i] MeCN–$NaClO_4$ [174].
[j] CH_2Cl_2–AcOH–$(CF_3CO)_2O$–$NaClO_4$ [135].
[k] MeCN–Bu_4NBF_4–Al_2O_3 [175].
[l] CH_2Cl_2–CF_3COOH–$(CF_3CO)_2O$–Bu_4NBF_4 [12].
[m] C_6H_5Cl–Bu_4NBF_4 [176].
[n] MeCN–$(CF_3CO)_2O$–Bu_4NBF_4 [177].

demonstrated that the reaction was following a rate law [Eq. (59)], second order in 9,10-$DPA^{+\cdot}$ and first order in PYR. These data indicate a transition from rate-determining nucleophilic attack at high concentrations of 9,10-DPA^+ to rate-determining electron transfer at low concentrations [56]. The same rate law was found for attack by Cl^- [60].

$$-d[9,10\text{-DPA}^{+\cdot}]/dt = k_{58}[9,10\text{-DPA}^{+\cdot}]\,[\text{PYR}] \tag{58}$$

$$-d[9,10\text{-DPA}^{+\cdot}]/dt = k_{59}[9,10\text{-DPA}^{+\cdot}]^2\,[\text{PYR}] \tag{59}$$

The rate constant for the corresponding reaction with rubrene radical cation is approximately one order of magnitude lower [185]. The solvent used in these studies, MeCN, is in itself a nucleophile, but much too weak to interfere kinetically in the presence of pyridines. For instance, the pseudo-first-order rate constant for the reaction between unsubstituted anthracene and MeCN has been estimated to be $125\,s^{-1}$ [66].

B. Arylalkenes

Oxidation potentials for typical arylalkenes are summarized in Table 2.

Oxidation of tetraphenylethylene (TPE) in CF_3COOH or CH_2Cl_2–CF_3COOH [20,23] gives a radical cations table on the CV time scale, but that undergoes second-order decomposition according to this rate law: rate $= k_{obs}[TPE^{+\cdot}]^2/[TPE]$. The product is 9,10-diphenylphenanthrene [Eq. (43)], and the reaction seems to be a clear-cut example of disproportionation followed by rate-determining intramolecular cyclization of the resulting dication. The rate constant for the coupling reaction at 298 K was determined by derivative LSV and found to be equal to $3.2 \times 10^3\ s^{-1}$ and the Arrhenius activation energy was equal to $11.4\ kcal\ mol^{-1}$. This relatively high value was believed to reflect charge–charge repulsion in the transition state. The activation entropy at 298 K was $-6\ cal\ K^{-1}, mol^{-1}$, indicating solvent reorganization around the more localized charges in the transition state.

C. Alkyl-Substituted Arenes

As it appears in the preceding discussion, the radical cations of unsubstituted or aryl-substituted arenes are usually long-lived species under nonnucleophilic conditions. This is at variance with the radical cations of most alkyl-substituted arenes, which as a rule are thermodynamically very strong acids [189–191]. For instance, the pK_a of toluene changes

Table 2 Oxidation Potentials of Arylalkenes, Alkenes, Alkadienes, and Carotenes

	$E_{1/2}$ (V)		E_p (V) or $E_{p/2}$ (V)	
Compound	vs. SCE[a]	vs. Ag/Ag^{+}[b]	vs. SCE[c]	vs. Ag/AgCl[d]
Styrene				1.68
Indene				1.56
cis-Stilbene				1.57
trans-Stilbene				1.40
2-Phenylnorbornene				1.1[e]
Ethylene		2.90		
1-Alkenes		2.7–2.8		
2-Alkenes		2.2–2.3		
Cyclohexene	2.14	2.05; 1.95[f]		
1,3-Butadiene		2.09		2.0
Biadamantylidene				1.65[g]
Norbornadiene	1.54			1.62
Norbornene	2.02			
1,4-Cyclohexadiene	1.74	≈ 1.3		
β-Carotene	0.51[h]		0.54	

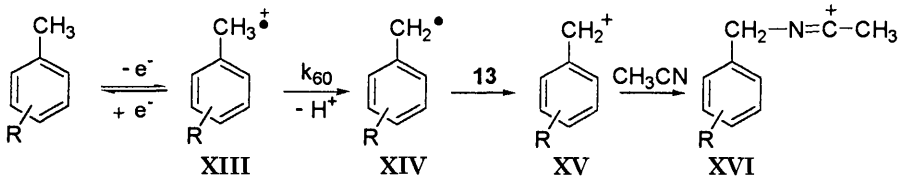
[a] MeCN–$LiClO_4$ [70].
[b] MeCN–Et_4NBF_4 unless otherwise stated [186].
[c] CH_2Cl_2–Bu_4NPF_6 [187].
[d] MeOH–$NaClO_4$ unless otherwise stated [85].
[e] MeCN–Bu_4NClO_4 (V vs Ag/Ag^+) [90].
[f] MeCN–$NaClO_4$ [172].
[g] CH_2Cl_2–CF_3COOH–$(CF_3CO)_2O$–Bu_4NBF_4 (V vs. SCE) [121].
[h] MeCN/benzene (2/1)–Et_4NClO_4 [188].

from approximately 40 to −13 upon oxidation to the radical cation. Accordingly, the radical cations of alkyl arenes would be expected to deprotonate readily, which is indeed the case.

The application of CV in the $kV \cdot s^{-1}$ range has allowed for the determination of $E^{\circ\prime}$ (Table 1) for the oxidation of a series of methylbenzenes [152,153] and $E^{\circ\prime}$ was observed to correlate linearly with the corresponding IP values. The value of the slope, a in Eq. (56), in this case was only 0.71, indicating that the free energy change associated with the electron transfer process decreases with approximately $10\,kcal\,mol^{-1}$ in going from hexamethylbenzene to toluene. However, reexamination of the data [155] showed that slopes close to unity were observed if the methylbenzenes were, rather arbitrarily, divided into two classes, one including benzenes with the number of methyl groups larger than three and another including benzenes with the number of methyl groups less than or equal to three. The difference between the intercepts, b in Eq. (56), amounted to $2.5\,kcal\,mol^{-1}$, reflecting the difference in solvation energies between the two series of compounds.

The voltammetry of methylbenzenes and related compounds has been studied extensively as examples of a reaction in which the initial electron transfer is followed by proton loss [78–80,133,152,153,173,192–201]. Cyclic voltammetry of these compounds at low voltage sweep rates in MeCN typically gives two irreversible oxidation peaks, both corresponding to the transfer of two electrons. The first of these oxidation processes results in the formation of the corresponding benzyl cation, presumably formed in an ECE/DISP-type process, with the chemical step being deprotonation of the initially formed radical cation [Eq. (3)]. The fate of the benzyl cation depends on the composition of the solvent. For instance, in CF_3COOH or CH_2Cl_2–CF_3COOH the intermediate pentamethylbenzyl cation, formed by oxidation of hexamethylbenzene, is converted to $ArCH_2OOCCF_3$. Further oxidation of this product leads to the radical cation, which is stable on the time scale of slow-sweep CV [133].

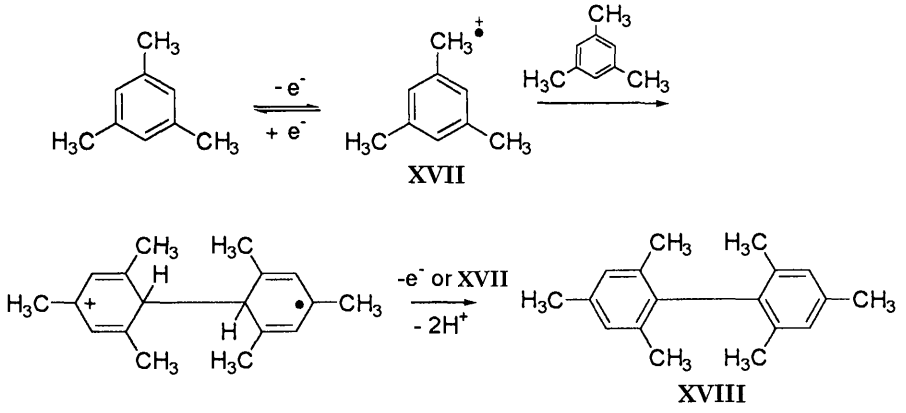
The mechanistic details of the anodic alkylbenzene oxidation have been under intense investigation. In the early stages of this research the major issue was the order of the electron and proton transfer steps leading to the benzyl cations and whether the second electron-transfer reaction takes place at the anode (ECE) or in solution (DISP); see Eq. (7). By the application of a combination of voltammetry and specular reflectance spectroscopy [173,192–195], it has been possible to monitor the electrode surface by UV-visible spectroscopy during electrolysis at controlled potential or to monitor the absorption at a predetermined λ_{max} value as a function of potential. In this way absorption spectra, which were attributed to the radical cation, **XIII**, the benzyl radical, **XIV**, formed by deprotonation, Eq. (60), the benzyl cation **XV**, and the N-benzylnitrilium ions, **XVI**, have been recorded in MeCN.



(60)

The total analysis of the data from this and other electrochemical techniques was found to be in agreement with mechanism (60) and allowed for the evaluation of the deprotonation rate constants, k_{60}, for a number of methylbenzene radical cations. The values of k_{60} measured in this way varied from $100\,s^{-1}$ (1,3,5-trimethylbenzene) to $870\,s^{-1}$ (1,2,4-trimethylbenzene). On the other hand, reoxidation of the radical cation of hexamethylbenzene in MeCN at −40°C could not be observed by CV [197], which led to the conclusion that the lifetime was less than 10^{-4} s, corresponding to a pseudo-first-order rate constant approximately one order of magnitude higher than the range reported above.

The simplest compound to study with respect to deprotonation of the radical cation is hexamethylbenzene because the nucleus is blocked to competing substitution reactions. For other alkylaromatics an alternative reaction is available, that is, attack by starting material on the radical cation or benzyl cation. The balance between these pathways has been studied by the combination of LSV and specular reflectance spectroscopy for durene and mesitylene. The conclusion was that proton loss is slower from the radical cation of mesitylene than from that of durene [79,173]. Consequently, bimolecular reaction with substrate [Eq. (61)], resulting in formation of the dimer, **XVIII**, is more likely for mesitylene than for durene, which will be acetamidated after proton loss and further oxidation. Attack of radical cation on mesitylene rather than dimerization of two radical cations is preferred, since the yield of **XVIII** increases appreciably with increasing concentration of mesitylene but is not affected by changes in the current density. However, it should be pointed out that some authors have suggested that dimer formation may take place as a coupling between two radical cations, as in the formation of 6,6′-bibenzo[a]pyrene from benzo[a]pyrene [202].



(61)

The exact nature of the base is not clear in these studies, and the difference in the rate constants might be attributed to differences in solvent quality. More insight into the nature of the proton transfer reaction has been gained through studies in MeCN of the homogeneous electron transfer from a series of methylbenzenes to Fe(III) complexes followed by proton transfer from the resulting methylbenzene radical cations to a series of pyridine derivatives [153,198]. For hexamethylbenzene radical cation, the rate constants for proton transfer varied between $4 \times 10^2\,M^{-1}\,s^{-1}$ and $9 \times 10^5\,M^{-1}\,s^{-1}$ in going from 2-fluoropyridine to 2,4,6-trimethylpyridine. The rate of deprotonation followed a general Brønsted relationship with a slope of 0.26, which suggested an overall free energy change

in the exergonic region of the driving force. This, together with a deuterium kinetic isotope effect that was observed to decrease with increasing driving force for proton transfer, seems to indicate an early transition state in which the proton transfer has not proceeded beyond the symmetrical situation.

Results reported by Parker have cast some doubt on the general validity of the mechanism including simple deprotonation of the radical cations [Eq. (60)] [199]. Experimental results obtained for durene and for penta- and hexamethylbenzene in MeCN indicated a rate law [Eq. (62)] second order in radical cation. This, together with the unusual observation that the apparent rate constant decreased with increasing temperature at $t > 20°C$, resulting in a curved Arrhenius plot and a deuterium kinetic isotope effect that decreased with decreasing temperature, pointed toward a reaction scheme including the reversible dimerization of the radical cation followed by the irreversible formation of $ArCH_2^+$, $ArCH_3$ and a proton as in Eqs. (63) and (64).

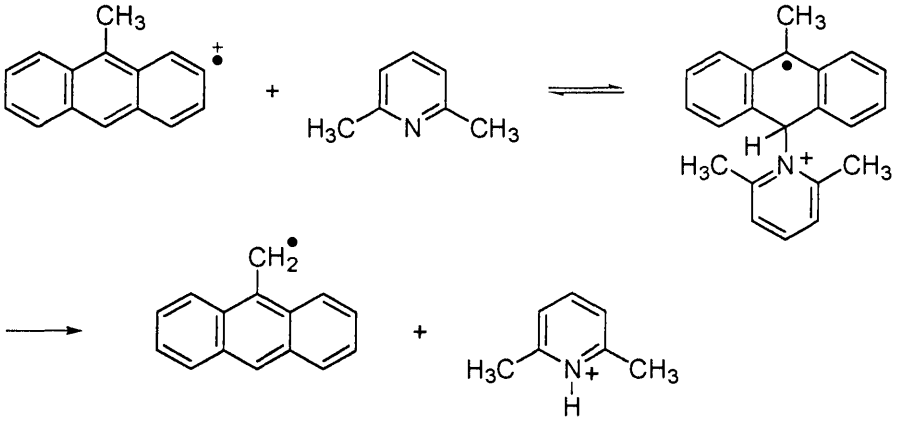
$$-d[ArCH_3^{+\cdot}]/dt = k_{62}[ArCH_3^+]^2 \tag{62}$$

$$2Arch_3^{+\bullet} \rightleftharpoons (ArCH_3^{+\bullet})_2 \tag{63}$$

$$(ArCH_3^{+\bullet})_2 + B \longrightarrow ArCH_2^+ + ArCH_3 + BH^+ \tag{64}$$

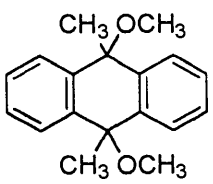
The implications of these unexpected results for the conclusions drawn from previous studies, in particular the work based on spectroelectrochemical measurements, are not clear. The structure of the dimer dication, $(ArCH_3^+)_2$, is not known. However, the reversible formation of dimers from hydrocarbon radical cations has been observed in other cases [203], and is probably a general phenomenon, but usually the dimers do not manifest themselves kinetically.

Another unexpected result is the observation that deprotonation of the 9-methylanthracene radical cation in the presence of 2,6-lutidine appears to proceed via an addition–elimination reaction [Eq. (65)] rather than by direct proton transfer [Eq. (3)] [204]. The important feature of the reaction, which led to the proposal of the addition–elimination mechanism, was the inverse deuterium kinetic isotope effect, $k_H/k_D = 0.83$, observed for the exchange of H by D in the 10-position together with the primary effect, $k_H/k_D = 3.5$–5.9, observed for the exchange of CH_3 by CD_3 in the 9-position.

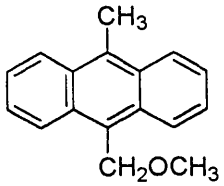


(65)

Related to this is the observation that Ce^{4+} oxidation of, for example, 9,10-DMA in MeOH–MeCN at 0°C leads exclusively to the 9,10-adduct, **XIX**, which upon heating to 45°C was converted to the side chain oxidation product, **XX**, by elimination of MeOH.



XIX



XX

In the absence of a proton in the α-position, such as when the alkyl group is *tert*-butyl, the radical cation may instead undergo slow C–C cleavage, resulting in formation of the parent hydrocarbon and a *tert*-butyl fragment. This has been observed during the voltammetric oxidation of a 9-*tert*-butylanthracene in HFP [205].

D. Simple Alkenes, Alkadienes, and Related Compounds

The electrochemical oxidation of nonbenzenoid unsaturated hydrocarbons is believed to include also the formation of the corresponding radical cation as the first step. However, radical cations derived from alkenes are only in rare cases sufficiently stable to allow for the observation of their reduction back to starting material during CV. Accordingly, the oxidation potentials, such as those listed in Table 2, have in most cases no thermodynamic significance. A notable exception is the oxidation of hydrocarbons of the carotenoid type, which are oxidized in two closely spaced reversible or quasireversible one-electron transfers to the corresponding dications [187,188], and even the quasireversible oxidation to the radical trication has been observed [206].

E. Alkanes

The anodic limit of MeCN containing a perchlorate salt is not high enough to allow a more general study of aliphatic hydrocarbons, except in a few favorable cases [172,207,208]. With the introduction of tetrafluoroborates and hexafluorophosphates [186] as supporting electrolytes, the anodic limit in MeCN can be extended considerably, so that certain saturated aliphatic hydrocarbons can be studied voltammetrically. The application of ultramicroelectrodes has even made it possible to record voltammograms for short-chain alkanes in MeCN in the absence of intentionally added supporting electrolyte [209]. Oxidation potentials for a number of aliphatic and alicyclic hydrocarbons are listed in Table 3. The table is organized to include a representative range of alkanes; common conditions for voltammetry are displayed, as are the relationships between oxidation potentials measured against different reference electrodes. From the diffusion currents it can be estimated that two electrons are involved in the majority of these oxidations [186,207,210].

It will be apparent from Table 3 that, apart from the use of tetrafluoroborates and hexafluorophosphates, extended anodic limits can be obtained at low temperatures [212] or by the use of acidic solvents such as CF_3COOH [81,211,216], FSO_3H [186,217–221], HF [222], and CF_3SO_3H (without supporting electrolyte) [213]. In addition to the electrolyte systems included in the tables, hydrocarbon oxidation has been realized in nitromethane,

nitroethane, propylene carbonate, sulfolane, and dichloromethane [223]. The observed potentials, invariably for irreversible oxidation, vary in a reasonably predictable manner. Good correlations are often found with IP [208,210,224] and σ^+ parameters [70,85,107].

There remains some doubt about the first step of the overall reaction; in MeCN the final products are usually the *N*-alkylacetamides, as shown in Eq. (35). In neutral solution, at extreme anodic potentials, it is difficult to decide between direct [Eqs. (1), (2), and/or (3)] and indirect electron transfer [Eqs. (16), (17), and/or (18)]. For oxidation in MeCN–BF_4^- solutions the variation in potentials is best explained in terms of the direct mechanism. An indirect oxidation mechanism involving hydrogen abstraction by electrogenerated nitrate radical has recently been proposed for the electrolysis of linear alkanes in *tert*-$BuOH/H_2O$ mixtures containing HNO_3 and saturated with O_2 [25].

In strongly acidic solution it has been proposed that electron transfer is from the protonated alkane [220,221]. The CV of alkanes in FSO_3H was studied as a function of added AcOH (a base under these conditions) and/or $KFSO_3$; diffusion-controlled two-electron oxidation was found, and the current-potential curves shifted as base was added. Similar results for cyclohexane oxidation in CF_3COOH–FSO_3H, CF_3COOH–CH_3SO_3H, and CH_2Cl_2-FSO_3H were also interpreted in terms of initial protonation of the alkane [216]. The experimental basis for this conclusion has been challenged. First it was claimed

Table 3 Oxidation Potentials of Alkanes

	$E_{1/2}$ (V)			E_p (V) or $E_{p/2}$ (V)
Compound	vs. SCE	vs. Ag/Ag^+	vs. Pd/H_2	vs. Ag/Ag^+
n-Alkanes		3.4[a]; 2.7[b]		3.5[c]
		3.5–3.9[d]		
		1.14–1.46[e]		
		1.7–2.3[f]		
2,2-Dimethylbutane		3.28[a]		3.90[c]
2-Methylpentane		3.01[a]	1.68[g]	
Cyclopropane		3.41[d]		
1,1,2,2-Tetramethylcyclopropane	2.05[h]			
Phenylcyclopropane	1.87[i]			
Cyclopentane			2.01[g]	
Cyclohexane			1.77[g]	
Adamantane				2.36[j]; 1.75[k]; 2.38[l]
Cubane	1.73[m]			

[a] MeCN–Et_4NBF_4 [186].
[b] MeCN–Bu_4NBF_4 [211].
[c] MeCN–Et_4NBF_4, −45°C [212].
[d] MeCN [209].
[e] vs. Ag/AgCl, CF_3SO_3H, H_2O [213].
[f] HF–BF_3/BF_4^- ($H_0 \approx -15.6$).
[g] FSO_3H–CH_3COOH [186].
[h] MeCN–Et_4NBF_4 [111].
[i] MeCN–$LiClO_4$ [110].
[j] MeCN–$LiClO_4$ [214].
[k] vs. an Ag wire, CF_3COOH–Bu_4NBF_4 [210].
[l] MeCN–Bu_4NBF_4 [215].
[m] MeCN–$LiClO_4$ [208].

that the addition of base assisted alkane oxidation, which made it unlikely that oxidation of protonated alkane was involved [217]. Second, for cyclopentene, no oxidation peak could be observed for a solution of the alkene in FSO_3H; ^1H nuclear magnetic resonance (NMR) spectroscopy showed that in such solution the cyclopentene was substantially converted by proton addition into the secondary carbenium ion [218]. It was suggested that this cation should be oxidized at a potential similar to those claimed for the oxidation of protonated alkanes. The issue has been confused further by the use of different reference electrodes and by variations in voltammograms with temperature, which are difficult to interpret unambiguously, as well as nonelectrochemical reactions of the alkanes in these highly acidic media [222]. However, there seems now to be general agreement on a mechanism involving electron transfer from unprotonated RH involving steps (1), (3), and (6).

V. CONCLUSIONS

In most cases, hydrocarbon oxidations occur via an initial one-electron transfer to the anode to form a radical cation. The further fate of the radical cation depends on its reactivity toward other reagents present. By suitable blocking of reactive sites and/or extensive delocalization of the positive charge, the radical cation may be stable for long periods or at least during the time scale of slow-sweep voltammetry. In the majority of cases, the radical cation is very reactive as an electrophile, a proton donor or electron acceptor, and interacts with nucleophiles or bases present; cases are also known where it can react as a radical, as in dimerization processes. The factors that govern the reactivity of radical cations are becoming increasingly better understood as a result of kinetic work using conventional and voltammetric methods and also by theoretical studies.

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14
Carboxylic Acids

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I. INTRODUCTION

The coupling reaction of alkyl radicals provided by electrodecarboxylation of alkanoates gives the Kolbe dimer:

$$2\,R\text{–}CO_2^- \longrightarrow R\text{–}R + 2\,CO_2 + 2e^- \quad (1)$$

The Kolbe reaction sounds historical in electroorganic chemistry, but it is still alive as an important synthetic tool in today's organic synthesis.

Since the discovery of the Kolbe reaction [1], a vast number of investigations have been carried out to unveil the features of its synthetic potentiality. The first finding of the

versatility by Wurts (1855) [2] is that the electrolysis of two different carboxylates gives the mixed dimer together with two possible symmetrical dimers:

$$R\text{–}CO_2^- + R'\text{–}CO_2^- \longrightarrow R\text{–}R' + R\text{–}R + R'\text{–}R' + 2\,CO_2 + 2e^- \quad (2)$$

The most versatile extension of the Kolbe reaction was done by Brown and Walker (1891) [3], which opened a simple entry to the synthesis of a variety of dicarboxylic acids:

$$2\,RO_2C\text{–}(CH_2)_n\text{–}CO_2^- \longrightarrow RO_2C\text{–}(CH_2)_{2n}\text{–}CO_2R + 2\,CO_2 + 2e^- \quad (3)$$

Actually, this modification, the Brown–Walker reaction, is a well-established method for the synthesis of long-chain carboxylic acids:

$$R\text{–}CO_2^- + R'O_2C\text{–}(CH_2)_n\text{–}CO_2^- \longrightarrow R\text{–}(CH_2)_n\text{–}CO_2R' + 2\,CO_2 + 2e^- \quad (4)$$

$$RO_2C\text{–}(CH_2)_m\text{–}CO_2^- + R'O_2C\text{–}(CH_2)_n\text{–}CO_2^- \longrightarrow RO_2C\text{–}(CH_2)_{m+n}\text{–}CO_2R' + 2\,CO_2 + 2e^- \quad (5)$$

Brown and Walker first proposed the generally accepted mechanism of the Kolbe reaction, which involves the initial discharge of carboxylates at the anode followed by decarboxylation and subsequent combination of the resulting radicals, leading to the Kolbe dimer [3]. The radical formed may also undergo disproportionation to afford olefins and alkanes as the result of hydrogen abstraction [Eq. (6)]. Actually, olefins and alkanes are found as by-products.

$$R\text{–}CO_2^- \xrightarrow{-e} R\text{–}CO_2^{\bullet} \xrightarrow{-CO_2} R^{\bullet} \longrightarrow 1/2\,R\text{–}R \quad (6)$$

Olefin R–H

In the 1960s, a more promising expansion of the electrodecarboxylation reaction in terms of synthetic utility was recorded in which a carbenium intermediate R^+ formed at the anode plays an important role [Eq. (7)] [4]. Depending on the structural characteristics of the carboxylates and/or electrochemical variables, the cation intermediate R^+ may undergo the so-called non-Kolbe reactions, for example, substitution, deprotonation, C–C bond cleavage, and rearrangement to provide alcohols, ethers, esters, amides, olefins, and others.

$$R\text{–}CO_2^- \xrightarrow[-CO_2]{-2e} R^+ \quad (7)$$

R^+ → Substitution → R–Nu (Nu = OH, OMe, OAc, NHAc, etc)
R^+ → Deprotonation → Olefins
R^+ → C–C Bond Cleavage, Rearrangement

The electrochemical hydroxylation and esterification in aqueous media, the so-called Hofer–Moest reaction, initially were regarded as a side reaction, but sometimes become the major reaction in the aqueous Kolbe reaction [5]. Such puzzling phenomena encountered in the early Kolbe reaction can be rationalized on the basis of the assumption just described above.

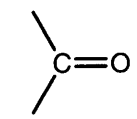
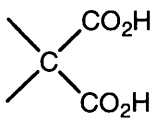
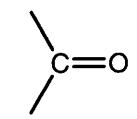
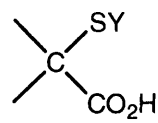
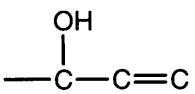
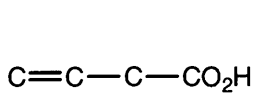
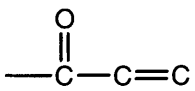
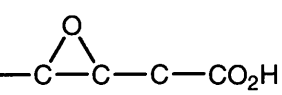
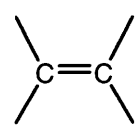
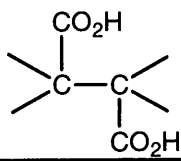
In the past three decades, more sophisticated electrolysis conditions suited for the Kolbe dimerization, for hydrogen abstraction, for substitution, for rearrangement, and for other radical- or cation-induced reactions have accumulated for a number of carboxylic acids and have been used for many synthetic purposes. Most recently, in the field of the

two-electron transfer process, significant progress has been made in exploiting preparative use of the cation intermediates for the functionalization, such as alkoxylation, acetoxylation, acetamidation, formation of olefins and carbonyl groups, and rearrangements. The concept of modern electrodecarboxylation of carboxylic acids tends to be far from that of the old-fashioned Kolbe reaction. Nowadays, electrodecarboxylation is available as a potential tool for building up the functional groups in complex molecules. Indeed, recent progress in this field enables us to design various synthetic equivalents to, for example, carbonyl groups, α,β-enones, and double bonds by virtue of electrodecarboxylation. Some selected examples are listed in Table 1 [6–17]. Today's synthetic potentialities of the electrogenerated carbenium intermediates are discussed in Sec. IV.

II. EXPERIMENTAL CONDITIONS

Electrodecarboxylation has been examined in a variety of electrolysis systems, and a proper combination of solvent, supporting electrolyte, electrode material, pH, concentration of salt and substrate, and other variables has been chosen according to the synthetic requirements in each case. As briefly mentioned before, the electrodecarboxylation may provide two competing pathways that give rise to either radical $R^{\cdot}$ or cation R^{+} intermediates, leading to various products. The optimum conditions for promoting a particular reaction have been accumulated. Thus far, one can in many cases design a suitable electrolysis system, making the reaction products selective via either the radical or cation pathway.

Table 1 Synthetic Equivalents Based on Electrodecarboxylation[a]

Target molecule	Synthetic equivalent	Reference
		6
		7-10
		11, 12
		11
		13-17

[a]Y = Ph or benzothiazolyl.

A. Constant-Current-Density Electrolysis (Electrode Potential and Current Density)

The Kolbe reaction is usually performed with constant current density, and control of the anode potential by using a potentiostat is seldom essential. A high current density, higher than 0.25 and often up to 1.0 A/cm^2, is in general recommended for the Kolbe dimerization, since the rate of the radical combination should be proportional to the concentration of the radical species per unit area of the electrode. It has been reported that if the anode potential is plotted against the logarithm of the current density (Tafel plots) (Fig. 1), there is a special value of current density at which the anode potential jumps from 2.1 to 2.4 V [18]. At a current density higher than that causing such a potential jump, discharge of the carboxylates proceeds almost exclusively and may completely suppress undesirable reactions that normally take place at a lower potential, such as oxygen evolution from water.

The critical potentials at which the decarboxylation starts have been compiled for a variety of carboxylic acids; it is normally observed in a region of 2.0–2.8 V (vs. normal hydrogen electrode; NHE) [19]. In practice, however, it is not necessary to control the anode potential since the anode potential may shift to higher values than the critical potential even if the electrolysis is operated at a constant current density of around 1 mA/cm^2.

The radical R$^{\cdot}$ thus generated may undergo a further one-electron oxidation to give a cation R$^+$. Owing to the high discharge potential of carboxylates, easily oxidizable radicals are believed to couple prior to the second electron transfer. Easily oxidizable functional groups such as amine, sulfide, and formyl, attached to the carbon atom bearing a carboxylic group, cannot survive under the electrolysis conditions. The decarboxylation of carboxylic acids may proceed at lower discharge potentials than usual in systems combining a heteroatom and a carboxylic acid. In such systems, concerted decarboxylations may proceed. The details are discussed in the following sections.

B. Electrode Material

The influence of anode materials on the electrodecarboxylation in aqueous solutions has been well documented; platinum, iridium, and vitreous carbon electrodes favor the cou-

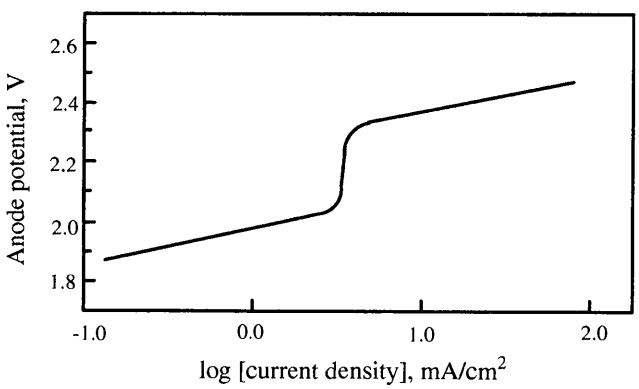


Figure 1. Anode potential (vs. NHE) as a function of log(current density) in an H_2O–AcONa (0.5M) system.

pling product; graphite and porous carbon anodes facilitate the two-electron process, giving cation intermediates. In contrast, in nonaqueous solvents, a variety of anode materials may be employed. The choice of electrode material is less critical, although platinum is still recommended for the one-electron process and carbon for the two-electron process. Other electrode materials, such as gold, palladium, lead dioxide [20], iron-impregnated carbon [21], and shungite (a nongraphitized carbon) [22], are useful in some cases for the Kolbe coupling.

The nature of the cathode material is not critical in Kolbe reactions. In most cases, neither starting material nor products are reducible at potentials less negative than that required for hydrogen evolution.

C. Solvent, Electrolyte, and Additives

Neutral and slightly acidic media have been recommended for the Kolbe reaction. To keep the electrolyte acidic during electrolysis, the reaction is simply performed in an aqueous solution of the acid, neutralized by an alkali metal hydroxide or trialkylamine to an extent of 2–5%. Since hydroxyl ions are formed at the cathode at the same rate as carboxylate ions are consumed at the anode, the concentration of carboxylate ion remains approximately constant during the whole run. Water is now seldom used as a solvent in Kolbe oxidations. Methanol or aqueous methanol is regarded as the best choice as a solvent [23]. Dimethylformamide (DMF) and wet acetonitrile can also be used in particular cases [24–26]. Special attention should be paid to assessing the solvent system for the generation and reaction of carbenium intermediates under electrolysis conditions [23]. A variety of solvent systems elaborated for the electrodecarboxylation has been compiled [27]. On the basis of a rough statistical treatment of experimental findings, the combinations or interrelations among three kinds of solvent [water (W), protic solvent (P), and dipolar aprotic solvent (DA)], two reactive intermediates (cation and radical), and four typical reactions (Kolbe dimerization, substitution, rearrangement, and olefin formation) are schematically illustrated in Fig. 2 [27]. One can select the first choice of the solvent system that may be suited to undertaking certain reactions. For example, a dipolar aprotic solvent–water (DA–W type), such as pyridine–water, should be the first choice when aiming to obtain olefins as the exclusive electrodecarboxylation product.

Most of electrodecarboxylations have been carried out with partially neutralized carboxylic acid. Alkaline and alkaline earth metal as well as ammonium (pyridinium) carboxylates work efficiently as supporting electrolytes. Some metal ions (such as Fe^{2+} and Co^{2+}) are found to favor selectively radical reactions in electrodecarboxylation. Addition of certain salts, such as perchlorate, fluoroborate, sulfate, dihydrogen phosphate, bicarbonate, and fluoride, tends to inhibit the radical reaction and favor the formation of cation intermediates [28–31]. The remarkable effects of the salts are well explained in terms of competitive adsorption between the anions and carboxylates.

D. Other Variables (Temperature, Pressure, and Magnetic Field)

Temperature is usually not a critical variable but may improve viscosity and mass transport. An increase in temperature generally results in an increased yield of the Kolbe dimer [32,33]; however, increasing it over 50°C causes in some cases a total change in the product obtained [34,35]. For example, the electrolysis of ω-bromoundecanoic acid in methanol at

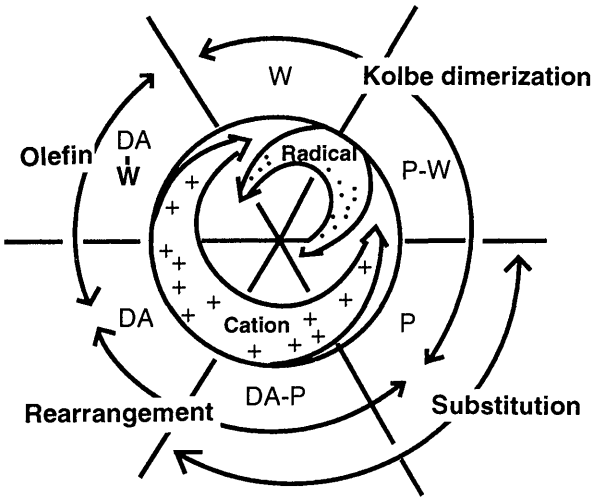


Figure 2. Correlation between reaction type, solvent, and reactive intermediate: W, water; P, protic solvent; DA, dipolar aprotic solvent.

50°C gives the Kolbe dimer (64%), but at 65°C methyl ω-bromoundecanoate (71%) is obtained:

$$1/2\ \underset{64\%}{Br(CH_2)_{20}Br} \xleftarrow{50℃} Br(CH_2)_{10}CO_2^- \xrightarrow{60℃} \underset{71\%}{Br(CH_2)_{10}CO_2Me} \quad (8)$$

Under high-pressure conditions, volatile species, such as hydrogen, carbon dioxide, and in some cases olefins or alkanes, are accumulated on the anode surface, which may affect the product distribution [33,36]. An aqueous Kolbe electrolysis of an alkanoic acid (in the range C_4–C_6) tends to give higher yields of the Kolbe dimers when run at elevated pressure (100 kPa) than an equivalent experiment at atmospheric pressure.

A magnetic field may affect the flow of electron and ion, resulting in perturbation of the mass transport process near the electrode [37]. For example, in the decarboxylation of phenylacetic acid, the presence of a magnetic field increases the yield of aldehyde, presumably because the supply of molecular oxygen from the bulk solution of the electrode surface is enhanced.

E. Conclusion

Experimental variables affecting the course of the electrolytic decarboxylation of carboxylic acids are summarized in Table 2. For the Kolbe dimerization, the conditions specified for a one-electron process are recommended; otherwise the reaction through carbenium ion (non-Kolbe reaction) may occur predominantly. It should be emphasized that even under the conditions most favorable for the Kolbe dimerization, the cation-derived products are usually formed to some extent or, in particular cases, as a major product, depending on the structure of the employed carboxylic acid.

Table 2 Effect of Experimental Variables on Electrodecarboxylation

Variable	One-electron process	Two-electron process
Current	High current density	Low current density
Electrode material	Pt electrode	Carbon electrode
Reaction media	Acidic Neutral	Basic
	Water (W)	Dipolar aprotic (DA)
	Protic (P)	DA-W
	W-P	P
Additive	None	ClO_4^-, SO_4^{2-}, HCO_3^-, and others
Temperature	<50°C	Not critical

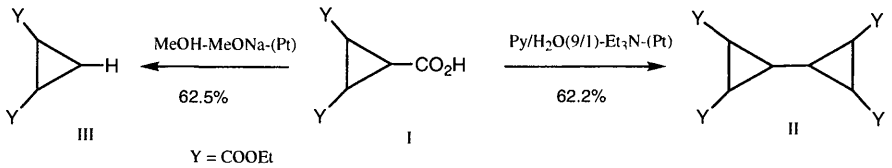
III. RADICAL REACTION (ONE-ELECTRON OXIDATION)

A. Kolbe Coupling Reaction

The Kolbe reaction can be regarded as a chemical process involving the control of a one-electron oxidation reaction. Thus, the generated radicals R undergo so-called Kolbe coupling, hydrogen abstraction, and in some cases radical addition to olefins, each of which allows many useful synthetic applications. Further one-electron oxidation leading to a carbenium ion is another reaction pathway that normally competes with the reactions mentioned. Preparative use of the Kolbe coupling reported up to 1970s has been well documented in several excellent reviews [18,27,38–43]. Here some characteristic features of the early reactions as well as recent advances in this field are discussed.

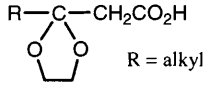
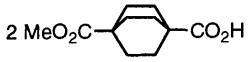
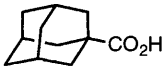
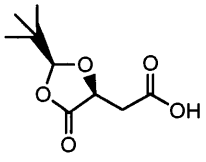
Some results on Kolbe couplings are listed in Table 3 [42,44–51]. The electrolysis of carboxylic acids is usually carried out in an alkaline protic solvent–(Pt electrodes) system. Most frequently, MeOH–MeONa, MeOH-H_2O–NaOH, MeOH–KOH, MeOH–Py–Et_3N, and MeOH–Py–Na salt systems are used as electrolysis media. Aprotic media, such as DMF–KOH, MeCN–Et_3N, MeCN–Et_4NBF_4, and Py–H_2O–Et_3N, are also utilized and, in particular cases, acetone–H_2O–NaOH is usable.

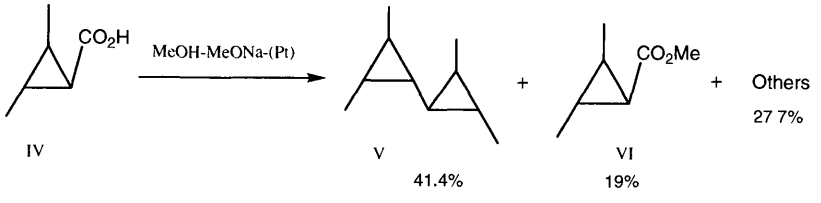
The proper choice of the electrolysis medium may provide significant product selectivity in each reaction. For instance, in the electrolysis of cyclopropane carboxylic acids (**I**) [Eq. (9)], a dramatic change in products is observed [52]; in a pyridine–H_2O–Et_3N–(Pt) system the Kolbe dimer (**II**) is mainly obtained, but in an MeOH–MeONa–(Pt) system predominantly cyclopropane (**III**) is formed via hydrogen atom abstraction. The cyclopropane carboxylic acid (**IV**), however, undergoes decarboxylative coupling even in an MeOH–MeONa–(Pt) system to afford the dimer (**V**) as a major product along with the ester (**VI**) [Eq. (10)] [53]:



(9)

Table 3 Kolbe Dimerization

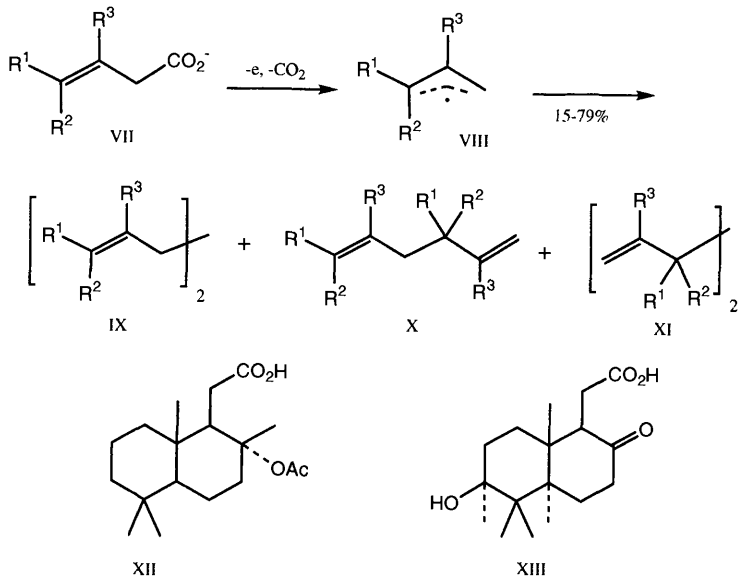
Carboxylic acid	Conditions	Dimer Yield, %	Reference
$CH_3(CH_2)_nCO_2H$ n = 5-15	MeOH, EtOH	60-90	42
$RO_2C(CH_2)_nCO_2H$ R = Me, Et; n = 2-16	MeOH, EtOH	43-80	44
$AcO(CH_2)_nCO_2H$ n = 3-5	MeOH	73-83	44
$RCH(CO_2Et)CO_2H$ R = alkyl, H	MeOH	61-74	44
$FCH_2(CH_2)_nCO_2H$ n = 3-9	MeOH	45-69	44
$CH_3CH_2CO(CH_2)_4CO_2H$	MeOH	75	45
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	MeOH-MeOK-(Pt)	75	46
 R = alkyl		63-69	47
$CH_3CO(CH_2)_2CO_2H$	MeOH-MeONa-(Pt)	–	48
$HOCH_2CH(CF_3)CO_2H$	MeOH-MeONa-(Pt)	95	49
	MeOH–MeONa–(Pt)	30	50
	MeOH–MeONa–(Pt)	3.2	50
	MeOH–MeONa–(Pt)	0.6	50
	MeOH-Et_3N-(Pt)	56	51



(10)

Many functional groups, such as halogen, acetal, ketone, and acetate, and in some cases alcohol, aldehyde, and amide, can survive during the Kolbe decarboxylation [44]. Double bonds isolated from the carboxylic acid moiety are usually not affected under the

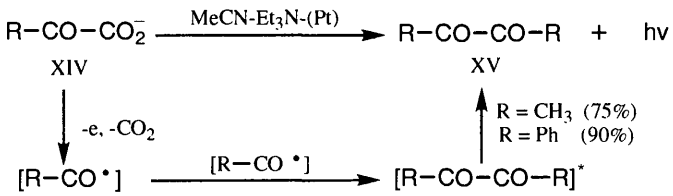
Kolbe electrolysis conditions. The β,γ-unsaturated carboxylic acids (**VII**) give the isomeric 1,5-dienes (**IX–XI**) via the allylic radicals (**VIII**) [Eq. (11)] [54]. Through this reaction, the configuration of the double bonds is almost totally (> 90%) retained.



(11)

The synthetic potentiality of the Kolbe dimerization has been well documented for a variety of symmetrical target molecules. For example, the dimerization of acids (**XII** and **XIII**) is the key step of the pentacyclosqualene [55] and α-onocerin [56] syntheses. A large-scale production of sebasic acid has been realized by the Kolbe dimerization of methyl adipate half-ester [57].

The Kolbe reaction of pyruvic acid and phenylglyoxylic acid (**XIV**) (R = CH_3 and Ph) affords the corresponding diketones (**XV**) in high yields [Eq. (12)] [58,59]. Interestingly, electroluminescence can be observed during the electrolysis, which probably can be attributed to phosphorescence due to the generation of excited triplets of α-diketones in the acyl radical recombination.



(12)

Electrodecarboxylative polymerization of dicarboxylic acids has been examined [60–63]. Under the Kolbe electrolysis conditions, dicarboxylic acids (XVI) (n = 4–8), such as adipic acid and sebasic acid, give rise to polymer along with oligomeric carboxylic acids and oligomeric hydrocarbons. The polymer produced has the character of a cross-linked and branched polyethylene having ester and methoxyl groups. The polymer formation is explained by assuming an α,ω-biradical intermediate (**XVII**):

$$\underset{\text{XVI}}{HO_2C-(CH_2)_n-CO_2H} \xrightarrow[-CO_2]{-2e} \underset{\text{XVII}}{\bullet(CH_2)_n\bullet} \longrightarrow \text{Polymer} \qquad (13)$$

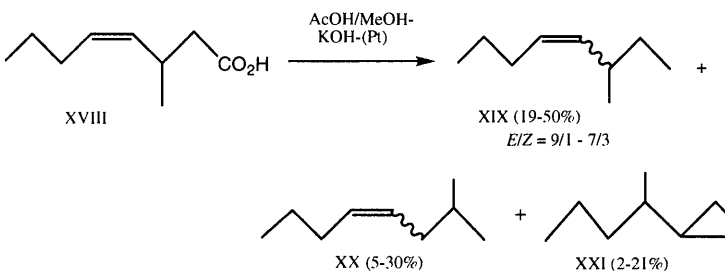
The formation of grafted films on carbon electrode surfaces is attained by electrooxidation of arylacetates under Kolbe electrolysis conditions [64].

B. Kolbe Cross-Coupling Reaction

Electrolysis of two different carboxylic acids may give a cross-coupling product. The product is, however, always accompanied by two symmetrical dimers owing to the statistical coupling of each radical intermediate R· and R′· [Eq. (14)]. Although a few attempts toward selective cross-coupling—for example, square-pulse electrolysis of unsymmetrical acyl peroxide [65–67]—have been made, these are still far from the goal. The disadvantageous but unavoidable formation of the two symmetrical dimers can be reduced to a single product when one of them is used in 5- to 10-fold excess [68].

$$R-CO_2^- + R'-CO_2^- \longrightarrow R-R' + R-R + R'-R' \qquad (14)$$

The Kolbe cross-coupling may permit a variety of applications in natural product synthesis. By using this method, carotenoids, fatty acids, muscone, fumulene [42], and pheromones [43] have been synthesized. Reported results of Kolbe cross-couplings are summarized in Table 4 [69–88]. Under the cross-coupling conditions, the double bond of unsaturated acids generally retains its configuration. Partial Z/E isomerization of olefins is, however, observed in the electrolysis of Z-4-enoic acids [89]. The electrolysis of Z-3-methyl-4-octenoic acid (**XVIII**) with acetic acid gives a mixture of Z and E isomers of the cross-coupling product (**XIX**) (9 : 1–7 : 3) together with **XX** and **XXI** [Eq. (15)]. This can be well understood by assuming a Z/E isomerization via a reversible ring closure to cyclopropylcarbenyl radicals (**XXII**).



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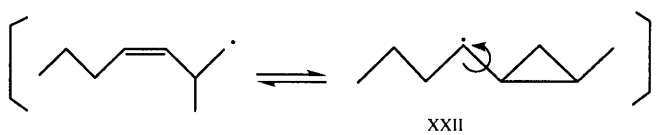
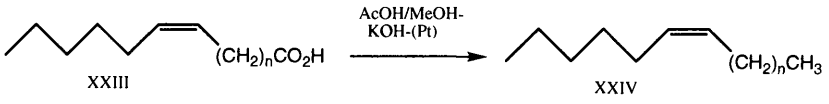


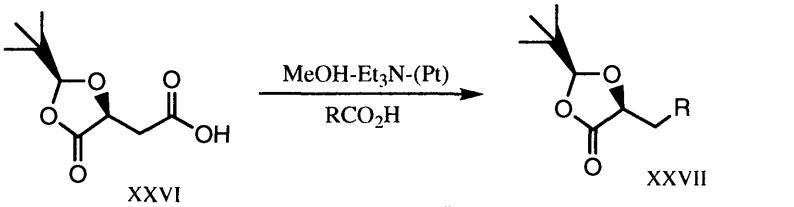
Z-*n*-Enoic acids (**XXIII**) ($n > 5$) fully retain the olefin configuration in the Kolbe electrolysis, but cyclic products (**XXV**) are obtained, to some extent, for 6- and 7-alkenoic acids (**XXIII**) ($n = 4$ and 5):



Compound XXIII n	Yield, % XXIV	XXV
3	68	--
4	46	21
5	65	5
6	72	--
7	73	--

(16)

Enantiomerically pure carboxylic acids (**XXVII**), chiral building blocks for the synthesis of natural products, are prepared by cross-Kolbe electrolysis of chiral carboxylic acids, R* CO_2H (**XXVI**) [51]:



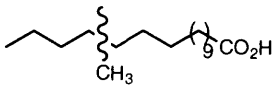
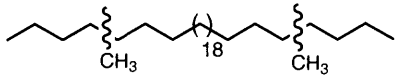
R	Isopr	$(CH_2)_3NHCHO$
yield, %	35	51

(17)

C. Decarboxylative Radical Addition

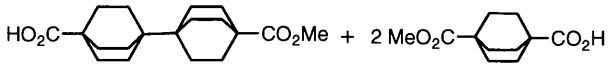
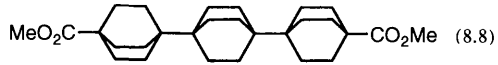
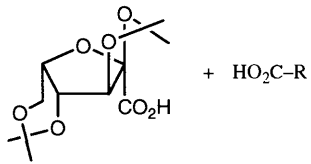
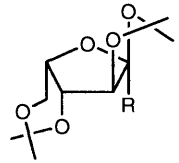
Electrolysis of carboxylates RCO_2^- in the presence of olefins (**XXVIII**) may afford the radical addition products **XXX, XXXI, XXXII**, and **XXXIII**. Plausible reaction pathways are illustrated in Eq. (18). The radical R˙ generated by electrodecarboxylation of RCO_2^- first combines with the olefin (**XXVIII**) to give the radical intermediates (**XXIXa**), which may provide the dimers (**XXX**) or the radical coupling products (**XXXI**). Further one-electron oxidation of **XXIXa** may provide cations (**XXIXb**), which subsequently react with the nucleophiles Nu^- or liberate H^+ to give substituted products (**XXXII**) or olefins (**XXXIII**).

Table 4 Kolbe Cross-Coupling

Carboxylic acids[a]	Conditions	Product (yield, %)	Reference
$C_2H_5CO_2H + C_5H_{11}CO_2H$	H_2O-Na_2SO_4 / NaOH-(Pt)	C_4H_{10}, C_7H_{16}, $C_{10}H_{22}$ (9.2) (42)	84
$C_3H_7CO_2H + C_5H_{11}CO_2H$	H_2O-Na_2SO_4 / NaOH-(Pt)	C_6H_{14}, C_8H_{18}, $C_{10}H_{22}$ (total 26.8)	84
R^1-CO_2H + R^2-O-CH_2-CO_2H	DMF–KOH–(Pt)	R^2-O-CH_2-R^1 a: R^1 = C_5H_{11}, R^2 = C_5H_{13} (32); b: R^1 = $C_{11}H_{23}$, R^2 = $C_{12}H_{25}$ (58)	69
$HO_2CCH_2CH(CH_3)CH_2CO_2Me + CH_3(CH_2)_{16}CO_2H$	MeOH-Hexane-MeOK-(Pt)	$CH_3(CH_2)_{17}CH(CH_3)CH_2CO_2Me$ (25)	70
CbzNHCH(CO_2Me)$(CH_2)_2CO_2H$ + BocNHCH(CO_2t-Bu)$(CH_2)_2CO_2H$	MeOH-Py-MeONa-(Pt)	CbzNHCH(CO_2Me)$(CH_2)_4$CHNHBoc(CO_2t-Bu)	71
$MeO_2C(CH_2)_3CO_2H$ + BocNHCH(CO_2t-Bu)$(CH_2)_2CO_2H$	MeOH-Py-MeONa-(Pt)	$MeO_2C(CH_2)_5$CHNHBoc(CO_2t-Bu)	71
$HO(CH_2)_{18}CH(CH_3)CH_2CO_2H + MeO_2C(CH_2)_3CO_2H$ (1:6)	MeOH-KOH-(Pt)	$HO(CH_2)_{18}CH(CH_3)(CH_2)_4CO_2Me$ (31)	72
$MeCO(CH_2)_2CO_2H$ + $MeO_2C(CH_2)_3CO_2H$	MeOH-NaOH-(Pt)	$MeCO(CH_2)_5CO_2Me$ (55.5)	73
		 (63)	74
$HO_2C(CH_2)_7CO_2Me$ + $C_6F_{13}CH_2CO_2H$		$C_6F_{13}(CH_2)_8CO_2Me$ (41)	74
$HO_2C(CH_2)_7CO_2Me$ + $C_8F_{17}(CH_2)_2CO_2H$		$C_8F_{17}(CH_2)_9CO_2Me$ (68)	74

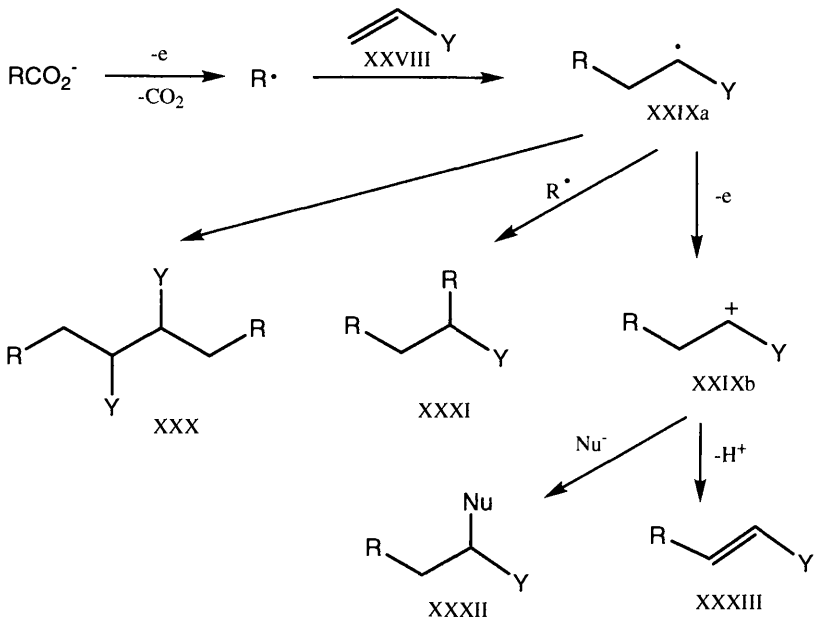
Carboxylic acids[a]	Conditions	Product (yield, %)	Reference
$HO(CH_2)_{17}CO_2H + HO_2CCH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2CO_2Me$ (2:1)	MeOH-KOH-(Pt)	$HO(CH_2)_{18}\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2CO_2Me$ (47)	72
$CH_3(CH_2)_{16}\text{-}CO_2H + HO_2CCH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2CO_2Me$	MeOH-MeOK	$CH_3(CH_2)_{17}\text{-}\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2CO_2Me$ (25)	83
$CH_2{=}CH(CH_2)_8CO_2H + HO_2C(CH_2)_7CO_2Me$	MeOH-MeONa-(Pt)	$CH_2{=}CH(CH_2)_{15}CO_2Me$ (85-97)	77
$CH_2{=}CH(CH_2)_8CO_2H + HO_2C(CH_2)_8CO_2Me$	MeOH-MeONa-(?)	$CH_2{=}CH(CH_2)_{16}CO_2Me$ (40)	77
$CH_3CH_2CH{=}CHCH_2CO_2H + HO_2C(CH_2)_8CO_2CH_3$	MeOH–KOH–(Pt)	$CH_3CH_2CH{=}CHCH_2(CH_2)_8CO_2CH_3$	78
$MeO_2C(CH_2)_2CH{=}CH(CH_2)_2CO_2H + CH_3(CH_2)_7CO_2H$ (1:10)	MeOH-KOH-(Pt)	$MeO_2C(CH_2)_2CH{=}CH(CH_2)_9CH_3$ (48)	79
$CH_3(CH_2)_7CH{=}CH(CH_2)_{10}CO_2H + CH_3CH_2CO_2H$ (1:10)	MeOH-MeONa-(Pt)	$CH_3(CH_2)_7CH{=}CH(CH_2)_{11}CH_3$ (59)	68
$CH_3(CH_2)_3CH{=}CH(CH_2)_2CO_2H + MeO_2C(CH_2)_3CO_2H$ (1:10)	MeOH-KOH-(Pt)	$CH_3(CH_2)_3CH{=}CH(CH_2)_5CO_2Me$ (55)	80
$C_2H_5CH{=}CHCH_2CO_2H + CH_3CO(CH_2)_2CO_2H$ (5:1) (trans)	MeOH-MeOK-(Pt)	$CH_3CO(CH_2)_3CH{=}CHC_2H_5$ (33) (trans)	81
$Me(CH_2)_4(\overset{cis}{CH{=}CHCH_2})_2(CH_2)_6CO_2H + RCO_2H$	MeOH-KOH-(Pt)	$Me(CH_2)_4(\overset{cis}{CH{=}CHCH_2})_2(CH_2)_6R$ R = C_2H_5 (49), n-C_3H_7 (49), n-C_4H_9 (51)	82
$Me(\overset{cis}{CH{=}CHCH_2})_3(CH_2)_6CO_2H + RCO_2H$	MeOH-KOH-(Pt)	$Me(\overset{cis}{CH{=}CHCH_2})_3(CH_2)_6R$ R = C_2H_5 (50), n-C_3H_7 (43), n-C_4H_9 (52)	82
$CH_3CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}H(CH_2)_2CO_2H + THPO(CH_2)_7C{\equiv}C(CH_2)_2COOH$ (1:1)	MeOH-KOH-(Pt)	$CH_3CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}H(CH_2)_4C{\equiv}C(CH_2)_7OTHP$	75

Table 4 (Continued)

Carboxylic acids[a]	Conditions	Product (yield, %)	Reference
$RCH_2C\equiv C(CH_2)_3CO_2H + MeO_2C(CH_2)_nCO_2H$ R = Me,Et, Pr	MeOH-KOH-(Pt)	$RCH_2C\equiv C(CH_2)_{n+3}CO_2Me$ (45-59)	76
$CH_3(CH_2)_{17}CH(CH_3)CH_2CO_2H + MeO_2C(CH_2)_3CO_2H$ (1:6)	MeOH-KOH-(Pt)	$CH_3(CH_2)_{17}CH(CH_3)(CH_2)_4CO_2Me$ (66)	70
$CH_3(CH_2)_{17}CH(CH_3)(CH_2)_4CO_2H + CH_3COCH(CH_3)(CH_2)_3CO_2H$ (1:5)	MeOH-KOH-(Pt)	$CH_3(CH_2)_{17}CH(CH_3)(CH_2)_7CH(CH_3)COCH_3$ (42.5)	70
$Br(CH_2)_{10}CO_2H + MeO_2C(CH_2)_7CO_2H$ (5:1)	MeOH-KOH-(Pt)	$Br(CH_2)_{17}CO_2Me$ (76)	72
		 (8.8)	50
		 R = C_7H_{15} (32); $C_{11}H_{23}$ (33); $(CH_2)_{10}$–Br (33)	74
$HOCH_2CH(CF_3)CO_2H + R(CH_2)_2CO_2H$ (1·6)	MeOH-MeONa-(Pt)	$HOCH_2CH(CF_3)(CH_2)_2R$ R = Cl(70), Me(50), OH(14)	85
$CF_3CO_2H + EtOCOCH_2CO_2H$	H_2O-KOH-(Pt)	$CF_3CH_2CO_2Et$ (46)	86
$CF_3CO_2H + CD_3CO_2H$	KOAc-d3-(Pt)	CF_3CD_3 (68)	87
$R^1N(Ac)(CH_2)_2CO_2H + MeOCO(CH_2)_nCO_2H$	MeOH/Py–RCO_2Na–(Pt)	$R^1N(Ac)(CH_2)_2(CH_2)_nCO_2Me$	88

R^1	n	
C_{12}	3	(56)
	4	(60)
C_{18}	4	(57)

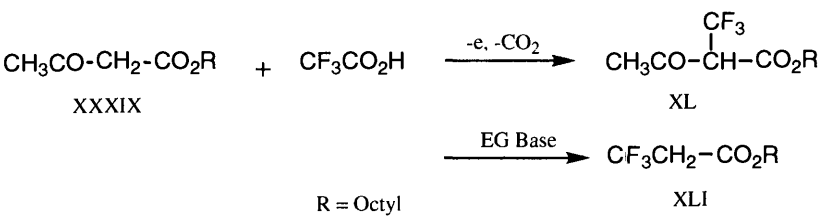
[a]Cbz = benzyloxycarbonyl; Boc = t-butoxycarbonyl; THP = tetrahydropyranyl.



(18)

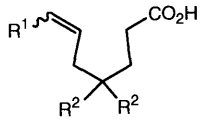
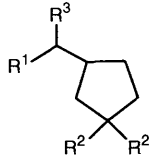
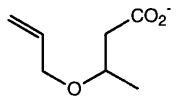
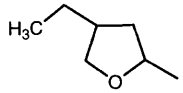
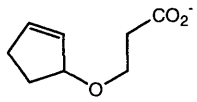
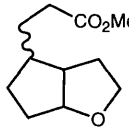
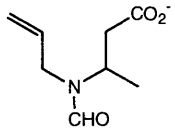
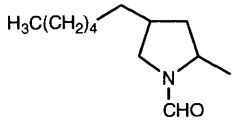
The radical addition to the olefins (**XXVIII**) generally gives rise to a mixture of products but, in some particular cases, gives reasonable yields of the radical adducts (**XXX** and **XXXI**). Some typical examples are shown in Table 5 [90–104]. Both styrene (**XXVIII**, Y = phenyl) and conjugated dienes (**XXVIII**, Y = vinyl) afford the corresponding radical adducts in fairly good yields. Addition of the electrogenerated trifluoromethyl radical $CF_3^{\cdot}$ to olefins has been found to be a good procedure for the preparation of trifluoromethylated products. The electrolysis of partially neutralized trifluoroacetic acid and olefins (**XXVIII**) generally gives a mixture of mono- and bis-trifluoromethylated derivatives, types **XXX** and **XXXI** (R = CF_3), and it is quite hard in some cases to separate the products in a pure state. Recently, however, several devices have been made to overcome such difficulties. ω-Trifluoromethylalkanoic acids (**XXXIV** and **XXXV**) [95,96], β-trifluoromethylaldehyde (**XXXVI**) [97], α-trifluoromethylketones (**XXXVII**) [98], and 5-trifluoromethyluracil (**XXXVIII**) [100] have thus been synthesized efficiently.

The cross-coupling of the electrogenerated trifluoromethyl radical with active methylene compounds may open another access to trifluoromethylated products. Electrolysis of octyl acetoacetate (**XXXIX**) in an MeCN–H_2O–TFA–(Pt) system gives a mixture of octyl 2-trifluoromethylacetoacetate (**XL**) and octyl 3,3,3-trifluoropropionate (**XLI**), the latter of which is probably produced by deacetylation of **XL**, with a base electrogenerated at the cathode [105]:



(19)

Table 5 Decarboxylative Olefin Addition

Carboxylic acid	Olefin	Product (yield, %)	Reference
EtO_2CCO_2H	CH_2=CH-CH=CH_2	$[EtO_2CCH_2CH$=$CHCH_2$-$]_2$ (66) (70)	90, 74
$MeO_2CCH_2CO_2H$	CH_2=CHPh	$[MeO_2CCH_2CH_2\underset{\displaystyle Ph}{\underset{\vert}{C}}H$-$]_2$ (38)	90
$MeO_2CCH_2CO_2H$	CH_2=CMePh	$[MeO_2CCH_2\underset{\displaystyle Ph}{\underset{\vert}{C}}MeCH_2$-$]_2$ (50)	74
EtO_2CCO_2H	$CH_2=C(Me)_2$	$EtO_2CCH_2C(Me)_2CO_2Et$ (9)	74
$MeO_2C(CH_2)_4CO_2H$	CH_2=CH-CH=CH_2	$[MeO_2C(CH_2)_4CH_2CH$=$CHCH_2$-$]_2$ + $[$=$CHCH_2(CH_2)_4CO_2Me]_2$ (47) (47)	91
R^3–CO_2H		 R^1 = CN, R^2 = CH_3, R^3CO_2H = HO_2C–$(CH_2)_4$–CO_2CH_3 (75) R^1 = CO_2Et, R^2 = CH_3, R^3CO_2H = HO_2C–$(CH_2)_4$–CO_2CH_3 (75) R^1 = CN, R^2 = H, R^3CO_2H = HO_2C–$(CH_2)_4$–CO_2CH_3 (71)	74
CH_3CO_2H		 (72)	74
CH_3O_2C–CH_2–CO_2H		 (43)	74
$H_3C(CH_2)_4CO_2H$		 (67)	74

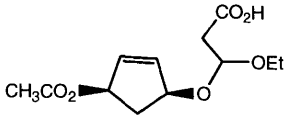
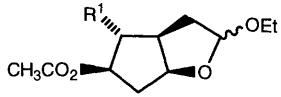
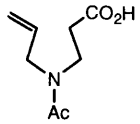
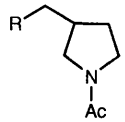
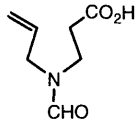
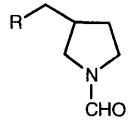
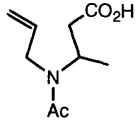
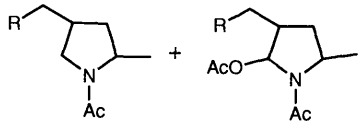
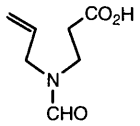
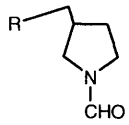
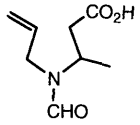
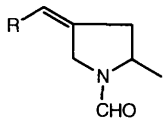
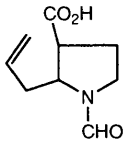
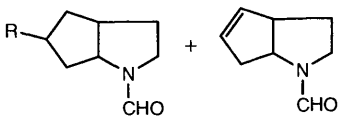
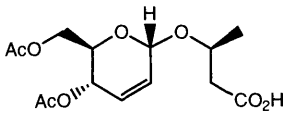
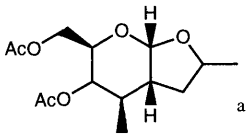
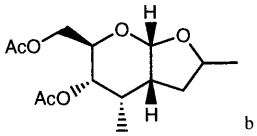
Carboxylic acid	Olefin	Product (yield, %)	Reference
R^1CO_2H		 R^1 = Me (35); $(CH_2)_2CO_2Me$ (33)	92
$MeCO_2H$ $C_5H_{11}CO_2H$ $MeO_2C(CH_2)_4CO_2H$		 R = Me (58); C_5H_{11} (46); $MeO_2C(CH_2)_4$ (53)	93
$MeCO_2H$ $C_5H_{11}CO_2H$		 R = Me (58); C_5H_{11} (45)	93
$MeCO_2H$		 R = Me (56)	93
$MeCO_2H$ $C_5H_{11}CO_2H$		 R = Me (67); C_5H_{11} (63)	93
$MeCO_2H$		 R = Me (45)	93

Table 5 (Continued)

Carboxylic acid	Olefin	Product (yield, %)	Reference
$MeCO_2H$		 R = Me (60)	93
CH_3CO_2H		 a  b a:b = 1.8:1 (50)	74
CH_3CO_2H	$CH_2{=}CCH_3$ (CHO)	$[CH_3CH_2C(CH_3)\text{-}]_2$ (CHO) (80)	94
CF_3CO_2H	$CH_2{=}CH(CH_2)_6CO_2H$	$CF_3(CH_2)_8CO_2H$[a] (16) XXXIV	95
CF_3CO_2H	$CH_2{=}CHCO_2H$	$CF_3CH_2CH_2CO_2H$ (8) XXXV	96
CF_3CO_2H	$CH_2{=}CHCH_2OH$	$CF_3(CH_2)_2CHO$[c] (25) XXXVI	97
CF_3CO_2H	$CH_2{=}C(CH_3)OAc$	$CF_3CH_2COCH_3$ (17) XXXVII	98

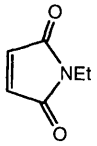
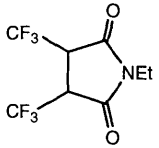
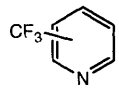
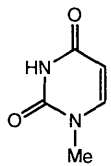
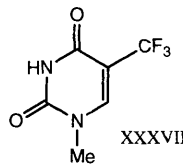
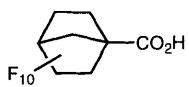
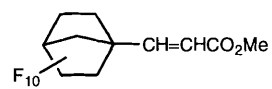
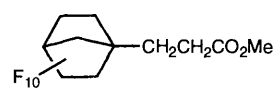
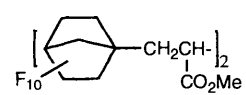
Carboxylic acid	Olefin	Product (yield, %)		Reference
CF_3CO_2H	$CH_2=C(CH_3)CH_2CN$	$CF_3CH_2C(CH_3)CH_2CN$ (good)		99
CF_3CO_2H	$CH_2=CHCO_2R$ R = Me, Et	$[CF_3CH_2\underset{\displaystyle CO_2R}{\underset{\vert}{C}}H\text{-}]_2$ (24-50)		86, 100-102
CF_3CO_2H	$CH_2=CHCONH_2$	$CF_3CH_2\underset{\displaystyle CF_3}{\underset{\vert}{C}}HCONH_2$ (37)	$CF_3CH=CHCONH_2$ (9)	102
CF_3CO_2H	$CH_2=CHCN$	$CF_3CH_2\underset{\displaystyle CF_3}{\underset{\vert}{C}}HCN$ (5)	$[CF_3CH_2\underset{\displaystyle CN}{\underset{\vert}{C}}H\text{-}]_2$ (30)	101
CF_3CO_2H	$CH_2=CHSO_2R$ R = Ph, Et	$CF_3CH_2\underset{\displaystyle CF_3}{\underset{\vert}{C}}HSO_2R$ (24, 25)	$[CF_3CH_2\underset{\displaystyle SO_2R}{\underset{\vert}{C}}H\text{-}]_2$ (22, 22)	102
CF_3CO_2H	$EtO_2CCH=CHCO_2Et$	$EtO_2C\underset{\displaystyle CF_3}{\underset{\vert}{C}}H\underset{\displaystyle CF_3}{\underset{\vert}{C}}HCO_2Et$ (47)	$[EtO_2C\underset{\displaystyle CF_3}{\underset{\vert}{C}}H\underset{\displaystyle CO_2Et}{\underset{\vert}{C}}H\text{-}]_2$ (27)	100
CF_3CO_2H		 (43.8)		100
CF_3CO_2H	$CH\equiv C(CH_2)_3CH_3$	$CF_3CH=\underset{\displaystyle CF_3}{\underset{\vert}{C}}(CH_2)_3CH_3$		101

Table 5 (Continued)

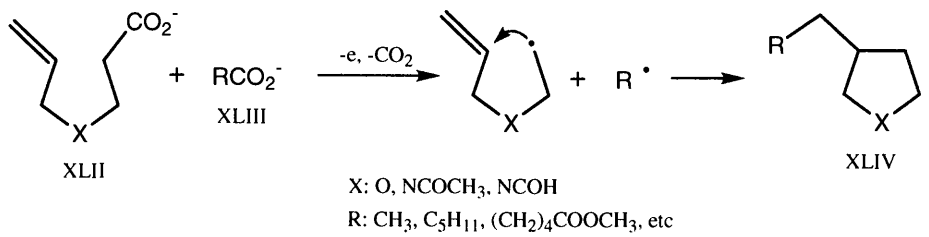
Carboxylic acid	Olefin	Product (yield, %)	Reference
CF_3CO_2H		 (7) $\alpha:\beta:\gamma = 27:38:35$	103
CF_3CO_2H		 (40) XXXVIII	100
	$CH_2{=}CHCO_2Me$	  	104

[a]After hydrogenation (Pd/C).

[b]After hydrogenation (Pd/C) and hydrolysis (aqueous NaOH).

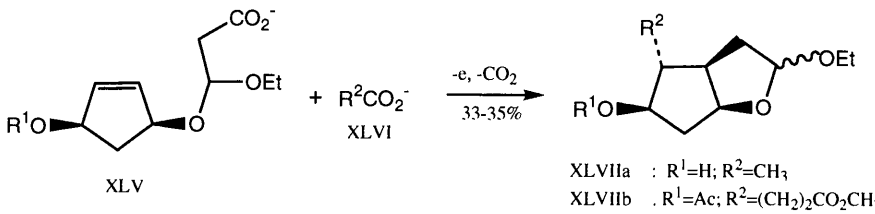
[c]After hydrolysis (aqueous H_2SO_4).

Intramolecular radical addition may furnish a simple and straightforward access to cyclic compounds. Mixed coupling of 6-alkenoic acids (**XLII**) and various carboxylic acids (**XLIII**) successfully gives cyclic compounds (**XLIV**) [106,107]:



(20)

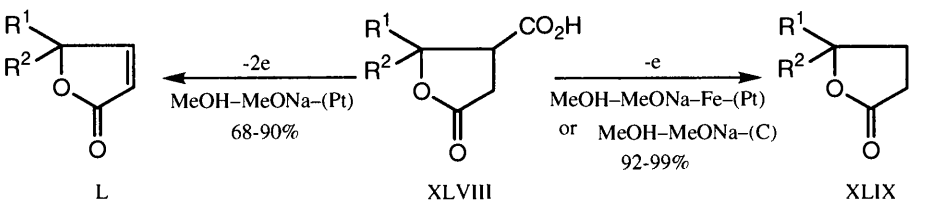
A stereoselective synthesis of prostagrandin precursors (**XLVII**) has been performed by coelectrolysis of **XLV** and **XLVI** [108]:



(21)

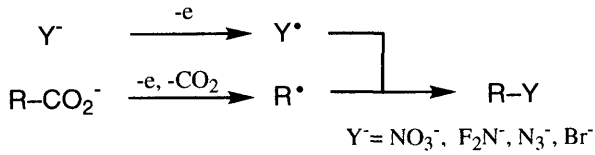
D. Miscellaneous

Further applications of the radical-induced reactions in the Kolbe decarboxylation reactions involve hydrogen abstraction and coupling with in situ generated radical species from additives. For example, hydrogen abstraction by radical intermediates derived from paraconic acids (**XLVIII**) occurs selectively in MeOH–MeONa–Fe powder–(Pt) and MeOH–MeONa–(C) systems [Eq. (22)] [20]. The effect of Fe powder is significant since butenolides (**L**) are obtained exclusively in an MeOH–MeONa–(Pt) system.



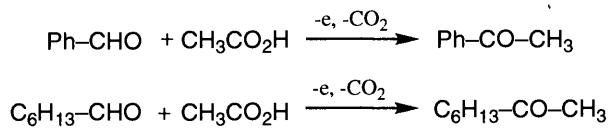
(22)

Electrolysis of carboxylic acids in the presence of nitrate [109,110], difluoroamide [111], azide [112], and bromide ions [113] has been examined in which radical species generated from both carboxylic acids and additive anions are formally coupled to give substituted products:



(23)

Substitution of an aldehyde hydrogen with methyl has been performed by electrolysis of acetic acid in the presence of aldehydes yielding methyl ketones [114,115]:



(24)

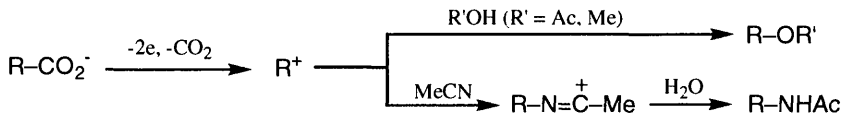
Initiation of polymerization of olefins with radicals formed in the Kolbe electrolysis has been studied to some extent [116–120].

IV. CARBENIUM ION REACTION (TWO-ELECTRON OXIDATION)

The two-electron process in the electrodecarboxylation of carboxylates has been intensively investigated from the mechanistic and synthetic viewpoints. Significant progress of such carbenium reactions has been recognized in alkoxylation, acetoxylation, acetamidation, olefin formation (β-elimination), rearrangement, C–C bond cleavage, and so on. Typical reaction patterns of the electrogenerated cation intermediates R^+ and their synthetic potentialities are discussed next.

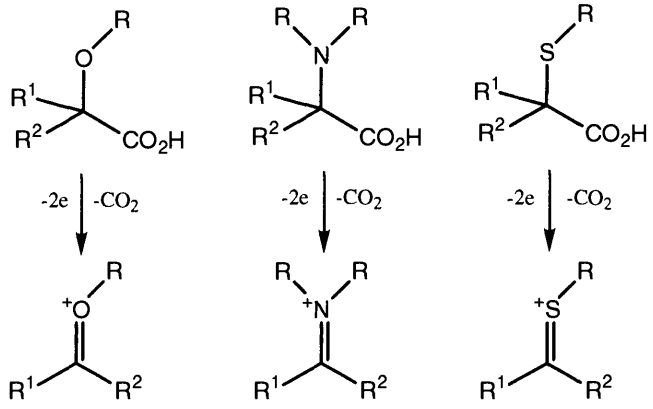
A. Acyloxylation, Alkoxylation, and Acetamidation

Sufficiently stable electrogenerated carbenium ions can be trapped with nucleophiles or nucleophilic solvents. Acetoxylation and methoxylation proceed by electrolysis in either acetic acid or methanol. Acetamidation occurs in wet acetonitrile, in which the nucleophilic attack of the nitrile group on the carbenium ions R^+ tends to give iminium cations; subsequent hydrolysis with water in the medium completes the reaction:



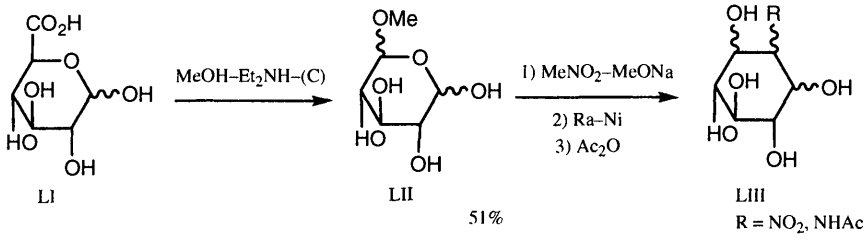
(25)

Electrogenerated carbenium ions, which are stabilized by neighboring hetero atoms, that is, oxygen nitrogen, sulfur, and others, can lead smoothly to the corresponding acetoxylated and/or methoxylated product [Eq. (26)]. This method can play an important role in synthetic applications. Some typical examples are shown in Table 6 [74,121–137].



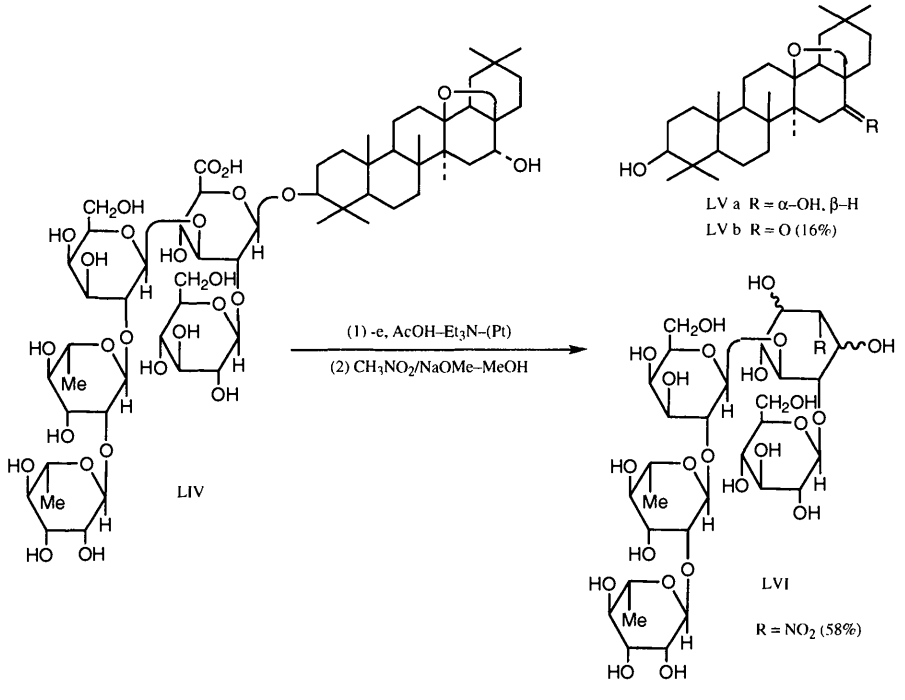
(26)

α-*O*-Substituted carboxylic acids can give mixed acetals; the electrolysis of uronic acid derivative (LI) in methanol thus affords the mixed acetals (**LII**) [Eq. (27)]. The method has been successfully applied to aminocyclitol synthesis as well as to the selective fission of glucuronide linkages in oligoglycosides (**LIV**) [Eq. (28)] [138].



LI LII 51% LIII R = NO_2, NHAc

(27)



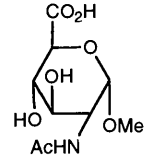
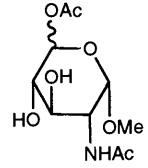
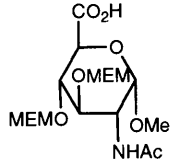
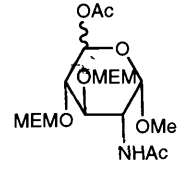
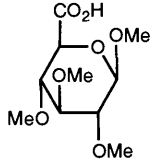
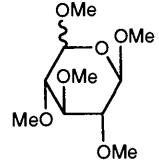
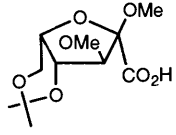
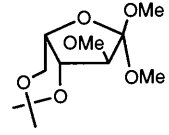
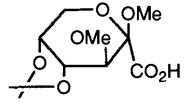
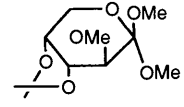
LIV

LV a R = α-OH, β-H
LV b R = O (16%)

LVI R = NO_2 (58%)

(28)

Table 6 Acyloxylation and Alkoxylation of α-Hetero-Substituted Carboxylic Acids

Carboxylic acids[a]	Conditions	Products (yield %)	Reference
	$AcOH\text{-}Et_3N\text{-}(Pt)$	 (43)	121
	$AcOH\text{-}Et_3N\text{-}(Pt)$	 (89)	121
	$MeOH\text{-}NaClO_4\text{-}(Pt)$	 (96)	122
		 (93)	74
		 (92)	74

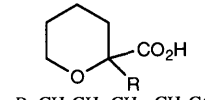
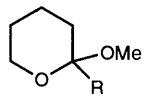
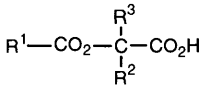
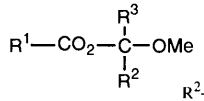
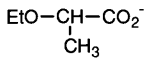
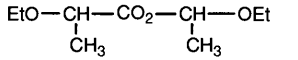
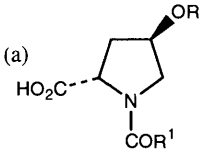
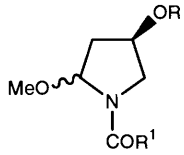
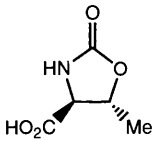
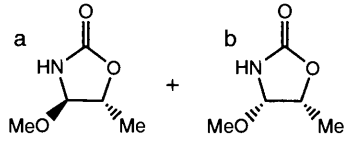
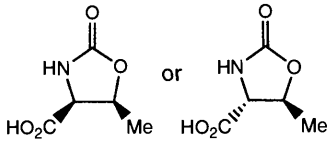
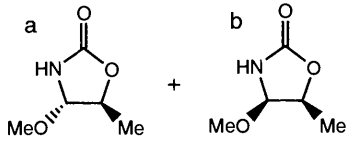
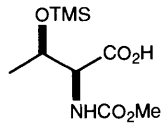
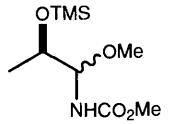
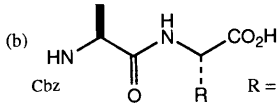
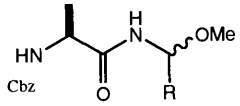
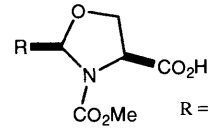
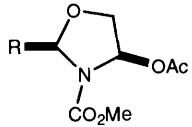
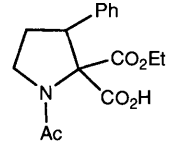
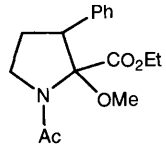
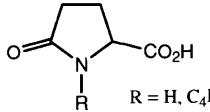
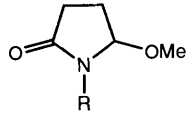
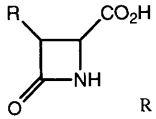
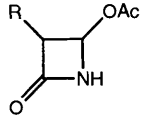
Carboxylic acids[a]	Conditions	Products (yield %)	Reference
 R: $CH_2CH{=}CH_2$, $CH_2C(CH_3){=}CH_2$, etc.	$MeOH\text{-}K_2CO_3\text{-}Et_4NClO_4\text{-}(Pt)$	 (67-90)	123
 $R^1 = Ph, CH_3, OC_2H_5$ $R^2, R^3 = H, CH_3, Ph, -(CH_2)_5-$	MeOH-(C) or $MeCN\text{-}Et_3N$-(C)	 $R^2\text{-}CO\text{-}R^3$, etc	124,125
	MeCN-(C)	 (81)	126
 $R = H, Si(t\text{-}Bu)Me_2$ $R^1 = Me, OMe$	$MeOH\text{-}Et_3N$-(Pt)	 (89-97)	127, 128
	MeOH–AcONa–(?)	 (95(a/b=77/23))	129
	MeOH–AcONa–(?)	 (95(a/b=77/23)	129

Table 6 (Continued)

Carboxylic acids[a]	Conditions	Products (yield %)	Reference
	MeOH-Et_3N-(Pt)	 (75)	130
(b)  R = H, *i*-Pr	MeOH-Et_3N-(Pt)	 (95)	130
 R = *i*-Pr, *t*-Bu	AcOH	 (85-87)	130
	MeOH-MeONa-(C)	 (98)	131, 132
 R = H, C_4H_9	MeOH-MeONa-(C)	 (75-98)	133
 R = H, Et	MeCN-AcOH-AcONa-(Pt)	 (76)	134

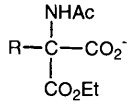
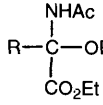
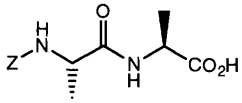
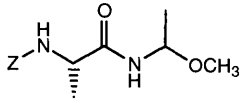
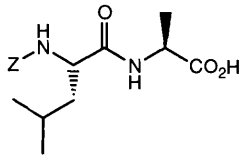
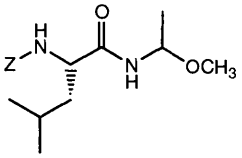
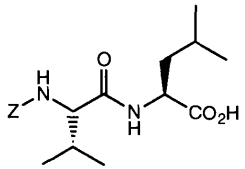
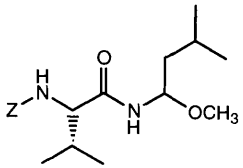
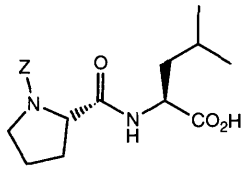
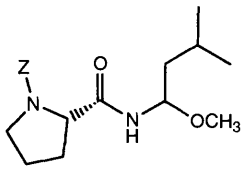
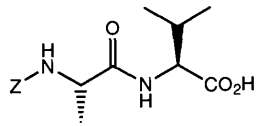
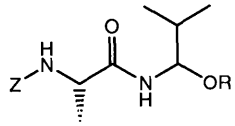
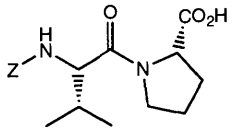
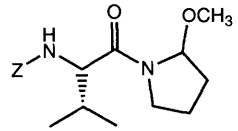
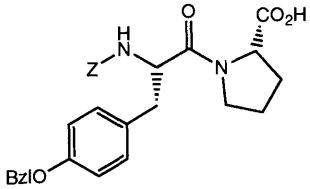
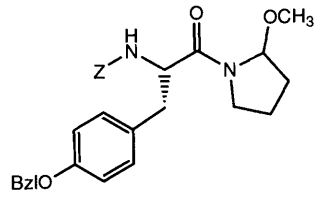
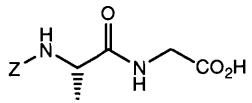
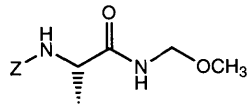
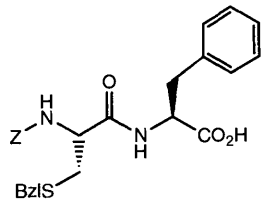
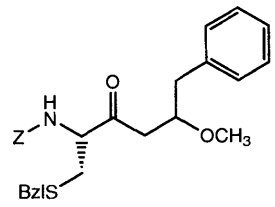
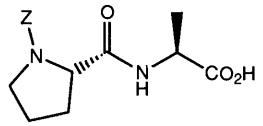
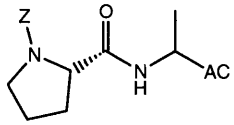
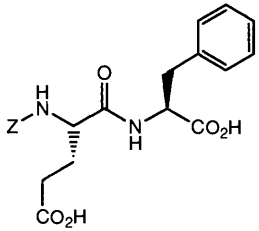
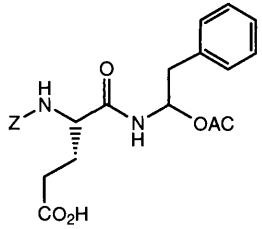
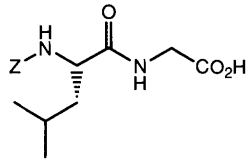
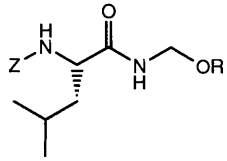
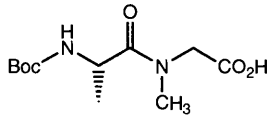
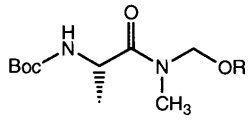
Carboxylic acids[a]	Conditions	Products (yield %)	Reference
 R = H, alkyl, allyl, etc.	R'OH-(C)	 (79-97) R' = Me, Et, *i*-Pr	135, 136
	MeOH 2.3 F/mol	 (82)	137
	MeOH 2.3 F/mol	 (98)	137
	MeOH 2.3 F/mol	 (98)	137
	MeOH 2.3 F/mol	 (93)	137

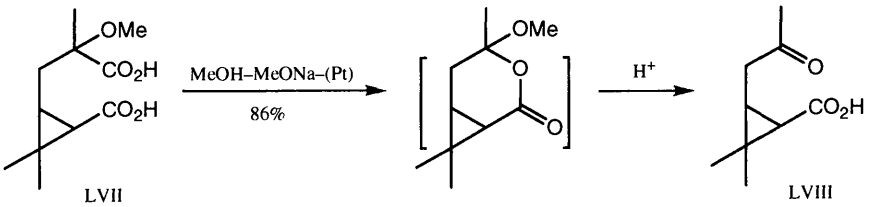
Table 6 (Continued)

Carboxylic acids[a]	Conditions	Products (yield %)	Reference
	MeOH 2.3 F/mol AcOH 2.3 F/mol		R = Me (98) R = Ac (67)	137
	MeOH 2.3 F/mol		(50)	137
	MeOH 2.4 F/mol		(50)	137
	MeOH 2 2 F/mol		(98)	137
	MeOH 2.2 F/mol		(44)	137

Carboxylic acids[a]	Conditions	Products (yield %)	Reference
	AcOH 13.4 F/mol	 (50)	137
	AcOH 3.4 F/mol	 (25)	137
	MeOH 7.0 F/mol AcOH 1.5 F/mol	 R = Me (60) R = Ac (48)	137
	MeOH 2.5 F/mol AcOH 3.2 F/mol	 R = Me (58) R = Ac (69)	137

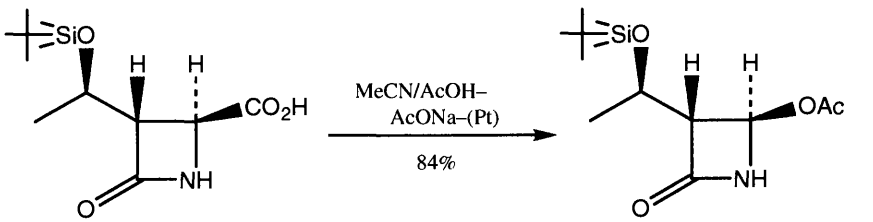
[a]MEM = 2-methoxyethoxymethyl; Cbz = benzyloxylcarbonyl.

Electrolysis of the dicarboxylic acid (**LVII**) in an MeOH–MeONa–(Pt) system and subsequent workup afford the keto acid (**LVIII**), a precursor of chrysanthemic acid (**LVIII**), in 86% yield via intramolecular acyloxylation and acid-promoted hydrolysis [139]:



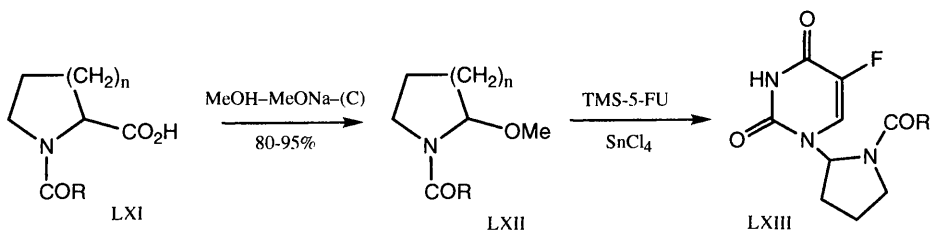
LVII LVIII (29)

Decarboxylative acetoxylation and methoxylation of α-aminocarboxylic acids proceed smoothly, yielding synthetically useful intermediates. For example, the versatile intermediate (**LX**) for the synthesis of thienamycine is prepared by electrodecarboxylative acetoxylation of 4-carboxy-2-azetidinone (**LIX**) in an AcOH–MeCN–AcONa–(Pt) system [134]:



LIX LX (30)

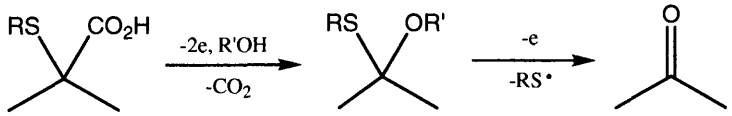
Electrolysis of *N*-carbamoylaspartic acid or *N*-ethoxycarbamoylaspargine in MeOH–MeONa–(C) affords the corresponding methoxylated products [140]. A 5-fluorouracil derivative (**LXIII**), a potent antitumor agent, can be prepared via electrolytic methoxylation of *N*-acylazacycloalkane-2-carboxylic acids (**LXI**) in MeOH–MeONa–(C) and subsequent condensation of (**LXII**) with 2,4-bis-(trimethylsilyl)-5-fluorouracil (TMS-5-FU) [Eq. (31)] [133,141]. Recently, the decarboxylative methoxylation of α-amino acids has been extended to prepare useful chiral building blocks [127–130].



LXI LXII LXIII

n = 1,2; R = H, CH_3, CH_2NHCO_2Bn (31)

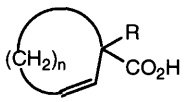
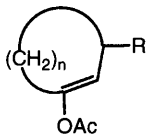
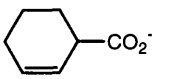
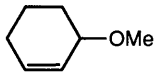
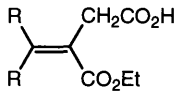
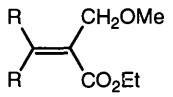
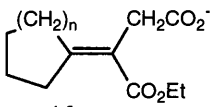
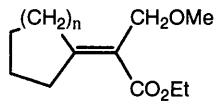
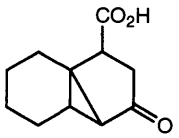
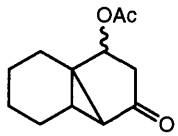
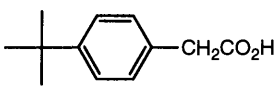
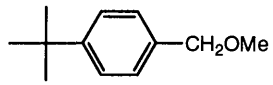
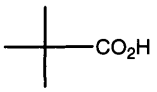
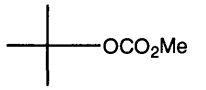
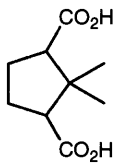
Electrolysis of α-sulfenyl carboxylic acids in protic solvents gives ketones, presumably via replacement of the carboxyl group with alkoxyl or acetoxyl groups and a subsequent two-electron oxidation of the sulfenyl moiety [Eq. (32)]. (This discussion is postponed to Sec. IV.D.)



(32)

Further selected examples of the decarboxylative acetoxylation and methoxylations are listed in Table 7 [11–13,17,30,142–147]. The electrogenerated stable carbenium ions, such as benzylic, allylic, homoallylic, and tertiary carbocation intermediates, are likely to

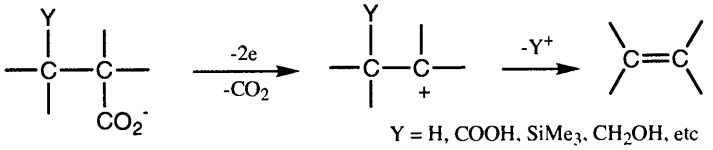
Table 7 Electroacyloxylation and Alkoxylation

Carboxylic acid	Conditions	Products (yield %)	Reference
 R = CH_3 : phenyl, hexyl cis 3-hexenyl	AcOH/AcOEt/ *t*-BuOH-Et_3N-(Pt)		11, 12
	MeOH	 (100)	13, 17, 142
 R: CH_3 Ph	MeOH-NaOMe-(C)	 (22-31)	143
 n; 1,2	MeOH-NaOMe-(C)	 (35, 28)	143
	AcOH-*t*-BuOH-Et_3N-(Pt)	 (72)	144, 145
			13, 142, 30
	MeOH-NaOMe-CO_2-(Pt)	 (78)	146
	MeOH-(Pt)	(77)	147

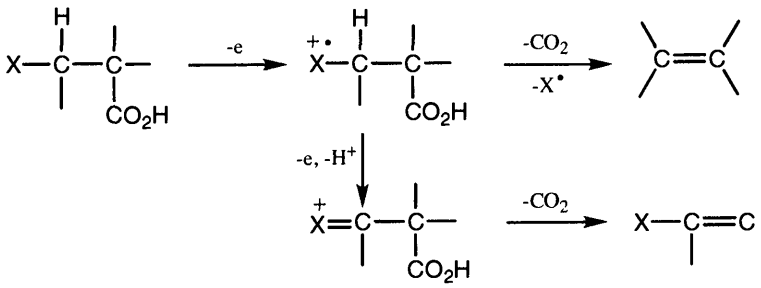
be trapped by suitable nucleophiles, yielding the corresponding acetates, methyl esters, and, in some cases, intramolecular acyloxylation products.

B. Olefin Formation

The electrodecarboxylation becomes a good procedure for the formation of carbon–carbon double bonds, which involves roughly two types of reactions: (1) decarboxylative discharge of carboxylates followed by releasing a vicinal leaving group [Eq. (33a)], and (2) initial discharge of hetero atoms at the β-position to carboxylic acid, which causes an elimination of the carboxyl group in a concerted manner [Eq. (33b)].



(33*a*)

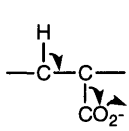
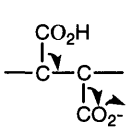
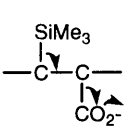
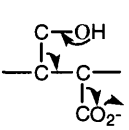
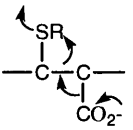
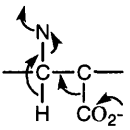
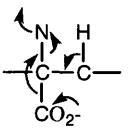


(33*b*)

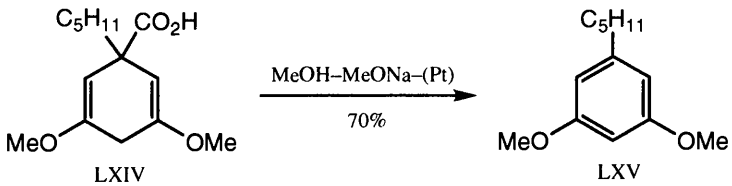
Various sets of functional groups have been devised for both types of decarboxylative carbon–carbon double-bond formation. Typical examples of a set of functional groups together with their electrolysis conditions are summarized in Table 8 [13–17,21,148,150–153].

In such olefin formation reactions, an electrodecarboxylation–deprotonation sequence is also involved. Electrochemical aromatization of the nonconjugated dienes (**LXIV** and **LXVI**) can be successfully performed by this method as in Eqs. (34) and (35) [154]. Decarboxylation of the γ-lactone α- and β-carboxylic acids (**LXVIII** and **LXX**) in a Py–H_2O–Et_3N–(Pt or C) proceeds smoothly, yielding the corresponding bute-

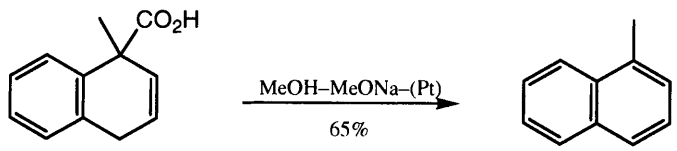
Table 8 Decarboxylative Carbon–Carbon Double-Bond Formation

Direct discharge of carboxylates				Concerted decarboxylation		
						
Py/H_2O Et_3N (Pt)	Py/H_2O Et_3N (C)	MeCN EtOH KOH (C)	MeOH Et_3N (Pt)	H_2O Et_3N $LiClO_4$ (Pt)	H_2O KOH (C)	MeCN Et_4NBF_4 (Pt)
References						
21	13-17	148	150, 14	151	152	153

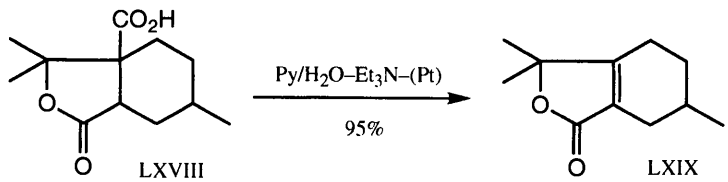
nolides (**LXIX** and **LXXI**), respectively, as in Eqs. (36) and (37) [155,156]. In a similar fashion, 2-substituted cyclopentenones (**LXXIII**) have been obtained starting from 2-carboxycyclopentanones (**LXXII**) [Eq. (38)] [157].



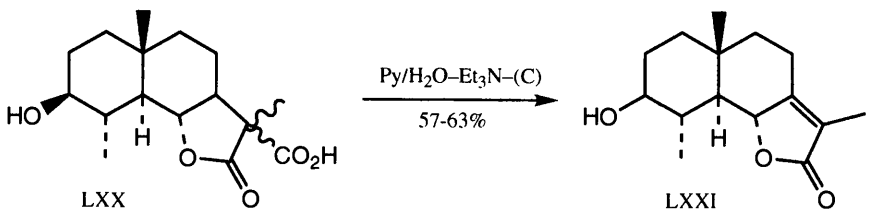
LXIV LXV (34)



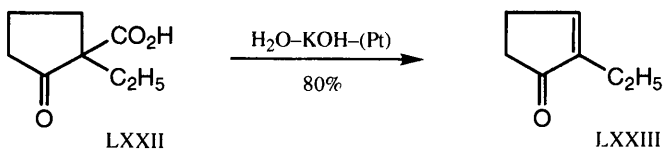
LXVI LXVII (35)



LXVIII LXIX (36)

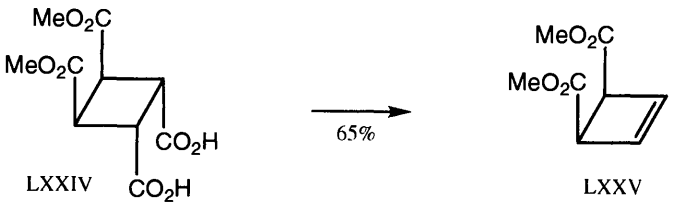


LXX LXXI (37)

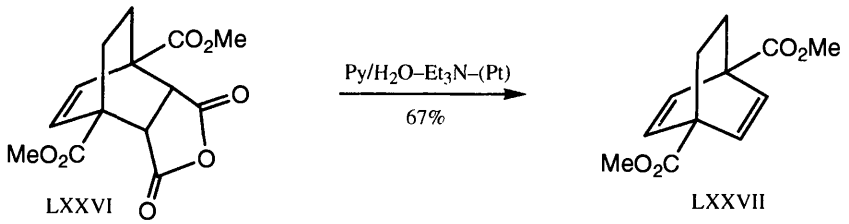


LXXII LXXIII (38)

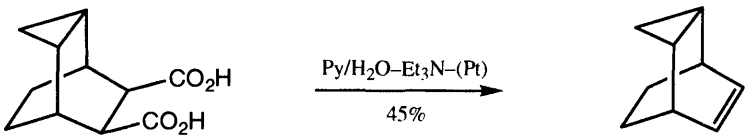
Double decarboxylation of 1,2-dicarboxylic acids may take place smoothly in an aqueous 90% pyridine–Et_3N–(Pt) electrolysis system to give olefins in fair yields [158–160]. Some representative examples are shown in Eqs. (39) [14], (40) [13,15,16], and (41) [160]:



LXXIV LXXV (39)

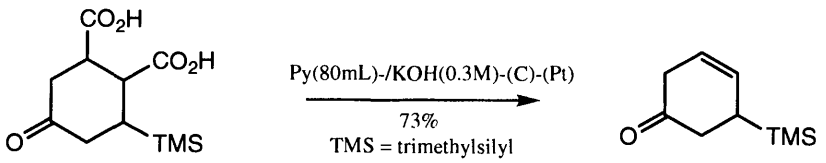


LXXVI LXXVII (40)



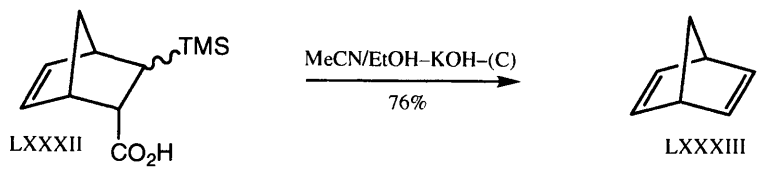
LXXVIII LXXIX (41)

Equation (42) demonstrates that the double decarboxylation of the dicarboxylic acid (**LXXX**) preferentially proceeds rather than the decarboxylation–desilylation reaction to give the olefin (**LXXXI**) in 73% yield [149].

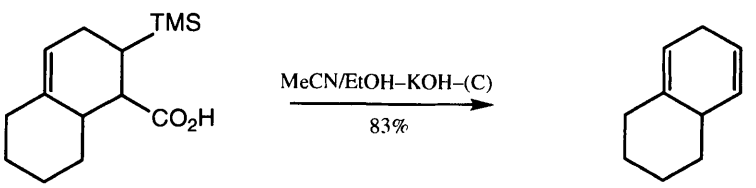


LXXX LXXXI (42)

A new device for olefin formation via decarboxylation–desilylation has been achieved successfully by electrolysis of β-trimethylsilyl carboxylic acids in an MeCN–EtOH–KOH–(C) system [148]. For example, norbornadiene (**LXXXIII**) and cyclohexadiene (**LXXXV**) have been obtained in good yields:

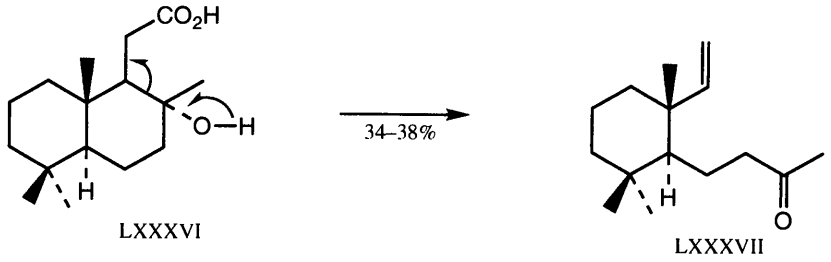


LXXXII LXXXIII (43a)



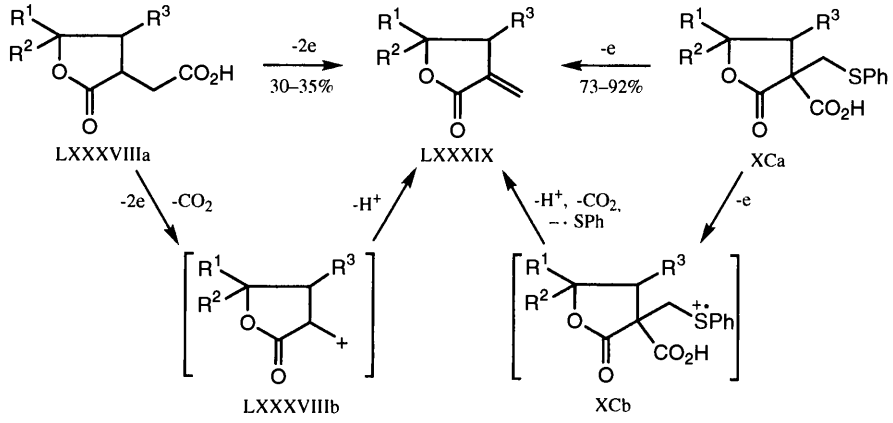
LXXXIV LXXXV (43b)

Electrolysis of γ-hydroxy carboxylic acid may give rise to decarboxylative β,γ-bond fission, leading to olefinic ketones. An example is given in Eq. (44) [150]:



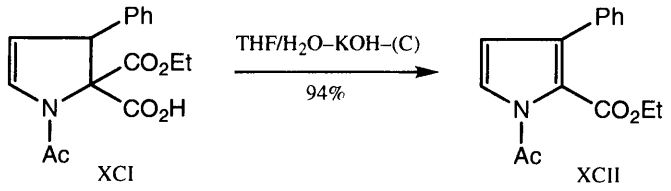
LXXXVI LXXXVII (44)

The α-exomethylene-γ-lactone framework has been successfully constructed via two electrosynthetic pathways, that is, both by the direct and by the concerted decarboxylation processes as mentioned earlier [Eq. (45)] [151]. The electrodecarboxylation of **XCa** is probably initiated by a one-electron oxidation of the sulfur atom, giving first the cation radical (**XCb**) and subsequently a concerted elimination of the thiyl radical and carbon dioxide to **LXXXIX**. On the other hand, the electrochemical decarboxylation of **LXXXVIIIa** involves an E1-type elimination of a proton from the cation intermediate (**LXXXVIIIb**) generated from direct two-electron oxidation of the carboxyl group. The latter method generally requires a higher oxidation potential than that required for the concerted method. Therefore, the concerted electrodecarboxylation method becomes more advantageous, especially when the substrates or products are unstable under oxidative conditions.

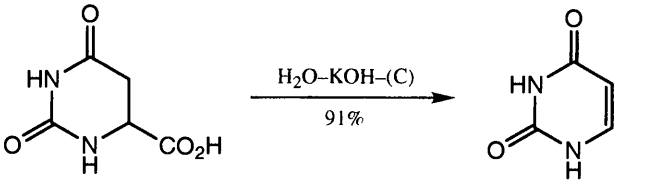


(45)

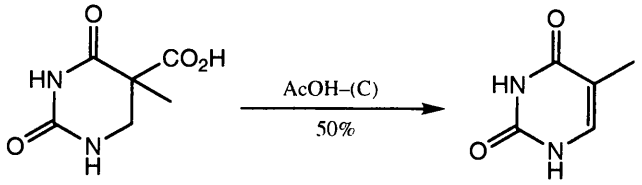
The decarboxylation started by the oxidation of a nitrogen atom promises versatile synthetic applications for making unsaturated nitrogen-containing heterocyclic frameworks. Pyrrole [132], uracil [152,161–163], thymine [152], 2-pyrazoline [153], β-carboline [164], and dihydroquinoline [165], useful intermediates for drug syntheses, have been prepared by using the electrodecarboxylation procedure. Some typical examples are given in Eqs. (46) through (51):



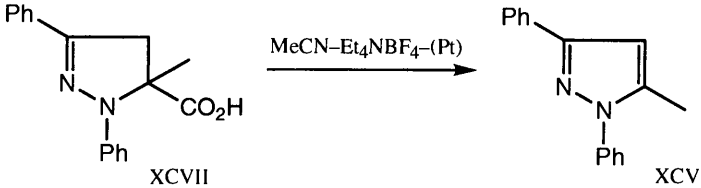
XCI XCII (46)



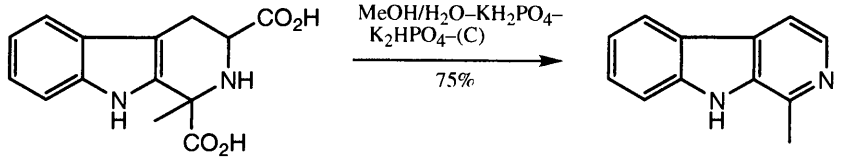
XCIII XCIV (47)



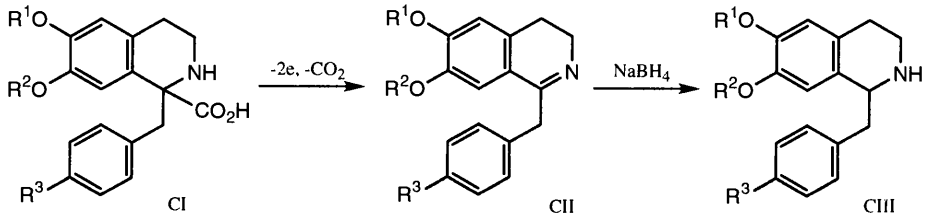
XCV XCVI (48)



XCVII XCVIII (49)



XCIX C (50)

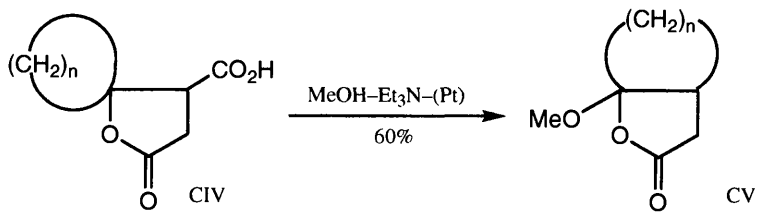


CI CII CIII (51)

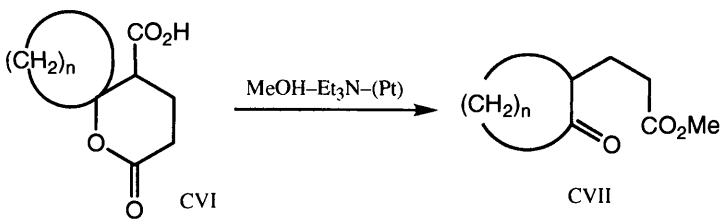
C. Rearrangement

A carbocation formed by an electrodecarboxylation process is expected to be different in nature from carbocations generated in homogeneous media, for example, by solvolysis or deamination [166,167]. It is very likely that the carbocation produced in the electrodecarboxylation should be highly reactive, possessing an unsolvated vacant p-orbital, and having no counterion in the near vicinity. Actually, certain carboxylic acids bearing not only suitably oriented β-substituent but also a heteroatom linked to the β-carbon are liable to undergo a carbocation rearrangement. Some reactions are exemplified as follows.

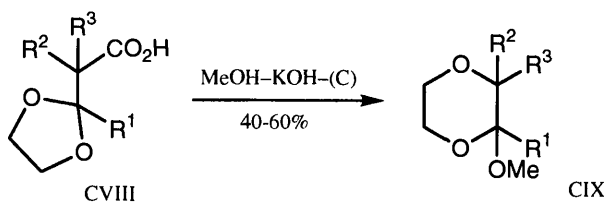
The electrochemical rearrangement of paraconic acids (**CIV**) [Eq. (52)], γ-carboxy-δ-lactones (**CVI**) [Eq. (53)] [168], and β-keto carboxylic acid ethylene acetals (**CVIII**) [Eq. (54)] [169,170] has been known to proceed smoothly. γ-Keto carboxylic acids (**CX**) and acetals (**CXII**) undergo decarboxylative rearrangement to afford esters (**CXI** and **XCIII**) as in Eqs. (55) and (56) [171,172].



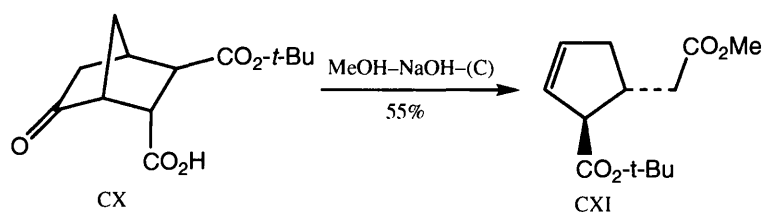
(52)



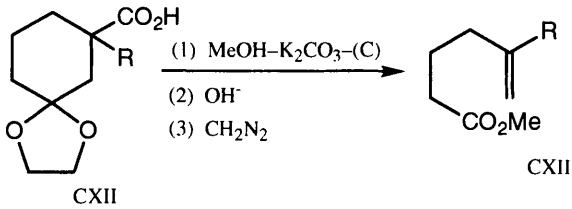
(53)



(54)

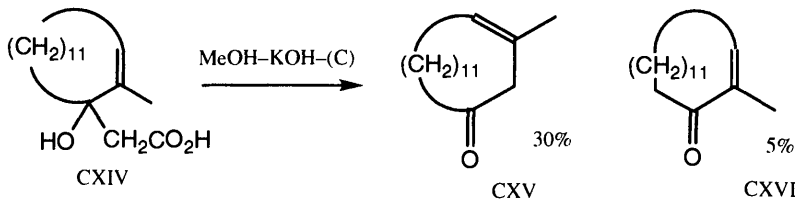


(55)



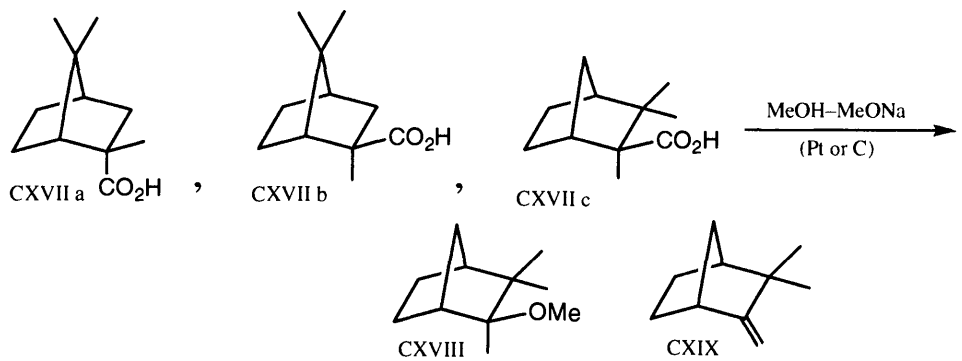
(56)

The electrodecarboxylation of β-hydroxycarboxylic acids, easily accessible by Reformatsky reaction on cyclic ketones, furnishes a promising route for the ring enlargement of cyclic ketones; for example, electrolysis of 1-hydroxy-2-cyclotetradecenylacetic acid (**CXIV**) in an MeOH–KOH–(C) system gives the sp^2 carbon migration product (**CXV**, 30%) together with the sp^3 carbon migration product (**CXVI**, 5%) [173]:

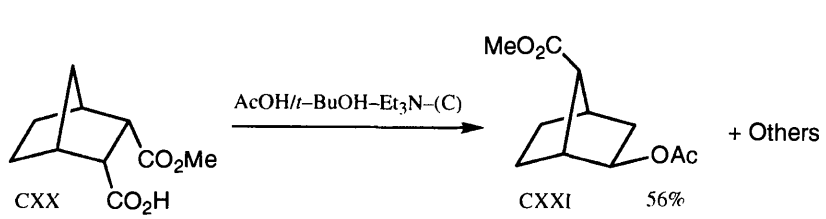


(57)

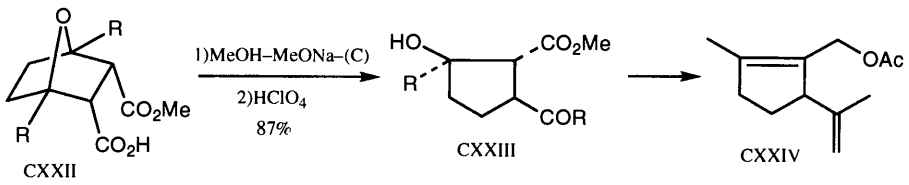
A Wagner–Meerwein rearrangement via a bridged carbenium ion has been observed in the electrodecarboxylation of bicyclo[2.2.1]heptane-2-carboxylic acids (**CXVIIa**, **CXVIIb**, and **CXVIIc**), leading to the formation of the same products (**CXVIII** and **CXIX**) [Eq. (58)] [174]. This method has been successfully applied to synthesis of useful intermediates for natural product synthesis. Some examples are given in Eqs. (59) and (60) [175–179].



(58)



(59)

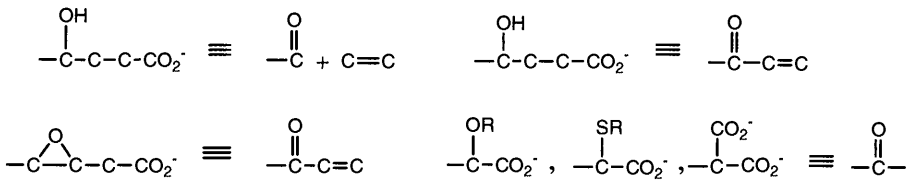


CXXII CXXIII CXXIV

(60)

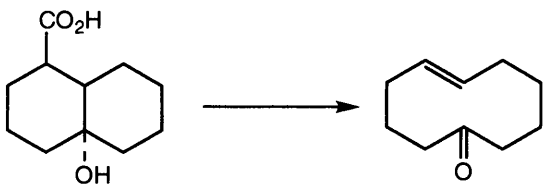
D. Formation of Aldehydes, Ketones, Acetals, and α,β-Enones

Electrodecarboxylation procedures for preparing aldehydes, ketones, acetals, and enones have been intensively investigated. The following sets of functional groups are found to be electrosynthetically equivalent to carbonyl groups:



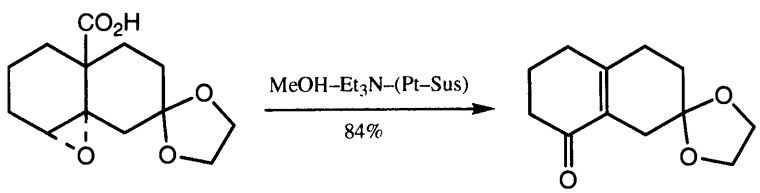
(60a)

As mentioned in preceding sections, γ- and β-hydroxy carboxylic acids undergo decarboxylative rearrangement to afford ketones. An additional example is given in Eq. (61), in which the electrodecarboxylation of a γ-hydroxyl carboxylic acid moiety in a bicyclo[4.4.0]decane system (**CXXV**) gives a 10-membered nonconjugated enone (**CXXVI**) [180]. On the other hand, the electrolysis of a β,γ-epoxy carboxylic acid moiety arranged in the same ring system (**CXXVII**) provides a conjugated enone (**CXXVIII**) in good yield [Eq. (62)] [11]. Electrodecarboxylation of α-hydroxy or α-alkoxy carboxylic acids proceeds smoothly, affording aldehydes [181] or acetals (see preceding sections).



CXXV CXXVI

(61)

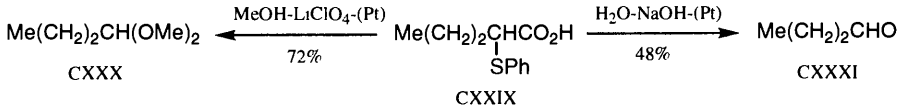


CXXVII CXXVIII

(62)

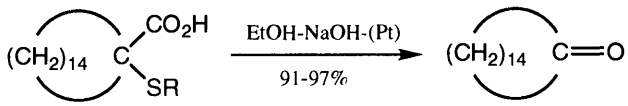
α-Sulfenylcarboxylic acids can be transformed into aldehydes and ketones via electrodecarboxylation. For example, the electrolysis of α-phenylthiocarboxylic acid (**CXXIX**) gives aldehyde (**CXXXI**) in an H_2O–NaOH–(Pt) system and the corresponding acetal (**CXXX**) in an MeOH–$LiClO_4$–(Pt) system [Eq. (63)] [9]. Cyclopentadecanone

(**CXXXIII**) is prepared by electrolysis of α-phenylthio- and methylthio-substituted cyclopentadecanecarboxylic acids (**CXXXII**) [Eq. (64)] [8].



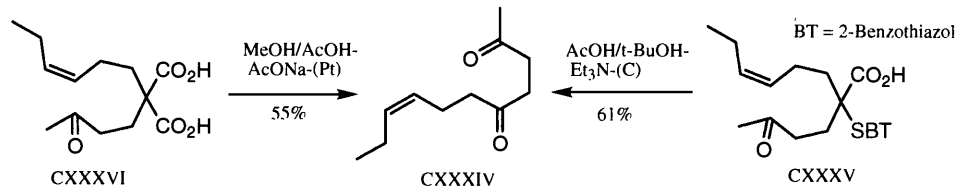
CXXX CXXIX CXXXI

(63)



CXXXII CXXXIII (64)

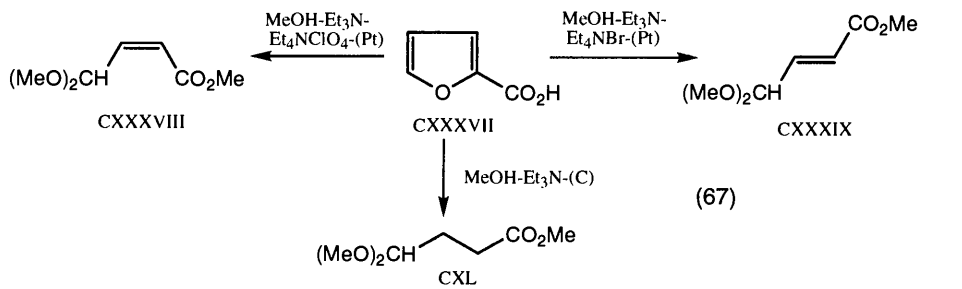
The α-sulfenyl group can be replaced by a benzothiazolthio group, as demonstrated in the synthesis of the 1,4-diketone (**CXXXIV**), a precursor of *cis*-jasmone [Eq. (65)] [10]. The geminal dicarboxylic acid (**CXXXVI**) can also be transformed into the 1,4-diketone (**CXXXIV**) by electrochemical decarboxylation as in Eq. (66) [6], suggesting that the substituted malonic acid group is synthetically equivalent to a carbonyl group.



CXXXVI (66) CXXXIV (65) CXXXV

E. Miscellaneous

Further synthetically meaningful reactions induced by electrochemical decarboxylation are briefly discussed in this section. Potent stereoselective routes to methyl *cis*- and *trans*-4,4-dimethoxy-2-butenoates (**CXXXVIII** and **CXXXIX**) and methyl 4,4-dimethoxybutanoate (**CXL**) from 2-furoic acid (**CXXXVII**) have been achieved mostly by simple selection of an appropriate electrolyte and electrode, that is, MeOH–Et_3N–Et_4NClO_4–(Pt) for **CXXXVIII**; MeOH–Et_3N–Et_4NBr–(Pt) for **CXXXIX**; and MeOH–Et_3N–Et_4NBr–(C) for **CXL**, respectively [182,183]:



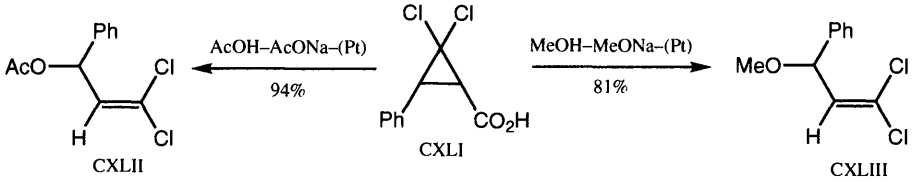
CXXXVIII CXXXVII CXXXIX

CXL

(67)

(67)

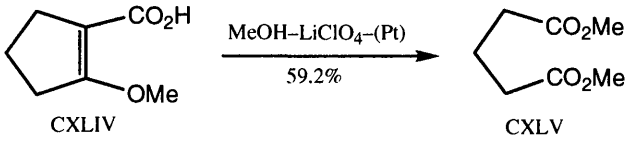
Electrodecarboxylation followed by C–C bond cleavage has been investigated for three- and four-membered ring systems. The dichlorocyclopropane carboxylic acid (**CXLI**) undergoes decarboxylation in either acetic acid or methanol to give the ring-opened acetate (**CXLII**) or methyl ether (**CXLIII**) in good yields [184]:



CXLII CXLI CXLIII

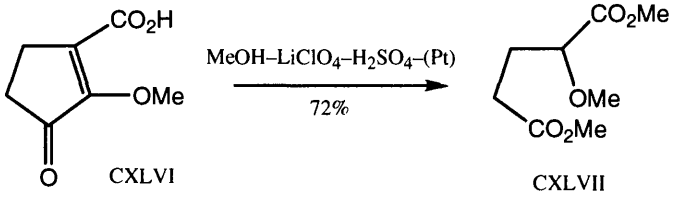
(68)

The double bond in alicyclic β-keto acid enol ethers (**CXLIV** and **CXLVI**) can be cleaved by electrodecarboxylation [185]:



CXLIV CXLV

(69)



CXLVI CXLVII

(70)

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Anodic Oxidation of Nitrogen-Containing Compounds

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References

I. INTRODUCTION

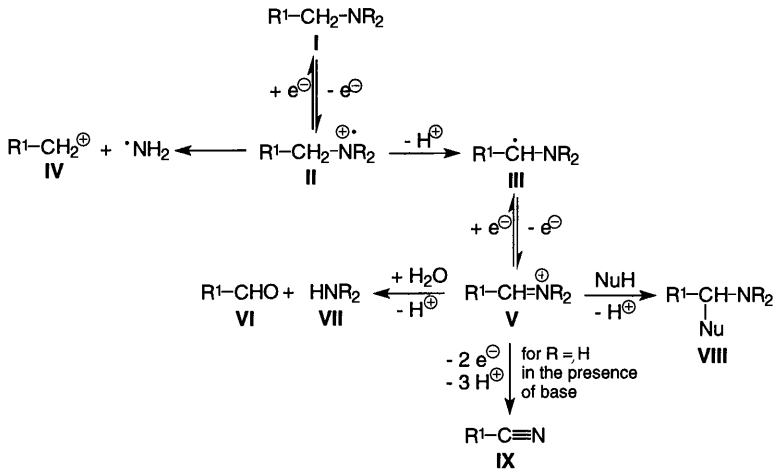
Nitrogen-containing compounds having lone-pair electrons are usually relatively easy to oxidize. Therefore the anodic behavior of such compounds has been studied quite intensively. However, the ease of oxidation is not always paralleled by the selectivity of the

[†]Deceased.

reaction. For example, electrochemical oxidation and aliphatic and aromatic amines in many cases leads to a variety of products while the anodic oxidation of amides or carbamates results in the formation of only one major product. Therefore, synthetic application of amine oxidation is more seldom found than that of amide and carbamate oxidation.

II. ALIPHATIC AMINES

The oxidation potentials of aliphatic amines depend on their structure. Primary amines (E_p^{ox} between 1.6 and 1.7 V vs. NHE) are more difficult to oxidize then secondary or tertiary (E_p^{ox} between 1.3 and 1.0 V vs. NHE) ones. The electrochemical oxidation of simple aliphatic amines is quite complex and may lead to a variety of products. Scheme 1, which is based on studies by Mann [1–4], gives a general survey of the possible reaction pathways. In the first step the amine **I** is oxidized to the radical cation **II**, which may decompose by C–N bond cleavage if a relatively stable carbenium ion **IV** can be formed which may solvolyze, add to a nucleophile, or polymerize. Usually, however, **II** is deprotonated and further oxidized to give the iminium ion **V**. Compound **V** can hydrolyze to give the aldehyde **VI** and amine or ammonia **VII**, or it adds to a nucleophile, giving substitution product **VIII**. Under basic conditions using certain metal oxide electrodes, **V** with R being H may be further deprotonated and oxidized to finally yield the nitrile **IX**.



Scheme 1

Nelsen et al. [5] pointed out that the usually assumed extremely high acidity of the cation radical **II**, at least in the case of trialkylamines, does not exist, so that the radical cations do not usually decompose by deprotonation if bases no stronger than R_3N are the only ones present. Instead, **II** (R = alkyl) shows exceptionally weak C(α)-H bonds. Therefore, hydrogen atom abstraction from **II** leading to **V** might be the first step in its decomposition.

A. Primary Amines

Anodic oxidation of primary amines at platinum or carbon electrodes is not of significant preparative interest. The common products in acetonitrile are the aldehydes **VI**, NH_4^+, nitrogen from the oxidation of ammonia, protonated starting material, and hydrocarbons

[1,2]. Valuable, however, is the anodic oxidation of primary amines in basic aqueous media at silver oxide, copper oxide, or, more effectively, at nickel hydroxide electrodes to form the nitriles **IX** in good to excellent yields [6–11]. In this case the primary step in the reaction mechanism is the hydrogen atom abstraction at C(α) by the in situ generated nickel oxide hydroxide, which is formed at about 0.63 V (vs NHE):

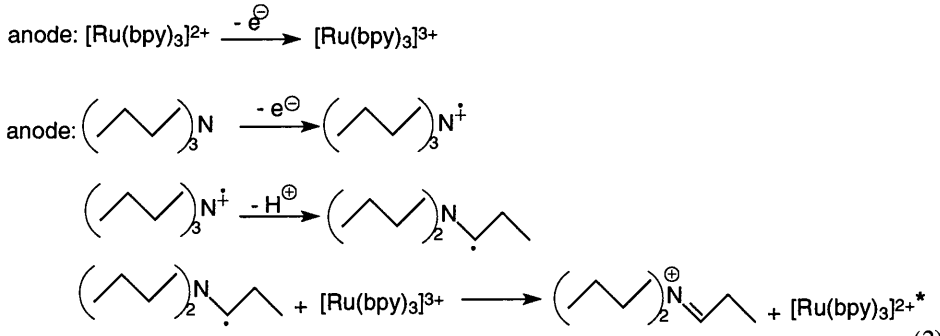
$$H_2N{-}CH_2{-}(CH_2)_8{-}CH_2{-}NH_2 \xrightarrow[\text{0.1 N KOH}\ \text{in t-butanol/water (1:1)}]{\text{NiOOH-anode}} N{\equiv}C{-}(CH_2)_8{-}C{\equiv}N \quad (90\ \%) \tag{1}$$

α-Branched primary amines are oxidized to ketones presumably via hydrolysis of the intermediate imines. Alanine is cleaved to acetonitrile, while 6-aminohexanoic acid yields the cyanocarboxylic acid in excellent yield.

Primary amines may be oxidized by a two-electron process to give hydrazines, which generally are further oxidized to the azo compound. As the oxidation potential of the primary amines is higher than that of the hydrazine, the latter very often is largely decomposed during the reaction. The amide ion, however, which may be obtained in the presence of a base, is easier to oxidize than the amine, so that under these conditions azo compounds are generated in moderate yields [12]. *tert*-Butylamine is coupled to the azo compound (41%) also in the absence of a base using an aqueous electrolyte [13], because in the absence of α-hydrogens further oxidative degradation is hindered.

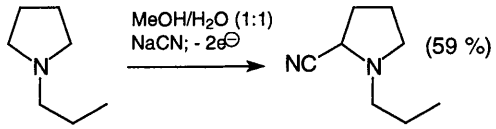
B. Secondary and Tertiary Amines

In acetonitrile, secondary and tertiary aliphatic amines are degraded according to Scheme 1 to the aldehydes **VI**, the lower amines **VII**, and protonated starting material. The lower amines may be further degraded along the same pathways [1,4]. The anodic dealkylation of aliphatic tertiary amines was also studied in aqueous alkaline solution [14]. In this case, it was found that the relative amount of dealkylation in unsymmetrical amines is predominantly governed by the number of α-protons and their acidity. Interestingly, the coelectrolysis of tripropylamine (TPA) and tris(2,2′-bipyridine) ruthenium(II) [$Ru(bpy)_3^{2+}$] in phosphate buffer at a potential at which both compounds are oxidized leads to electrochemiluminescence (ECL). The luminescent $Ru(bpy)_3^{2+*}$ is formed by the highly exergonic oxidation of the intermediate TPA radical (species **III** in Scheme 1) by the electrogenerated ruthenium(III) complex [Eq. (2)] [15]. Although the light-delivering step is only a minor part in the complex reaction scheme, this system is used as the detection mode for a commercial high-throughput immunoassay analyzer employing tris(2,2′-bipyridine) ruthenium-labled antibodies.



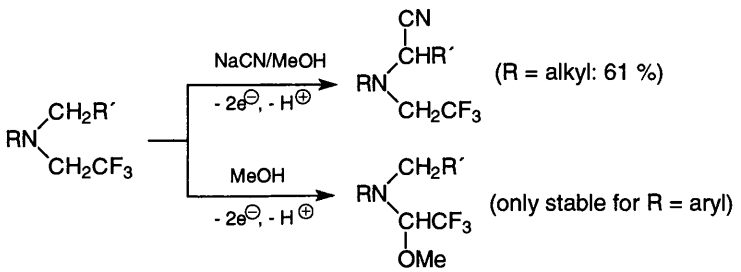
(2)

A synthetically very useful reaction sequence would be the anodic oxidation of **I** via the iminium ion **V** to the substitution product **VIII**. The addition of nucleophiles to **V** in the case of purely aliphatic amines has, however, only found limited application. For example, the cyanide ion may be used as a nucleophile, giving α-cyanation products or α-amino acids after hydrolysis. Thus, anodic oxidation of methyl-diisopropylamine in methanol/water (1 : 1) in the presence of sodium cyanide leads to the formation of cyano-methyl-diisopropylamine in 55% yield, and 2-cyano-*N*-*n*-propylpyrrolidine is formed from *N*-*n*-propylpyrrolidine in 59% yield [16]:



(3)

In the case of *N*-(2,2,2-trifluoroethyl)amines, Fuchigami et al. studied the influence of the trifluoromethyl group on the regioselectivity of the nucleophilic substitution in the α-position to nitrogen using cyanide and methanol as nucleophiles. While the methoxy function was introduced into the α-position to both the nitrogen and the trifluoromethyl group with *N*,*N*-dialkyl anilines, the cyanide nucleophile substituted the hydrogen in α-position to nitrogen in the nonfluorinated alkyl substituent [17]:



(4)

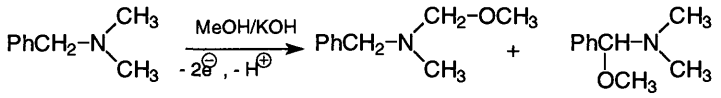
In a special case of tertiary amine oxidations, the electrogenerated diiminium ion obtained from the indole alkaloid cantharanthine couples in the 16-position with the electron-rich aromatic subunit of vindoline in the 10-position to give the highly cytostatic anhydrovinblastine. In the presence of methanol, the methoxy group is introduced in the 16-position, yielding, after a follow-up reduction, 16-methoxyclea-vamine [18].

The electrochemical oxidation of the aspidofractinine-type alkaloid kopsingine in a dichloromethane/acetonitrile medium at a platinum anode in the presence of 2,6-lutidine results in the intramolecular cyclization of an hydroxy group to the intermediate iminium ion of the tertiary amine structure. Thus, kopsidine A was formed in 72% yield [19].

In the case of tribenzyl and trimethyl amine, α-substitution products could be obtained using diethyl malonate or diethylphosphonate as nucleophiles, if 2,4,6-collidine was used as base in an acetonitrile electrolyte [20]. In this way, dialkyl aminomethyl phosphonates and malonates could be obtained in good yield.

If methanol is used as nucleophile, the substitution products are usually not stable and decompose to the aldehyde and lower amine. Exceptions are *N*,*N*-dialkyl anilines,

which are treated later. In the case of *N*, *N*-dimethylbenzylamine **X**, however, two isomeric substitution products **XI** and **XII** could be obtained in a ratio of 4 : 1 [21]:

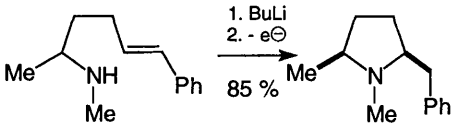


X **XI** **XII** (5)

The reason for the unexpected predominant substitution at the methyl group instead of the benzyl group was the matter of some discussion [22–24]. In the case of the *N*-benzyl-*N*-methylethanolamine, anodic oxidation in MeOH/KOH leads to the intramolecular cyclization by attack of the hydroxy function onto the positively charged benzylic α-C atom. Thus, 3-methyl-2-phenyl-1,3-oxazolidine is formed in 60% yield [20].

Shono [25] pointed out that the microsomal oxidation of tertiary amines and amides occurs via the same intermediates as the anodic oxidation in methanol solution. The dealkylation of *N*-methyl-*N*,*N*-dialkyl amines by both methods results in almost the same *N*-demethylation/*N*-dealkylation ratio. This method has been used in the pharmaceutical industry for the easy supply of metabolites of pharmaceuticals.

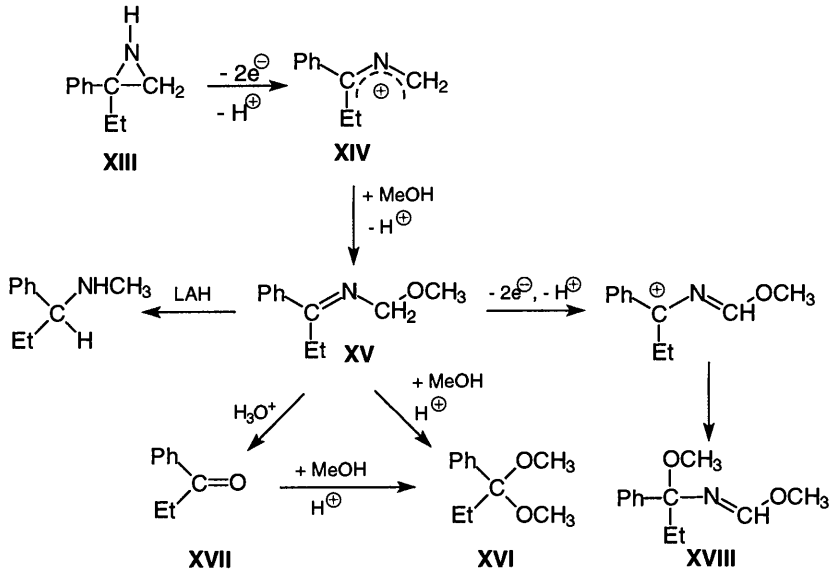
Lithium 1,2-dialkyl-1-(4-pentenyl)amide ions obtained from secondary pentenylamines may be anodically oxidized to form aminyl radicals which undergo cyclization to give regio- and stereoselectively *cis*-*N*-alkyl-2,5-disubstituted pyrrolidines [26]:



(6)

Otherwise, lithium amides of secondary amines undergo anodic dimerization to form hydrazines in moderate yields [12]. Hydrazines are also generated, if secondary amines are electrochemically oxidized in the presence of an alkali hydroxide [27,28]. This reaction is mainly effective if the coupling takes place intramolecularly to give cyclic hydrazine derivatives [28]. If lithium amides of secondary amines are anodically oxidized in tetrahydrofuran (THF) solution in the presence of the free amine, 2-aminotetrahydrofurans are formed in reasonable yields. In contrast, the respective aminomagnesium bromides only gives *N*,*N*-coupling products [29].

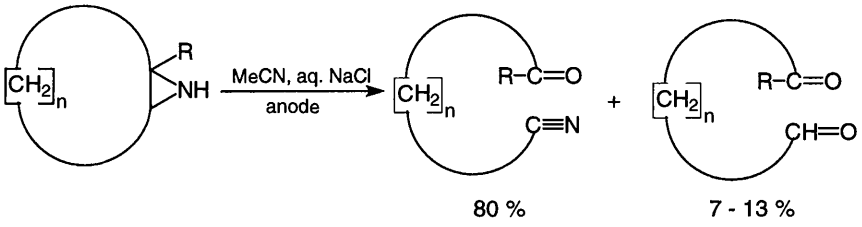
Aziridines, which may be regarded as cyclic secondary or tertiary amines containing a β-amino substituent, undergo ring cleavage by anodic oxidation (Scheme 2). Thus, in the electrochemical oxidation at a platinum anode in a methanol solution 2-ethyl-2-phenylaziridine (**XIII**) forms propiophenone dimethylacetal (**XVI**) (50%), propiophenone (**XVII**) (6%), and **XVIII** (12%) [30]. The reaction is supposed to proceed via the intermediate azaallyl cation **XIV** leading to imine **XV**. This is supported by the fact that **XV** can be trapped by lithium aluminum hydride (LAH) reduction to give *N*-methyl-*N*-(1-phenylpropyl) amine. Hydrolysis of **XV** may lead to propiophenone, while its further two-electron oxidation and deprotonation forms **XVIII**. Compound **XVI** may be generated either by proton-catalyzed acetalization of propiophenone or **XV**.



Scheme 2

At a potential of 1.1 to 1.3 V (vs. Ag/Ag^+ 0.1 *M*), (*N*-benzylaziridine is opened to form a cyclic tetramer, which may be explained by an electron transfer chain mechanism [31]. The same reaction may also be performed by redox catalysis using tris(4-bromophenyl)amine as mediator at a potential of about 0.75 V (vs. Ag/Ag^+). The possibility of catalysis by electrogenerated acid was excluded.

Indirect electrooxidation of cyclic aziridines using NaCl or NaBr as a redox catalyst results in C(1)–C(2) bond cleavage under formation of the corresponding keto nitriles. This reaction is explained by the intermediate generation of an azaallenyl cation, which is hydrated to the α-hydroxyimine. Further oxidation by "Cl^+" then would lead to the open-chain keto *N*-chloroimine, which by HCl elimination forms the keto nitrile, while its hydrolysis leads to the keto aldehyde as a side product [32]:



(7)

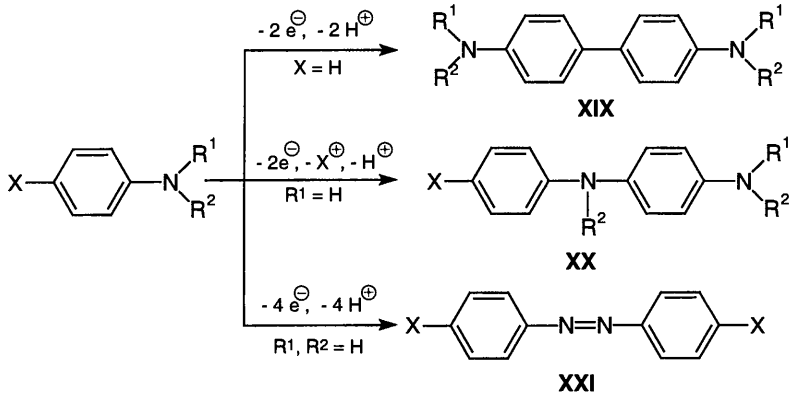
III. AROMATIC AMINES

Usually, aromatic amines are very easy to oxidize. Unsubstituted, *N*-alkyl-, and *N,N*-dialkylanilines show anodic potentials in the range of 0.4 to 1.0 V (vs. NHE). Diphenylamines cover a broader spectrum of potentials depending on their substitution pattern. Triphenylamines have oxidation potentials between 0.7 and 2.0 V (vs. NHE). For aromatic amines, a large number of potentials has been tabulated [33]. The anodic oxida-

tion of aromatic amines is quite complex leading to a variety of products depending on their structure and the electrolysis conditions. Products may vary largely by using aqueous or nonaqueous, neutral, acidic, or basic conditions. In general, the anodic oxidation of tertiary aromatic amines shows a higher selectivity in product formation, thus being more valuable for synthetic purposes. The anodic oxidation of aromatic amines has been reviewed several times in detail [34–36]. Therefore, mainly typical reaction patterns and more recent developments are discussed here.

A. Aniline Derivatives

Aniline and its derivatives may form three types of products (Scheme 3): If no *para*-substituent is present, tail-to-tail coupling results in the formation of benzidine derivatives (**XIX**); anilines and *N*-alkylanilines also can undergo head-to-tail coupling to give 4-aminodiphenylamines (**XX**) even in the presence of certain *para*-substituents, one of which is eliminated; head-to-head coupling forming azo compounds (**XXI**) is possible with *N*-unsubstituted anilines.



Scheme 3

1. Primary Aniline Derivatives and *N*-Alkylanilines

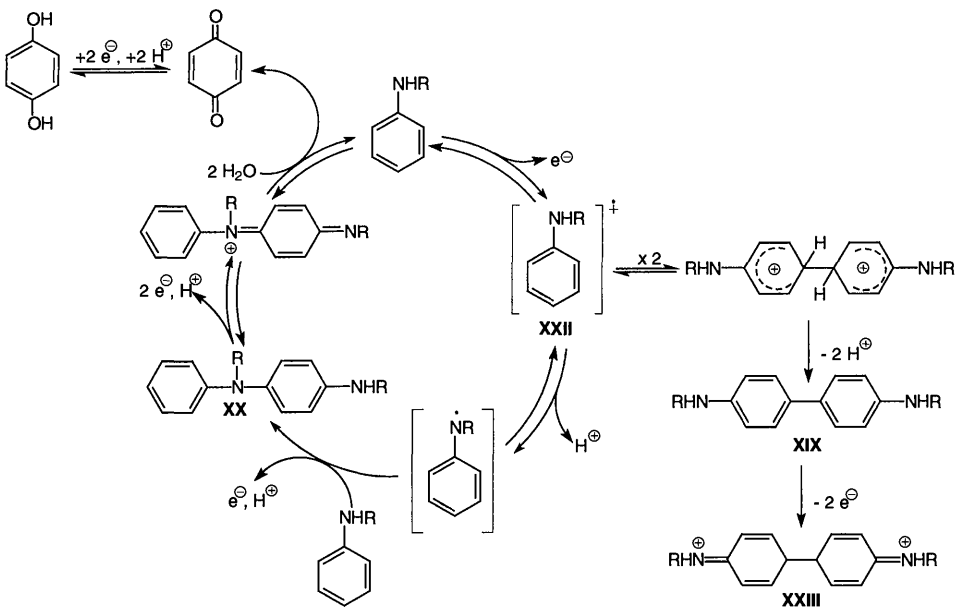
A generalized reaction scheme for anilines and *N*-alkylanilines based on results by Nelson [37] is shown in Scheme 4.

The primary intermediate formed by one-electron abstraction is the cation radical **XXII**, which can either undergo dimerization or deprotonation. Dimerization and subsequent deprotonation leads to the benzidine (**XIX**), which is easier to oxidize than the starting material. Thus, in a reversible two-electron oxidation, the stable diiminium species **XXIII** is formed. Dimerization is favored at high current densities, leading to high cation radical concentrations and low concentrations of the parent molecule at the electrode surface. At low current densities, high concentrations of starting material, and in the presence of a strong enough base, deprotonation is favored to form a resonance-stabilized radical. This undergoes C–N coupling with a parent molecule, which after loss of an electron and a proton leads to the 4-aminodiphenylamine (**XX**). This compound is easily oxidized to the diimine form, which may be hydrolyzed to give *para*-benzoquinone and the parent amine. The influences of the reaction parameters on the results of electrolyses of aniline and *N*-alkylanilines are given in Table 1 [37].

Table 1 Influence of Electrolysis Conditions on Product Distribution for Anodic Oxidation of Aniline and *N*-Alkylanilines

Compounds	Electrolysis conditions	Products (%)[a]
Aniline	MeCN–TEAP, low current density	4-Aminodiphenylamine (40)
Aniline	0.5*M* H_2SO_4, high or low current density	*p*-Benzoquinone (90–100)
Aniline	6*M* H_2SO_4, high current density	*p*-Benzoquinone (80–90); benzidine (10–20)
N-Ethylaniline	MeCN–TEAP, low current density, low parent concentration	*N,N'*-Diethylbenzidine (60–70)
N-Ethylaniline	MeCN–TEAP, high current density	*N,N'*-Diethylbenzidine (70–80)
N-Ethylaniline	MeCN–TEAP, low current density, high parent concentration	*N*-Ethyl-4-ethylaminodiphenylamine (70); *N,N'*-diethylbenzidine (15)
N-Ethylaniline	6*M* H_2SO_4, high current density	*p*-Benzoquinone (40); *N,N'*-diethylbenzidine (60)
N-*tert*-Butylaniline	MeCN–TEAP, high current density	*N,N'*-Di-*tert*-butylbenzidine (100)

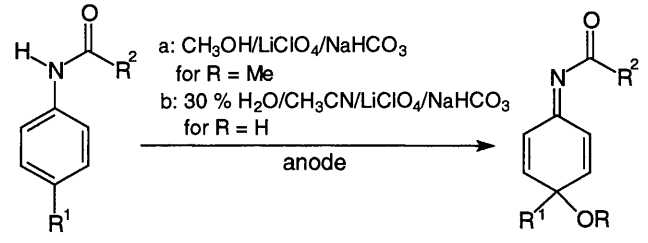
[a] Based on consumed parent compound.
Source. From Ref. 37; controlled-potential electrolyses.



Scheme 4

The formation of *p*-aminodiphenylamine is supposed to be the key intermediate in the formation of a dark green precipitate at the electrode surface during continued electrolysis of acidic aniline solutions. This has been characterized as an oligomer of aniline, for example, as the octamer emeraldine formed by a cascade of head-to-tail condensations [38,39]. Nelson, however, explained it as a mixture of mainly quinhydrone with a small amount of benzidine salt [37]. Today the electropolymerization of aniline under strongly acidic conditions is intensively studied as an important way to form the conducting polymer polyaniline [40] (see Chapters 31 and 32).

Para-substituted anilines undergo head-to-head coupling in an electrolyte of acetonitrile in the presence of pyridine [41] to give the azo compounds **XXI**. Hydrazo compounds are supposed to be the intermediates. Under acidic conditions, anilines with *para*-substituents, like methoxy, ethoxy, chloro, or carboxy groups, react via head-to-tail coupling, giving the corresponding 4′-substituted *p*-amino diphenylamines **XX** in the partially oxidized form as an *N*-aryl *p*-benzoquinone diimine. The leaving group is supposed to be the anion X^-, thus forming the product already in an oxidized state [42]. *Para*- and *ortho*-aminophenols are intensively studied. They undergo two-electron oxidation to the quinone imines, which readily undergo hydrolysis to *p*- or *o*-benzoquinone [43,44]. *N*-Acylated quinone imine ketals are formed in yields between 60 and 80% by anodic oxidation of *p*-methoxyanilide derivatives in methanol solution [45]. Starting from *p*-alkylanilides, *N*-acylated quinol and quinol ether imines can be obtained in good to moderate yields [46]:



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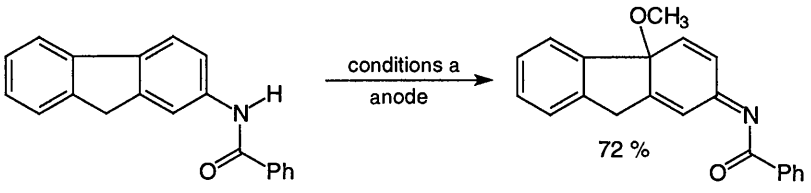
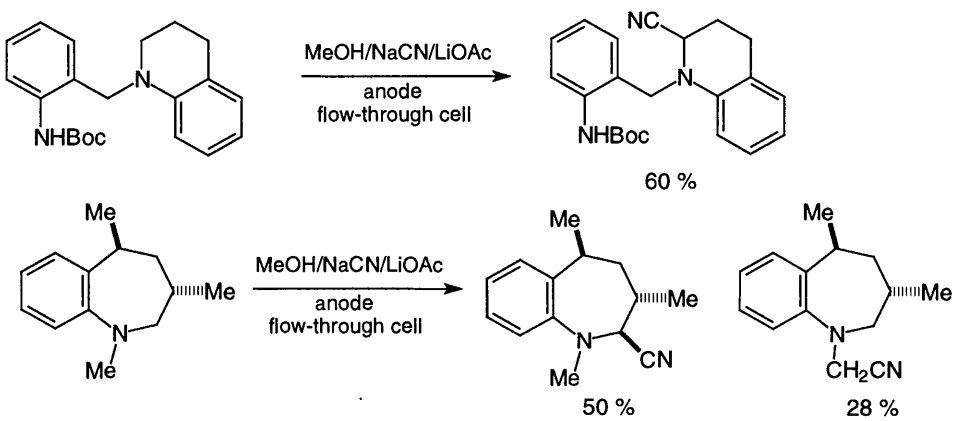


If the anodic oxidation of *N*-alkylanilines is performed in the presence of nucleophiles like enol ethers, nucleophilic substitution in the α-position to nitrogen by the enol ether can be observed in low yields. The electrophilic intermediate is the *N*-aryl iminium ion or the *N*-aryl imine after loss of two electrons and one or two protons. These intermediates add to the enol ether to give acetals (up to 26%) as addition products, or the first addition step is followed by an electrophilic aromatic substitution to form tetrahydroquinolines (13–39%) [47]. It should be noted at this point that better results for the nucleophilic α-substitution to nitrogen can be obtained with *N,N*-dialkylanilines (see next subsection). Optimum results, however, are obtained with *N*-acylated compounds via the intermediate *N*-acyl iminium ions (see Ref. 8).

2. *N,N*-Dialkylanilines

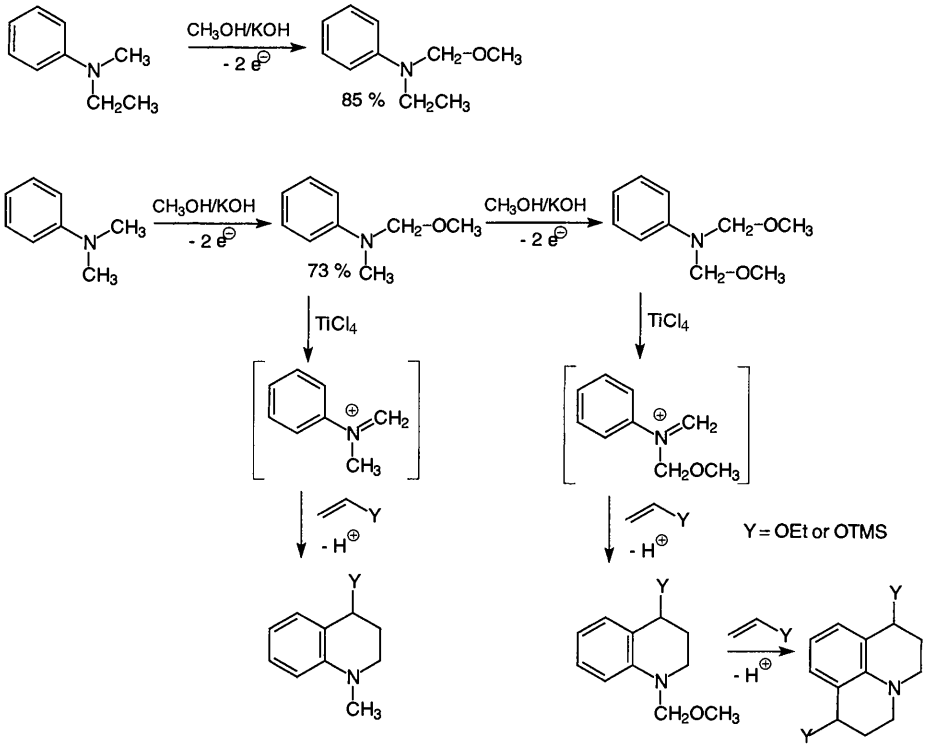
The most thoroughly studied compound of this class is *N,N*-dimethylaniline. The details of the anodic oxidation of *N,N*-dialkylanilines are well documented [48]. If the *para*-position of the aromatic ring is unsubstituted, tail-to-tail coupling via the intermediate cation radical under formation of the benzidines (Schemes 3 and 4, **XIX**) is dominating in acetonitrile or under acidic conditions. Benzidine, which has a lower oxidation potential than the starting material, is further oxidized to the corresponding quinoidal diimino dication.

In contrast to that, nucleophilic substitution in α-position to nitrogen by cyanide or methoxide predominates, if the electrolysis is carried out in acetonitrile or methanol in presence of cyanide [49], respectively, in basic methanol [50,51]. This reaction, which is supposed to occur via the iminium ion, is interesting for application in organic synthesis. The formation of synthetically valuable α-aminonitriles from *N,N*-dialkylanilines has been reported by Andreades and Zahnow [49]. More recently, a series of papers was published by Hurvois, Moinet, Tallec, et al. on the anodic α-cyanation of *N*-substituted 1-benzazepines, tetrahydroquinolines, and piperidines [Eq. (9)] [52]. The reactions were performed in a special flow-through cell. In the case of the 3-methyl-substituted benzazepines the reaction is stereospecific, leading only to the *trans*-α-cyano diastereomer.



(9)

If the α-methoxy group has been introduced electrochemically, it may be consecutively eliminated in the presence of a Lewis acid regenerating the iminium ion, which then can be trapped in situ by added nucleophiles. This sequence was performed in the case of *N*-ethyl-*N*-(2,2,2-trifluoro)ethylaniline by substitution of the anodically introduced α-methoxy function by the cyano group using trimethylsilylcyanide in the presence of borontrifluoride [53]. If electron-rich alkenes, like trimethylsilyl enol ethers, are used as C-nucleophiles in presence of $TiCl_4$, substituted tetrahydroquinolines are obtained in good to moderate yields [51]. Further anodic oxidation of α-methoxy-*N,N*-dimethylaniline in methanol leads to the formation of α,α'-dimethoxy-*N,N*-dimethylaniline, which forms julolidine derivatives by reaction with two molecules of vinyl ether in presence of $TiCl_4$ [51] [Eq. (10)].



(10)

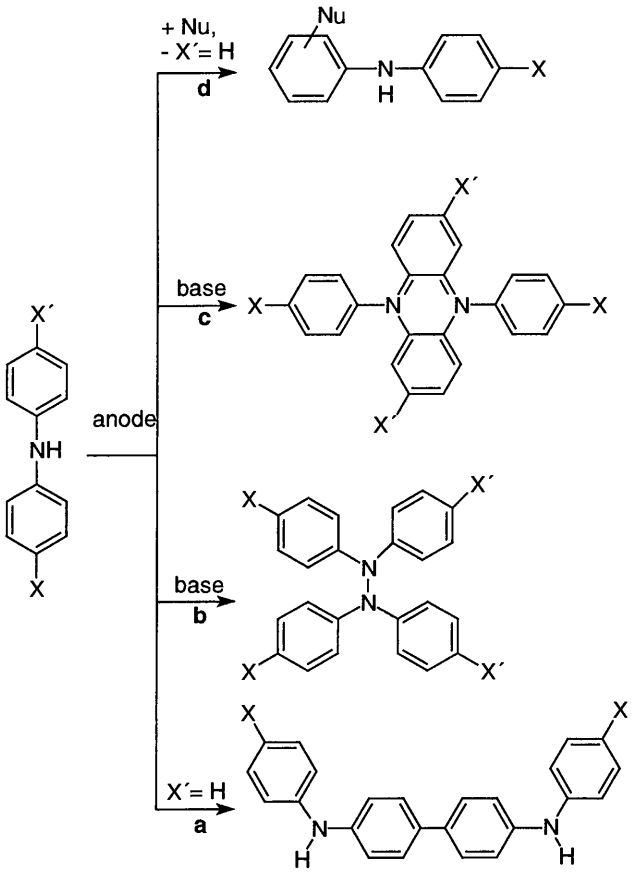
The reaction of ring-substitued *N,N*-dialkylanilines is depending on the type and position of the substituents. With halogen substituents in 2- or 3-position the corresponding substituted benzidines are formed as usual [34]. Bromo, iodo, and carboxy substituents in 4-position are eliminated to give the *N,N,N,N*-tetraalkylbenzidine [34,54]. 4-Alkoxy substituents result in the formation of 4-dimethylaminophenol, if the reaction is carried out in acetonitrile [55]. In aqueous solution, 4-hydroxy-*N,N*-dimethylaniline is oxidized to the quinone imine or its hydrolysis products *p*-benzoquinone and dimethylamine [56]. A methyl substituent in *p*-position like in *N,N*-dimethyl-*p*-toluidine leads to di(*p*-dimethylaminophenyl)-1,2-ethane [55,57] by coupling via the *p*-methyl group. Similar to tribenzyl and trimethyl amine (see Sec. II.B), α-substitution can be obtained with diethylphosphonate in presence of collidine giving (*N*-methyl-*N*-*p*-tolylaminomethyl)diethylphosphonate [20].

B. Diarylamines

The major pathways for the anodic oxidation of diarylamines are *N,N*- or aryl,aryl-coupling, *N*,aryl-coupling, and nucleophilic substitution in the aromatic ring. Which pathway actually will be followed depends on the reaction conditions and the substitution pattern of the substrate. With regard to the latter, one has to distinguish between *p*-unsubstituted, *p*-mono- and *p*-disubstituted diphenylamines.

Diphenylamine has been oxidized under various conditions (Scheme 5). In acetonitrile tail-to-tail coupling via the cation radical, forming *N,N'*-diphenylbenzidine is favored (pathway a) [58–61]. In the presence of cyanide or acetate acting as a base,

tetraphenylhydrazine is formed in high yield via coupling of the diphenylaminyl radicals (pathway b) [60]. These radicals may either be formed by deprotonation of the initial cation radical or by deprotonation of diphenylamine to the amide ion and subsequent oxidation to the *N*-radical.



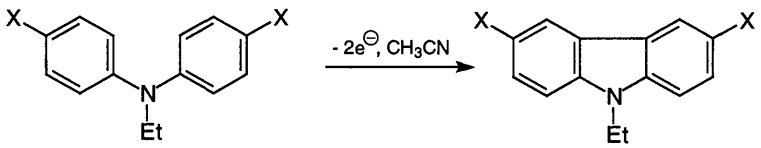
Scheme 5

The reaction of *p*-mono- and *p*-disubstituted diphenylamines has carefully been studied by Serve [59–64]. In acetonitrile medium, *p*-monosubstituted diphenylamines may form the following products: *N,N′*-diarylbenzidines via aryl,aryl-coupling of the cation radicals (pathway a); 5,10-diaryl-5,10-dihydrophenazines and *N,N,N′*-triaryl-*p*-phenylenediamines via *N*,aryl-coupling of a diarylnitrenium ion with the neutral substrate (pathway c) [61]; or tetraarylhydrazines via *N,N*-coupling of the aminyl radicals (pathway b) [60]. The last two compounds are only observed in basic media. *p,p′*-Disubstituted diphenylamines form quite stable cation radicals during anodic oxidation in acetonitrile under neutral conditions, while in the presence of pyridine-like bases the formation of diaryldihydrophenazine compounds (pathway c) is favored. In the presence of stronger bases, tetraarylhydrazines are generated [62–64]. The cyclization to the phenazine has also been studied by Nelson [65], who identified the *o*-phenylenediamine as intermediate.

Aromatic substitution reactions are also possible with diphenylamines (pathway d). In methanol solution containing sodium cyanide, diphenylamine is electrolyzed giving 4-

cyanodiphenylamine in 61% yield [66]. Similarly, a number of other substituted diphenylamines have been cyanated [66]. In methanol containing methoxide, diphenylamine could be methoxylated in *o*- or *p*-position only in low yield [67]. In the presence of water, *p,p'*-disubstituted diphenylamines containing at least one *p*-methoxy or *p*-hydroxy substituent are oxidized to the *p*-benzoquinoneimine [62,63,68]. By anodic oxidation of polysubstituted diphenylamines in acetonitrile containing TEACN, cyanated *N*-aryl-cyclohexadieneimines are obtained [63,69].

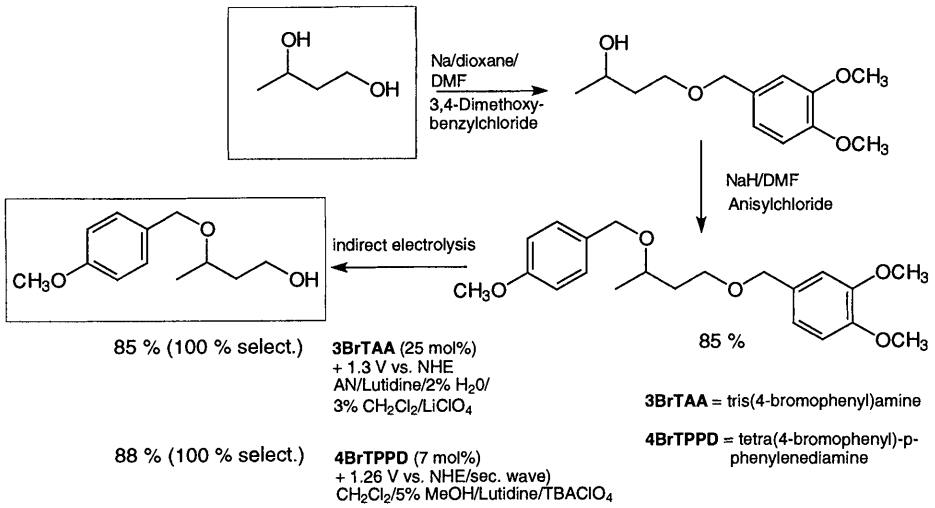
Tertiary diphenylamines like *N*-ethyl-di-*p*-substituted diphenylamines can be cyclized anodically in acetonitrile to give the corresponding carbazoles. This reaction occurs via the intermediate dication of the diphenylamine [Eq. (11)] [70]. In other cases, stable radical cations can be observed [61].



(11)

C. Triarylamines

The electrochemical oxidation of triphenylamines has been studied in detail [71–73]. With partially *p*-substituted compounds, tetraphenylbenzidines are generated. If all *p*-positions are blocked, very stable cation radicals are formed in acetonitrile and sometimes even in nucleophilic media. If the oxidation is performed to the dication stage, cyclization to the carbazoles is observed like in the case of *N*-alkyl-*p,p'*-disubstituted diphenylamines [70]. As the cation radicals of *p*-substituted triaryl amines are very stable toward the attack of nucleophiles, they can be applied as organic redox catalysts for many indirect electrochemical oxidations (see Chapter 29). This was first demonstrated in the oxidation of cyanide ions by electrogenerated trianisylamine cation radicals [74]. The advantage of triarylamines as mediators is the possibility to vary their oxidation potentials over a wide range by proper selection of the *ortho* and *para* substituents. Now about 40 different tri-*p*-substituted triarylamines covering a potential range from about 0.8 to 2.0 V (vs. NHE) are known [72,75–78]. In numerous cases they have been applied as mild and often highly selective oxidizing agents, either in stoichiometric amounts as stable radical cation salts or in catalytic amounts with electrochemical generation and in situ regeneration (redox catalysis; indirect electrolysis; see Chapter 29) [75,76]. These include deprotection of alcohols [79] [Eq. (12)] and carboxylic acids [80] from the substituted benzyl ethers and esters, cleavage of carbon–sulfur bonds [81] in dithioacetals, benzyl- and *p*-methoxybenzyl thioethers, thiol esters, *S*-glycosides, and in monofluro-desulfurizations [Eq. (13)], transformation of *o*-nitrophenylsulfenamides into their corresponding sulfenimines [82], side-chain oxidations of alkyl aromatic compounds [83], benzyl alcohol oxidations [84], α-methoxylations of aliphatic ethers and acetals [85], allylic oxidation of olefins [86], amine oxidations [87], α-oxidation of ketones via their enols [88], oxidation of azomethine derivatives for the formation of *N*-heterocycles [89], and disengagement of organic ligands from their iron carbonyl complexes [90]. Typical examples are given in Eqs. (12) and (13).



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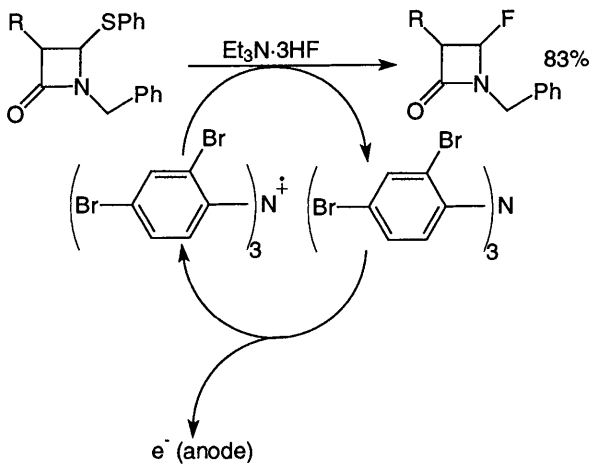
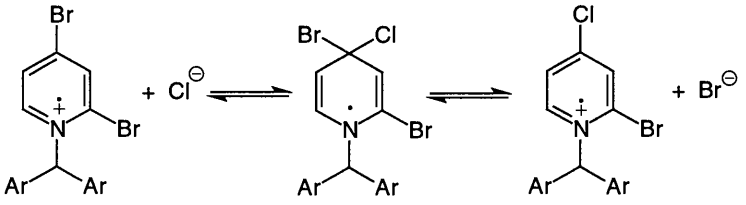


(13)

Polyelectrolytes and soluble polymers containing triarylamine monomers have been applied successfully for the indirect electrochemical oxidation of benzylic alcohols to the benzaldehydes. With the triarylamine polyelectrolyte systems, no additional supporting electrolyte was necessary [91]. Polymer-coated electrodes containing triarylamine redox centers have also been generated either by coating of the electrode with poly(4-vinyltriarylamine) films [92], or by electrochemical polymerization of 4-vinyl- or 4-(1-hydroxyethyl) triarylamines [93], or pyrrol- or aniline-linked triarylamines [94]. Triarylamine radical cations are also suitable to induce pericyclic reactions via olefin radical cations in the form of an electron-transfer chain reaction. These include radical cation cycloadditions [95], dioxetane [96] and endoperoxide formation [97], and cycloreversion reactions [98].

The stability of the triarylamine cation radicals in redox catalytic reactions strongly depends on their substitution pattern, the reaction medium, and also on the overall rate of the catalytic reaction. If the catalytic cycle is slow, higher stationary concentrations of the cation radicals are favoring side reactions. For example 4-bromo- and 4-iodo-substituted cation radicals can undergo 4,4′-coupling under loss of the halo substituents, leading to

the benzidine cation radical or dication, respectively [99]. This type of debromodimerization has been observed with tris(4-bromophenyl)amine in acetonitrile at 0°C [100]. Similarly, tris(2,4-dibromophenyl)amine undergoes successive slow exchange of the *p*-bromo against *p*-chloro substituents, if it is oxidized in methanol/dichloromethane in an undivided cell. This reaction may proceed as a nucleophilic ipso substitution in the *para*-position of the cation radical [78], in which the cathodically formed Cl^- (by reduction of CH_2Cl_2) acts as the nucleophile:



(14)

In the absence of dichloromethane, the radical cations of tris(2,4-dibromophenyl)-amine can undergo several thousand turnovers without considerable loss of material. This is different in the case of tris(4-bromophenyl)amine, which was found to form (2-methoxy-4-bromophenyl)-bis(4-bromophenyl)amine by anodic nuclear substitution, if used in pure methanol [78]. In the presence of acetate, the corresponding acetoxy compound has been isolated [100]. It is interesting to note that in the case of bromosubstituted triphenylamines, the electronic and steric effects of the *o*- and *p*-substituents could be discriminated by voltammetric studies. In addition, a linear relationship between the redox potentials of these amines and the long-wavelength ultraviolet–visible (UV/VIS) absorbance maxima of the cation radicals is observed [77]. The correlation of the long-wavelength absorbance maxima of a large variety of *p*-substituted triarylamines with the Hammett σ constants was unsuccessful and was called "non-Hammett-behaviour" by Walter [101]. A very good linear relationship is, however, obtained, if the redox potentials of the *p*-substituted triarylamines are correlated with σ/σ^+ values (for electron-donating groups, σ^+ values have to be used). To obtain a value for the reaction constant ρ, the redox potentials have to be converted into a ratio of equilibrium constants. This has been done by using the following equation, which was derived from the Nernst equation:

$$\log(K/K_0) = (1/0.059)(E^\circ - E) = \sigma\rho$$

As a standard, triphenylamine with $E^\circ = 1.17\,V$ was used. In this way, for ρ a value of -11.28 with a correlation coefficient of 0.993 was obtained [78]. The strongly negative value of ρ demonstrates the high sensitivity of the cation radicals toward the electronic effects of the *p*-substituents.

Voltammetric studies of macrobicyclic host molecules bearing triphenylamine units as trifunctional spacers demonstrate the influence of steric hinderance and strain upon the redox potentials [102,103].

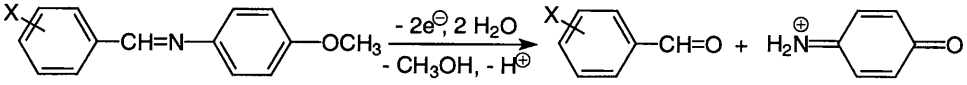
It should be noted here for triarylamine networks and dendrimers [104], respectively, the radical cations have interesting properties like the formation of high-spin polyradicals with ferromagnetic coupling [105] or conducting polymers [106]. Very often, triarylamines have been used as the hole-transport layer in electroluminescent devices [107].

D. Phenylenediamines

The anodic oxidation of phenylenediamines parallels that of aminophenols (see Sec. III.A.1) and has been reviewed by Adams [108]. If unsubstituted at the nitrogens, the two-electron oxidation leads to the quinone dimine. This compound either undergoes hydrolysis to the quinone imine and benzoquinone, or a 1,4-addition of a nucleophile, for example, the parent phenylenediamine itself, to the quinoidal systems occurs. Further oxidation of the products may take place. In acetonitrile, the one-electron oxidation to the cation radical predominates [109]. Under these conditions, *p*-phenylenediamine also leads to 1,4-coupling products [110,111]. *N*-Substituted phenylenediamines are forming more stable cation radicals. For example, tetrakis(*p*-bromophenyl)*p*-phenylenediamine ($E^\circ = 0.91$ V vs. NHE) and tetrakis(2,4-dibromophenyl)-*p*-phenylenediamine ($E^\circ = 0.94$ V vs. NHE) in acetonitrile even show reversible behavior for the second oxidation step to the dication [78].

IV. COMPOUNDS WITH C=N DOUBLE BOND: IMINES, OXIMES, HYDRAZONES, SEMICARBAZONES, FORMAZANES, AMIDINES, AND KETIMINES

In the anodic oxidation of imines, usually addition of a nucleophile to the carbon of the C=N double bond takes place. If the nucleophile is water, hydrolytic cleavage will occur. For example, controlled-potential oxidation of *N*-benzylidene-*p*-anisidines in acetonitrile at the first voltammetric wave yielded the protonated anisidine. At the second wave, benzaldehyde and protonated *p*-benzoquinone imine are formed by attack of residual water as nucleophile [112] [Eq. (15)].

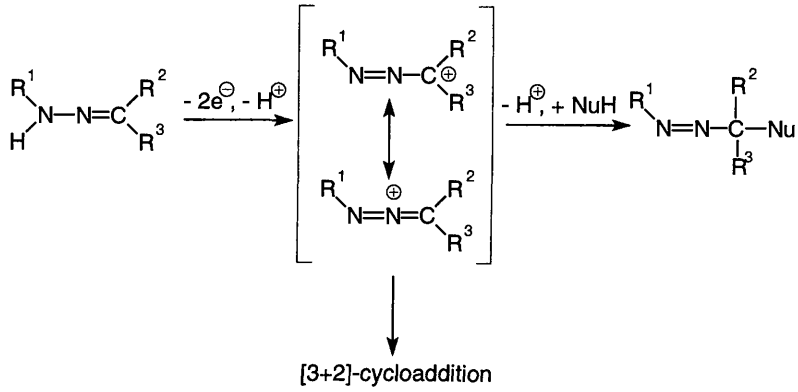


(15)

Instead, in the presence of pyridine the oxidation at the first wave resulted in the pyridination not at the α-carbon but in the *ortho*-position of the aromatic ring, which is followed by a second electron transfer and a deprotonation under rearomatization [113, 114].

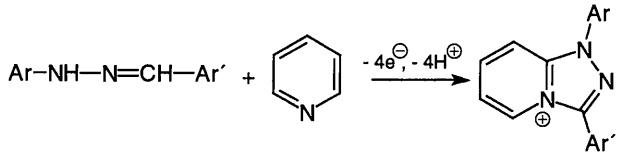
The formation of *N*-formyl-(*N*-methoxymethyl)-phenylalkyl amines during the anodic oxidation of primary phenylalkyl amines in methanol/KOH is explained by the intermediate generation of imines, which are further oxidized under addition of methanol. By anodic co-oxidation of methanol, formaldehyde and formic acid are formed. Formaldehyde is reacting with the amine under generation of the imine, while formic acid introduces the formyl group into the product [115]. If aldehydes are oxidized by an indirect process using catalytic amounts of KI in an NH_3–NaOMe–MeOH–KI medium, nitriles (50–90%) are formed via the intermediate aldimines [116]. To suppress methyl ester formation, high concentrations of ammonia are necessary. Under similar conditions, ketones afford 2,2-dialkyl-2,5-dihydro-1*H*-imidazoles via an oxidative cyclocoupling of the ketenimine intermediates [17].

As in the case of imines, during the oxidation of arylhydrazones nucleophilic attack occurs at the α-carbon [Eq. (16)]. If the nucleophile is water, and R^1 is an aryl substituent, cleavage under formation of the parent ketone, nitrogen, and ArH is observed [118].



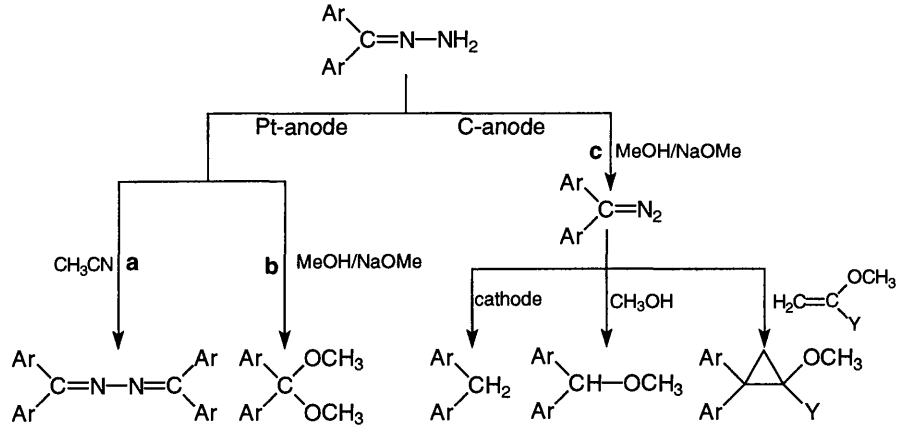
(16)

The intermediate 1-aza-2-azoniallene cations can undergo 1,3-dipolar cycloaddition reactions with inverse electron demand [119]. Thus, oxidation of a *N*-phenyl hydrazone in the presence of pyridine leads to the formation of a *s*-triazolo[4,3-a]-pyridinium salt by attack of pyridine as a nucleophile on the intermediate nitrilimine [Eq. (17)] [120]. Other examples are reported by Jugelt [121].



(17)

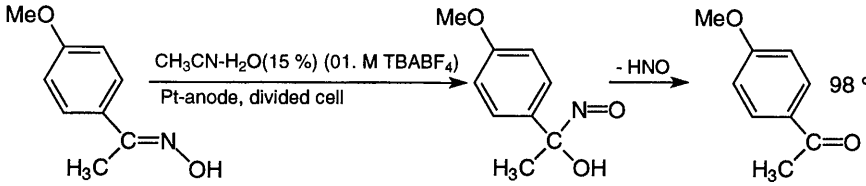
At platinum anodes and under aprotic conditions (CH_3CN–$LiClO_4$), benzophenone hydrazones afford exclusively benzophenone azines (Scheme 6, **a**), while in MeOH/NaOMe benzophenone dimethyl acetals are formed (Scheme 6, **b**). At graphite anodes (MeOH/NaOMe), diphenyldiazomethane is formed as an intermediate [122] (Scheme 6, **c**).



Scheme 6

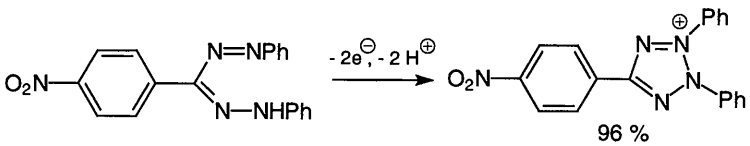
Cleavage of oximes to the parent carbonyl compound may be performed under mild conditions by anodic oxidation in CH_3CN/H_2O [123]. Thus, anodic oxidation of 4-substituted acetophenone oximes in wet acetonitrile furnishes the corresponding acetophenones in high yields, while the oxidation of benzaldoximes is unselective [124] [Eq. (18)]. By indirect electrochemical oxidation using the Mn(II)/Mn(III) mediator system in the

presence of benzyltriethylammonium chloride as a phase-transfer catalyst, aldoximes are cleaved to give the aldehydes in good yields [125].

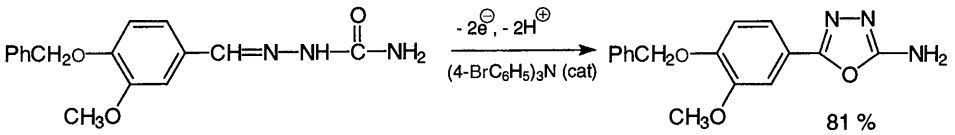


(18)

Anodic oxidation of azomethine, hydrazone, oxime, formazane, and semicarbazone structures has been used to initiate the intramolecular cyclization [119] under formation of heterocycles like triazoles [126,127], oxadiazoles [128,129], triazolinones [129], benzoxazoles [130,131], benzimidazoles [130,131], pyrazoles [132], indazoles [133], furoxanes [134], and tetrazolium salts [135] (see Chapter 18). Some of these reactions can be performed advantageously by indirect electrolysis using tris(4-bromophenyl)amin or 2,3-dihydro-2,2-dimethylphenothiazine-6(1*H*)-one as mediators [119,136]. Two examples are given in Eqs. (19) and (20).

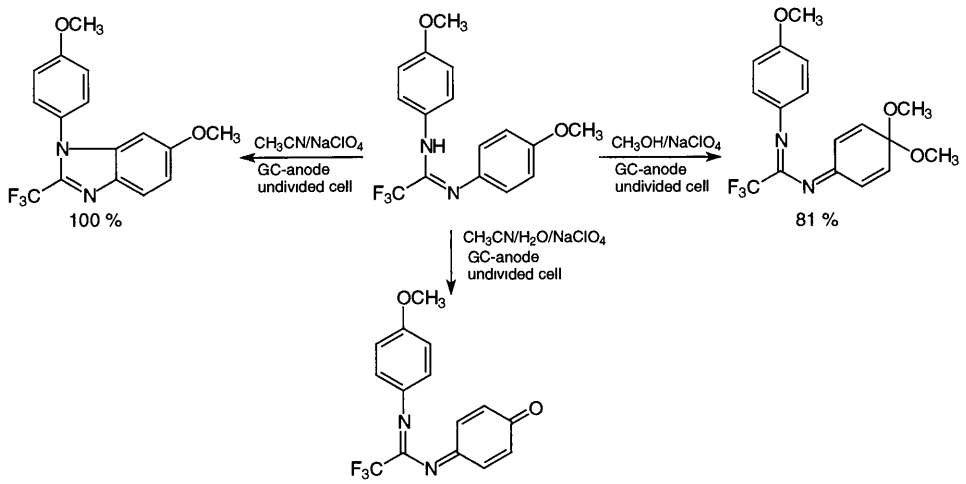


(19)



(20)

Trifluoroethanimidamines (amidines) undergo a two-electron electrochemical oxidation leading either to 2-trifluoromethyl benzimidazoles via intramolecular nucleophilic substitution or to *p*-benzoquinone imine derivatives by external nucleophilic addition depending on the reaction conditions [Eq. (21)] [137]. Another study of the indirect electrochemical amidine oxidation has been published by Lessard [138].

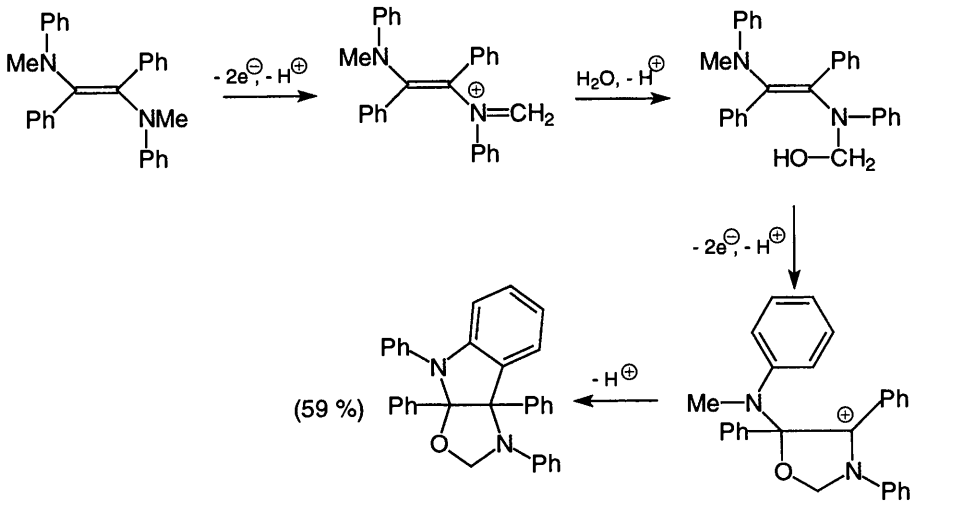


(21)

Becker, who intensively studied the anodic oxidation of heteroallenes, showed that electrooxidation of aryl-substituted ketene imines leads to mono- and multiannulated heterocyclic dimers [139].

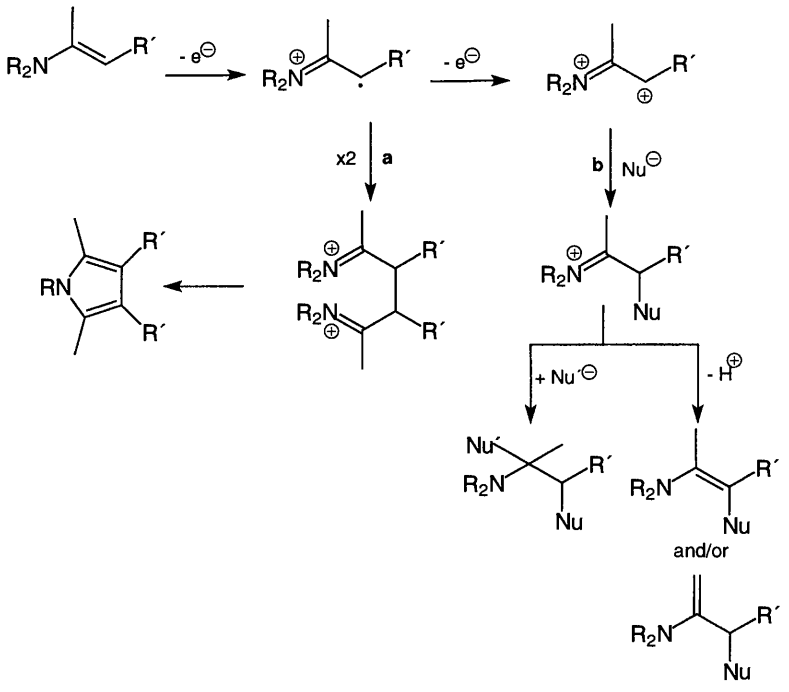
V. COMPOUNDS WITH C=C DOUBLE BOND: ENAMINES, ENAMINOESTERS AND KETONES, ENAMIDES, AND ENECARBAMATES

The anodic behavior of *N*-substituted alkenes can be described as the oxidation of an electron-rich double bond. Tetraamino-substituted alkenes are extremely easily oxidized. Tetrakis(dimethylamino)ethylene exhibits two reversible one-electron processes at −0.75 and −0.61 V vs. SCE at a dropping mercury electrode in acetonitrile [140]. The anodic behavior of *N,N*-dimethylaminoalkenes has been studied intensively by cyclic voltammetry and electron spin resonance (ESR) spectroscopy [141]. The anodically ($E^{\circ'} = 0.48$ V vs. SCE) generated cation radical of 1,1-bis(*N,N*-dimethylamino)ethylene is shown to undergo C–C coupling, forming 1,1,4,4-tetrakis(*N,N*-dimethylamino)butadiene, which subsequently is further oxidized to its dication at −0.8 V [141,142]. With vicinal diamino ethylenes, usually two reversible one-electron oxidations are observed [143], while geminal diamino ethylenes exhibit an irreversible behavior [141]. Aryl-substituted vicinal diamino ethylenes (endiamines) can undergo a double cyclization to give an indolooxazoline when oxidized at 0.4 V vs. SCE in acetonitrile in the presence of 2,6-lutidine [144]:



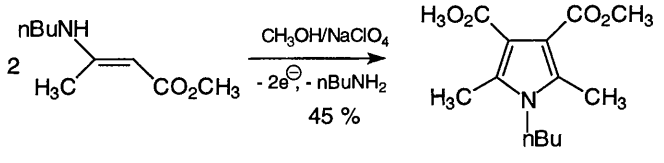
(22)

Generally, enamines, enamino esters and ketones, enamides and enecarbamates can give the following products after anodic oxidation (Scheme 7):

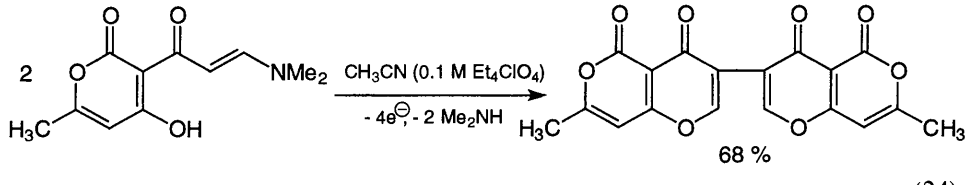


Scheme 7

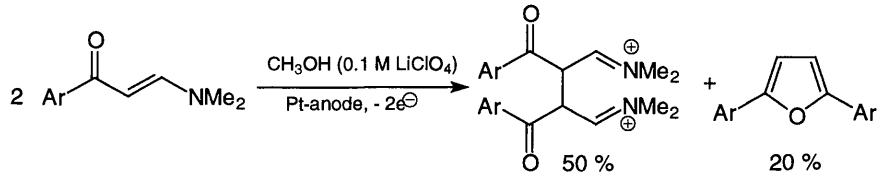
1. The primarily formed radical cation can undergo dimerization (path **a**), which very often is followed by intramolecular cyclization via an amino group to give symmetrically substituted pyrrols [Eq. (23)] [145]. In other cases, cyclization takes place via oxygen functions leading to bischromones [Eq. (24)] [146] or to furans [Eq. (25)] [147].



(23)



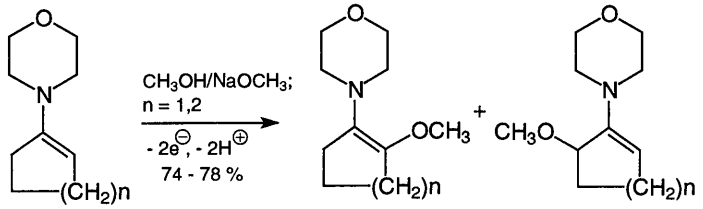
(24)



(25)

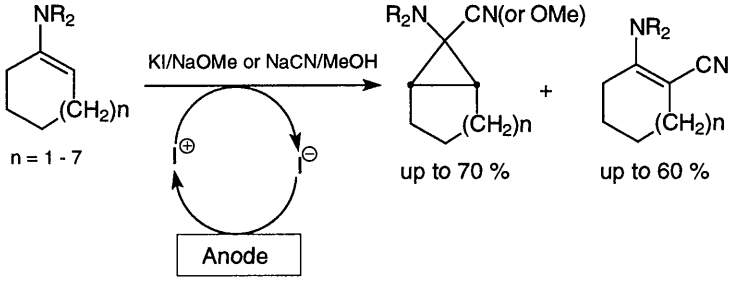
In the case of 2-cyano-2-phenylvinylamines, coupling is also observed. Here it takes place between the phenyl ring in *para*-position to the enamino group and C-2 of the enamine, leading to diphenylmethane derivatives [148]. Dimerization or trimerization takes place, too, with 2-phenyl- or 2-cyano-substituted *N*-methyl-*N*-phenyl-1,2-diphenylvinylamines by coupling between the *p*-positions of the *N*-phenyl and 2-phenyl substituents. The reaction strongly depends on the medium and the base [149,150]. It can be assumed that the primary radical cation attacks the nucleophilic aromatic system as an electrophile according to pathway **b** in Scheme 7. A similar coupling has been observed in the anodic oxidation of the β-anilinoacrylic alkaloid tabersonine to give stereoselectively a 16,10′-didehydro dimer [151].

2. The other possibility is the nucleophilic substitution or addition to the radical cation or the dication (path **b**) in the presence of external or internal nucleophiles. Thus, electrochemical oxidation of morpholino cycloalkenes in methanol/methoxide leads to the formation of a compound with an allyl or vinyl methoxy substituent [Eq. (26)] [152].



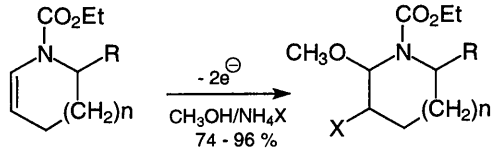
(26)

Similarly, carbanions from 1,3-dicarbonyl compounds can act as nucleophiles [153]. In a somewhat related reaction, enamines of cyclohexanone or cycloheptanone are oxidized in an iodide-mediated indirect electrochemical process leading to a Favorskii-type rearrangement. Thus, bicyclo[(n − 1).1.0] systems containing a nucleophile like a cyano or a methoxy function are formed [Eq. (27)] [154].



(27)

Addition to the double bond of enecarbamates is observed during anodic oxidation in methanol in presence of an ammonium halide, leading to the product of halomethoxylation [Eq. (28)] [155]. The enecarbamates are available through electrochemical α-methoxylation of the carbamate followed by methanol elimination (see Sec. VIII.B).

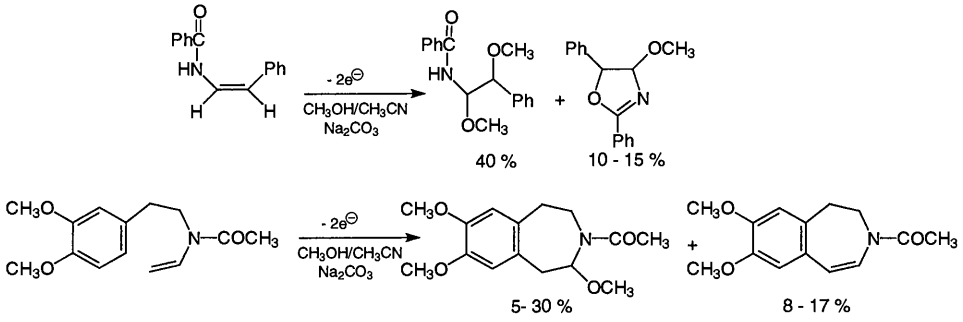


(28)

By electrochemical oxidation of enamines, in situ prepared from an aldehyde and a secondary amine, using KI as mediator system, β-ketoamines were formed in 30 to

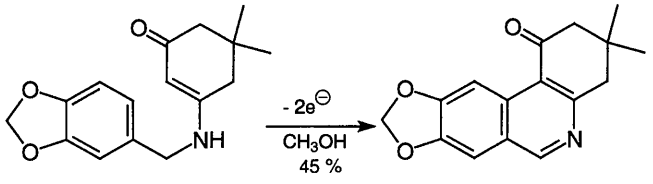
60% yield [156]. The reaction is explained by the formation of a iodohydrine as intermediate.

Anodic oxidation of an *N*-benzoylated enamine in acetonitrile/methanol/Na_2CO_3 leads not only to the formation of the dimethoxylated starting material but also to a methoxy-substituted oxazoline through intramolecular nucleophilic attack of the benzoyl oxygen [157]. In another case, an electron-rich aromatic system can act as a nucleophile in an intramolecular cyclization with the enamine radical cation or dication [Eq. (29)] [157].



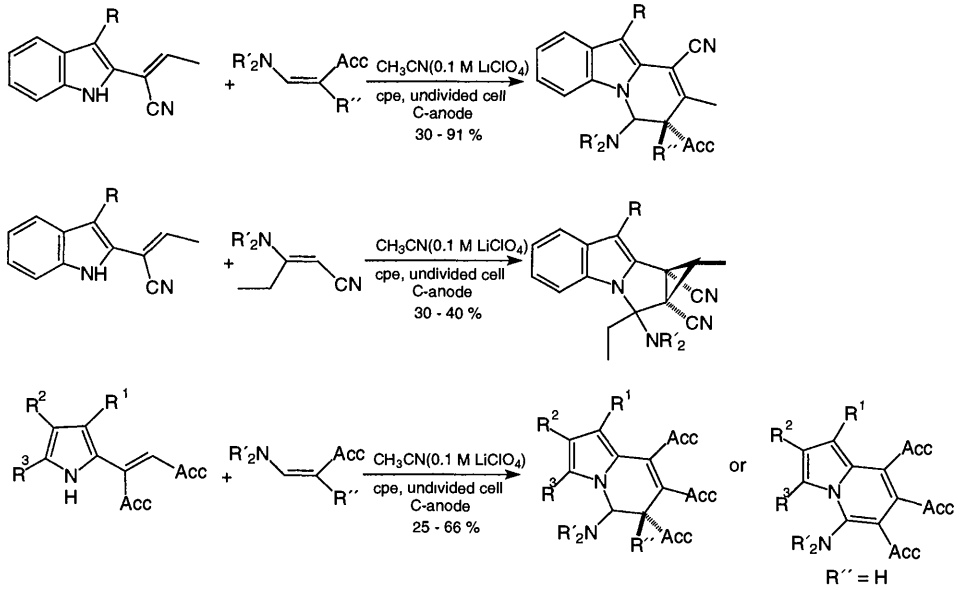
(29)

Intramolecular cyclization is a general reaction in the anodic oxidation of substituted amino alkenes. Thus, the already mentioned *N*-methyl-*N*-phenyl-1,2,2-triphenylvinylamine leads to a new 3*H*-indole by anodic oxidation in the presence of 2,6-lutidine [149,150]. The corresponding enediamine undergoes an electrolytic double cyclization to form an indolooxazolidine [149]. The formation of isoquinolines, benzazepines, and tetrahydrocarbazoles may also be obtained by anodically initiated intramolecular cyclization of *N*-benzyl, *N*-β-phenethyl, and anilino enaminones [Eq. (30)] [158].



(30)

Enaminoesters, -ketones, and -nitriles have also successfully been applied in electrochemically induced radical cation cycloaddition reactions, especially with 2-vinylindoles or 2-vinylpyrroles. Some examples are given in Eq. (31). Depending on the structures, the reaction starts with the formation of either the vinylindole or vinylpyrrole radical cation or the radical cation of the enamidoester, -ketone, or -nitrile. In Eq. (32), a representative reaction pathway for the cycloaddition between a 2-vinylpyrrole and an acceptor-substituted enamine is formulated via the enamine radical cation [159].



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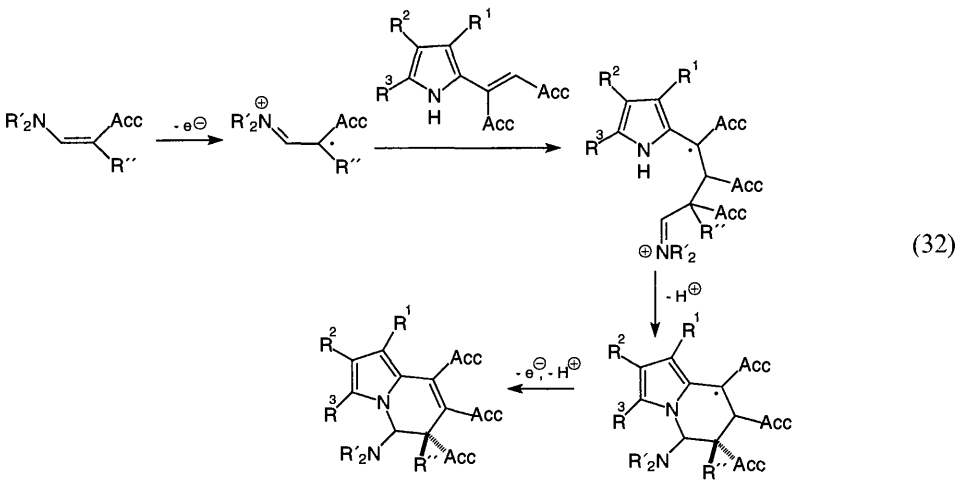


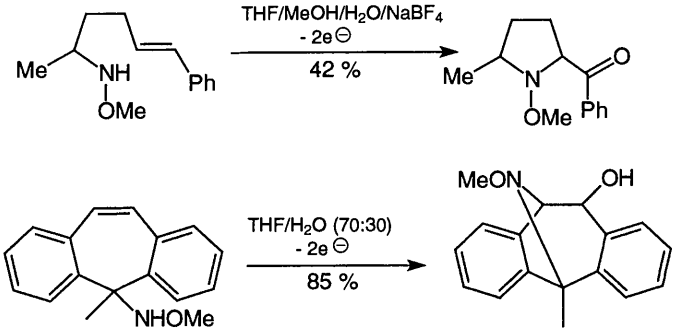
(32)

VI. *N*-HETEROSUBSTITUTED COMPOUNDS

Aromatic hydroxylamines are easily electrochemically oxidized to the nitroso compounds, which subsequently may combine with the starting material to give azoxy compounds [160]. Benzylhydroxylamines are anodically transformed to the oximes in good yields because of the facile deprotonation in benzylic position [161]. Electrolysis of methylhydroxylamine leads to the formation of the corresponding oxime and azoxymethane via the intermediate nitroso compound [162]. *N*,*N*-Disubstituted hydroxylamines may be oxidized to the corresponding nitroxides [163]. An interesting acylation and ethylaminocarbonylation reaction of amines and alcohols is observed, if benzo- or acetohydroxamic

acids or *N*-ethyl-hydroxyurea is electrochemically oxidized in acetonitrile in presence of nucleophiles [164].

Similar to hydroxylamines, alkoxyamines may be oxidized to the nitroso compounds under loss of the alkyl group [165]. Radical cations or radicals obtained from *N*-alkoxyamines may undergo intramolecular cyclization to double bonds like in pentenyl-alkoxyamines [26] or in 5-methoxyamino-5-methyl dibenzocycloheptene [166] [Eq. (33)].

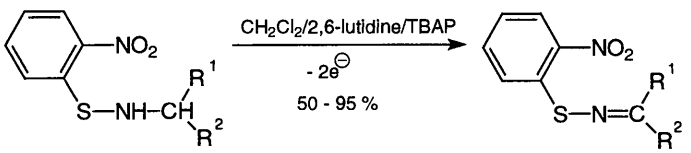


(33)

N-Alkoxycarbamates form dimers by *N*,*N*-coupling, if anodically oxidized in acetonitrile in the presence of collidine [167].

The electrochemical oxidation of *N*-nitrosodialkylamines leads to the formation of the corresponding nitramines together with β-ketonitrosamines, in which the carbonyl oxygen results from dissolved O_2 [168].

The anodic oxidation of 2-nitrophenylsulfenamides, which are easily obtained by the reaction of amines or amino acid esters with 2-nitrophenylsulfenyl chloride, to form the corresponding 2-nitrophenylsulfenimines, can be realized either by direct or indirect electrochemical methods. In most cases the direct electrochemical method is preferred because of the convenient reaction procedure and the simple workup [Eq. (34)] [82,169].



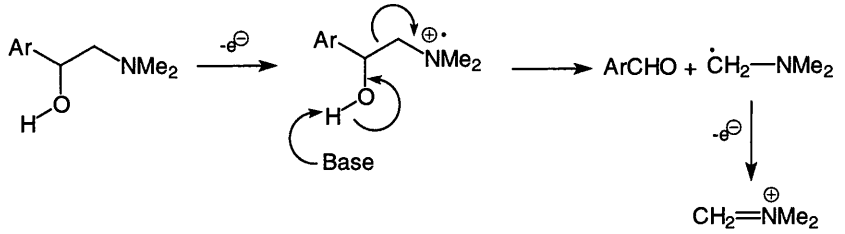
(34)

In the case of the double NPS-protected lysine methyl ester, oxidation selectively takes place at the ε-sulfenamide function under spontaneous cyclization via the α-sulphenamido group as nucleophile. Only one diastereoisomer of the *N*,*N*′-bis(NPS)-protected methyl 6-amino-piperidine-2-yl-carboxylate seems to be formed. The transformation of α-amino alkanoates and diaryl or dialkyl disulfides to the aryl- or alkylsulfenimine derivatives can be performed electrochemically using $MgBr_2$ as a mediator system. This reaction can either proceed in one step or starting from the corresponding sulfenamide [170].

The anodic oxidation of hydrazine derivatives has not been used synthetically to a larger extent due to the decomposition of the intermediates that are most often observed. Thus, 1,1-dimethyl hydrazine undergoes an electrooxidative dimerization to the 1,1,4,4-tetramethyl tetrazane, which decomposes to give nitrogen and dimethylamine. 1,2-Dimethyl hydrazine is oxidized to give nitrogen, ethene, and methylamine [171]. Starting from 1-acyl-2,2-dimethyl hydrazine, the stable 2,3-diacyl-1,1,4,4-tetramethyl tetrazane is formed [172]. The relatively stable radical cations of tetraalkyl hydrazines were intensively studied by Nelsen et al. [173].

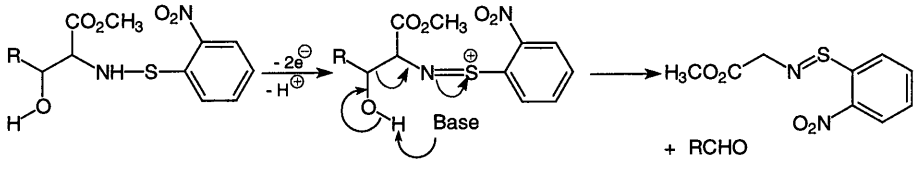
VII. AMINO ALCOHOLS AND AMINO ACIDS

Amino alcohols may either be oxidized at the hydroxy or the amino function. Oxidation at the hydroxy function will lead to the amino acid. This reaction can be performed at lead dioxide or platinum anodes in aqueous sulfuric acids with moderate material and current yields [174]. In the case of the oxidation of 3-phenyl-2-*N*-acetylaminopropanol to acetylphenylalanine, an indirect electrochemical ex-cell process was proposed using anodically generated $Cr_2O_7^{2-}$ as reagent [175]. Oxidation under basic or neutral conditions usually starts at the nitrogen atom. *β*-Amino alcohols, similar to 1,2-diols and 1,2-diamino compounds, undergo cleavage to aldehydes or ketones. Thus, 1-(*N*,*N*-dimethylaminomethyl)-*p*-methoxybenzyl alcohol is oxidized in acetonitrile to yield *p*-methoxybenzaldehyde, dimethylamine, and formaldehyde [Eq. (35)] [176] or ephedrine is decomposed in an aqueous buffer of pH 10 mainly to benzaldehyde, acetaldehyde, and *N*-methylamine [177]. Other *β*-alkanolamines behave similarly [178,179]. These reactions are explained by a fragmentation of the primarily formed amino cation radical into the aldehyde or ketone and, after further oxidation, an iminium ion, which subsequently hydrolyzes to aldehyde and amine.



(35)

Moeller et al. attempted an electrochemically initiated intramolecular cyclization of the protected dipeptide Boc–Ser–Pro–OME between the intermediate *N*-acyliminium ion of the proline subunit and the hydroxy group of the serine side chain. However, using methanol as solvent they found predominant elimination of formaldehyde under cleavage of the serine side-chain followed by methoxylation of the thus obtained *N*-acyliminium ion of the serine subunit. In acetonitrile as solvent, the cleavage reaction could be minimized yielding the cyclized product in 25% yield [180]. In a very similar manner [Eq. (36)], the *o*-NPS derivatives of serine and threonine are fragmented under loss of formaldehyde or acetaldehyde to give the *ortho*-nitrophenyl sulfenimine of glycine methyl carboxylate [82,169].



(36)

Anodic oxidation of *N*-benzyl-*N*-methylethanolamine leads to the formation of a mixture of 3-methyl-2-phenyl- and 3-benzyloxazolidine by intramolecular attack of the hydroxy group at the intermediate iminium ion, mainly in the benzylic position [181]. The typical fragmentation of *β*-amino alcohols occurs as a side reaction, in this case giving formaldehyde and *N*-benzyl-*N*-methoxymethyl-*N*-methyl amine. The direct anodic oxida-

tion of 2-amino-1-cycloalkanols using NaCl as redox catalyst in aqueous acetonitrile leads to the formation of ω-keto nitriles (50–60%) under cleavage of the C–C bond. The β-hydroxy-*N*-chloroamine is supposed to be the intermediate [32].

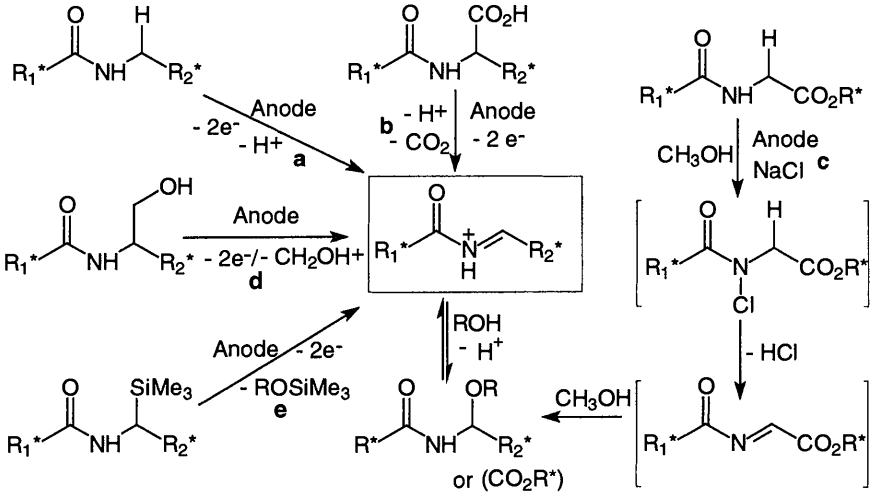
The electrochemistry of amino acids has been studied in strong acid solutions. In general, the compounds are decomposed to carboxylic acids, aldehydes, ammonia, and carbon dioxide. The results are reviewed by Weinberg [35]. The anodic oxidation mechanism has been studied in pH 10 buffer solution. Decarboxylation accompanied by C–N bond cleavage is the main reaction process [182]. The synthetically interesting Hofer–Moest decarboxylations of *N*-protected amino acids and α-amino malonic half esters under the formation of *N*-acyliminium ions is treated in the following section.

VIII. AMIDES, CARBAMATES, LACTAMS, *N*-ACYLATED AMINO ACIDS OR ESTERS, AND RELATED COMPOUNDS

The anodic oxidation of amides, lactams, carbamates, and *N*-acylated amino acids is of considerable synthetic value because in contrast to aliphatic amines, the *N,O*-acetals formed by α-oxidation are quite stable precursors of *N*-acyliminium ions and can be used effectively in amidoalkylation reactions [183–186]. Electrochemical oxidation can be considered to be the most flexible way for the synthesis of *N*-acyliminium ions. The application of this reaction sequence has been used intensively during the past several years, but the anodic oxidation of amides and carbamates has been known for a much longer time. As early as 1954, electrooxidation of a number of amides and lactams was studied by Mizuno in acidic aqueous media [187]. Under these conditions, dealkylation by scission of the carbon–nitrogen bond is observed leading to carboxylic acids, amino acids, ketones, and imides. O'Donnell and Mann [188] investigated the cyclic voltammetry of a number of aliphatic amides in acetonitrile. Electrode potentials of about 2.0 V for primary amides, 1.8 V for secondary amides, and 1.2 to 1.5 V (vs. SCE) for tertiary amides were found. In all cases, a one-electron oxidation occurs. Finckelstein and Ross and colleagues [189–192], and later Nyberg and Eberson and colleagues [193–196], Shono [183], Callens [197], Steckhan [198–202], Wistrand [203], Lhommet [204], and others, showed that in the presence of alcohols, acetic acid, or formic acid, the anodic oxidation of *N*-alkyl- and *N,N*-dialkylamides and carbamates, urethanes, urea derivatives, and *N*-acyl- and *N*-carbamoylamino acid esters leads to stable α-alkoxylated and α-acyloxylated products as precursors for amidoalkylation reactions with a large variety of nucleophiles. Moeller [205] used this strategy intensively for the intramolecular cyclization of a variety of nucleophilic functions toward the intermediate *N*-acyliminium ion for the formation of conformationally restricted peptide mimetics.

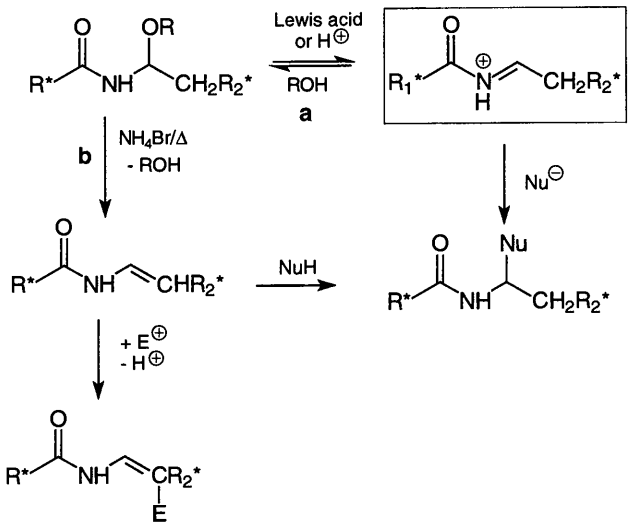
In Scheme 8, five possible electrochemical pathways for the formation of *N*-acyliminium ions are represented. Pathway **a** (see Sec. VIII.A) describes the direct anodic oxidation of amides and carbamates to the intermediated *N*-acylium ions via removal of one electron from the nitrogen lone pair followed by deprotonation in α-position of the nitrogen atom and further one-electron oxidation. In pathway **b** (see Sec. VIII.C), a decarboxylative methoxylation of an *N*-acylated amino acid (Hofer–Moset reaction) leads to the same intermediate. The radical that is formed after anodic decarboxylation is immediately further oxidized to the cation due to the electron donation of the nitrogen. Pathway **c** (see Sec. VIII.B) describes the anodic oxidation of an *N*-acylated amino

acid ester under conservation of the ester function. This process is only possible under the conditions of an indirect electrochemical oxidation using sodium chloride as the mediator. Methyl hypochlorite, which is formed as the reactive intermediate, generates the *N*-chloro compound. HCl elimination leads to the intermediate *N*-acylimino acid ester. Additionally, as described before (see Sec. VII), an *N*-acylated *β*-amino alcohol can be cleaved (path **d**) to generate the *N*-acyliminium ion. Anodic oxidation of *α*-silyl- or *α*-thio-substituted carbamates [206] or azetidin-2-ones [207] in methanol, acetic acid, or Et3N · 3HF results in smooth and regioselective cleavage of the C–Si or, respectively, the C–S bond and introduction of the methoxy, acetoxy, or fluoro function at the *α*-carbon in high yields. The silyl or thio group not only lowers the oxidation potential but also controls the regiochemistry of the methoxylation in unsymmetrical carbamates. These intermediates are finally trapped by water, alcohols, or carboxylic acids. If water acts as the nucleophile, the product is unstable and dealkylation occurs with formation of aldehyde and amide.



Scheme 8

Scheme 9 demonstrates the further synthetic application of the thus obtained *N,O*-acetals. Substitution of the alkoxy or acyloxy group by nucleophiles like enol ethers, enol esters, enamines, other electron-rich olefins, CH-acidic compounds, electron-rich aromatics, isocyanides, trimethylsilyl cyanide, organometallics, vinyl and allyl silanes, hydroxy functions, or trialkylphosphites either catalyzed by Lewis acids or proton acids leads to the product of the amidoalkylation reaction (path **a**). In the presence of stereocenters as control elements, diasteroselective amidoalkylation reactions can be performed as shown in a large number of examples. On the other side, as Nyberg showed for the first time [196], elimination with formation of enecarbamates [208] and enamides [196,208,209] followed by reaction with electrophiles or nucleophiles (path **b**) also is possible.

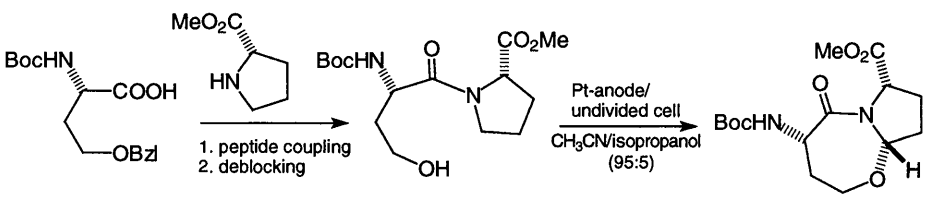


Scheme 9

Intramolecular anodic coupling of diaryl amides is a synthetically interesting reaction that may be applied to the synthesis of alkaloidal structures [210]. However, this aryl coupling is initiated by the oxidation of an aromatic ring (aryl ether or phenol) and not by oxidation of the nitrogen. Therefore, it is not discussed further in this chapter.

A. Anodic Oxidation of Amides, Carbamates, and Lactams

For the electrochemical oxidation of amides, carbamates, and lactams with formation of the *N,O*-acetals as amidoalkylation reagents, countless interesting synthetic applications have been described [183–209], especially in the field of alkaloid synthesis [183,204,211–213], the generation of enantiopure nonproteinogenic amino acids [201,202], the formation of peptido mimetics [205], dichiral β-amino alcohols and 1,2-diamino derivatives and enantiopure aza sugar precursors [198,199], and many more. In many cases, diastereoselective amidoalkylation reactions under control of the configuration of the newly formed stereogenic center by chiral elements in the substrate are described. Moeller [205] used this strategy to synthesize conformationally restricted peptide mimetics via intramolecular cyclization to the intermediate *N*-acyliminium ion, as exemplified in Eqs. (37) and (38).



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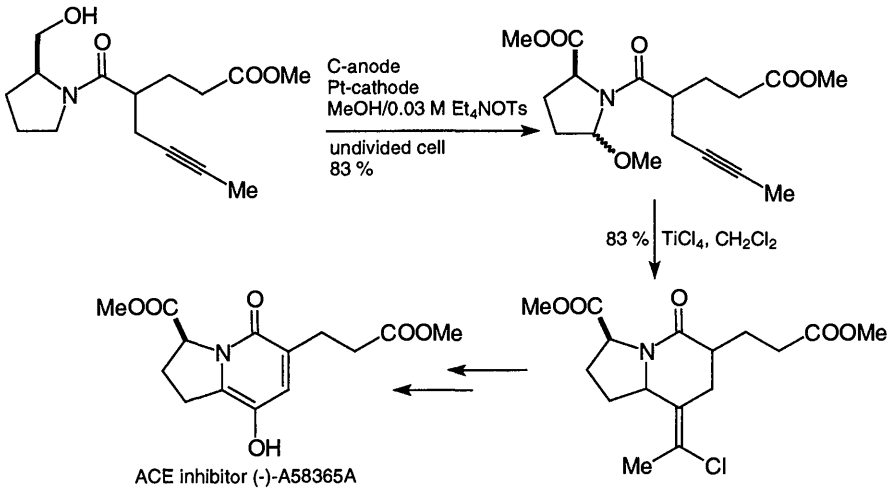
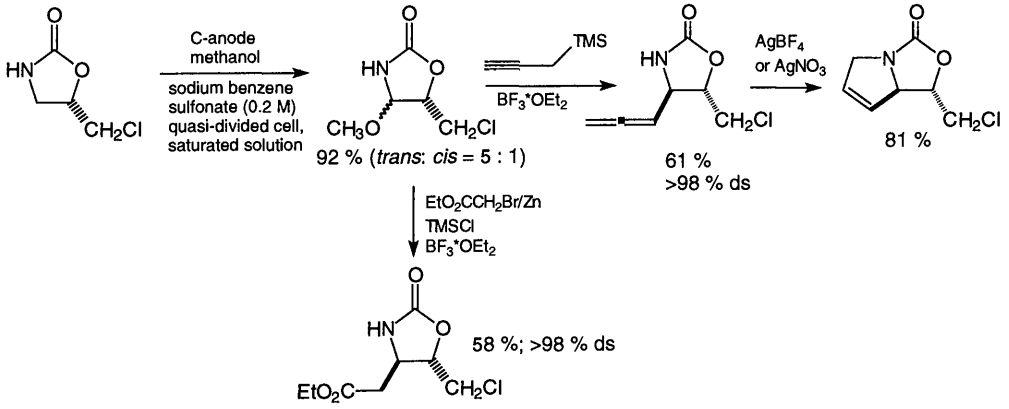


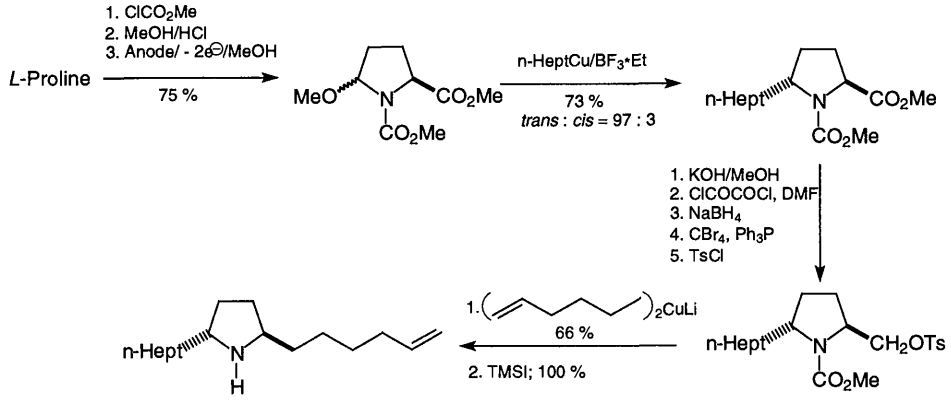
(38)

Enantiopure (5*S*)-5-chloromethyl 1,3-oxazolidinone, which is easily obtained from either malic acid or epichlorohydrine, is efficiently methoxylated in a quasi-divided cell [198]. Follow-up methoxy group exchange under Lewis acid catalysis can be performed with a large variety of silyl nucleophiles or organometallics with very high diastereoselectivity [199]. Also, ring annulation reactions to generate aza sugar precursors are possible [Eq. (39)].



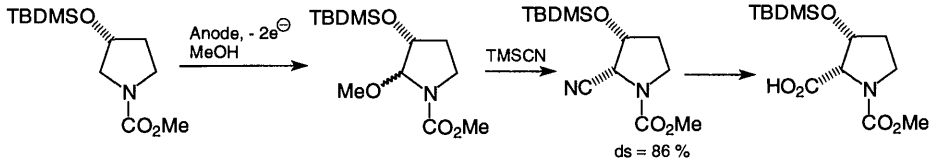
(39)

Wistrand [203] described the highly diastereoselective synthesis of an enantiopure ant pheromone starting from *L*-proline using an organocopper nucleophile in the presence of borontrifluoride for the amidoalkylation reaction as shown in Eq. (40).



(40)

Similarly, Shono studied the diastereoselective introduction of the allyl group into the 5-position of *N*-acylated *L*-proline derivatives by reaction of the *N*,*O*-acetal with allyltrimethylsilane in the presence of titanium tetrachloride [214]. Substitution of the anodically introduced methoxy group by cyanide using trimethylsilyl cyanide [215,216] or an isocyanide [217] as the nucleophile can be used to generate α-amino acids via hydrolysis of the cyano function. Equation (41) shows an example [216].



(41)

Usually the anodic oxidation of amides and carbamates can be performed under constant-current conditions in an undivided cell at platinum or graphite anodes using $R_4N^+BF_4^-$, sodium benzenesulfonate, or KPF_6 as supporting electrolyte. A different and technically important approach is the application of the Solid Polymer Electrolyte (SPE) technology using an ion-exchange membrane, mostly a Nafion cation exchange membrane, as polyelectrolyte in the absence of any supporting electrolyte for the efficient methoxylation of amides [218,219].

Polyalkoxylation of amides is more difficult to obtain than monoalkoxylation. In the case of *N*,*N*-dimethylformamide and *N*-methyl-*N*-methoxymethylformamide, it can be performed in methanol/$TBABF_4$ at Pt anodes [182]. Another example is the 2,5-dimethoxylation of *N*-acetyl pyrrolidine [220] and *N*-methoxycarbonyl pyrrolidine [221]. Bisacetoxylation has also been reported [222].

The methoxylation of *N*-ethyl carboxamides has been studied especially intensively, as the produced *N*-(α-methoxyethyl)amides may be transformed to the technically interesting vinyl amides by methanol elimination [209]. Glassy carbon anodes together with graphite or steel cathodes and tetramethylammonium methyl sulfate as conducting salt proved to be the best conditions. Alternatively, the SPE cell using Nafion as polyelectrolyte is practicable [218,219].

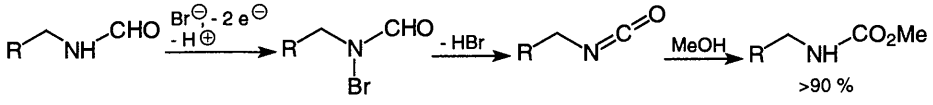
Also, lactams could be hydroxylated [223] or alkoxylated [224,225] in the α-position. In the case of five- and six-membered *N*-alkyl lactams oxidation occurs regioselectively at the endocyclic carbon in α-position to nitrogen and at the exocyclic α-carbon with seven-

membered rings [223]. This procedure has also been applied to intramolecular cyclizations [226].

The anodic oxidation of *N*-alkyl- and *N*-benzyl-β-lactams in methanol at Pt anodes in the presence of Et_4NBF_4 as an electrolyte leads to the methoxylation of both the endo- and exocyclic carbon in α-position to nitrogen. Usually the exocyclic carbon was more easily oxidized than the endocyclic carbon. With a tertiary exocyclic α-carbon, the formation of the endo-oxidation product was increased. *N*-Benzyl-β-lactams were predominantly oxidized in the exocyclic α-position. In case of *N*-4-methoxybenzyl-β-lactam exocyclic oxidation occurred with total regioselectivity [227,228].

Similar to carboxamides, sulfonamides [229,230] and amidophosphates [230] may also be α-methoxylated at the anode. *p*-Tolysulfonamides of primary amines undergo a rearrangement during anodic oxidation in methanol in the presence of KBr and KOH, leading to α-amino aldehydes [231]. Bromide ion is involved as inorganic redox catalyst.

Another interesting bromide ion-catalyzed reaction is the anodic oxidation (undivided cell) of secondary formamides in methanol leading to urethanes [232]. This reaction proceeds via the intermediate *N*-bromo amide, which under elimination of HBr forms the isocyanate, which is attacked by methanol. Thus, a phosgene-free technical synthesis of urethanes is made possible. Urethanes can be used as stable isocyanate equivalents [Eq. (42)].



(42)

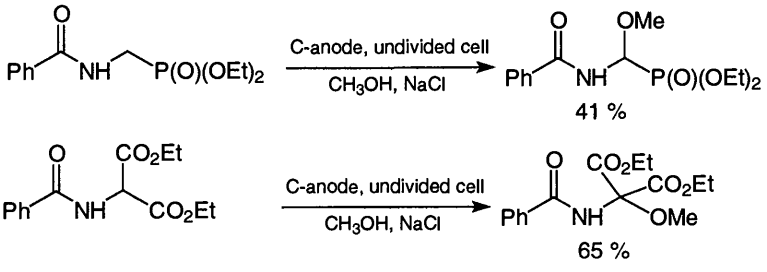
If the direct anodic oxidation of tertiary formamides, which do not possess an α-hydrogen, is performed, the formyl function is transformed into a carboxymethyl group [233].

Regioselectivity and stereochemistry have been studied in the case of the anodic methoxylation of *N*-acylpiperidines and *N*-acylmorpholines [234]. Because of steric constraints imposed by the intermediate formation of the planar *N*-acyliminium ions, substitution is directed to the secondary carbon rather than to the tertiary position. The same reason accounts for the axial methoxylation in this reaction.

B. Anodic Oxidation of *N*-Acyl and *N*-Carboalkoxy α-Amino Acid Esters

Electrochemical oxidation in the α-position of protected α-amino acid esters and dipeptides is synthetically interesting, as the α-carbon is transformed into an electrophilic center by the redox-umpolung principle. Direct electrochemical oxidation of *N*-acyl amino acid esters is not successful, presumably because of the electron-withdrawing effect of the ester function. Indirect anodic oxidation under application of NaCl as redox catalyst, however, is possible [200,235,236]. In methanol using an undivided cell the α-methoxylation of protected amino acids occurs according to Scheme 8, path **c**. In this way, *N*-carbomethoxylated branched α-amino acid esters and α-amino β-lactams have been methoxylated in 83–91% material yield at Pt anodes in presence of 0.5 equivalents of NaCl after consumption of 10 F/mol. In case of phenylglycine, 31 F/mol was necessary to obtain the α-methoxylated product in 62% yield [235]. Under these conditions, the glycine derivative was α-dimethoxylated in 95% material yield [235]. Steckhan and Ginzel [200] showed that in the presence of very high concentrations of chloride ions, already after consumption of 3 F/mol over 90% turnover of the protected amino acid esters could be obtained. In the

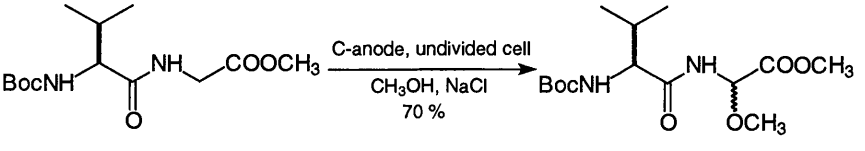
case of *N*-acyl glycine methyl ester, a 5 : 1 ratio of mono- and dimethoxylated product could be obtained. *N*-Acyl phenylglycine methylester could be methoxylated in 98% yield after consumption of 3 F/mol. Obviously, high chloride concentrations diminish the competing methanol oxidation. The reaction rate increases with increasing electron-withdrawing effect of the *N*-protecting group; it decreases with increasing electron-donating ability of the substituents in the α-position. *N*-Acylamino malonates are faster and *N*-acylamino methylphosphonates are slower reacting than the corresponding *N*-acylamino acid esters [Eq. (43)].



(43)

These effects can best be interpreted assuming the HCl elimination from the *N*-chloro amino acid intermediates to be the rate-determining step [200].

Similarly, *N*-acyl or *N*-carboalkoxylated dipeptides can be anodically oxidized in α-position to the nitrogen using NaCl as a mediator [200]. In the case of dipeptides, however, two regioisomers may be obtained by oxidation at the N- or the C-terminal amino acid. The results show that the α-methoxylation occurs selectively and in high yields at the C-terminal amino acid, if *N*-benzoyl protecting groups without electron-donating substituents are used. The *Z*-protecting group predominantly leads to oxidation at the C-terminus, accompanied by small amounts of products from oxidation at the N-terminus and some hydantoine formation. The Boc protecting group leads to selective monomethoxylation at the C-terminus, if glycine is the C-terminal and valine the N-terminal amino acid [see Eq. (44)], while in the case of proline as the N-terminal amino acid, the monomethoxylated product (39%) is accompanied by smaller amounts of the product which is dimethoxylated at the glycine residue [202]. Monomethoxylation can be obtained selectively if aminomalonic acid is used as the N-terminal amino acid, which is an equivalent of glycine because of the easy monodecarboxylation. This principle has been used in the formation of a chiral cationic glycine equivalent based on a dipeptolide [202].

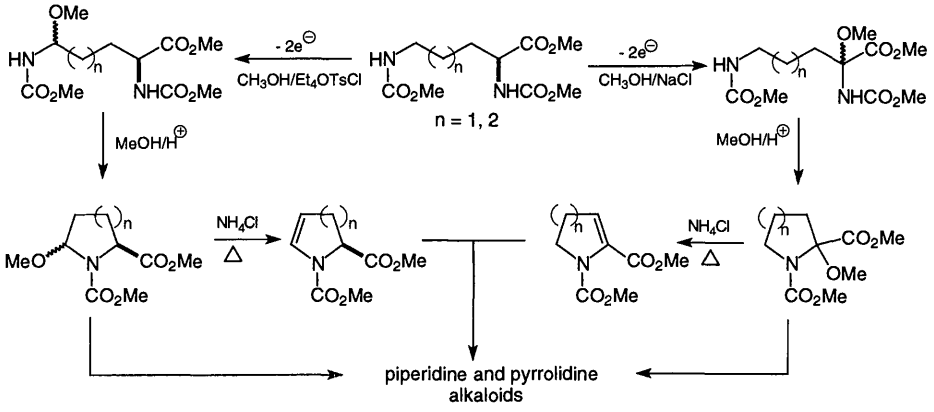


(44)

In the case of branched C-terminal amino acids, methoxylation at the C-terminus is accompanied by formation of imidazolidine-4-ones by α-oxidation at the C-terminus followed by intramolecular attack of the nitrogen of the N-terminal amino acid. This reaction can be performed in high yields, if the electrooxidation is performed in acetonitrile/5% methanol [200].

In the case of basic amino acids like lysine or ornithine, the regioselectivity of the direct and indirect electrochemical oxidation can be demonstrated. Direct anodic oxidation of *N*,*N*′-dimethoxycarbonylated *L*-lysine and *L*-ornithine in methanol regioselectively resulted in the methoxylation at the ω-amino group, while indirect

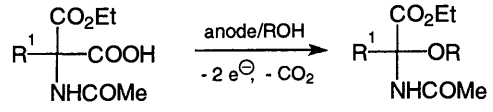
electrochemical oxidation in the presence of NaCl according to Scheme 8, path **c**, regioselectively formed the α-methoxylated α-amino acid ester [236–238] [Eq. (45)]. The species thus formed are very useful for the synthesis of optically active alkaloids [183,204,208,212,236–238].



(45)

C. Anodic Oxidation of *N*-Acyl and *N*-Carboalkoxy α-Amino Acids

N-Acylated amino acids are anodically oxidized in methanol or acetic acid solution under decarboxylative methoxylation or acetoxylation via the intermediate *N*-acyliminium ion in the course of a Non-Kolbe reaction (Hofer–Moest reaction) according to Scheme 8, path **b**. This type of reaction has been used intensively for amidoalkylation reactions by Mori, Seebach, and Steckhan. These reactions were based on the results of Iwasaki applying *N*-acyl aminomalonic acid half esters [Eq. (46)] [239].



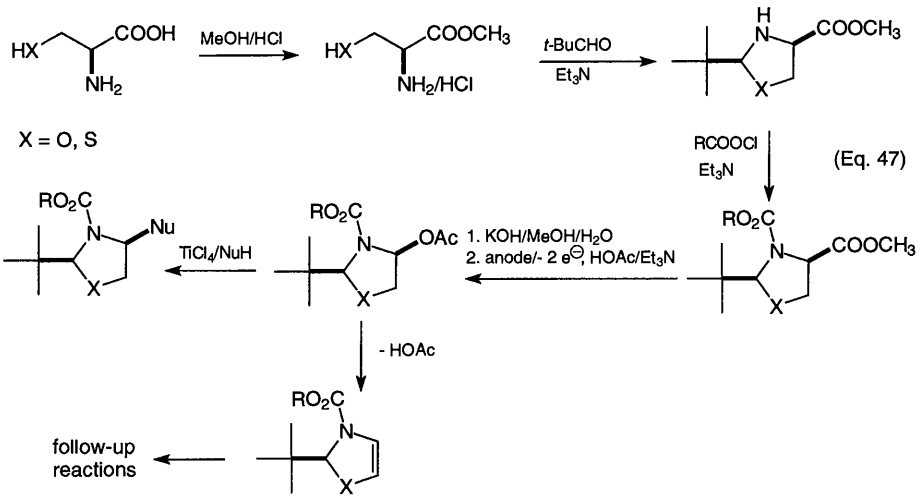
(46)

R^1 = H, Me, Et, ^{i}Pr, $PhCH_2$

R = Me, Et, ^{i}Pr, CH_3CO

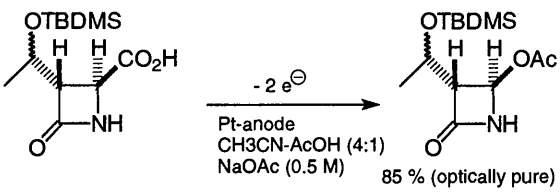
Seebach applied this reaction type in diastereoselective syntheses. In the case of *Z*-Ala-Gly-OH and *Z*-Ala-Val-OH, the decarboxylative methoxylation went smoothly [240]. However, the $TiCl_4$-catalyzed nucleophilic substitution of the methoxy group via the intermediate *N*-acyliminium ion resulted in very low diastereoselectivity. Starting from (4*R*)-*N*-acetyl-4-hydroxy-*L*-proline, anodic decarboxylative methoxylation followed by nucleophilic substitution of the methoxy group by allyl trimethylsilane in the presence of a Lewis acid resulted in the formation of the *cis*-2-allyl substitution product with more than 97% diastereoselectivity [241]. For his concept of self-regeneration of stereo centers [242], Seebach started from the enantiopure amino acids swerine, threonine and cysteine. After formation of the methyl ester, the compounds are cyclized mostly using pivalaldehyde to give the oxazolidine or thiazolidine carboxylic acids. The chirality at the α-carbon of the amino acid is effectively transferred to the *N*,*O*- or *N*,*S*-acetal carbon (C-2), usually in the *trans*-configuration. Anodic decarboxylative acetoxylation leads to the *cis*-4-acetoxy compound with a diastereoselectivity of 90 to more than 97% diastereoselectivity. In

follow-up reactions, the acetoxy group can be substituted by nucleophiles with high *cis*-diastereoselectivities [243]. Other follow-up reactions are possible after elimination of acetic acid leading to the enantiopure oxazoline and thiazoline derivatives. The double bond can undergo diastereoselective cycloaddition reactions and also electrophilic and nucleophilic substitution and addition reactions. Thus, the chirality of the α-carbon of the amino acid has been transferred to C-2 and then back to the α-carbon and other stereogenic centers [Eq. (47)].



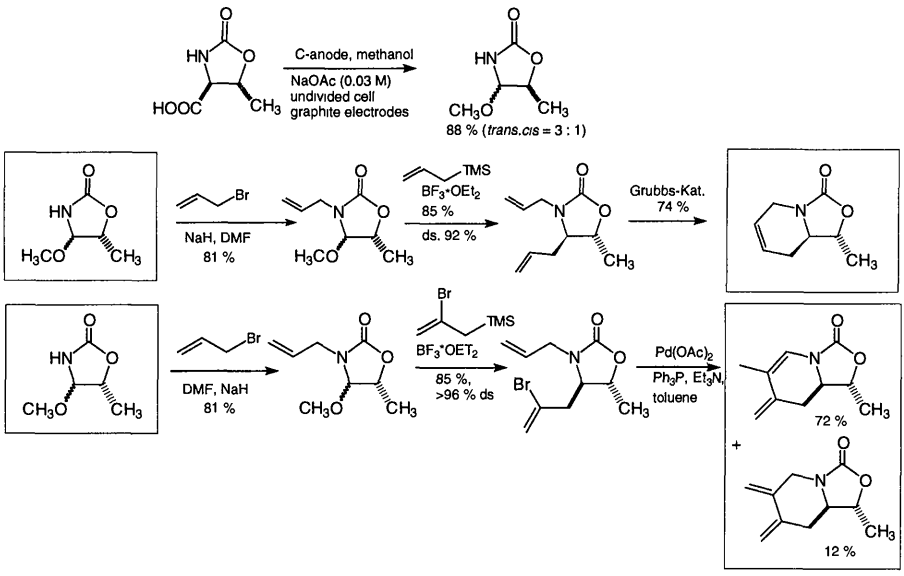
(47)

Mori used the anodic decarboxylative acetoxylation for the synthesis of the valuable penem precursors 4-acetoxy-2-azetidinones. Thus, 4-carboxy-2-azetidinone was electrolyzed in acetonitrile/AcOH (3 : 1) in the presence of NaOAc (4.5 equivalents) to give the desired product in 76% yield. Starting from the enantiopure 4-carboxy-3-[1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone, the enantiopure 4-acetoxy compound was obtained in 85% yield [Eq. (48)] [244].



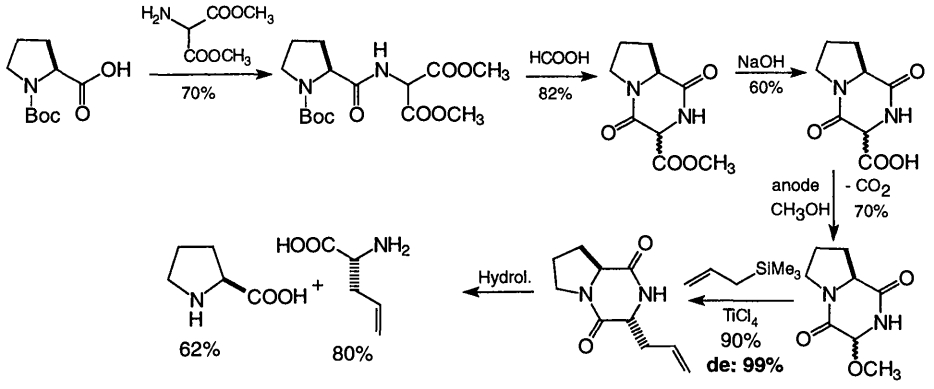
(48)

Steckhan applied the anodic decarboxylative methoxylation to (4*S*,5*R*)-, (4*S*,5*S*)-, and (4*R*, 5*S*)-5-methyl-oxazolidin-2-one-4-carboxylic acid, which can be obtained in almost quantitative yield from *L*-, *L*-allo-, and *D*-threonine. The 4-methoxy derivatives are obtained in 88% yield. Diastereoselective substitution of the methoxy group is possible with a large variety of nucleophiles including CH-acidic compounds and aromatics like furan in the presence of Broensted acids, or silyl nucleophiles, cuprates, and Grignard reagents in the presence of Lewis acids. Diastereoselectivities are in most cases very high, up to more than 98%, giving enantiopure β-amino alcohols, peptide mimetics, and other biologically active compounds [199,245]. Follow-up cyclizations to precursors of aza sugars and alkaloids are also possible. Two examples are represented in Scheme 10 [199].



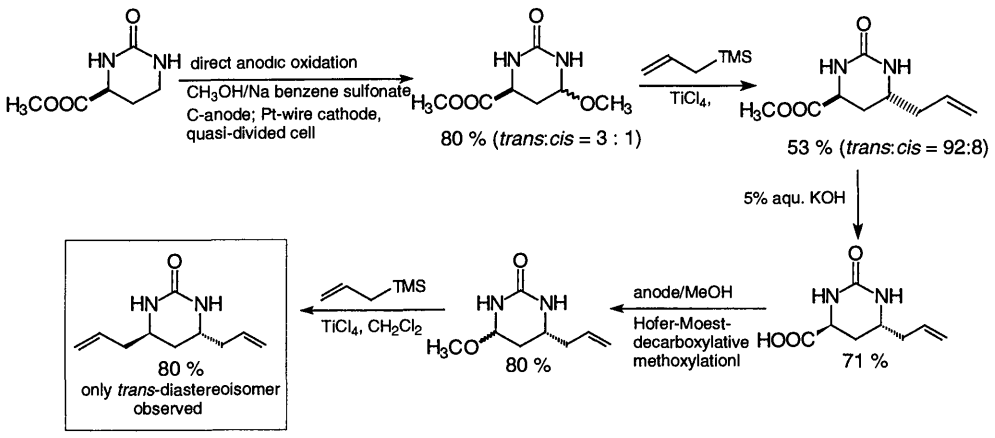
Scheme 10

Anodic decarboxylative methoxylation has also been used to generate an efficient electrophilic chiral glycine equivalent. This is produced from the cyclic dipeptide of *L*-proline and aminomalonic acid diester. Anodic decarboxylation of the remaining carboxylic function leads to the chiral *N,O*-acetal, which can undergo nucleophilic substitution followed by hydrolysis to give back *L*-proline and the nonproteinogenic new enantiopure *D*-amino acid [Eq. (49)] [201].



(49)

In another application, the totally regioselective direct anodic methoxylation of (4*S*)-pyrimidinone-4-methyl carboxylate obtained from *L*-2,4-diamino butyric acid followed by diastereoselective substitution of the methoxy group by allyl trimethylsilane can be combined with the follow-up decarboxylative methoxylation of the carboxy function after hydrolysis. A second methoxy group exchange by allyl trimethylsilane yields the C_2–symmetrical (4*R*,6*R*)-4,6-diallyl-pyrimidin-2-one enantiomerically pure [Eq. (50)] [246].



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16

Anodic Oxidation of Oxygen-Containing Compounds

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I. INTRODUCTION

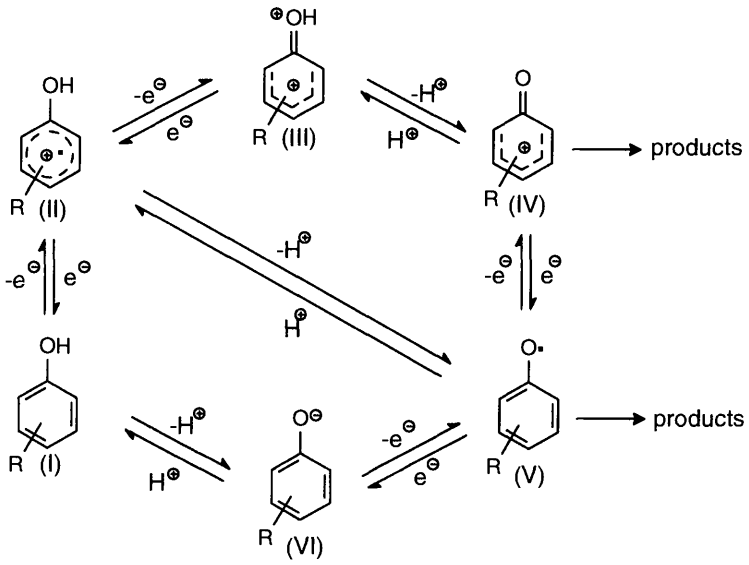
The anodic oxidation of oxygen-containing compounds continues to be an active area of research. Significant progress has been made in recent years, particularly with respect to preparatively useful anodic transformations of oxygenated aromatics. It is hoped that by highlighting the significance and practical value of these reagentless electroorganic reactions, more synthetic practitioners will be encouraged to apply them with confidence to appropriate problems in organic synthesis.

As much of the organizational spirit of the chapter from previous editions has been retained as possible, and the obviously large debt owed to the work of the previous authors is hereby acknowledged. Any modest changes in coverage were introduced primarily for the sake of balancing depth with timeliness and economy. As before, to compensate for the somewhat arbitrary coverage that necessarily attends the limited treatment of broad subjects, as many leading references have been furnished as possible.

II. ANODIC OXIDATION OF PHENOLS, HYDROQUINONES, AND DERIVATIVES

A. Phenols, Hydroquinones, and Hydroquinone Monoethers

The course of the electrooxidation of phenols and derivatives is remarkably complex, as indicated in Eq. (1). The many species involved are related to one another by a series of proton and electron transfers that may occur as the result of bimolecular interactions as well as by primary electrode processes [1–6].

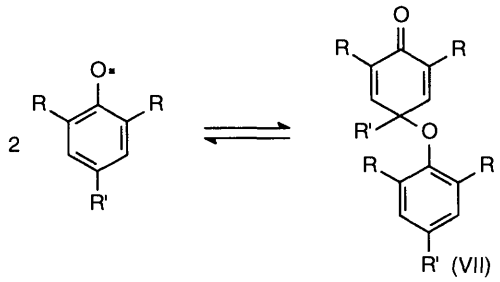


(1)

The predominance of one species over another has been shown to be a function of a number of experimental variables including medium pH, electrode potential, solvent–electrolyte system, and electrode material [7,8]. Voltammetry studies of suitably substituted phenolate ions at elevated pH show the expected reversible one-electron process leading to formation of phenoxy radicals (**V**), with peak potentials on the order of −0.16 to −0.31 vs. SCE [8,9]. Oxidation of nonionized phenols in media sufficiently acidic to suppress ionization of the resulting cation radicals (**II**) ($pK_a \approx -5$ to 0 [10–13]) reveals positive peak potentials in the range of 1.3–1.65 V versus SCE [14,15]. As indicated earlier, the principal product-producing species from these oxidations are the phenoxy radical (**V**) and the phenoxonium ion (**IV**).

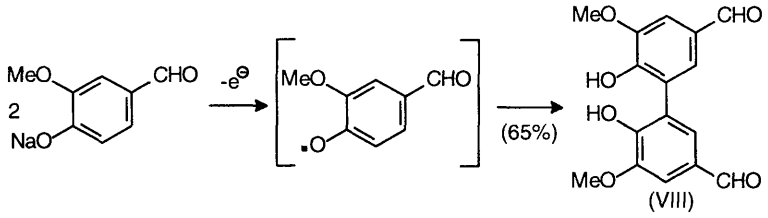
1. Phenoxy Radical Products

The products obtained via phenol oxidations involving phenoxy radicals range from simple *ortho-* or *para*-benzoquinones and quinol ethers to biphenyls arising via C–C coupling processes. Suitably substituted phenoxy radicals with sterically bulky *ortho*-substituents R and nonbulky *para*-substituents R′ (Me, Et, Bu) have been found to exist in equilibrium with their corresponding *para*-quinol ether derivatives (**VII**), as in Eq. (2). The results are more complex when R′ is bulkier [9,16,17].



(2)

Oxidative C–C coupling of phenoxy radicals to give symmetrical biphenyl derivatives has been observed in the anodic dimerization of sodium vanillate to biphenyl (**VIII**), as in Eq. (3) [18] and in anodic oxidation of 2,6-dihydroxy-acetophenone at a Pt anode in aqueous methanolic NaOH to give biphenyl (**IX**), as in Eq. (4) [19].



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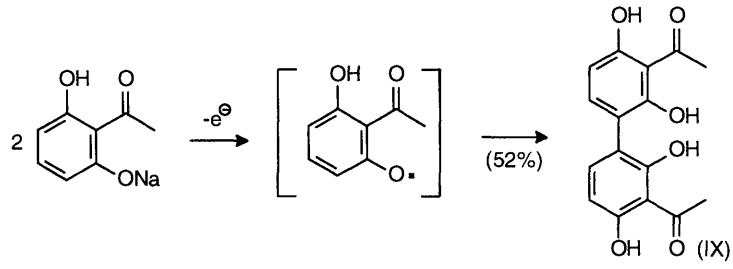


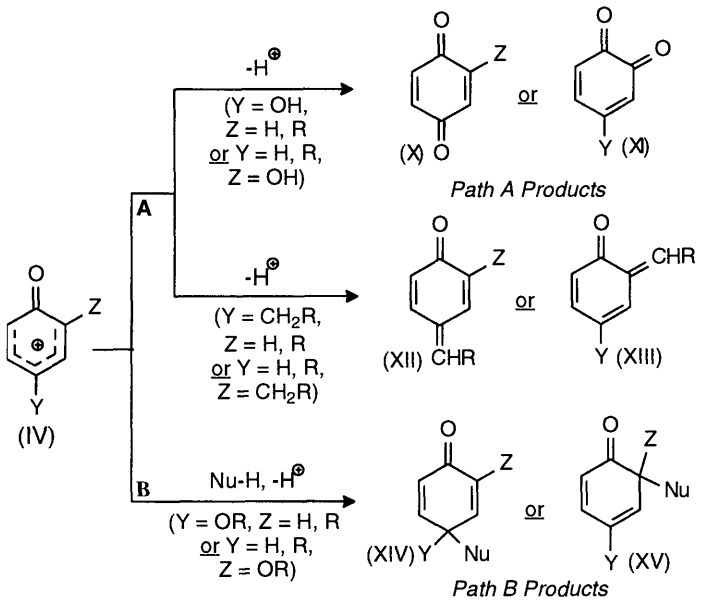
(4)

2. Phenoxonium Ion Products

The possible products derived from phenoxonium ion intermediates (**IV**), as in Eq. (5), may be conveniently divided into two groups, depending on the reaction pathway followed.

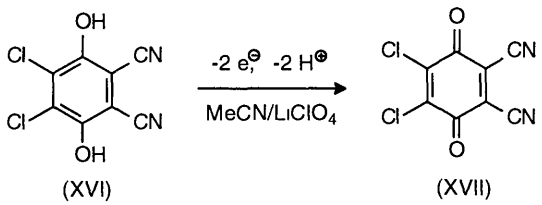
Path A products (**X**)–(**XIII**) arise via simple proton loss from *para*– or *ortho*-substituents on the phenoxonium ion. When the substituent is OH, *para*- or *ortho*-benozoquinone derivatives (**X** and **XI**) are formed [20], with the latter being highly reactive and subject to dimerization and other complex side reactions in the absence of suitable trapping agents [21–23]. When the phenoxonium ion substitution involves *ortho*- or *para*-alkyl groups with at least one ionizable hydrogen, the generation of highly reactive *para*- or *ortho*-benozoquinone methide derivatives (**XII** or **XIII**) may be involved [24–26]. While their formation under anodic conditions has been challenged in at least one study [27], quinone methides have clearly been implicated as the key intermediates in the anodic oxidation of *ortho*-(1-phenylthio)alkyl phenols, although the *ortho*-quinone methides thus formed apparently arise via sulfur oxidation and subsequent loss of thiophenyl radical and a proton rather than via direct oxidation of the phenol ring itself [28].

Alternatively, path B gives rise to substituted dienones (**XIV** or **XV**), which are derived from nucleophilic trapping of the phenoxonium ion followed by proton loss. This is the most preparatively significant anodic reaction of phenols and is treated at length in the ensuing discussion [29 and references cited therein].



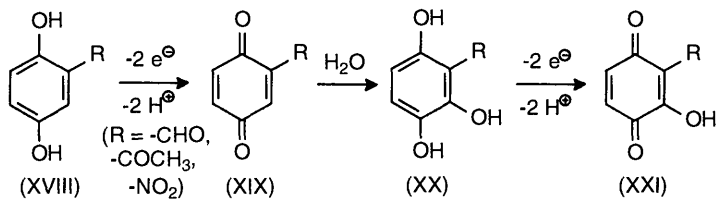
(5)

a. Formation of Simple Quinone Derivatives. A simple but useful example of oxidative conversion of hydroquinones to quinones on a multigram scale is the anodic preparation of DDQ (**XVII**) from DDH (**XVI**) in 77% yield in a divided cell [30]:



(6)

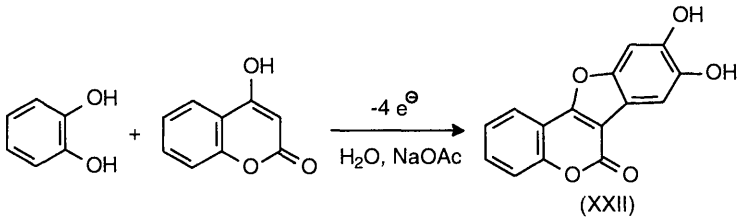
When conducted in water or aqueous solvent mixtures, anodic oxidation of hydroquinones (**XVIII**) bearing electron-withdrawing groups in the 2-position leads to conjugate addition of water to the resulting quinone (**XIX**), as in Eq. (7) [31]. Subsequent aromatization to the corresponding trihydroxybenzene (**XX**) followed by a second anodic oxidation gives the corresponding hydroxyl-substituted quinone derivatives (**XXI**).



(7)

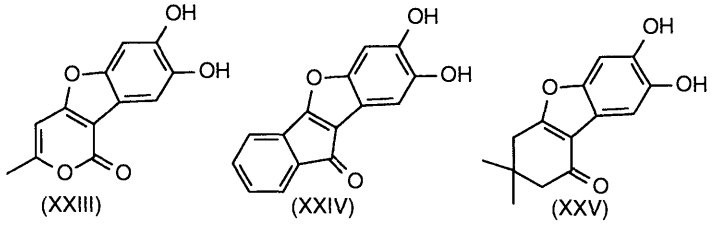
As mentioned earlier, the high reactivity of *ortho*-quinones generally precludes their direct isolation. However, if oxidation of the corresponding hydroquinone is conducted in

the presence of a suitable nucleophilic partner, useful intermolecular coupling can take place, as in the preparation of **XXII** in 95% yield by controlled potential oxidation of catechol at a carbon anode in the presence of 4-hydroxycoumarin [32]:

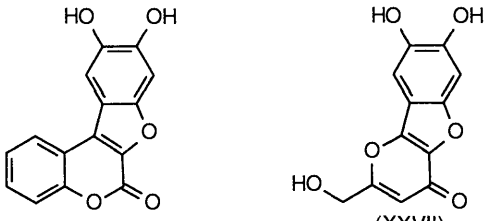


(XXII) (8)

Similarly, catechol undergoes anodic oxidation in the presence of other β- or α-dicarbonyl compounds to give what are formally the corresponding [3 + 2]-cycloadducts, as in **XXIII** through **XXVII** [33]:

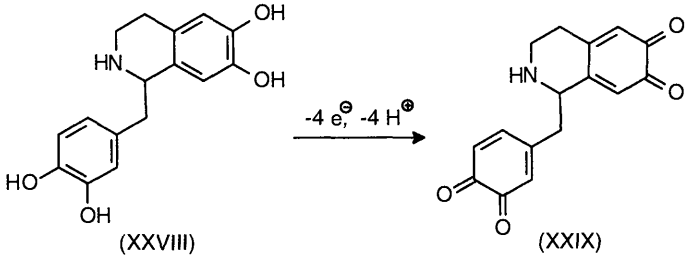


(XXIII) (XXIV) (XXV)



(XXVI) (XXVII) (9)

In anodic oxidation studies on neurotransmitters, generation of *ortho*-quinone (**XXIX**) occurred during controlled potential oxidation of tetrahydropapaveroline (**XXVIII**), a dopamine metabolite [Eq. (10)] [34]. In the absence of strong nucleophiles, **XXIX** underwent intramolecular Michael addition to give a transient intermediate, which oxidized at a lower potential than **XXVIII**.



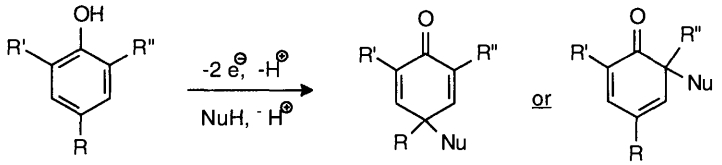
(XXVIII) (XXIX) (10)

b. Products Via Bimolecular Processes. Phenoxonium ions are highly electrophilic species that react with a variety of O, N, and C nucleophiles as solvents, electrolytes, additives, or impurities to give predominantly the corresponding 2,5-cyclohexadienone derivatives, as in Eq. (11) and Table 1.

Table 1 Anodic Formation of Some Cyclohexadienones Via Bimolecular Nucleophilic Trapping of Phenoxonium Ions[a]

Starting material, phenol	Product, dienone[b]	Yield (%)	Anode	Solvent/electrolyte system	Reference
Phenol	4,4-Dimethoxy	46	C	MeOH, $LiClO_4$, 2,6-lutidine	29
4-Methyl	4-Methyl-4-hydroxy	50	Pb	H_2SO_4(2N)	35
2,6-Dimethyl	4,4-Dimethoxy	28	Pt	MeOH, $LiClO_4$, $NaHCO_3$	29
2,6-Di-*t*-butyl	4,4-Dimethoxy	78	C	MeOH, $LiClO_4$, $NaHCO_3$	29
2,6-Di-*t*-Bu-4-Me	4-Methoxy-4-methyl	95	C	MeOH, $LiClO_4$, $NaHCO_3$	29
2,6-Di-*t*-Bu-4-Me	4-Methoxy-4-anisyl	81	Pt	MeCN-anisole, Bu_4NBF_4	36
2,6-Di-*t*-Bu-4-Et	4-Ethyl-4-hydroxy	93	Pt	MeCN–H_2O, $NaClO_4$	37
4-Methoxy	4,4-Dimethoxy	97	Pt	MeOH, $LiClO_4$	41
4-Phenyl	4-Methoxy-4-phenyl	87	Pt	MeOH, $LiClO_4$	29
2,6-Di-*t*-Bu-4-Ph	4-Ph-4-(L-ala-O-)	94	Pt	Ch_2Cl_2, Bu_4NBF_4, 2,6-lutidine	38
2,6-Di-*t*-Bu-4-Ph	4-Ph-4-$((AcO)_4$-Glu-O-)[c]	14	Pt	CH_2Cl_2, Et_4NBF_4, 2,6-lutidine	38
2,6-Di-*t*-Bu-4-Ph	2-*t*-Bu-2-(Gly-O-)[d]	62	Pt	CH_2Cl_2, Et_4NBF_4, 2,6-lutidine	38

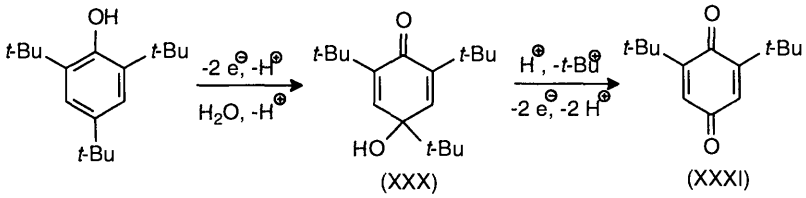
[a] See references for other examples.
[b] Only substitution at the 4-position is reported.
[c] α:β anomer ratio = 0:100.
[d] Substitution occurred at the 2-position.



(11)

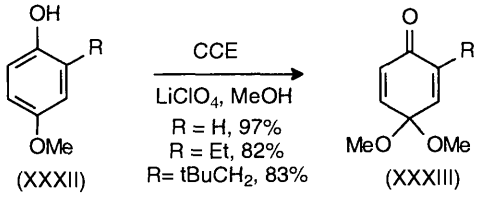
NuH = H_2O, ROH, RCO_2H, RCN, ArOH, ArOR, ROCH=CHR', RSCH=CHR'

Table 1 provides a highly abbreviated list and some leading references for the preparation of 2,5-cyclohexadienone derivatives via bimolecular nucleophilic trapping of phenoxonium ions. Not included in the table are examples of the synthesis of quinone and substituted quinones from anodic oxidation of phenols in the presence of water as nucleophile. Such quinone syntheses have been carried out via anodic oxidation of phenol itself as well as from *para*-alkoxyphenols, which give quinones via the corresponding hemiacetals [29,35,39]. In a related example, 2,4,6-tri-*tert*-butylphenol was anodically oxidized to the phenoxonium ion in the presence of water to give the corresponding *para*-quinol (**XXX**), which underwent aromatization to the hydroquinone via loss of *tert*-butyl cation and subsequent anodic oxidation to give 2,6-di-*tert*-butylquinone (**XXXI**) [40]:



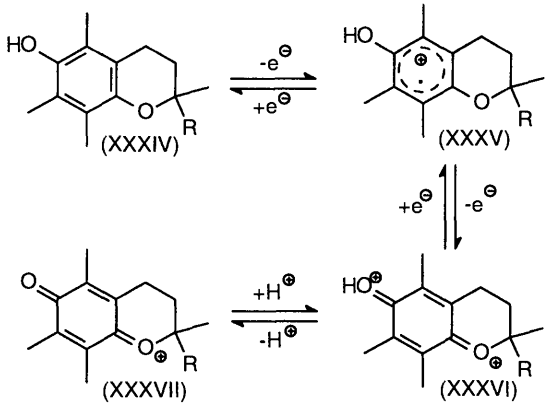
(12)

Constant-current electrolysis (CCE) of *para*-alkoxyphenols (**XXXII**) in alcohol solvents, usually methanol, provides ready access to the synthetically useful quinone monoketals (**XXXIII**), as in Eq. (13) [41]. In many cases, the yields are superior to those obtained via chemical oxidation of the phenols with $Tl(NO_3)_3$, DDQ, or $FeCl_3$ [42 and references cited therein].



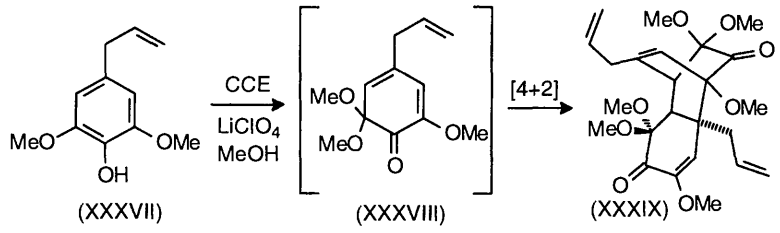
(13)

Interest in the antioxidant properties of the naturally occurring *para*-alkoxyphenol α-tocopherol (vitamin E) led to cyclic voltammetry (CV) studies on the radical cations (**XXXV**) and dications (**XXXVI**) of model compounds (**XXXIV**). Both the dication and phenoxonium ion (**XXXVII**) were found to possess surprising stability when prepared in MeCN [43,44]:



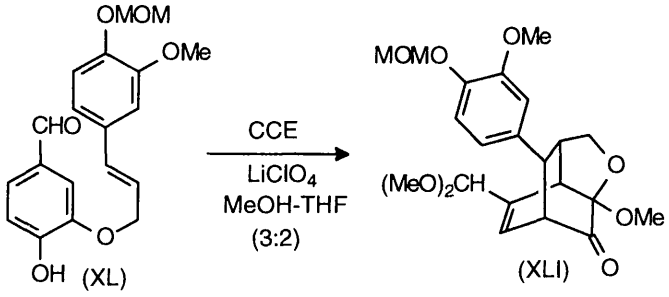
(14)

Oxidation of *ortho*-alkoxyphenols in alcohol solvents leads to highly reactive *ortho*-quinone monoketals, which undergo spontaneous dimerization unless appropriately substituted. In one useful example of such a [4 + 2]-cycloaddition, monoketal (**XXXVIII**), derived from constant current electrolysis of phenol (**XXXVII**), dimerized to give the neolignan natural product asatone (**XXXIX**) in 34% yield [45]:



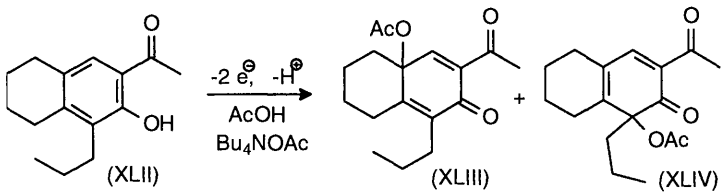
(15)

Intramolecular variants of this chemistry have also proved to be useful in the synthesis of complex ring systems. For example, anodic oxidation of phenol (**XL**) afforded oxaisotwistenone (**XLI**) in 79% yield in an approach to the antihepatotoxic agent silydianin [45]:



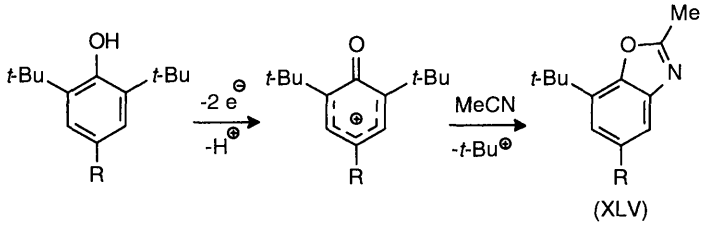
(16)

Mixtures of *para*- and *ortho*-substituted products are sometimes obtained, as in the anodic oxidation of electron-deficient tetrahydronaphthol (**XLII**), which gave a 5 : 2 mixture of *para*- and *ortho*-quinol acetates (**XLIII** and **XLIV**), as in Eq. (17) [46]. Similar results were reported for the anodic methoxylation of eugenol and isoeugenol [47].



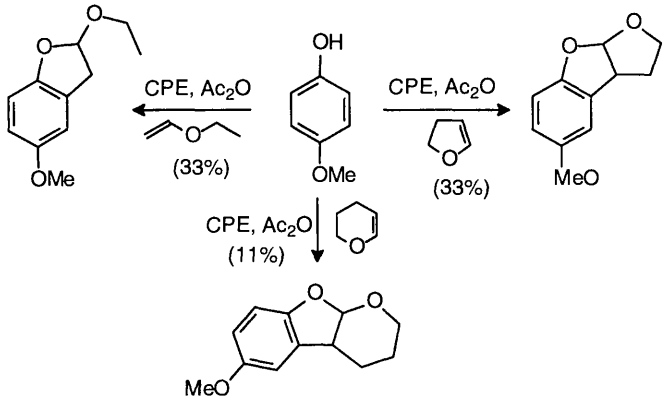
(17)

Bimolecular trapping of phenoxonium ions by nucleophilic π-bonds can lead to cyclized products when attack occurs at the *ortho*-position. For instance, a Ritter-type reaction occurs when MeCN is used as solvent in the absence of other nucleophiles, leading to a useful synthesis of benzoxazoles (**XLV**) [48]:



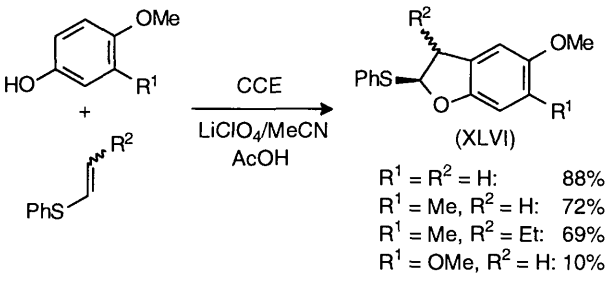
(18)

In an analogous fashion, use of the π-bonds of vinyl ethers, vinyl sulfides, and electron-rich styrenes as nucleophiles has been developed as a surprisingly versatile anodic C–C bond-forming reaction, particularly for the synthesis of complex neolignan structures. Early controlled-potential electrolysis studies on *para*-methoxyphenol and vinyl ethers gave the corresponding dihydrobenzofuran acetals in what is formally a [3 + 2]-cycloaddition process, shown in Eq. (19). A 20-fold excess of the vinyl ether component was used to obtain the modest yields indicated [49].



(19)

The need for a large excess of the vinyl ether was circumvented to some extent through the use of phenyl vinyl sulfides, as in Eq. (20) [50]. Yields of dihydrobenzofuran cycloadducts (**XLVI**) were generally good using only 2 equivalents of the vinyl sulfide component, although in one case (R^1 = OMe) the cycloadduct was subject to further oxidation under constant current conditions.



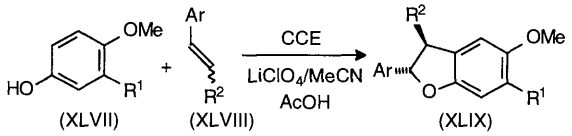
$R^1 = R^2 = H$: 88%
R^1 = Me, R^2 = H: 72%
R^1 = Me, R^2 = Et: 69%
R^1 = OMe, R^2 = H: 10%

(20)

Detailed studies on the constant current anodic cyclization of phenols (**XLVII**) and electron-rich styrenes (**XLVIII**) leading to neolignan-type dihydrobenzofurans (**XLIX**) have been carried out, with some of the results summarized in Table 2 [51]. Comparable results were obtained using 4-methoxynaphthol as the phenol component. As in the phenol-vinyl sulfide cyclizations, good results were obtained using only a modest excess of the alkene component.

The mechanism of these cycloadditions is conveniently rationalized via attack at a phenoxonium ion center by the styrene π-bond followed by cyclization onto the resulting cation via phenol tautomerization, as in Eq. (21). An alternate mechanism involving initial coupling between a phenoxy radical and a styrene radical cation has also been proposed, but either mechanism leads to a common benzylic cation intermediate (**L**). Significantly, the substitution pattern of the phenolic component can drastically alter the mode of cyclization of cation (**L**), leading to bridged bicyclic structures (**LI**) via a [5 + 2]-cycloaddition rather than the [3 + 2]-process that affords the benzofurans (**XLIX**). The bridged cycloadducts are favored when R^1 is strongly electron-releasing and when R^2 is a sub-

Table 2 Anodic Cyclizations of Phenols and Electron-Rich Styrenes

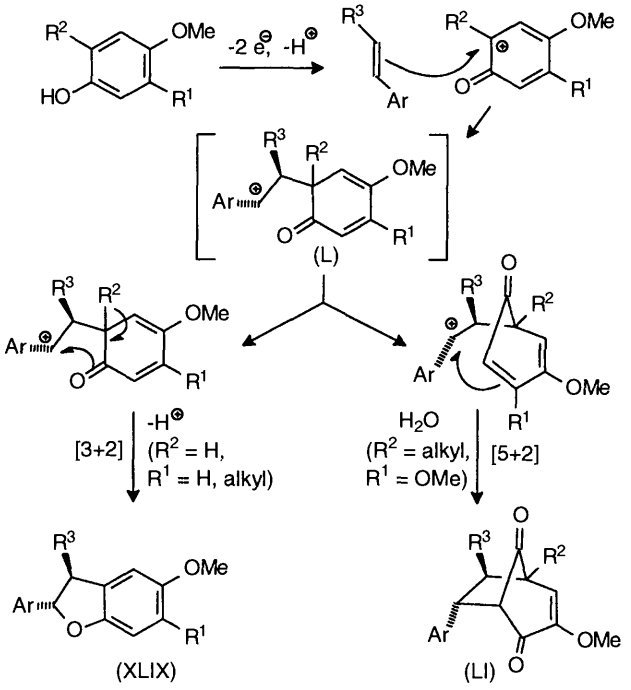


(XLVII) (XLVIII) (XLIX)

(XLVII) *M*	(XLVIII) *M*	R^1	R^2	mA	T (mins)	% yield (XLIX)
0.05	0.05	OMe	*t*-Me	80	110	14
0.05	0.18	OMe	*t*-Me	80	120	61
0.04	0.04	Me	*t*-Me	80	90	75
0.05	0.05	H	*c*-Me	80	95	50
0.05	0.05*	H	H	80	120	18
0.05	0.18*	H	H	80	120	40
0.03	0.03*	H	t-Me	40	120	80

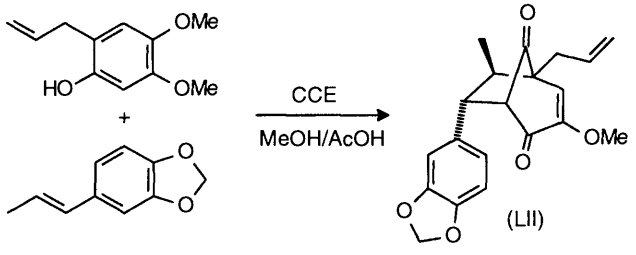
*Ar = 4-(MeO)Ph; for all others, Ar = 3,4-$(MeO)_2$Ph

stituent other than H. This trend has also been observed in analogous cycloadditions of styrenes with chemically generated phenoxonium ions [51 and references cited therein].



(21)

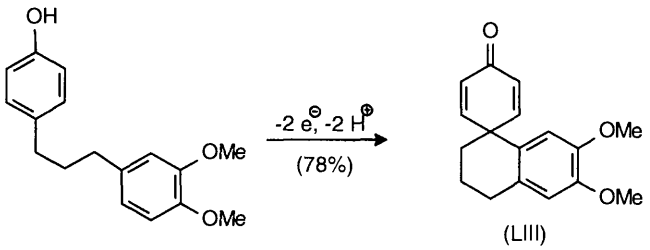
The anodic method, which often gives superior yields, has been effectively used in the total synthesis of a number of natural products, as in the preparation of *Aniba* neolignan (**LII**) in 81% yield [52]:



(22)

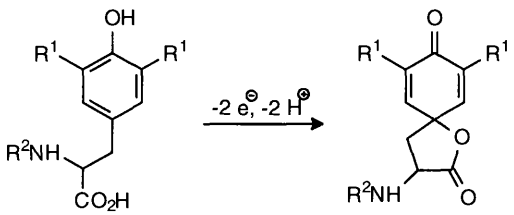
3. Products Via Unimolecular Processes

Numerous investigations have centered on the trapping of anodically generated phenoxonium ions with nucleophilic centers tethered to the reacting phenol ring. Much of the early work in this area centered on anodic phenolic coupling reactions, which are essentially Friedel–Crafts type cyclizations, affording spirodienones such as (**LIII**), often in excellent yield [Eq. (23)] [53]. Anodic cyclizations are treated in detail elsewhere in this edition.



(LIII) (23)

More recently, quinonoidal spirolactones (**LV**), which can react with amino acid esters to give dipeptides, have been conveniently prepared via anodic oxidation of tyrosine derivatives (**LIV**) [Eq. (24)] [54]. Anodic phenolic coupling of tyrosine and phenylglycine derivatives to afford isodityrosine, dityrosine, and related compounds has also been recently reported [55].

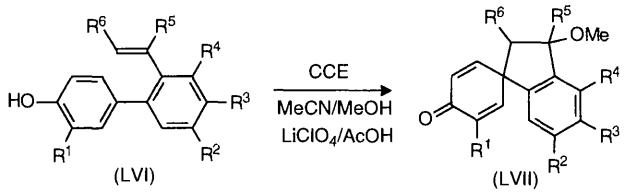


(LIV) (LV) (24)

Continuing interest in the development of preparatively useful anodic C–C bond-forming reactions has led to detailed investigations of the intramolecular trapping of phenoxonium ions by alkenyl side chains in anodic oxidation of phenolic biphenyl derivatives [56–58]. In this process, solvent trapping by methanol occurs after the phenoxonium ion has been intercepted by the side-chain π-bond. As shown in Table 3, a variety of substituted spirodienones (**LVII**) may be prepared from the corresponding phenolic biphenyls (**LVI**) under constant-current electrolysis conditions.

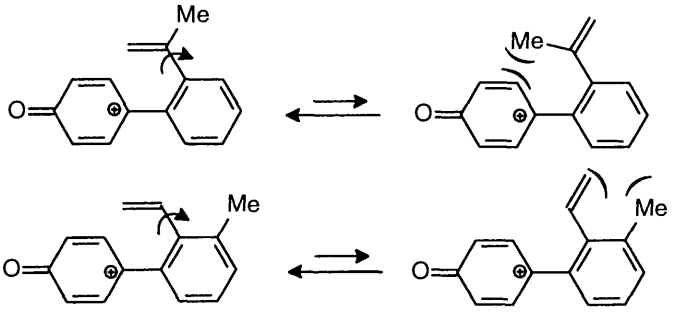
The success of these reactions depended on a number of factors. A mildly acidic reaction medium (5–20 equivalents of AcOH) markedly improved yields, but even more significant were the effects of substitution on the side-chain π-bond or the *para*-aryl ring. A change in side-chain π-bond substitution from $R^5 = H$ to $R^5 = Me$ caused a dramatic increase in spirodienone yield (Table 3, entries 1 and 2). This was attributed either to enhanced nucleophilicity for the methyl-substituted π-bond or to a more favorable reaction conformation for the side chain when substitution was present. The latter hypothesis was subsequently supported by examination of a system in which a side-chain buttressing effect was introduced via methyl substitution at R^4, adjacent to the alkenyl side chain (Table 3, entry 6) [Eq. (25)]. The superiority of the vinyl sulfide vs. vinyl ether moiety as a nucleophile in phenoxonium ion trapping was again observed (Table 3, entry 8 vs. entry 7). Enhanced side-chain nucleophilicity via resonance was also examined through electron-donating oxygen substituents on the *para*-aryl ring. Interestingly, oxygen substitution *para* to the alkenyl side chain proved beneficial for the cyclization even when the side-chain π-bond was unsubstituted (Table 3, entry 13), while oxygen substitution *para* to the phenolic ring gave no cyclized product at all unless the side-chain π-bond was alkyl-substituted (Table 3, entries 15 and 16).

Table 3 Anodic Cyclizations of Alkenyl-Substituted Phenolic Biphenyls[a]



Entry	R^1	R^2	R^3	R^4	R^5	R^6	% yield (LVII)
1	H	H	H	H	H	H	16
2	H	H	H	H	Me	H	85
3	H	H	H	H	Ph	H	65
4	H	H	H	H	H	Me	35
5	H	H	H	H	$-(CH_2)_3-$		65
6	H	H	H	Me	H	H	70
7	H	H	H	H	OMe	H	21[b]
8	H	H	H	H	SPh	H	72[b]
9	H	OMe	OMe	H	H	H	70
10	H	$-O-CH_2-O-$		H	Me	H	70
11	H	$-O-CH_2-O-$		H	H	H	12
12	H	OMe	OMe	H	Me	H	92
13	H	OMe	H	H	H	H	47
14	H	OMe	H	H	Me	H	84
15	H	H	OMe	H	Me	H	84
16	H	H	OMe	H	H	H	---[c]
17	OMe	H	H	H	Me	H	---[d]

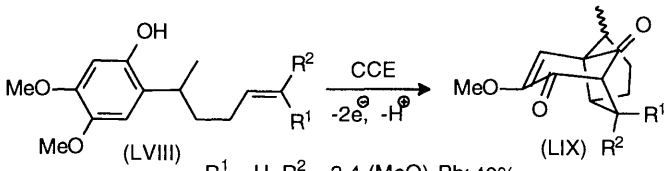
[a]Pt anode and cathode were used in all reactions; [b]product was isolated as the diketone; [c]only *para*-quinol ether was isolated; [d]only *ortho*-quinone monoketal was isolated.



(25)

In other studies, various complex ring systems useful in the synthesis of natural products have been prepared by anodic oxidation of electron-rich phenols bearing alkenyl side chains of varying substitution and stereochemistry [59–65]. In some instances, the

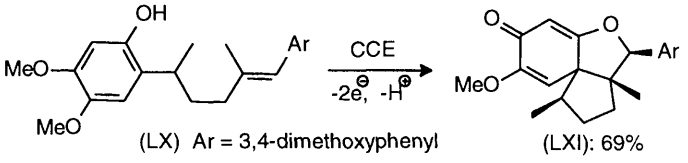
process is essentially an intramolecular variant of the previously examined cationic [5 + 2]-cycloaddition processes leading to bridged bicyclic adducts, as in the anodic cyclization of **LVIII** to **LIX** [61,63]:



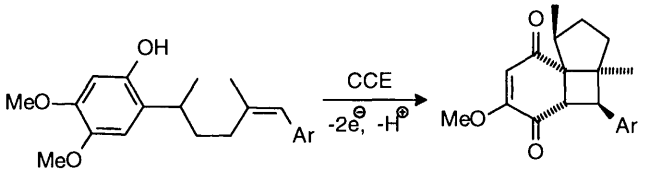
(LVIII) (LIX)

R^1 = H, R^2 = 3,4-$(MeO)_2$Ph: 40%
R^1 = Me, R^2 = CH_2OAc: 80% (26)

The effect of double-bond stereochemistry and substitution on the course of these reactions is illustrated in Eqs. (27) and (28), wherein cycloadducts **LXI** and **LXIII** of quite different structure are obtained in good yield [62]. Note that when the methyl group is absent from the double bond of **LX**, the cyclization leading to **LIX** in Eq. (25) occurs. Since the process leading to **LXIII** occurs even in the absence of light, a simple [2 + 2]-cycloaddition between an electrochemically generated quinone and the alkenyl side chain is an unlikely mechanism. The chemistry illustrated here has been employed in the total synthesis of natural products such as cendranoxide and silphinene [66], as well as in the synthesis of both linear and angular triquinane ring systems [65] and 2-*epi*-cedrene analogs [67].



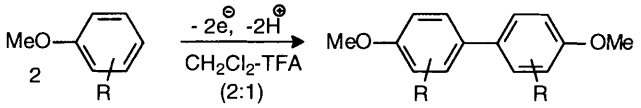
(LX) Ar = 3,4-dimethoxyphenyl (LXI): 69% (27)



(LXII) Ar = 3,4-dimethoxyphenyl (LXIII): 66% (28)

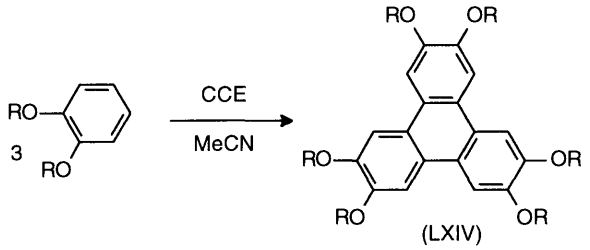
B. Aryl Ethers and Aryl Esters

The radical cations derived from anodic oxidation of simple aryl ethers have been found to be quite stable, especially in trifluoroacetic acid or trifluoroacetic acid–dichloromethane mixtures [68–71]. Thus, aryl ethers with unsubstituted *para*-positions may be coupled anodically to form the corresponding biphenyls, as in the anodic dimerization of anisole derivatives [Eq. (29)]. Yields are on the order of 90–100% on a preparative scale. The biphenyl products are ultimately obtained by reversing the cell polarity in order to reduce the product radical cations, which are more readily formed than those of the starting ethers [69].



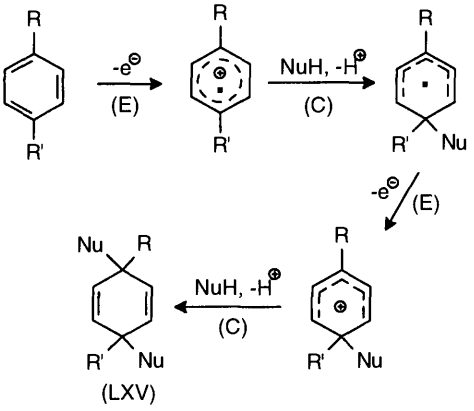
(29)

In a related process, *ortho*-dialkoxybenzenes undergo an unusual anodic trimerization reaction, leading to hexaalkoxytriphenylenes (**LXIV**) [Eq. (30)], certain of which have found application in the field of liquid crystal technology [72,73].



(30)

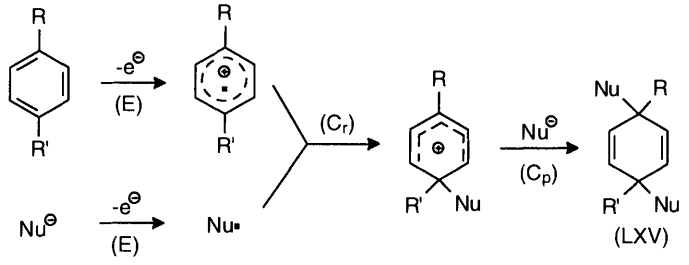
Generation of substituted aryl radical cations in the presence of nucleophiles can lead to products of side-chain substitution (processes such as anodic benzylic substitution of toluenes, which are dealt with in a separate chapter) or to products of addition to the aromatic ring itself. Nuclear addition products in *para*-substituted systems have been proposed to form in essentially one of two ways, depending on substitution pattern and reaction conditions. Radical cations formed by electrochemical reaction (E) may be trapped by chemical reaction (C) with a nucleophile (or its anion). Repeating this sequence leads to nuclear addition products (**LXV**), formed by what is referred to as the ECEC mechanism [Eq. (31)] [74]. An analogous pattern may be inferred for *ortho*-substituted systems.



(31)

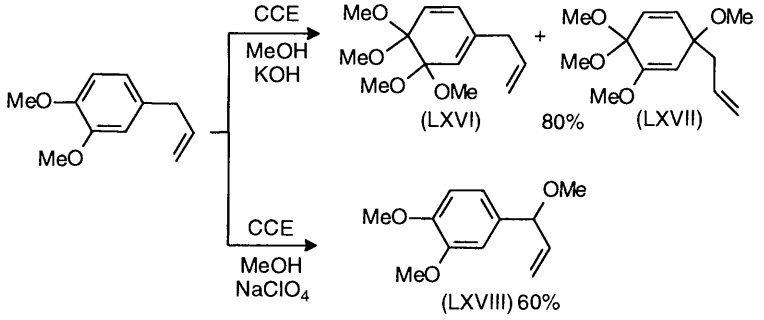
In certain basic reaction media, an alternative mechanism has been proposed [Eq. (32)], involving initial electrochemical oxidation (E) of the aromatic substrate accompanied by simultaneous electrochemical oxidation (E) of the nucleophile anion to its corresponding radical. A radical–radical coupling (C_r, chemical reaction, radical) between the aromatic radical cation and the nucleophile radical at the anode is then followed by chemical trapping (C_p, chemical reaction, polar) of the resulting carbocation by unox-

idized nucleophile or nucleophile anion to again give the nuclear addition products (**LXV**). This so-called EEC_rC_p mechanism [75,76] represents a useful working hypothesis for predicting the products derived from anodic addition reactions of a variety of substituted aromatic ethers, especially anodic methoxylations conducted in basic media at a Pt anode.



(32)

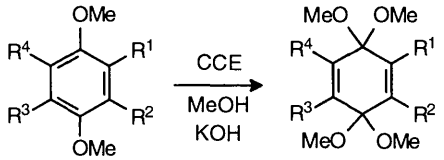
The constant current electrolysis of methyl eugenol serves to illustrate some of the effects of ring substitution and electrolyte on the course of such reactions. When carried out in methanol containing 2% NaOH or KOH (with or without added $NaClO_4$), an approximately 1 : 1 mixture of *ortho*-quinone bisketal (**LXVI**) and *para*-quinol ether (**LXVII**) was obtained. In contrast, when the oxidation was carried out in methanol–$NaClO_4$ in the absence of base, only side-chain substitution product (**LXVIII**) was obtained [Eq. (33)] [77]. This work clarified an earlier mechanistic interpretation of the reaction [78].



(33)

Anodic methoxylation of aromatic ethers via the EEC_rC_p mechanism has found its widest application in the synthesis of quinone bisketals (**LXX**) from *para*-dimethoxybenzenes (**LXIX**) [79]. Yields are generally excellent, and the reaction is conveniently carried out at constant current in a single cell [42,80]. The reaction has also been shown to work well for naphthalenes [81] and benzothiophenes [82]. As shown in Table 4, a variety of substituents may be present on the ring. When substituents sensitive to cathodic reduction such as –CHO and $-CH{=}CHCO_2Me$ are present, a divided cell apparatus may be required to obtain reasonable yields of the corresponding bisketals.

Table 4 Anodic Methoxylation of Some *para*-Dimethoxyaromatic Compounds[a]

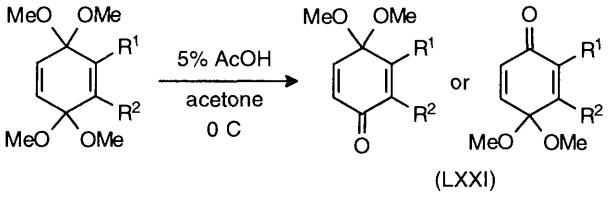


(LXIX) (LXX)

R^1	R^2	R^3	R^4	% yield (LXX)
H	H	H	H	88
Br	H	H	H	78
Br	H	Br	H	58
Me	H	H	H	80
$Si(Me)_3$	H	H	H	93
Me	Me	Me	H	63
CH(OMe)Me	H	H	Me	92
CH(OH)Me	H	H	H	50
$(CH_2)_3OH$	H	H	H	48
$CH_2CH{=}CH_2$	H	H	H	81
SMe	H	H	H	54[b]
H	H	R^3, R^4 =		74
Me	H			75
OMe	H			83
Me	OMe			82
Me	$Si(Me)_3$			80
SOTol	H	OMe	H	71[c]

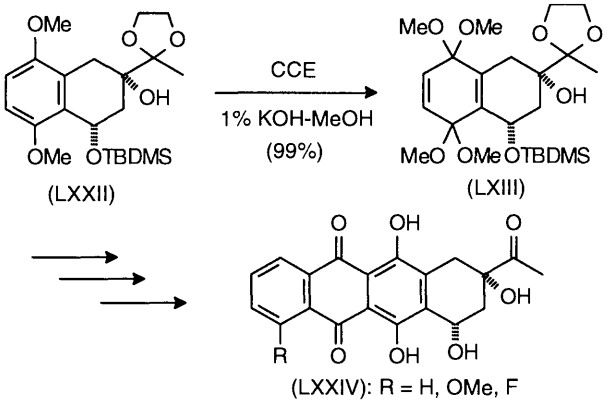
[a]All results from Ref. 81, using Pt anode and cathode at constant current in a single cell; [b]product was isolated as the quinone monoketal after hydrolysis; [c] from Ref. 83.

Monohydrolysis of the bisketal products under mildly acidic conditions leads to the synthetically useful quinone monoketals (**LXXI**) [Eq. (34)]. Considerable regioselectivity in the hydrolysis chemistry is possible, depending on the substituents present [42]. This chemistry has found wide application in the field of anthracycline synthesis, as illustrated by the anodic oxidation of highly functionalized dimethoxyaromatic **LXXII** to the corresponding bisketal (**LXXIII**) in essentially quantitative yield [Eq. (35)]. Compound **LXXIII** was subsequently elaborated in a convergent fashion via the monoketal (obtained as a 91:9 mixture of regioisomers) into several anthracycline aglycones (**LXXIV**), including (+)-daunomycinone and (+)-4-demethoxydaunomycinone [84] as well as several D-ring-fluorinated analogues [85].



(LXXI)

(34)

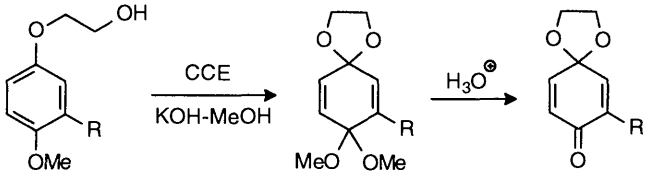


(LXXII) (LXIII)

(LXXIV): R = H, OMe, F

(35)

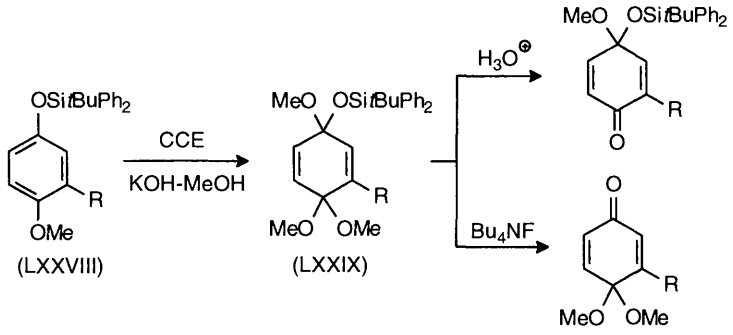
Useful strategies have been developed for the synthesis of unsymmetrically substituted bisketals that have their respective ketal functions differentiated in a way that facilitates regioselective monohydrolysis to an unsymmetrical quinone monoketal product. The first method involved anodic oxidation of hydroxyethyl ether derivatives (**LXXV**) to the mixed quinone bisketals (**LXXVI**) in 81–83% yield [Eq. (36)]. When R was -Br or -Me, the lower hydrolytic reactivity of the ethylene glycol ketal versus the dimethyl ketal allowed regioselective monohydrolysis to occur. Since **LXXV** was derived from a phenol that could be anodically oxidized to a quinone monoketal with regiochemistry opposite to that of **LXXVII**, the two methods were complementary. One exception involved bisketal **LXXVI** with R = OMe, which underwent selective hydrolysis of the ethylene glycol ketal moiety, due to the strong electron-donating resonance effect of the methoxyl substituent [86].



(LXXV) (LXXVI) (LXXVII)

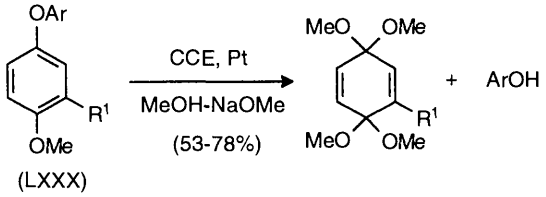
(36)

An alternate strategy involved anodic oxidation of *para*-methoxyphenol TBDPS ether derivatives (**LXXVIII**). The resulting mixed *O*-silyl *O*-methyl bisketals (**LXXIX**) underwent selective monohydrolysis of the dimethyl ketal moiety [87]. Alternatively, desilylation of **LXXIX** with Bu_4NF gave dimethyl monoketals of the opposite regiochemistry [Eq. (37)]. This work was in contrast to earlier studies on similar silyl ethers systems, wherein O–Si bond cleavage predominated during electrolysis [88].



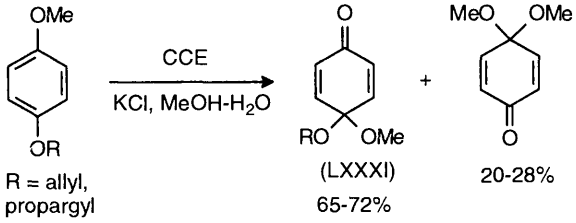
(37)

In studies of methods for lignin depolymerization [89–91], diaryl ethers (**LXXX**) were found to undergo anodic cleavage in methanolic sodium methoxide at constant current to give the corresponding bisketals and substituted phenols, the latter of which were recovered following acidification of aqueous extracts of the reaction mixture [Eq. (38)]. For unsymmetrical systems, the direction of cleavage of the diaryl ether was found to be a function of the presence of a methoxyl group at the 4-position of one of the rings [89].



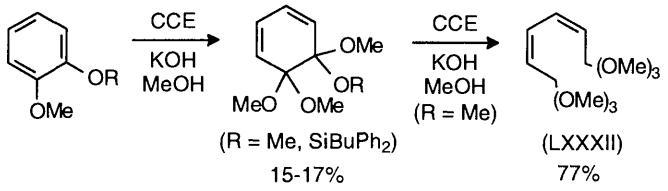
(38)

Apparently proceeding via the ECEC mechanism, oxidation of aryl propargyl and aryl allyl ethers in aqueous methanol–KCl at a Pt anode gave the corresponding mixed quinone monoketals (**LXXXI**) directly in reasonable yield, along with smaller amounts of the dimethyl monoketal [Eq. (39)]. No evidence was found for radical-cation-mediated 3,3-sigmatropic rearrangements. Under anhydrous conditions in acetonitrile–Et_4NClO_4, electrolysis of the same substrates afforded only mixed aryl–aryl C–C coupling products [92,93].



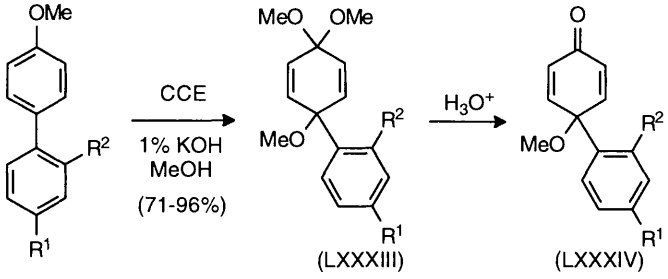
(39)

Anodic oxidation of *ortho*-dialkoxy aromatics has generally been less useful. Under conditions that gave a nearly quantitative yield of the *para*-bisketal from hydroquinone dimethyl ether, catechol ethers afforded the corresponding *ortho*-bisketals in low yield, along with other methoxylated products. Further oxidation of the *ortho*-bisketal derived from oxidation of catechol dimethyl ether afforded the ring-opened bis-*ortho*-ester (**LXXXII**) in 77% isolated yield [79,87]:



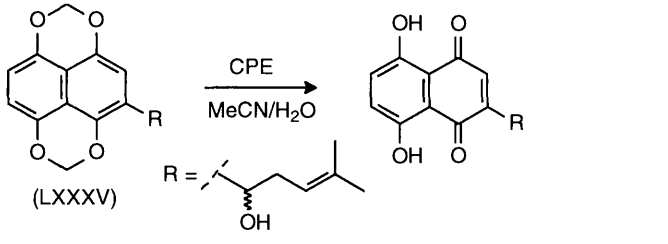
(40)

The anodic behavior of methoxylated biphenyls and dihydrophenanthrenes has been studied extensively. The stability of the radical cations in such systems was found to be a function of steric effects inhibiting a coplanar conformation for the two aryl rings [94]. From a preparative standpoint, methoxylated biphenyls have been found to undergo high-yield anodic methoxylation at a Pt anode in 1% KOH–methanol to afford the corresponding *para*-quinol ether ketals (**LXXXIII**) [Eq. (41)] [95]. These results are again consistent with an EEC_rC_p mechanism. Mild acid hydrolysis gave the *para*-quinol ethers (**LXXXIV**), which were subsequently functionalized using a variety of methods, affording unsymmetrical biphenyls. Analogous anodic transformation of a methoxylated 9,10-dihydrophenanthrene has also been reported [96].



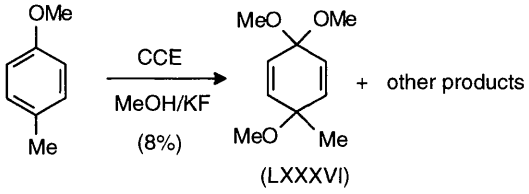
(41)

A novel O-deprotection protocol involving anodic cleavage of aromatic ether (**LXXXV**) was effectively used in the total synthesis of the natural products alkannin and shikonin [Eq. (42)]. The electrolysis was conducted at a carbon anode in MeCN/H_2O with $LiClO_4$ as electrolyte, giving an 80% yield at 50% conversion [97]. Although both naphthoquinone tautomers were initially formed after trapping of the radical cation by water and loss of CH_2O, the tautomer with alkyl substitution at the quinone double bond was more thermodynamically stable.



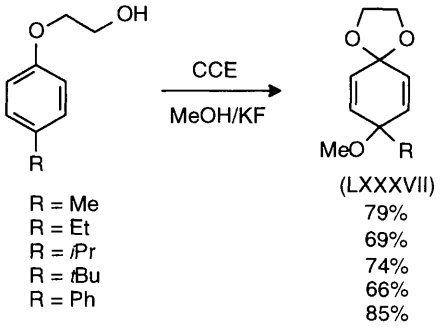
(42)

While anodic nuclear methoxylations of 1,4-dialkoxy or 1-alkoxy-4-aryl aromatics via the EEC_rC_p mechanism generally give excellent yields of the corresponding bisketals or quinol ether ketals, anodic oxidation of 1-alkoxy-4-alkyl aromatics often gave poor results, apparently due to competing alkyl side-chain anodic substitution processes [29]. For example, anodic oxidation of *para*-methoxytoluene in MeOH/KF gave only an 8% yield of the corresponding *para*-quinol ether ketal (**LXXXVI**) [Eq. (43)] [98]. Better results have been obtained using NaOMe as the electrolyte [74].



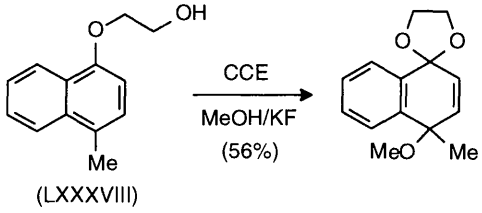
(43)

Replacement of the methoxy group with a hydroxyethyl ether function was found to largely overcome this limitation of the chemistry, affording the corresponding cyclic quinol ether ketals (**LXXXVII**) in good yield [Eq. (44)]. Mild acidic hydrolysis of the cyclic ketals to the quinol ether derivatives was nearly quantitative except when R = *t*-Bu [Eq. (44)], wherein loss of *t*-butyl led to reduction during the hydrolysis [98,99].



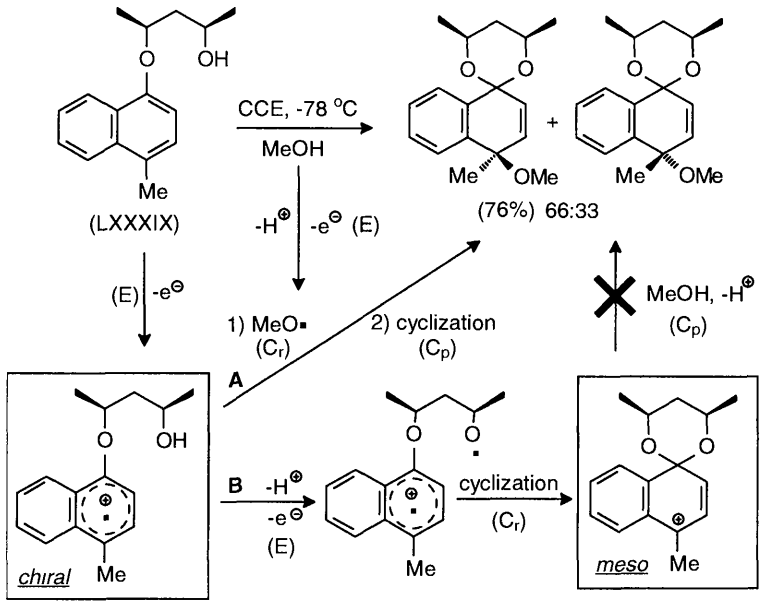
(44)

Anodic oxidation of the α-naphthol hydroxyethyl ether derivative (**LXXXVIII**) gave similar results [99]:



(45)

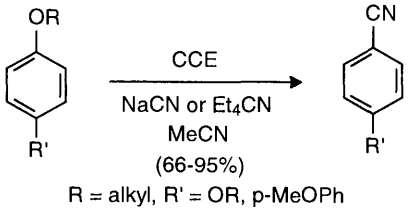
The predominance of nuclear methoxylation over competing alkyl side-chain oxidation processes for these systems was largely attributed to an intramolecular attack by the appended side-chain alkoxy radical on the anodically generated aromatic radical cation in the usual EEC_rC_p mechanism [99]. A more recent mechanistic study of anodic oxidation of chiral alkoxynaphthalene derivative (**LXXXIX**) sheds some additional light on this process [Eq. (46)] [100]. The isolation of a 2 : 1 mixture of enantiomeric methoxylated products indicated that intramolecular attack by the appended alkoxy radical on the aromatic radical cation (path B) was disfavored at −78°C (a nearly 1 : 1 mixture of enantiomers was obtained at 25°C), since the intermediate cyclic ketal resulting from such a process would be a *meso* form that would lead to a racemic mixture of methoxylated products. Note that the chirality of the appended hydroxyether side-chain disappears upon cyclization to the acetal.



(46)

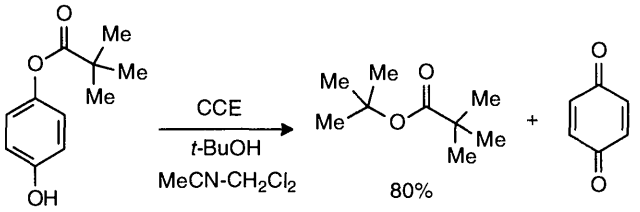
This result argued for the alternate view of the EEC_rC_p mechanism sequence, involving initial face-selective attack on the chiral radical-cation intermediate by methoxyl radical (path A), followed by acetal cyclization and proton loss. A rationale for the increased chemical yields observed for the systems studied in Eqs. (44) and (45) was not addressed in this work, although intramolecular solvation and stabilization of the intermediate radical cation by the appended hydroxyether side chain was suggested as one of the possible factors involved in the observed stereodifferentiation [101,102].

Anodic cyanation of alkoxylated biphenyls and other aromatic ethers is a limited but preparatively useful method for the formation of C–C bonds under mild conditions, as shown in Eq. (47) [103]. Mechanistic studies [104,105] supported a mechanism involving nucleophilic attack by cyanide ion on the aromatic radical cation rather than attack on the neutral aromatic nucleus by anodically generated cyano radicals, as had been proposed earlier [106].



(47)

Electrochemical oxidation of hydroquinone diesters generally gives only the corresponding quinones [20]. However, with hydroquinone monoesters, a useful anodic *trans*-acylation occurs when the reaction is carried out in alcohol solvents, probably via loss of acylium ion from the oxidized phenol monoester [107]. An example of the utility of the reaction is the conversion of hydroquinone monopivalate to highly hindered *t*-butyl pivalate in excellent yield:

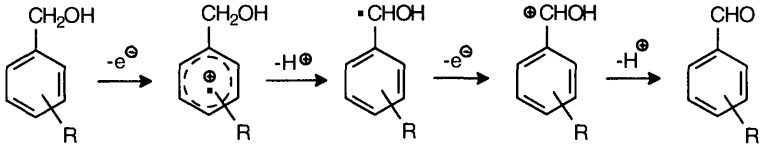


(48)

III. ANODIC OXIDATION OF ALCOHOLS AND DERIVATIVES

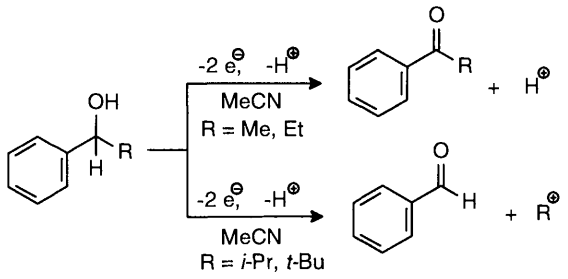
A. Benzylic, Allylic, and Aliphatic Alcohols

In general, the direct anodic oxidation of simple aliphatic primary alcohols to aldehydes and acids is often difficult to accomplish due to their high oxidation potentials, which are on the order of 2.5–2.7 V versus ferrocene/ferrocenium couple [108,109]. In contrast, for benzylic alcohols, oxidation of the ring π-system to the usual radical cation can occur, making transformations at the benzylic carbon more accessible. In the case of primary benzylic alcohols, direct anodic oxidation in acetonitrile gives benzaldehyde, apparently via an ECEC mechanism [Eq. (49)] [110,111]. The initially formed radical cation loses a proton to give the α-hydroxybenzyl radical, which undergoes subsequent oxidation and proton loss. Addition of bases like pyridine or sodium carbonate is helpful, though their role is not entirely clear beyond the likely suppression of acid-catalyzed ionization of the starting alcohol to benzyl cation, which can be trapped by solvent in a Ritter-type reaction. Overoxidation of the aldehyde to the acid also occurs, presumably via the hydrate, which may form via interception of the α-hydroxybenzyl carbocation by adventitious water [111,112]. Better results are usually obtained by indirect oxidation with mediators such as triarylamines [113]. *N*-oxyl radicals [114,115], chelated osmium complexes [116], and alkylammonium hypochlorites under phase-transfer catalysis conditions [117]. Such indirect methods are treated in detail elsewhere in this edition.



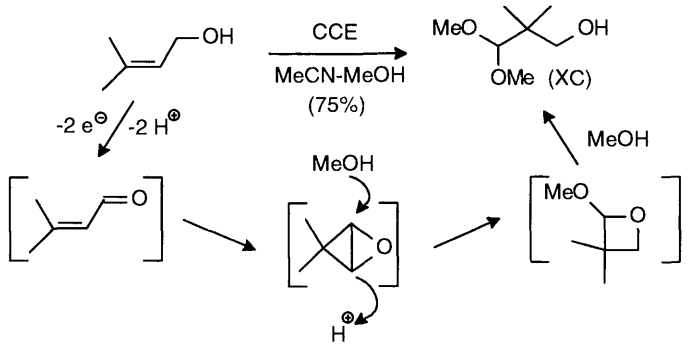
(49)

Under the same direct oxidation conditions, simple secondary benzylic alcohols ArCH(OH)R (R = Me or Et) undergo anodic oxidation in an analogous fashion to give the corresponding ketons [Eq. (50)]. However, when R is *i*-Pr or *t*-Bu, these groups are lost as carbocations from the intermediate α-hydroxybenzyl carbocation instead of a proton, giving benzaldehyde and the Ritter product derived from MeCN attack on the liberated carbocation [118]. As expected, cleavage of this type is the exclusive process observed in the oxidation of tertiary benzylic alcohols $ArC(OH)R_2$, regardless of R, with the usual leaving group ability—Me < Et < *i*-Pr < *t*-Bu—being observed. Examples of other anodic cleavages including tertiary alkylbenzyl carbinols [119] and benzpinacols [120] are treated mechanistically in the chapter on anodic cleavages.



(50)

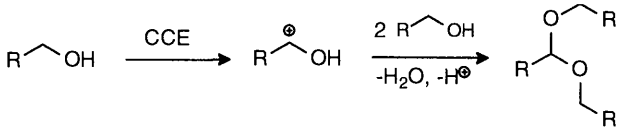
In spite of the abundance of naturally occurring allylic alcohols, such compounds have only recently become targets for initial anodic oxidation studies. For example, when prenol was subjected to constant-current oxidation at a carbon anode in acetonitrile–methanol in an undivided cell, an unusual rearrangement occurred, ostensibly at the surface of the electrode via the indicated mechanism, leading to hydroxyacetal (**XC**) in good yield [Eq. (51)]. The same product was obtained in similar yield by anodic oxidation of acrylaldehyde, demonstrating its intermediacy. Oxidation of geraniol under the same conditions gave citral, but no rearranged product and farnesol remained unchanged [121].



(51)

Among the aliphatic alcohols, oxidation of methanol has been studied most extensively [122–125]. At a platinum anode in acidic aqueous solutions, methanol oxidizes completely to CO_2. Higher primary alcohols oxidize to aldehydes and acids under these conditions, though detailed mechanistic studies are lacking [126,127]. Anodic oxidation of secondary alcohols in aqueous acid leads to the corresponding ketones in high yield, but the reaction has received little attention over the years [126,128]. Indirect oxidation methods employing mediators are of considerable interest in this area and are treated elsewhere.

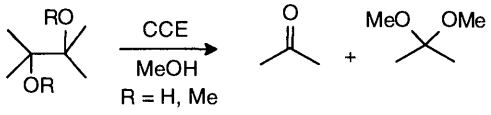
Under nonaqueous conditions, anodic oxidation of neat primary alcohols at a Pt anode gave the corresponding 1,1-dialkoxyalkanes, supposedly via the mechanism outlined in Eq. (52). Esters may also be formed, depending on electrolyte and anode material, though the reaction overall is of little preparative value [129–131].



(52)

B. Diols and Related Bifunctional Compounds

While anodic oxidation of simple alcohols is of limited utility, direct oxidation of vicinal diols and related compounds is an excellent method for achieving oxidative cleavage to the corresponding carbonyl or carbonyl-acetal products, as in Eqs. (53) and (54). Unlike certain chemical glycol cleavage reactions, the anodic method is not limited by the stereochemistry of the substrate oxygens [132].



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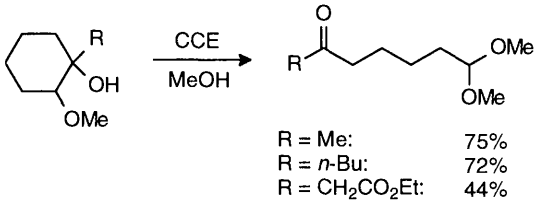
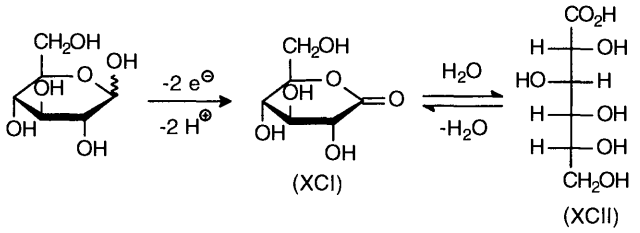


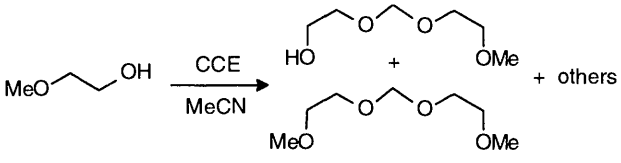
(54)

Anodic oxidation of glucose gives mainly the glucono-δ-lactone (**XCI**) or gluconic acid (**XCII**) [Eq. (55)] [133–135]. Formation of aldonic acids from aldoses is the most commonly observed process in other cases [126]. Additional work has been done in the area of indirect anodic oxidation of partially protected carbohydrates at a nickel hydroxide anode [136].



(55)

2-Methoxyethanol underwent anodic oxidation in acetonitrile to give a number of products, as in Eq. (56) [137]. Both tetrahydrofurfuryl alcohol and tetrahydropyranyl methanol have been oxidized indirectly at a nickel hydroxide anode to give a mixture of the corresponding alkoxy acids as well as lactones and ring-opened diacids [136].

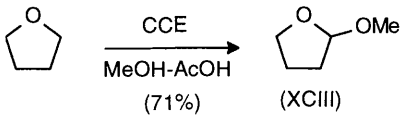


(56)

IV. ANODIC OXIDATION OF OTHER ALIPHATIC OXYGEN-CONTAINING COMPOUNDS

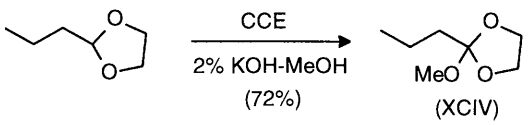
A. Saturated Ethers

Unlike the facile oxidation of vicinal diol ethers, the anodic oxidation of simple saturated aliphatic ethers is unsatisfactory under neutral or basic conditions, with the predominant reaction being -substitution in low yield [138]. Isoalkyl ethers such as di-*sec*-butyl ether, diisopropyl ether, and *t*-butyl methyl ether have been anodically oxidized in aqueous 1*M* H_2SO_4, giving, respectively, methyl ethyl ketone, acetone, and *t*-butanol as cleavage products in modest yields [139]. Anodic oxidation of ethers in alcohol solvents under acidic conditions gives the corresponding α-alkoxy ethers in good yield in some cases, as in the anodic α-methoxylation of tetrahydrofuran at a Pt anode to give acetal (**XCIII**) [140].



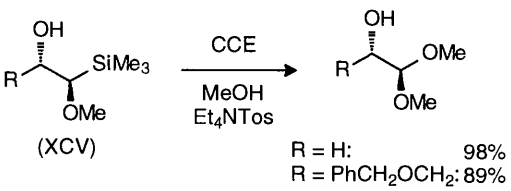
(57)

Under basic conditions using KOH as electrolyte, ethylene acetals are methoxylated at a Pt anode in good yield, giving the mixed *ortho*-esters, as in the anodic conversion of butyraldehyde ethylene acetal to *ortho*-ester (**XCIV**) [Eq. (58)]. In general, the corresponding dimethyl acetals give lower yields [141].



(58)

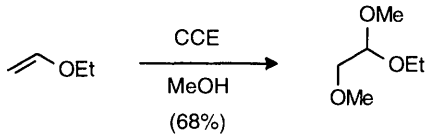
High-yield anodic oxidation of α-alkoxysilanes (**XCV**) to β-hydroxy aldehyde acetals was used as the key step in an iterative preparation of optically active polyols [Eq. (59)]. The reaction apparently involves formation of the ether radical cation, followed by rapid C–Si bond scission and nucleophilic trapping by solvent [142].



(59)

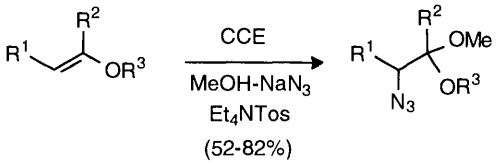
B. Unsaturated Ethers

Considerable progress has been made in recent years regarding the anodic oxidation of unsaturated ethers. In earlier studies, it was found that anodic methoxylation of simple vinyl ethers was a preparatively useful transformation, being essentially analogous to the anodic methoxylation of anisole derivatives, as in the preparation of 1-ethoxy-1,2-dimethoxyethane from ethyl vinyl ether [143]:



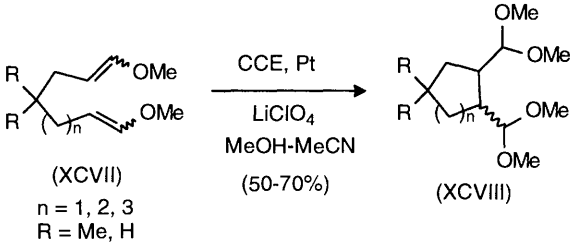
(60)

With growing interest in methods for the introduction of the azido function into organic compounds, anodic azidomethoxylation of simple vinyl ethers was more recently explored. This constant-current anodic functionalization was regiospecific and general, giving good to excellent yields of α-azidoacetals and ketals, as in Eq. (61). The methodology worked equally well using dihydropyran or vinyl ethers derived from cycloalkanone ketals [144].



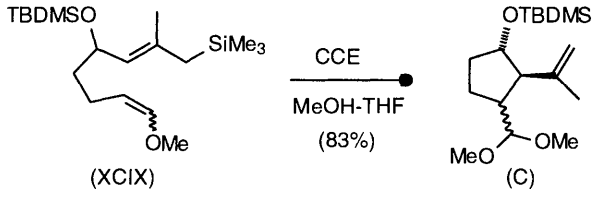
(61)

While it is a potentially useful anodic C–C bond-forming reaction, the bimolecular anodic dimerization of vinyl ethers in methanol generally proceeds in only modest yield under controlled-potential conditions [145]. More recently, the analogous anodic cyclization of bis-enol ether substrates (**XCVII**) was shown to give the corresponding cyclized bisacetals (**XCVIII**) in reasonable yield, although nonstereoselectively [Eq. (62)]. As in the bimolecular case, anodically generated vinyl ether radical cations are presumably the reactive intermediates in the process [146].



(62)

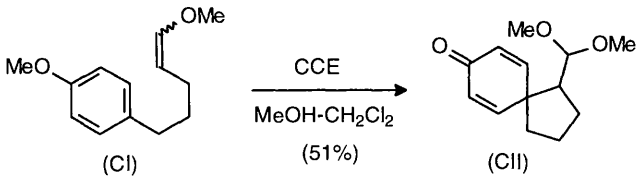
Similarly, at a carbon anode in 1 : 1 MeOH–THF, anodic cyclization of allylsilane enol ether (**XCIX**) proceeded stereoselectively to give (C) [Eq. (63)]. The use of allyl silanes as the unsaturated nucleophilic component in such radical-cation cyclizations proved to be beneficial, though the exact mechanistic details remain somewhat speculative [147]. The method represents an improvement over earlier methods involving anodic cyclization of alkenyl-substituted enol acetates [148].



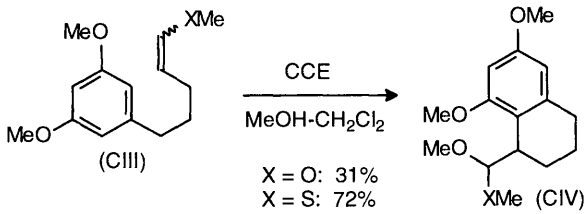
(63)

Vinyl ether radical-cation cyclizations using appended electron-rich aryl rings as the nucleophilic component have also been explored [149]. The nature of the products obtained was found in part to be a function of the position of electron donors on the

aryl ring. For example, constant-current oxidation of **CI** gave the corresponding spirodienone **CIII** [Eq. (64)], while anodic cyclization of **CIII** gave the cyclized acetal **CIV** [Eq. (65)]. Again, a vinyl sulfide moiety (X = S) proved to be superior to a vinyl ether (X = O) as a reaction partner, as was previously noted in anodic phenol–alkene oxidative cyclizations [50,58].

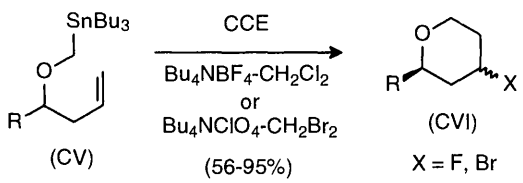


(CI) (CII) (64)



(CIII) (CIV) (65)

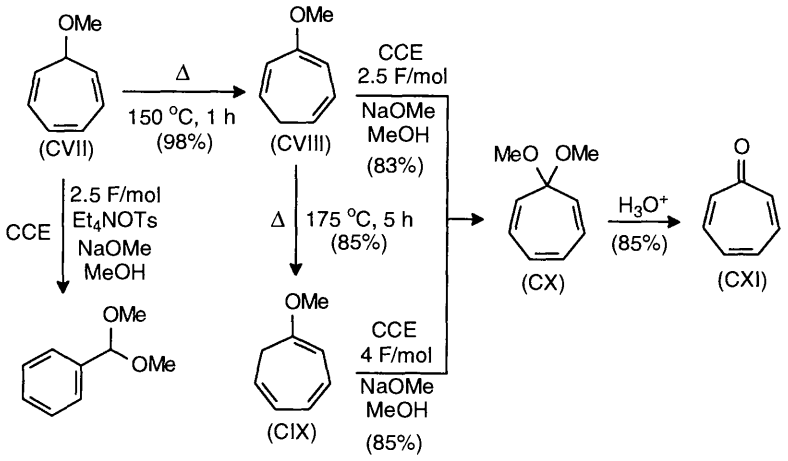
Intramolecular anodic C–C bond formation leading to F- or Br-substituted heterocycles (**CVI**) from α-stannyl ethers (**CV**) has been carried out at constant current in Bu_4NBF_4–CH_2Cl_2 [150] or in Bu_4NClO_4–CH_2Br_2 [151] [Eq. (66)]. Formation of six-membered rather than five-membered ring products suggested cyclization via a cationic rather than a radical intermediate after C–Sn bond cleavage via the α-stannyl ether radical cation. Interception of the cyclized cationic intermediates by halide ion terminates the process. Solvent-derived bromide ion serves as the terminator when the electrolysis is conducted in CH_2Br_2. No cyclization occurred using MeOH as solvent.



(CV) (CVI) (66)

X = F, Br

A number of interesting transformations of oxygenated cycloheptatrienes were found to be possible via anodic oxidation. As shown in Eq. (67), constant-current electrolysis of 6-methoxy-1,3,5-cycloheptatriene (**CVII**) (which is itself available by anodic oxidation of 1,3,5-cycloheptatriene [152]) gives benzaldehyde dimethylacetal, while thermal rearrangement of **CVII** to **CVIII** followed by electrolysis gives tropolone dimethyl ketal (**CX**), which may be readily hydrolyzed to tropolone (**CXI**) [153]. Likewise, further thermal rearrangement of **CVIII** to **CIX** followed by anodic oxidation also gives **CX**, though no explanation was offered for the lower current efficiency observed (4 F/mol vs. 2.5 F/mol for the **CVIII** → **CX** transformation). A number of substituted tropolones were also prepared in an analogous fashion, making the anodic method one of considerable importance in this area of study.



(67)

C. Miscellaneous Oxidations

An anodically induced controlled-potential cycloaddition reaction between ethyl vinyl ether and *N*-cyanomethyl oxazolidines was recently reported, though the reaction was thought to involve oxidation of the oxazolidines rather than the vinyl ether component [154].

A cyclic voltammetry study on a series of bicylic peroxides has been carried out, but little else is known about the anodic behavior of such ether derivatives [155].

Direct anodic oxidation of aldehydes to acids has long been known, but has been largely neglected in recent years due to its limited preparative value [156,157]. Likewise, the anodic oxidation of ketones leads mainly to C–C bond cleavage reactions or to Ritter-type products when conducted in acetonitrile, though the reaction in the latter case is of some mechanistic interest [158–160].

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17

Anodic Oxidation of Sulfur- and Selenium-Containing Compounds

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I. INTRODUCTION

Although organic compounds containing sulfur atoms are often considered a simple class, their electrochemical behavior depends on their structure and the experimental conditions used, with both having a pronounced influence upon the pathways followed during their anodic oxidation. Due to the variety of structures, we had to select subjects we considered to be representative of the electrochemical behavior of certain types of compounds; therefore, this chapter is not to be viewed as an exhaustive review. Even so, we had to restrain our presentation, giving only short summaries in most cases. Several reviews dealing with the anodic oxidation of different types of organic sulfur compounds have been published [1–6].

II. OXIDATION OF COMPOUNDS CONTAINING THE THIOL OR DISULFIDE GROUP

A. Thiols and Related Compounds

The RSH/RSSR interconversion is well known in organic chemistry due to its biological importance in systems like cysteine–cystine, glutathione and the corresponding disulfide, and α-lipoic acid and related dithiol.

The anodic oxidation of thiols, RSH, in aqueous solution on noble metal electrodes are complicated by adsorption phenomena [1, 7–12]. The oxidation peak potentials observed during cyclic voltammetry become more negative and vary linearly with pH by roughly 60 mV/pH when $pH < pK_a$ (RSH), and are independent of pH at $pH > pK_a$. These observations, together with product analysis and coulometric n values close to unity, suggest an oxidation process involving the initial formation of an $RS^{\cdot}$ radical, as in Eq. (1), followed by dimerization to the disulfide, as in Eq. (2). The corresponding sulfonic acid is formed during more extensive oxidation, probably via oxidation of adsorbed $RS^{\cdot}$ [Eq. (3)].

$$RSH \xrightarrow{-e} RS^{\cdot} + H^{+} \tag{1}$$

$$2RS^{\cdot} \longrightarrow RSSR \tag{2}$$

$$RS^{\cdot} + 3H_2O \xrightarrow{-5e} RSO_3^{-} + 6H^{+} \tag{3}$$

At Hg electrodes the oxidation of thiols in aqueous solution occurs at more negative potentials than on Pt and alkylmercury compounds are formed, as in Eqs. (4)–(6) [1, 7, 13–15].

$$RSH + Hg \xrightarrow[-H^{+}]{-e} (HgSR)_{ads} \tag{4}$$

$$(HgSR)_{ads} \rightleftharpoons (HgSR)_{soln} \tag{5}$$

$$2HgSR \longrightarrow Hg(SR)_2 + Hg \tag{6}$$

In nonaqueous solution, such as dimethylformamide (DMF) and MeCN, distinct peaks for the oxidation of RSH and RS^{-} to disulfides are observed on Pt and Au anodes, respectively [12–16].

Preparative electrolyses of aliphatic and aromatic thiols using a Pt anode in MeOH/NaOMe solution under controlled current conditions lead to the corresponding disulfides in high yields [17].

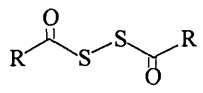
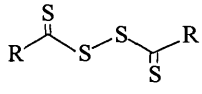
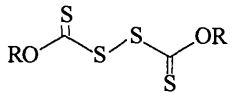
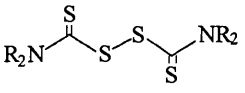
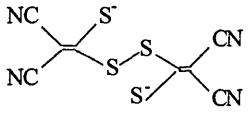
During the oxidation of sodium and mercury thiophenolate at an Hg electrode in dimethyl sulfoxide (DMSO) or DMF solutions [18] higher mercury complexes than those observed in aqueous solution are formed, as in Eqs. (7)–(8), with Ar = Ph.

$$3ArS^{-} + Hg \xrightarrow{-2e} Hg(SAr)_3^{-} \tag{7}$$

$$2Hg(SAr)_3^- + Hg \xrightarrow{-2e} 3Hg(SAr)_2 \quad (8)$$

It was shown [19] that $Hg(SAr)_2$, with Ar = Ph, or 4-XC_6H_4 (X = Me, OMe, Cl) are oxidized at Pt in DMF, 2 F mol^{-1}, affording as main products the corresponding disulfides, ArSSAr, and Hg^{2+}.

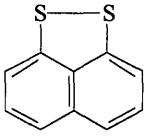
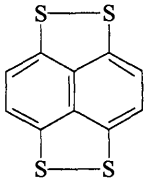
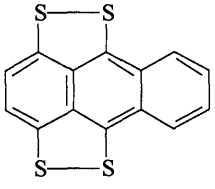
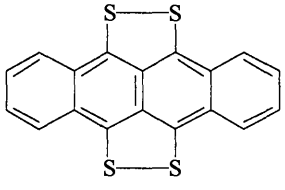
The anodic oxidation of a variety of organo-sulfur compounds containing the SH or S^- group, like thioacids, RCOSH [20], dithioacids, RCS_2H [21], alkyl xanthates, $ROCS_2^-$ [22], *N*, *N*-dialkyldithiocarbamates, $R_2NCS_2^-$ [23, 24], and 1,1-dicyanoethylene-2,2-dithiolate, $[(NC)_2C{=}CS_2]^{2-}$ [25], has been examined using solid electrodes, and the formation of the following products with a disulfide bond was established.

The electrochemical behavior of compounds as alkyl xanthates [26] and *N*, *N*-dialkyldithiocarbamates [27, 28] on Hg electrodes was shown to be diverse, and their mercury derivatives are formed when they are oxidized anodically.

B. Disulfides

Cation radicals are intermediates in the anodic oxidation of simple dialkyl and diaryl disulfides, RSSR, but are too short-lived to be observed at the time scale of slow-sweep voltammetry, although their existence has been established by pulse radiolysis [29] and electron spin resonance (ESR) spectroscopy [30]. Their detection by voltammetric technique was achieved in the case of more complex molecules like NDS [31], and when two disulfide linkages are present as in TTN, TTA, and TTT, even the generated dications are stable [32, 33].

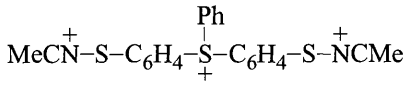





	NDS	TTN	TTA	TTT
E_1^{ox*}	0.86	0.55	0.41	0.24
E_2^{ox*}		0.93	0.85	0.67

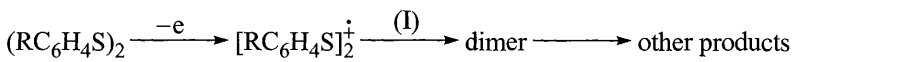
*V *versus* SCE

The electrochemical oxidation of organic disulfides, RSSR, has been investigated by several groups, and it was shown that the oxidation products depend markedly on the nature of R and the experimental conditions.

Diphenyl disulfide yields benzenesulfonic acid when electrolyzed in HOAc/HCl solution at a Pt anode [34]. A similar result was obtained in $MeCN/NaClO_4$ solution [35], but with Bu_4NBF_4 as supporting electrolyte the cation shown was suggested as the most probable product.



The oxidation of a series of diphenyl, $(RC_6H_4S)_2$, and methyl phenyl disulfides, 4-RC_6H_4SSMe, ring-substituted by several functional groups, was examined [36]. The potentials of the first oxidation wave turn out to be dependent upon the nature of the substituents (Table 1). With diphenyl disulfide and derivatives the calculated number of electrons n varies between 1 and 4.5, going from compounds with electron-donor groups toward compounds with electron-acceptor substituent groups, but n is close to unity for the methyl phenyl disulfides. A mechanism involving dimerization of the initially formed cation radicals followed by further transformations is suggested for the $(RC_6H_4S)_2$ oxidation, as in Eq. (9), whereas for 4-RC_6H_4SSMe a sulfur–sulfur bond cleavage or a deprotonation of the primary cation radical is likely to occur.



(9)

Preparative electrolyses of diphenyl disulfide and 4-bromophenyl 4-nitrophenyl disulfide afforded, respectively, sodium benzenesulfonate (20%) and bis(4-bromophenyl) and bis(4-nitrophenyl) disulfides with an overall yield of 80% [37].

Anodic oxidation of dialkyl disulfides in $MeCN/H_2O$ solutions at a Pt electrode yields alkyl alkanethiosulfonates both under controlled potential and current conditions, as in Eq. (10) [38].

Table 1 First Oxidation Wave Potentials of Some Diphenyl and Methyl Phenyl Disulfides

$(RC_6H_4S)_2$					
R	$E^a_{1/2}$	R	$E^a_{1/2}$	R	$E^a_{1/2}$
4-NMe_2	0.390	H	1.150	2-Me	1.200
4-OMe	0.895	4-Cl	1.250	2-Cl	1.500
4-Me	1.045	4-NO_2	1.590	2-NO_2	1.660

4-RC_6H_4SSMe				
R	OMe	Me	Br	NO_2
$E^a_{1/2}$	0.970	1.110	1.240	1.405

[a] V versus Ag/0.1 *M* $AgNO_3$, Pt oxide disk, $MeCN/Bu_4NClO_4$ (Ag/0.1 *M* $AgNO_3$ vs. SCE 0.337 V).

$$\text{RSSR} \xrightarrow[H_2O]{-4e} \text{RSO}_2\text{SR} \qquad (10)$$

R	Me	Et	*n*-Pr	*i*-Pr	*n*-Bu	*i*-Bu	*s*-Bu
Yield %	80	71	72	46	66	66	28

Conditions for Eq. (10) are MeCN-H_2O (9:1 v/v)–$NaClO_4$ (0.1 mol L^{-1}), Pt anode, 3.5–4 F.

Lower yields are observed when R is a secondary group, and no thiosulfonate is formed with $R = t$-Bu. Although thiosulfinates, RSOSR, are intermediate products, they are not oxidized under the electrolysis conditions. It was shown that thiosulfinates are transformed into thiosulfonates in the presence of disulfides being oxidized, presumably involving an intermediate species electrogenerated from the disulfide [38b]. Diaryl disulfides also lead to thiosulfonates in good yields when oxidized under similar conditions [39]. The disulfoxide, RSOSOR, supposedly obtained in the anodic oxidation of dibenzyl disulfide in a HOAc/HCl solution at a Pt anode [40], is probably also a thiosulfonate.

Anodic oxidation of diphenyl disulfides in CH_2Cl_2/Bu_4NBF_4 solution in the presence of trifluoroacetic acid yields oligo (*p*-phenylene) sulfides [41]. Under these conditions the oxidation proceeds via a one-electron transfer, and it is believed that in acidic medium nucleophilic reactions involving the initial cationic product are suppressed. A sulfonium cation formed by reaction of a cation radical with the starting material is suggested as an intermediate:

$$\text{PhSSPh} \xrightarrow{-e} [\text{PhSSPh}]^{+\cdot} \xrightarrow{\text{PhSSPh}} \text{PhS}\overset{+}{\underset{\text{SPh}}{\text{S}}}\text{Ph} + \text{PhS}^{\cdot}$$

$$\text{PhS}\overset{+}{\underset{\text{SPh}}{\text{S}}}\text{Ph} \xrightarrow{\text{PhSSPh}} \text{PhSC}_6\text{H}_4\text{SSPh} + \text{PhSSPh} + \text{H}^{+} \qquad (11)$$

$$\text{PhSC}_6\text{H}_4\text{SSPh} \longrightarrow \left(\text{C}_6\text{H}_4\text{S}\right)_n$$

It is noteworthy to mention that the oligomerization can also be achieved using mediators as hydroquinones and cerium acetylacetonate in catalytic amounts in solution or a polypyrrole modified electrode.

n-*t*-Butylamides are obtained by electrochemical oxidation of di-*t*-butyl disulfide using different nitriles as solvent and a Pt working electrode [42]. At lower oxidation potentials one carbon–sulfur bond is cleaved in a one-electron process to form a *t*-Bu cation, which reacts with the nitrile, and a radical, *t*-BuSS$^{\cdot}$, which dimerizes:

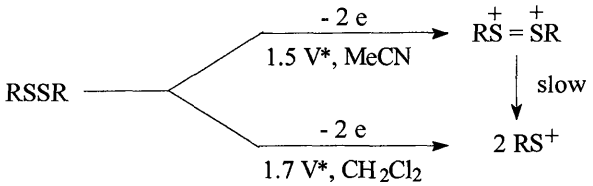
$$\text{t-BuSSBu-t} \xrightarrow[\text{1.3 V } \textit{vs.}\text{ SCE}]{-e} \begin{cases} \text{t-Bu}^{+} \xrightarrow{\text{RCN/H}_2\text{O}} \text{RCONHBu-t} \\ \text{t-BuSS}^{\cdot} \xrightarrow{\text{(II)}} \text{(t-BuSS)}_2 \end{cases} \qquad (12)$$

(II)

R = Me, Ph, $PhCH_2$, EtO_2CCH_2

At higher potentials (1.9 V vs. SCE), besides the amide, sulfur is formed in an overall two-electron process.

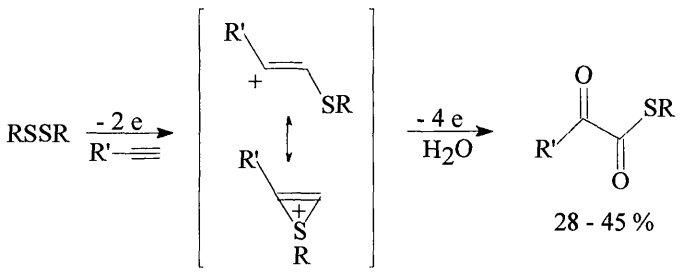
The mechanism of the anodic oxidation of aromatic disulfides at Pt in MeCN and CH_2Cl_2, was reexamined [43]. In CH_2Cl_2, under neutral conditions, the oxidation is a two-electron process leading to a sulfenium cation, RS^+, whereas in MeCN a dicationic species is postulated as intermediate that can partially evolve toward RS^+ [Eq. (13)]. The sulfenium cation seems to be very stable in solution even during several days.



(13)

*V *versus* SCE

As RS^+ is a much better electrophile and is considered to be the active species in reactions with organic substrates, better product yields are expected in CH_2Cl_2 solutions. This was observed when disulfides were electrolyzed in the presence of terminal alkynes, in solutions containing nucleophiles, as H_2O, MeOH, EtOH, and α-oxo-thioesters were obtained as major products:



(14)

R = Ph, $PhCH_2$, 4-MeC_6H_4 ; R' = Ph, *n*-Bu

Conditions: Pt anode, CH_2Cl_2/Bu_4NClO_4 (0.1 mol L^{-1}).

Yields in the range of 60–90% of unsymmetrical disulfides, $RSSR^1$, were obtained by reaction of a sulfenium cation, RS^+, prepared by anodic oxidation of several disulfides, RSSR, with thiols, R'SH, in CH_2Cl_2/Bu_4NClO_4 solutions using a Pt anode [44]:

$$RSSR \xrightarrow{-2e} 2RS^+ \xrightarrow[-H^+]{R'SH} RSSR' \qquad (15)$$

R = Ph, $PhCH_2$, Me; R' = *n*-Pr, *t*-Bu, Ph, $PhCH_2$

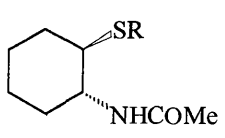
It was also observed that disulfides can be substituted for the thiols, but yields are lower.

When disulfides are oxidized in the presence of alkenes in MeCN solution, 2-acetamidosulfides are formed [45–48]. With cyclic alkenes a high selectivity for antiaddition is observed, whereas acyclic 1-alkenes yield the terminal sulfides with high regioselectivity [47]. Some of the results are summarized in Table 2.

Table 2 Oxidation by Controlled Potential of RSSR in the Presence of Cyclohexane and 1-Octene

	Product (yield %)[a] for RSSR			
Alkene	Me	Ph	$PhCH_2$	2-Pyridyl
Cyclohexene	**1** (58)	**2** (87)	**3** (112)	**4** (77)
1-Octene	**5** (52)	**6** (84)	**7** (17)	**8** (33)

Source: Ref. 47. Conditions: Pt anode, $MeCN/Bu_4NBF_4$ (0.1 mol L^{-1}).
[a]Yields based on RSSR.



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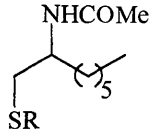

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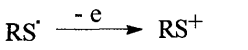
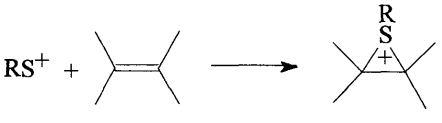
The mechanism proposed for the reaction is shown in Eqs. (16)–(20) [46, 47]:

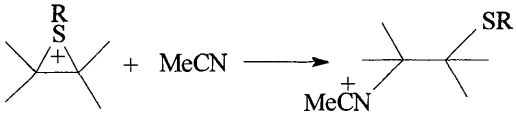
(16)



(17)



(18)



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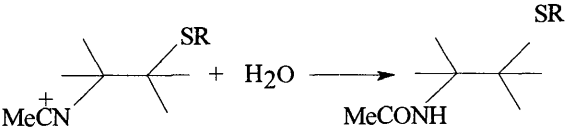
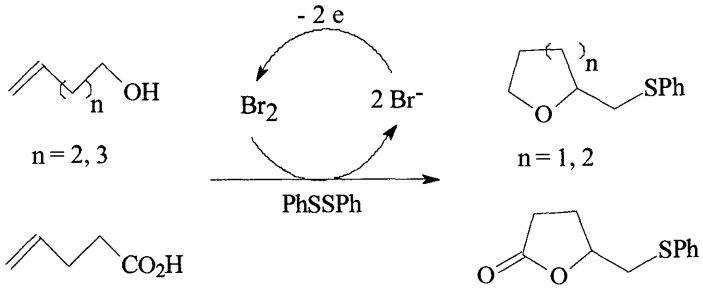


(20)

The reactive intermediate is considered to be RS^+, which adds to the carbon–carbon double bond, probably forming an intermediate episulfonium ion as in Eq. (18). This by a Ritter-type reaction followed by hydrolysis leads to the final products, as in Eqs. (19) and (20).

Cyclic ethers and lactones are obtained from alkenols and alkenoic acids through cyclizations initiated by sulfenium cations generated electrochemically from disulfides either by direct anodic oxidation or using bromide as a redox catalyst [49]. A variety of substrates were investigated using diphenyl disulfide bromide-mediated oxidation, and direct anodic oxidation involving diphenyl disulfide and some of its ring substituted derivatives. The most favorable results are obtained by the mediated reaction or utilizing the direct anodic oxidation of bis(4-methoxyphenyl)disulfide. Five- and six-membered

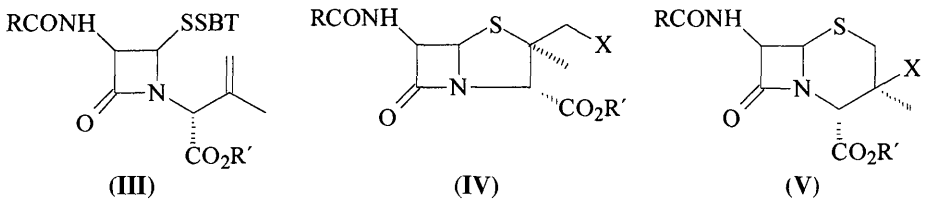
arylthio substituted cyclic ethers and lactones are formed when mono- or disubstituted alkenols and alkenoic acids are used as starting materials. Examples are shown in Eq. (21).



(21)

Conditions: Pt anode, CH_2Cl_2/Bu_4NBr, controlled current.

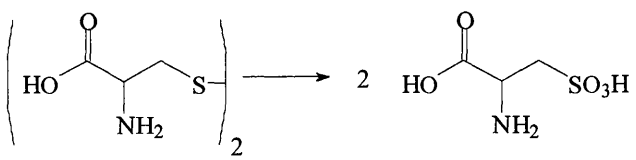
4-(2-Benzothiazolyldithio)azetidinones, **III**, are important intermediates related with the penicillin–cephalosporin conversion. A halide-mediated electrooxidative sulfur–sulfur bond cleavage of **III** leads to 2β-halomethyl penicillins (**IV**) and 3β-halocephams (**V**).



BT = 2-benzothiazolyl

Several disulfides (**III**) when electrolyzed at Pt electrodes in MeCN containing chloroacetic acid and Me_4NBr, under controlled current conditions, yield bis(2-benzothiazolyl) disulfide and compound **IV** (X = Br), which is transformed into **V** during isolation [50]. An intermediate episulfonium cation is suggested for this reaction. The electrochemical conversion of **III** was thoroughly examined under different experimental conditions and was reviewed [51].

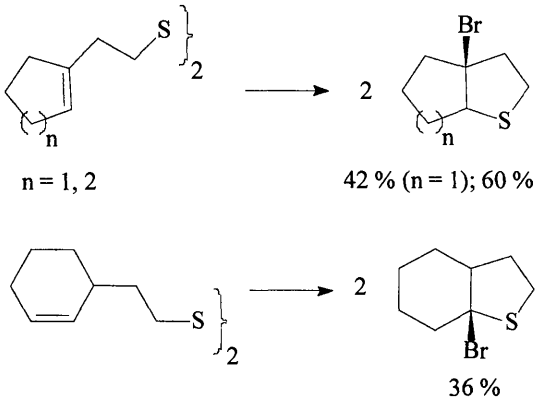
Attempts to obtain l-cysteic acid by direct electrochemical oxidation of l-cystine led to low material yields and mixtures of products [52], but bromide-mediated electrolyses in a divided cell afford the expected product in high yield, as in Eq. (22).



(22)

Conditions: C electrodes, HBr/H_2O, controlled current.

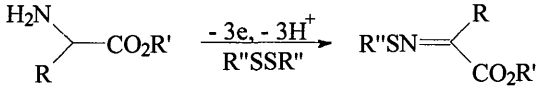
In the electrochemical oxidation of Δ^3 and Δ^4 unsaturated disulfides at Pt electrodes in MeCN, complex mixtures of products are obtained [53]. This situation was circumvented by performing the electrolyses in the presence of bromide salts under either controlled potential or controlled current conditions. A cleavage of the S–S bond occurred and cyclization products were formed. Examples are shown in Eq. (23). The formation of *cis* fused ring systems indicates high antistereoselectivity for addition to the C–C double bond.



(23)

Conditions: Pt anode, MeCN, Et_4NClO_4–Et_4NBr.

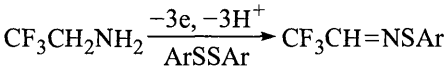
When mixtures of α-aminoalkanoates and disulfides are electrolyzed in CH_2Cl_2–H_2O–$MgBr_2$ using Pt electrodes, they are transformed directly into sulfenimines [Eq. (24)] [54]. Amino groups of penicillin and cephalosporin are conveniently sulfanylated by this procedure.



(24)

R = *i*-Bu, Ph, $(CH_2)_2CO_2Et$, CH_2CO_2Et; R' = Me, Et
R'' = Bu, *t*-Bu, Ph, 4-$O_2NC_6H_4$, 2-benzothiazolyl

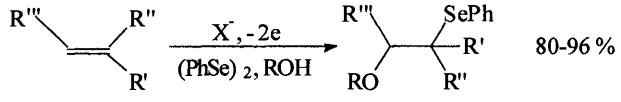
A similar reaction was performed involving 2,2,2-trifluoroethylamine and diphenyl and di-*p*-tolyl disulfides. The most suitable conditions were $MeCN/Et_4NClO_4/NaBr$ and utilizing Pt electrodes [55]:



(25)

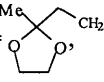
Selenium compounds are important reagents in organic synthesis [56]; therefore, some examples involving the electrochemical oxidation of diphenyl diselenide, PhSeSePh, in the presence of organic substrates are shown to illustrate their utilization in synthetic useful transformations.

Diphenyl diselenide has been used to convert alkenes into 2-acetoxy, 2-methoxy, and 2-hydroxy selenides by indirect oxidation in MeCN-H_2O, MeOH, and HOAc, respectively, in the presence of Et_4NX(X = Cl, Br, I) as supporting electrolytes [57]. High regioselectivities (Markownikoff-type adduct) are observed, and best current efficiency is obtained for X = Cl or Br. Examples are shown in Eq. (26).



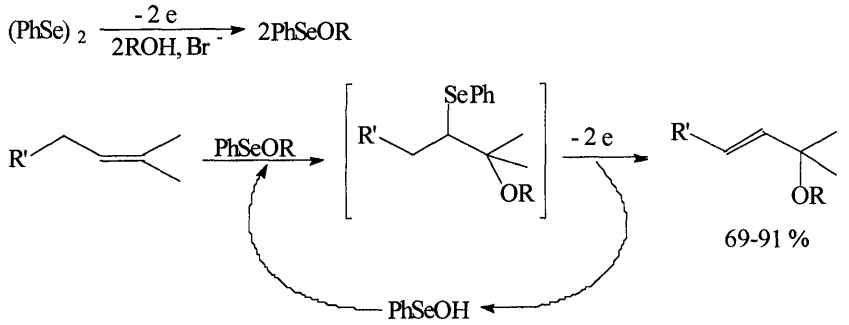
(26)

R' = R'' = H, R''' = Ph, $Me(CH_2)_5$; R' = H, R''/R''' = $-(CH_2)_4-$;

R' = R'' = Me, R''' =  $HO(CH_2)_2CH(Me)CH_2CH_2-$, $AcOCH_2CH{=}C(Me)CH_2CH_2-$

Conditions: Pt anode, controlled current, MeCN.

When the oxyselenides are further oxidized, PhSeOH is eliminated and allylic oxycompounds are formed [58]. This procedure can be accomplished using catalytic amounts of PhSeSePh, as in Eq. (27) [59, 60].



(27)

R = Me or H

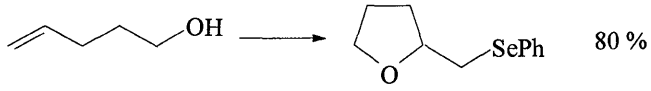
R' = CH ≡ CCMe(OAc)CH_2 ; $MeO_2CCH{=}CMeCH_2$;

$AcO(CH_2)_2CHMeCH_2$; $AcOCH_2CH{=}CMeCH_2$

Conditions: Pt anode, controlled current, MeCN (from ref. 59).

Direct anodic oxidation of PhSeSePh at a Pt anode in MeCN–Bu_4NBF_4 containing alkenes results in 2-acetamido selenides in good yields [61].

The Δ^4- and Δ^5-unsaturated acids [62, 63] and unsaturated alcohols [62] yield tetrahydrofuran-2-one or tetrahydropyran-2-one and tetrahydrofuran or tetrahydropyran derivatives, respectively, when electrolyzed in MeOH or CH_2Cl_2 containing PhSeSePh and NH_4Br or Et_4NBr. Examples of products and respective precursors are shown in Eqs. (28) and (29).



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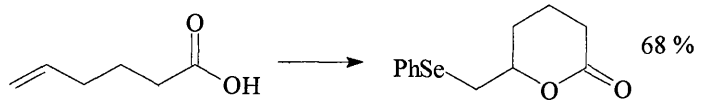
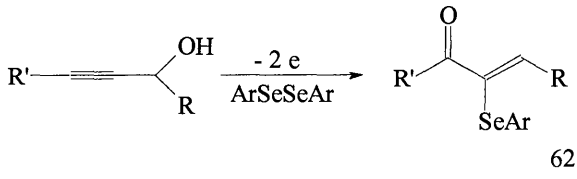


(29)

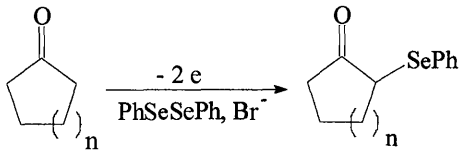
Electrochemical oxidation of bis(4-chlorophenyl)diselenide in MeCN–H_2O containing 3-hydroxyalkynes affords α-arylseleno-α, β-unsaturated aldehydes or ketones [64]:



(30)

Conditions: Pt electrodes, Et_4NClO_4 and H_2SO_4 in MeCN/H_2O, 60°C.

Ketones are transformed into the corresponding 2-phenylselenyl derivatives by a bromide-mediated electrolysis in mainly HOAc or MeOH and MeCN in the presence of PhSeSePh [65]. Some examples are shown in Eq. (31).



(31)

n = 1, 2, 3 84-97 %

Conditions: Pt electrodes, controlled current, HOAc, Et_4NBr, $MgBr_2$.

III. OXIDATION OF SULFIDES

A. Dialkyl Sulfides

The electrochemical oxidation of dimethyl sulfide was examined in MeCN [66], and it was shown that the nature of the products formed is dependent on the water content of the solvent. In the presence of 1% water the only product is dimethyl sulfone [Eq. (32)], but in dry MeCN the oxidation results in methanesulfonate and carbon monoxide involving the formation of an intermediate sulfonium salt by a two-electron process, as in Eqs. (33)–(35).

$$MeSMe \xrightarrow[H_2O/MeCN]{-4e,\ -4H^+} MeSO_2Me \tag{32}$$

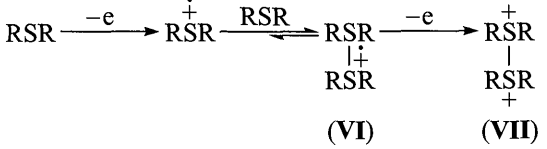
$$MeSMe \xrightarrow[MeCN]{-e} Me\overset{+\cdot}{S}Me \xrightarrow{-e,\ -H^+} MeS\overset{+}{C}H_2 \tag{33}$$

$$MeS\overset{+}{C}H_2 + MeSMe \longrightarrow MeSCH_2\overset{+}{S}Me_2 \tag{34}$$

$$MeSCH_2\overset{+}{S}Me_2 \xrightarrow[H_2O]{Cl_2O_7} \longrightarrow MeSO_3^- + CO \tag{35}$$

It is suggested that Cl_2O_7 is responsible for the transformation of the sulfonium cation into the final products [Eq. (35)], because with Et_4NBF_4 as supporting electrolyte no sulfonate was obtained.

The anodic behavior of aliphatic sulfides is quite different when the experiments are conducted in "superdry" conditions [67]. The number of electrons involved in this case was established to be 1.0 ± 0.1, the formation of a sulfonium ion $RSCH_2S^+R_2$ as an intermediate is excluded, and a dimeric dication is suggested as a transient product:



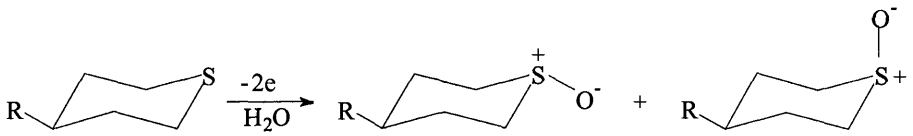
(36)

R = Me, Et, Bu, $-(CH_2)_5-$

The formation of cation radicals (**VI**) [68–71] and of dications (**VII**) [72–74] during the oxidation of organic sulfur compounds has been well established.

The formation of dialkyl sulfones in the oxidation of sulfides proceeds most likely through the corresponding sulfoxides [34, 40], which may be isolated. Sulfoxides are major products in the indirect oxidation of sulfides performed by a reagent electrochemically generated from crosslinked poly(4-vinylpyridine)hydrobromide [75].

Bromide ion-mediated electrolyses of substituted cyclic sulfides result in *cis* and *trans* isomeric sulfoxides [76]:



$R = 4\text{-}ClC_6H_4$

(37)

Conditions: Pt electrodes, organic solvents–H_2O, Bu_4NBr.

The *trans* isomer predominates (> 80%) in solvents with 10% of water, whereas in the presence of sulfuric acid and 0.5% water the *cis* isomer becomes the major product (67%).

Electrochemical oxidation of ethylene and propylene sulfides in MeCN–Bu_4NClO_4 medium results in poly(ethylenesulfide), and poly(propylenesulfide) films, respectively [77]. The propagation supposedly occurs by a cationic ring-opening step involving sulfonium salts.

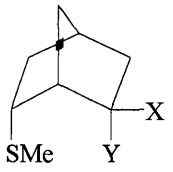
The anodic oxidation of a series of 1, *n*-halo(alkylthio)-, $X(CH_2)_nSR$ (X = Cl, Br, I), and 1,*n*-chloro(alkylsulfinyl)alkanes, $Cl(CH_2)_nSOR$, was studied by cyclic voltammetry and by controlled potential electrolyses in MeCN–Bu_4NPF_6 [78]. No influence of the alkyl substituents R nor of the number of methylene groups *n* with $n > 2$ upon the ease of sulfur oxidation, a two-electron irreversible process, was observed. Sulfoxides and sulfones are obtained in good yields by electrolysis in aqueous acetonitrile, as in Eqs. (38) and (39).

$$X(CH_2)_nSR \xrightarrow[H_2O/MeCN]{-2e} X(CH_2)_n\overset{+}{S}R \quad (O^-) \tag{38}$$

X = Cl, n = 3, 4, 5, 6
X = Br or I, n = 3, 4, 6
R = Me, Et, Pr, *i*-Pr, *t*-Bu

$$Cl(CH_2)_n\overset{+}{S}R \quad (O^-) \xrightarrow[H_2O/MeCN]{-2e} Cl(CH_2)_nSO_2R \tag{39}$$

The influence of various groups proximate to the sulfur atom on the electrochemical oxidation of thioethers is evaluated using 2-substituted 6-(methylthio)-bicyclo[2.2.1]heptanes (**VIII–XI**) in MeCN [79, 80].



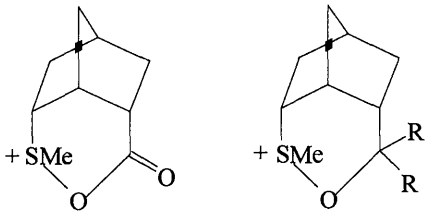
$X = H, Y = CO_2^-$ **(VIII)**

CH_2OH **(IX)**

CMe_2OH **(X)**

$X = \overset{+}{N}H_3, Y = CO_2^-$ **(XI)**

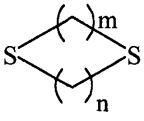
It is shown [79] that compounds **VIII–X** are oxidized much more easily in the presence of trace amounts of bromide ions when compared with their corresponding *exo* isomers, with $X = CO_2^-$, CH_2OH, CMe_2OH, $Y = H$. Controlled-potential electrolyses of **VIII–X** yield mixtures of diastereomeric sulfoxides (for **VIII**) or of diastereomeric alkoxysulfonium salts (for **IX** and **X**). These results are explained in terms of a neighboring carboxylate or alcohol participation in the bromide mediated oxidation of the thioethers.



R = H or Me

The electrochemical behavior of compound XI [80] is different as no catalytic effect is registered in the presence of bromide ions. Electrolysis under controlled-potential conditions in MeCN containing water and an excess of 2,6-di-*t*-butylpyridine provides the corresponding sulfoxides as a mixture of diastereomers in 60 and 25–30% yield, respectively.

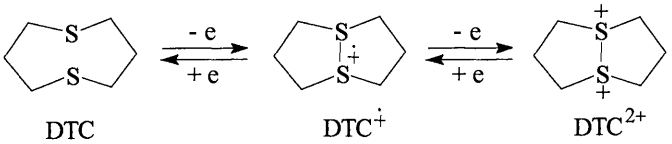
Neighboring group participation is also observed in cyclic bis-sulfides (**XII**) between the sulfur atoms, involving a transannular interaction, which results in a stabilization of the corresponding cation radicals and dications [81].



(XII)

Oxidation potentials determined by cyclic voltammetry in MeCN are considerable higher for monosulfides than those for the disulfides (**XII**) with $m = n = 3$, $m = 3$, $n = 4$, and $m = n = 4$, where five- or six-membered fused rings may be formed as result of a transannular interaction.

Cyclic voltammetry studies of 1,5-dithiocane (DTC) show its unusual electrochemical behavior, as in Eq. (40) [72–74]. An increase of current during the reverse scan occurs with decreasing sweep rates, which can be explained by assuming that the cation radical, $DTC^{+\cdot}$, exists in equilibrium with a dimer, $(DTC)_2^{2+}$, whose rate of formation is higher than that of its dissociation. Therefore, at high sweep rates, the direct reduction of the dimer to DTC is observed, whereas at low sweep rates the dissociation is sufficiently fast for the observation of the reduction current of the cation radical $DTC^{+\cdot}$.



(40)

$$2\ DTC^{+} \rightleftharpoons (DTC)_2^{2+} \qquad K = 5 \times 10^3\ mol^{-1}\ L$$

$$(DTC)_2^{2+} \xrightarrow{+2\ e} 2\ DTC$$

B. Alkyl Aryl Sulfides and Diaryl Sulfides

The oxidation of methylthio-substituted arenes in MeCN at a rotating Pt electrode was studied [82, 83]. The half-wave potentials were found to correlate linearly with Hückel HOMO energies, and the formation of cation radicals was judged to be reversible.

The products of the electrochemical oxidation of alkyl aryl sulfides, ArSR, are remarkably dependent upon the structure of R, the water content of the solvent, and the supporting electrolyte. If R can yield stabilized carbocations like benzyl or triphenylmethyl cations, extensive cleavage of the S–C bond occurs during the oxidation [84, 85]:

$$PhSR \longrightarrow PhSOR + ROH + RNHCOMe + (PhS)_2 \qquad (41)$$

$R = PhCH_2$	(36%)*	25%	3%	11%	12%
$R = Ph_3C$	(28%)*	0%	53%	0%	48%

Conditions: Pt electrodes, MeCN/0.5% H_2O, $LiClO_4$, undivided cell, *recovered starting material.

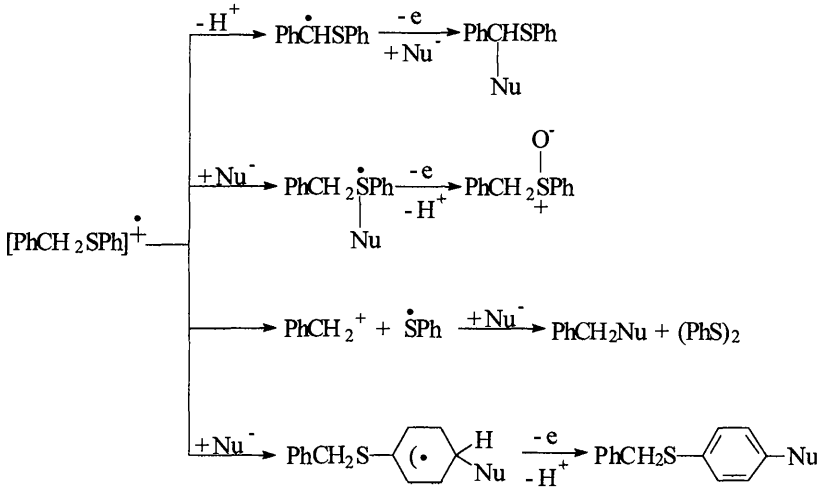
With other groups as methyl or phenyl, the corresponding sulfoxides are obtained in good yields when the electrolyses are performed in solvents containing water [40, 84, 86–88]. Further oxidation of the sulfoxide produces the corresponding sulfone, as in Eq. (42) [88].

$$PhSPh \xrightarrow[HOAc/H_2O]{-2\ e,\ -2H^+} PhS(O)Ph \xrightarrow[HOAc/H_2O]{-2\ e,\ -2H^+} PhSO_2Ph \qquad (42)$$

Alkyl aryl sulfides electrochemically oxidized on electrodes whose surfaces were modified by coating them with optically active compounds like camphoric acid [89] and poly(amino acids) [90, 91] afford mixtures of sulfoxides with variable enantiomeric excess. An optical yield of 93% is claimed when *t*-butyl phenyl sulfide is oxidized at a Pt electrode doubly coated with polypyrrole and poly(L-valine) [91].

Medium and structure effects on the anodic oxidation of benzyl phenyl sulfides, $XC_6H_4SCH_2C_6H_4Y$ (X = Y = H; X = H, Y = 4-MeO or 4-NO_2; X = 4-MeO or 3-Cl, Y = H), were established by investigating their electrochemical oxidation at Pt electrodes in a variety of reaction conditions, MeCN/ClO_4^-, HOAc/ClO_4^-, HOAc/NO_3^-, and HOAc/AcO^- [92]. Product analysis was employed to evaluate the relative weight of the various reaction paths available to the intermediate cation radical as follows: C_α-H deprotonation

[Eq. (43)], nucleophilic attack at sulfur [Eq. (44)], C–S bond cleavage [Eq. (45)], and nucleophilic attack at the aromatic ring [Eq. (46)].



(43)

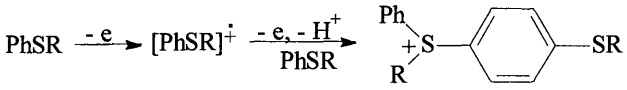
(44)

(45)

(46)

Three conclusions useful to conduct an anodic oxidation for synthetic purposes were drawn: (a) C_α-H deprotonation is strongly favored in HOAc/AcO^- and by the presence of electron-withdrawing groups in the benzylic ring but diminished by electron-donating groups linked to the other aromatic ring; (b) C–S cleavage is most likely in MeCN/ClO_4^- and is enhanced by electron-donating substituents in the benzylic ring; and (c) formation of sulfoxides occurs preferentially in HOAc/NO_3^- and to a lesser extent in HOAc/ClO_4^-. A 4-methoxy group in the sulfur-bearing ring seems to favor this reaction.

Oxidation of alkyl phenyl sulfides carried out in MeCN in absence of water affords sulfonium salts [93]:

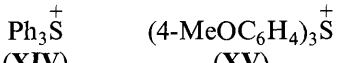


(XIII)

(47)

R	Me	CH_2=$CH(CH_2)_2$	cyclo-C_6H_{11}	Ph
% yield of XIII	60	67	57	71

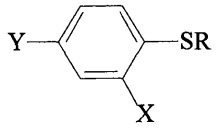
The formation of **XIII** (R = Ph) [Eq. (47)] [86, 93] is in agreement with the results obtained under similar conditions by other workers [94, 95]. Triphenylsulfonium ion (**XIV**), the expected product of the anodic oxidation of diphenyl sulfide in the presence of benzene as a nucleophile, was not formed [94], but with bis(4-methoxyphenyl)sulfide in the presence of methoxybenzene the formation of the self-coupling product was successfully suppressed and the tris(4-methoxyphenyl)sulfonium salt (**XV**) was obtained [95].



(**XIV**) (**XV**)

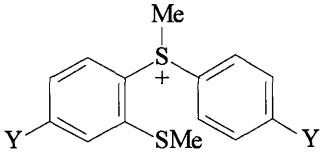
The anodic oxidation of several ring-substituted diphenyl sulfides in the presence of aromatic substrates as coupling partners aiming at the formation of triarylsulfonium ions has been further investigated [96].

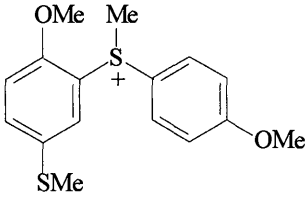
A large number of alkyl aryl sulfides were oxidized electrochemically under superdry conditions using MeCN as solvent and Bu_4NBF_4 or $LiClO_4$ as supporting electrolytes for cyclic voltammetry and preparative electrolyses, respectively [97].



X = H; Y = H; R = Me, Et, *i*-Pr, $PhCH_2$ (XVI)
X = H; Y = MeO, Me, Br, Cl, CN, NO_2; R = Me (XVII)
X = Br; Y = H, OMe; R = Me;

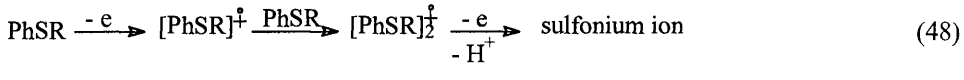
All sulfides exhibit a first voltammetric oxidation peak corresponding to an overall electricity consumption of one electron. For most of the *para*-substituted compounds (**XVII**), a first reversible step was observed, whereas for compounds **XVI** this step showed to be irreversible. Preparative electrolyses of all *p*-substituted sulfides (**XVII**) yield sulfonium salts under controlled-potential conditions, and all, except the *p*-MeO-substituted one, revealed the same regioselectivity for the S–C bond formation.



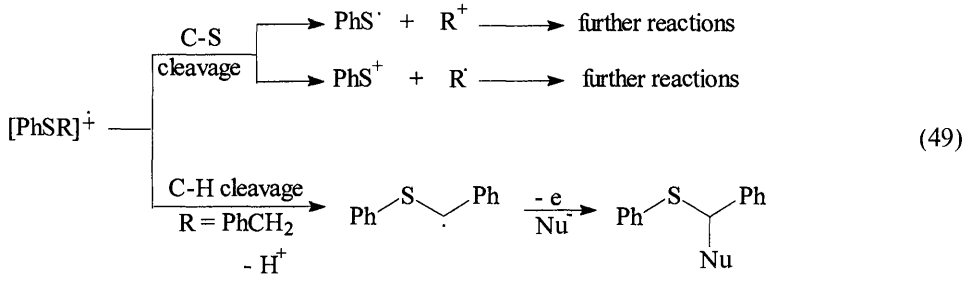


Y = Me, Br, Cl, CN, NO_2

The oxidation mechanism changes, influenced by the nature and location of substituents; therefore, no single proposal is adequate to explain all results of the electrochemical experiments. For the alkyl aryl sulfides (**XVI**), the reaction pathways to be followed depend on the type of R group. With R = Me or Et the reaction scheme of Eq. (48) is suggested, but for R = *i*-Pr or $PhCH_2$ additional pathways may be considered [Eq. (49)].

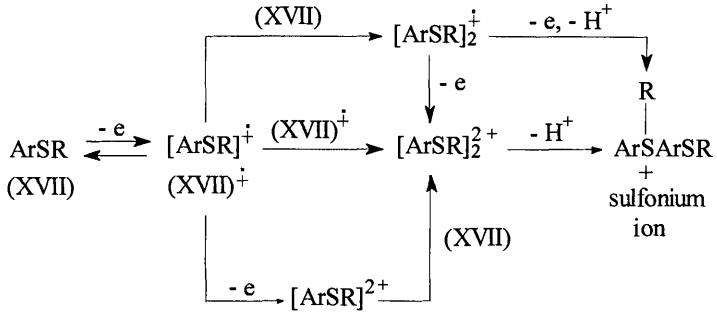


(48)



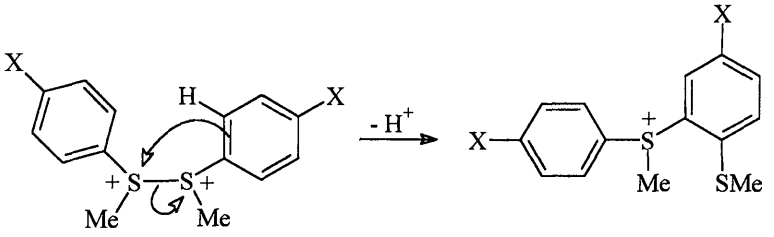
(49)

Based on the results of the electrochemical experiments performed with the sulfides **XVII**, a reasonable proposal for their oxidation mechanism seems to be as follows:



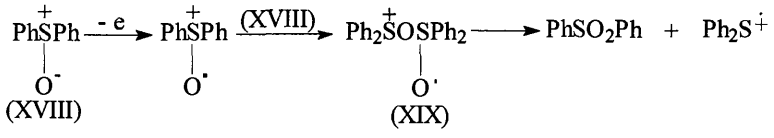
(50)

The structure of the proposed dication, $[ArSR]_2^{2+}$, is not clear. In the case of the anodic oxidation of dialkyl sulfides [67], the dicationic transient intermediate suggested involves an S–S bond, but with dimer $[ArSR]_2^{2+}$ its transformation into the sulfonium ion implies in a rather unusual although not demonstrated mechanistic path, as in Eq. (51).



(51)

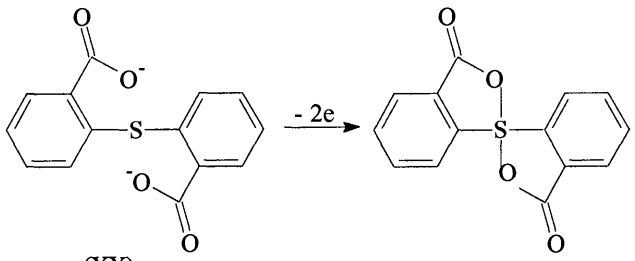
Diphenyl sulfone is obtained in 50% yield when diphenyl sulfoxide is anodically oxidized at a Pt electrode in MeCN [98]. The suggested reaction sequence is shown in Eq. (52).



(52)

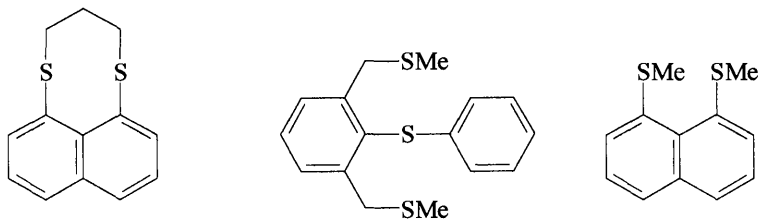
The formation of the cation radical, $PhS^{+\cdot}$, in a solution not containing diphenyl sulfide was established by the resulting triphenylsulfonium ion when the electrolysis is performed in the presence of benzene.

Anchimeric assistance in the anodic oxidation analogous to the neighboring group participation shown for **VIII–X** seems to operate in the oxidation of compound **XX** and similar ones, as in Eq. (53) [99]. Their oxidation potentials are strikingly low, 0.4–0.5 V versus Ag/Ag^+.



(XX) (53)

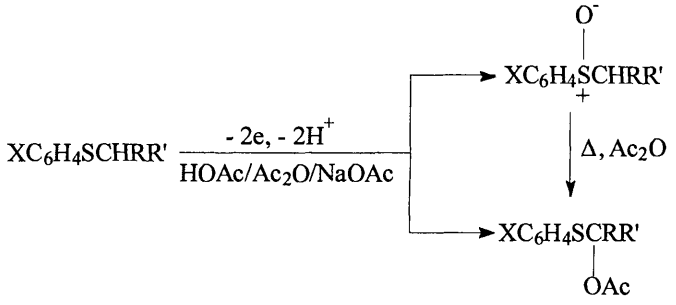
Neighbouring sulfur atom participation in the electrochemical oxidation of alkyl aryl sulfides was also shown to be occurring, such as in naphtho[1,8-*b*,*c*]-1,5-dithiocin (**XXI**) [101] and 2,6-bis[(methylthio)methyl]phenyl phenyl sulfide (**XXII**) [101].



(XXI) (XXII) (XXIII)

In compound **XXI**, whose first irreversible oxidation peak potential is 0.47 V versus Ag/Ag^+, an S–S transannular interaction is likely to operate when compared with the oxidation potential, 0.7 V versus Ag/Ag^+, of 1,8-bis(methylthio)naphthalene (**XXIII**). It is noteworthy to mention that 1,5-dithiocane (DTC), as in Eq. (40), the analogous saturated eight-membered ring compound of **XXI**, is oxidized reversibly, and it is suggested that the anchimeric assistance in oxidation of **XXI** and DTC is more effective in the latter [100]. When electrolyzed under controlled-potential conditions, **XXI** produces the corresponding monosulfoxide (80% yield). Cyclic voltammetric first peak potential of **XXII** was shown to be 400 and 670 mV, respectively, less positive than those of diphenyl sulfide and 1,3-bis[(methylthio)methyl]benzene [101].

Alkyl aryl sulfides, when oxidized in HOAc–Ac_2O–NaOAc, produce the corresponding sulfoxides and the α-acetoxy derivatives [102]. The formation of the latter compounds was ascribed to a Pummerer rearrangement of the initially formed sulfoxide. These compounds normally are obtained by heating sulfoxides with Ac_2O at elevated temperature, and it seemed attractive to perform the electrolyses in the boiling solvent to form the α-acetyoxy derivatives as the sole product. This approach was shown to be adequate, and yields are given in Eq. (54) [102].

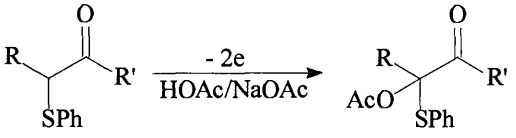


(54)

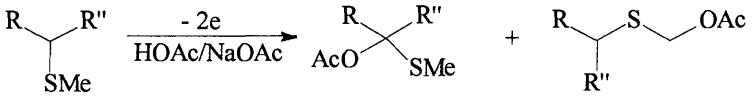
R = R' = H, X = H, 4-Me, 4-MeO, 4-Br (XXIV) 95 - 98 %
X = H, R = H, R' = Me or $PhCH_2$; R = R' = Me

C. Functional Derivatives of Dialkyl and Alkyl Aryl Sulfides

Electrochemical α-acetoxylation of octyl phenyl sulfide, methyl octyl sulfide, and several α-sulfanylated esters and ketones was achieved in HOAc–NaOAc solutions at Pt electrodes using high concentrations of the sulfur compounds [103]. Phenylthio derivatives produce a single α-acetoxy compound, whereas with the methylthio compounds two regioisomers are formed [Eqs. (55)–(56)].

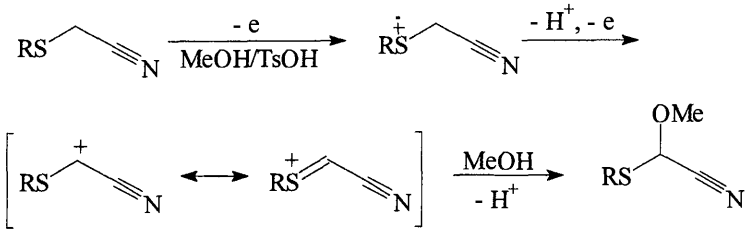


(55)



(56)

Alkylthioacetonitriles when oxidized anodically in methanol and *p*-toluenesulfonic acid as electrolyte produce α-methoxylated sulfides [104]. Their formation is tentatively explained by a Pummerer-type intermediate in which the presence of the cyano group appears to facilitate deprotonation at the α-position:

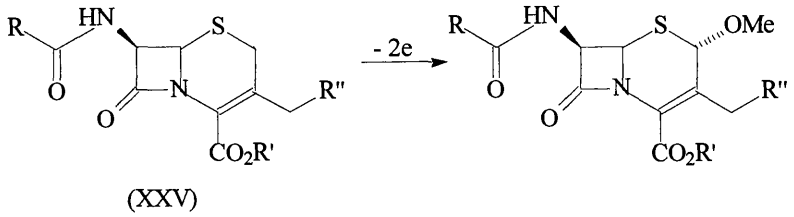


(57)

R = Me, Et, *t*-Bu, Ph

Conditions: Pt electrodes, constant current, 4–8 F.

Anodic oxidation of cephalosporins in methanol–tetrahydrofuran mixtures containing Et_4NOTs provides a useful synthesis of the corresponding 2-methoxy derivatives [105]. When ethanol, 2-propanol, or benzyl alcohol are substituted for methanol, the 2-alkoxy derivatives are formed in acceptable yields:

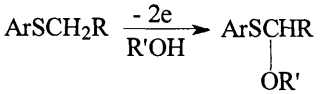


(XXV) (58)

Conditions: C electrodes, $MeOH/Et_4NOTs$, 1.1–1.2 V vs. Ag/Ag^+.

The functionalization at C-2 position of desacetoxycephalosporin is also achieved either by electrochemical acetoxylation of **XXV** ($R = CH_2OPh$, $R' = Me$, $R'' = H$), as in Eq. (58), in $HOAc–Ba(OAc)_2$, or methoxylation of **XXV** ($R = CH_2OPh$, $R' = CH_2Ph$, $R'' = H$) in $MeOH–CHCl_3–Bu_4NCl$ using Pt electrodes, with 70 and 43% yields, respectively [106].

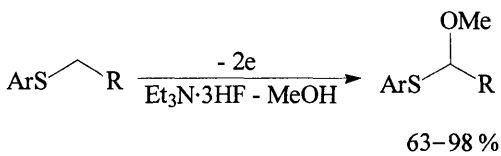
The anodic methoxylation and acetoxylation of phenyl 2,2,2-trifluoroethyl sulfides and various fluoroalkyl phenyl sulfides were investigated [Eq. (59)] [107–109]. It was found that the trifluoromethyl group remarkably promotes the side-chain functionalization, as do longer perfluoroalkyl groups, C_nF_{2n+1}, athough less effectively. Substituents at the benzene ring [109] also affect the reactions, and electron-donating groups interfere with them significantly. For methoxylations, $MeOH/Et_4NOTs$ and Pt electrodes produce the highest yields, and it was demonstrated that under these conditions $EtSCH_2CF_3$ and $PhSCH_2CH_3$ are unreactive [108]. HOAc/NaOAc solutions and Pt electrodes were used for the anodic acetoxylations. In both processes, undivided cells and controlled current were employed. An ECEC mechanism is proposed for this electrochemical oxidation.



(59)

$R = CF_3, C_2F_5, C_3F_7$; $R' = Me$ or Ac

When $Et_3N.3HF$ is used as supporting electrolyte in MeOH, the anodic oxidation of methyl phenyl sulfides bearing weak electron-withdrawing groups at the methyl group produces α-methoxy sulfides in much higher yields than those obtained in $MeOH/Et_4NOTs$, as in Eq. (60) [110]. If EtOH is substituted for MeOH, α-ethoxylation occurs.



63–98 % (60)

Ar = Ph or 4-$MeOC_6H_4$; $R = CH_2F, CHF_2, CH_2CF_3, CO_2Et, CONEt_2$

The anodic fluorination of organic sulfides has been intensively examined [111–115] (see Chapter 26). Most of these reactions were performed on Pt electrodes in MeCN containing $Et_3N \cdot 3HF$, although $Et_4NF \cdot 4HF$ in MeCN was shown to conduct to difluorinated sulfides with high current efficiencies [115]. The presence of electron-withdrawing groups in the α-position to the sulfur atom in the sulfides is an important structural feature for a successful regioselective fluorination, as in Eq. (61).

$$RSCHR'R'' \xrightarrow[Et_3N{\cdot}3HF]{-2e,\,-2H^+} RSCFR'R''$$

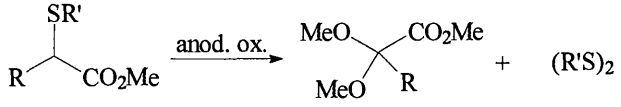
R = Ph, $PhCH_2$, $Me(CH_2)_6$
R′ = H, Me, CO_2Et, COMe
R″ = CF_3, CO_2Et, COMe, COPh, CN, $CONEt_2$, $PO(OEt)_2$
R′/R″ = $-(CH_2)_4CO-$ (61)

When R = $PhCH_2$, R′ = H, R″ = CF_3, for Eq. (61), the anodic fluorination produced a mixture of two regioisomers, $PhCHFSCH_2CF_3$ and $PhCH_2SCHFCF_3$ [113], but in the absence of an electron-withdrawing group, R = Ph, R′ = H, R″ = $Me(CH_2)_6$, the major product isolated was the corresponding sulfoxide [111].

Mono- and difluorination of alkyl aryl thioethers under electrooxidative conditions also proceed when the phenyl ring is substituted by strongly electron-withdrawing groups, such as NO_2, CN, SO_2Me, and SO_2Ph [116] (see Chapter 26).

Some interesting synthetic applications of the anodic oxidation of compounds containing alkyl- or arylthio functional groups are provided by the occurrence of the C–S bond cleavage in which the organothio group is removed from the substrate, and the intermediate generated may produce useful products through its follow-up reactions.

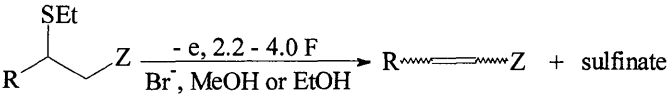
When α-(2-benzothiazolylthio)alkanoates are oxidized in the presence of $CuCl_2$ in MeOH-Et_4NClO_4 or MeOH-H_2SO_4 using Pt electrodes, α,α-dimethoxy esters are obtained in good yields [117]:



57 - 94 % (62)

R′ = 2-benzothiazolyl
R = C_6H_{13}, *i*-Bu, $MeO_2C(CH_2)_3$, $PhCH_2$

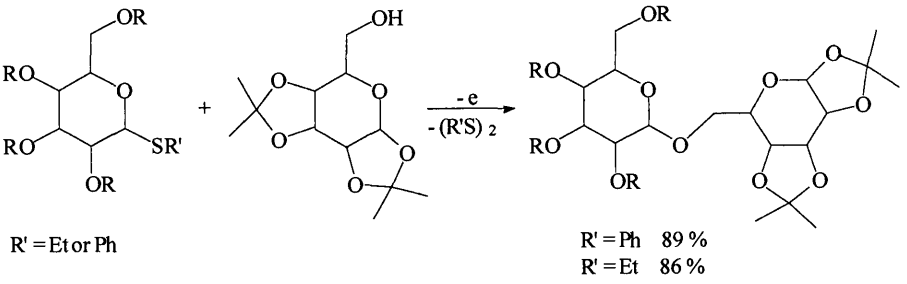
A convenient desulfanylation of Michael adducts of ethanethiol with α,β-unsaturated esters, ketones, and nitriles occurs under neutral conditions by a bromide ion-mediated oxidation, as in Eq. (63) [118]. If MeS, *t*-BuS, and PhS are substituted for EtS, the effect on the yield is relatively small.



(63)

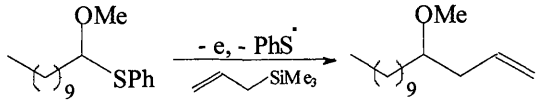
Z = CO_2Et, COMe, CN

Constant-current electrolyses of phenyl or ethyl l-thioglycosides in dry acetonitrile in the presence of various primary and secondary sugar alcohols, performed in an undivided cell, afford β-linked disaccharide derivatives in good yields [119]. An example is shown in Eq. (64).

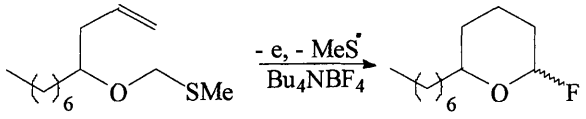


(64)

During the anodic cleavage of α-organothio ethers, performed in the presence of carbon nucleophiles, an inter- or intramolecular carbon–carbon bond formation was observed [120]. The electrolyses were run in CH_2Cl_2–Bu_4NClO_4 or Bu_4NBF_4 using a C rod anode. Two examples are summarized in Eqs. (65) and (66).

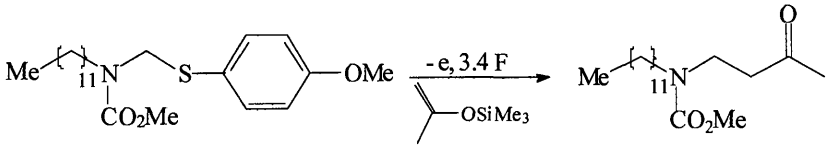


(65)

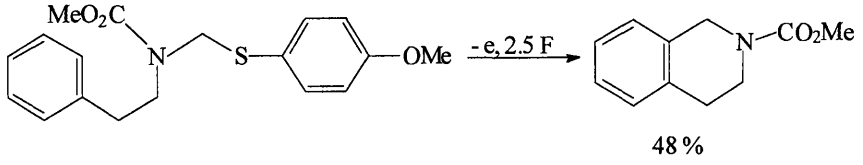


(66)

The same approach was used with α-organothio carbamates, as in Eqs. (67) and (68) [121].

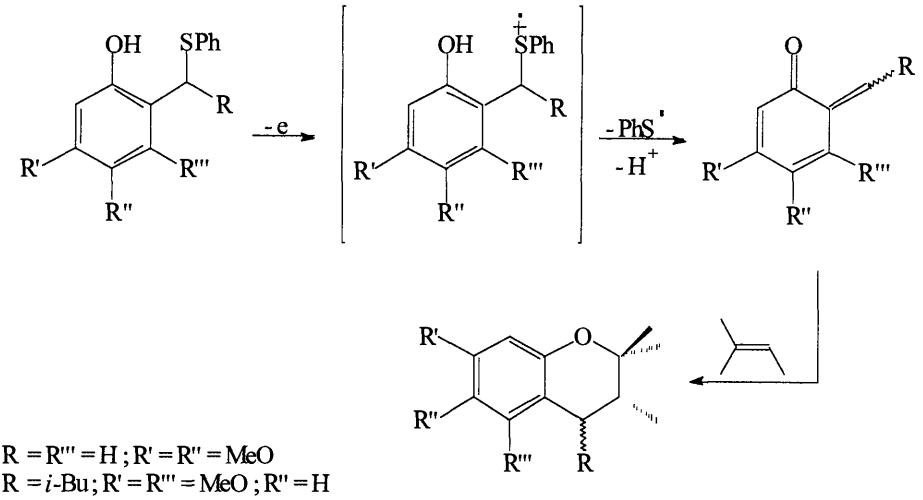


(67)



(68)

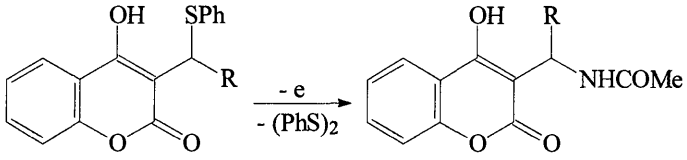
o-Quinone methides, generated electrochemically from *o*-[l-(phenylthio)alkyl]phenols in nitromethane or nitroethane containing $LiClO_4$ on a glassy C anode in an undivided cell, are trapped in situ by unactivated alkenes to produce chromanes [122]. The cycloaddition reaction probably proceeds by a one-electron oxidation of the sulfide followed by the elimination of PhS$^-$, producing the corresponding *o*-quinone methides as in Eq. (69).



R = R''' = H ; R' = R'' = MeO
R = *i*-Bu ; R' = R''' = MeO ; R'' = H

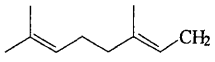
(69)

The anodic oxidation of substituted (4-hydroxy-3-coumarinyl) phenylthiomethanes in MeCN–$LiClO_4$ on a Pt electrode results in a C–S bond cleavage to give N-substituted acetamides by a Ritter reaction with MeCN [123]:

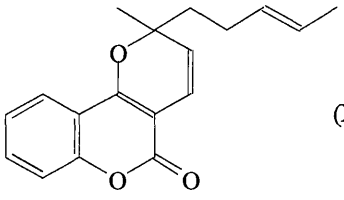


55 - 63 %

(70)

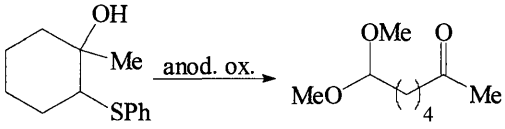
R = H, Ph, 3-$O_2NC_6H_4$,  (geranyl)

An intramolecular cyclization occurs when R = geranyl in Eq. (70), producing compound **XXVI** in 40% yield.



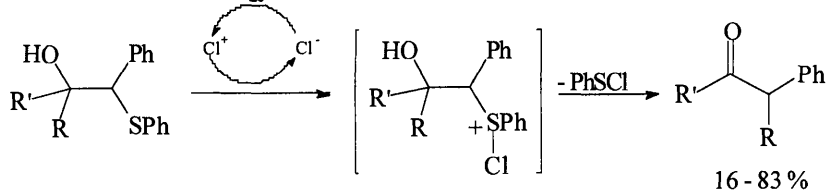
(XXVI)

β-Hydroxy cycloalkyl sulfides when electrolyzed in MeOH–Et_4NOTs suffer a C–C bond cleavage and ring-opened ketonic products are obtained. An example is shown in Eq. (71) [124].



(71)

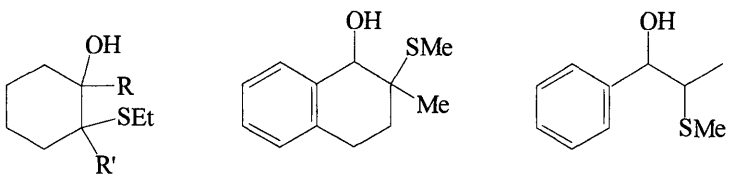
This C–C bond cleavage is avoided when the oxidation is performed in the presence of chloride ions. In this case, pinacol-type rearrangement products involving a C–S bond cleavage are obtained, as in Eq. (72) [125]. A chlorosulfonium intermediate is believed to participate in this type of reaction.



(72)

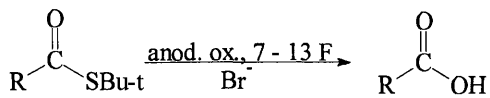
R/R' = -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-
R = R' = Ph or $PhCH_2$; R = Ph, R' = Me

Indirect electrochemical oxidation of β-hydroxy sulfides employing tris(4-bromophenyl)amine as mediator, in MeCN–H_2O (95:5 v/v)–$NaClO_4$ on a Pt anode, produces the corresponding sulfoxides as major products in 60–70% yield [126]. The substrate/mediator ratio used was between 5:1 and 10:1.



R = R' = H; R = H, R' = Me; R = Me, R' = H

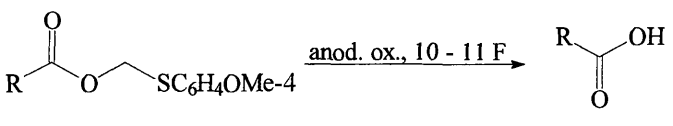
The C–C bond cleavage of *S*-*t*-butyl thioates and 4-methoxyphenylthiomethyl esters was achieved by an indirect bromide ion-mediated and a direct electrochemical oxidation, respectively, in MeCN–H_2O (9:1), as in Eqs. (73) and (74) [127], but no mention of the fate of the sulfur containing products was made.



94–96%

(73)

R = cyclo-C_6H_{11}, Ph, *n*-C_5H_{11}



71–84%

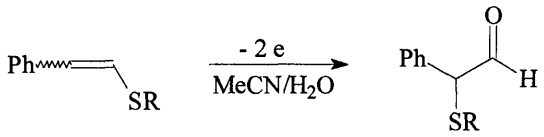
(74)

R = cyclo-C_6H_{11}, Ph, *n*-C_5H_{11}, *t*-Bu, 3-cyclohexenyl

D. Vinyl Sulfides

When alkyl or arylthio groups are linked to a C–C double bond, the anodic oxidation leads to products essentially derived from reactions involving the double bond.

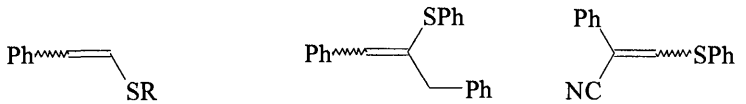
The electrochemical oxidation of phenyl styryl sulfides in MeCN–2% H_2O on a Pt plate electrode using a divided cell produces sulfanylated aldehydes in good yields determined by gas-liquid chromatography (GLC), as in Eq. (75) [128].



(75)

R = Ph, 4-*t*-BuC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$ 62–93%
R = Bu 50 %

The electrochemical behavior of a variety of vinyl sulfides (**XXVII–XXIX**) was investigated in superdry and H_2O- or MeOH-containing MeCN using Pt electrodes [129].



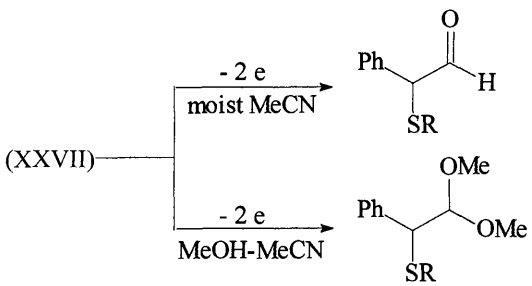
R = Ph, Pr, Bu, *i*-Bu, *s*-Bu (**XXVII**)

(**XXVIII**)

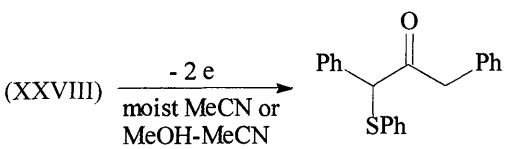
Z and *E* isomers (**XXIX**)

In superdry MeCN, all compounds exhibit an irreversible two-electron step in cyclic voltammetry experiments. The peak potentials versus Ag/Ag^+ for PhCH=CHSR (R = alkyl) (**XXVII**) are at about 0.9 V and become more positive for the other derivatives.

Preparative electrolyses were performed in moist MeCN or MeOH–MeCN (30–70% v/v), and sulfides **XXVII** yielded α-sulfanylated aldehydes (50% yield) or their corresponding dimethyl acetals (60% yield), as in Eq. (76), but different products were obtained starting from **XXVIII** and **XXIX** [Eqs. (77) and (78)].

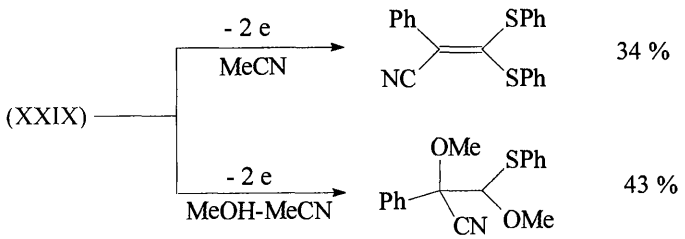


(76)



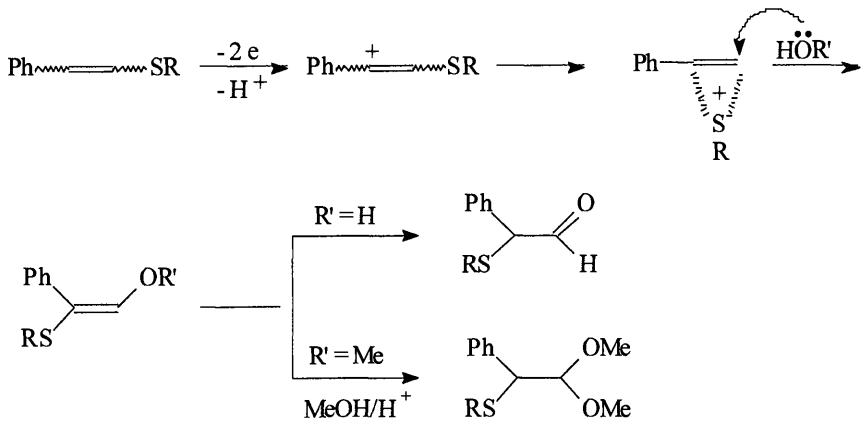
25 -30 %

(77)



(78)

To explain the results of these electrolyses of **XXVII**, a mechanism involving a nonclassical sulfonium ion was suggested, Eq. (79), which is prone to nucleophilic attack leading to the observed products.



(79)

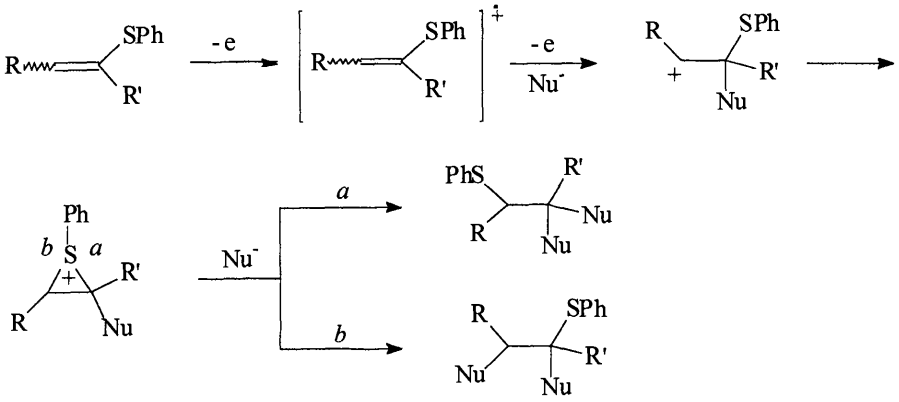
The anodic oxidation of a number of vinyl sulfides to produce fluorinated compounds was examined in MeCN–$Et_3N \cdot 3HF$ on Pt electrodes under controlled-potential conditions [130]. It became evident that the reactivity of the vinyl thioethers depends on, among others, their structure and the nucleophilicity of the medium. Two compounds, $PhSCH{=}CH_2$ and PhSCH=CHPh, were studied in more detail to evaluate the influence of the different factors upon their electrochemical behavior, and comparisons with that in $MeOH \cdot Et_3N \cdot 3HF$ and HOAc–KOAc, leading, respectively, to methoxylation and acetoxylation were made (Table 3).

Table 3 Electrochemical Oxidation of PhSCH=CHR

Substrates PhSCH=CHR R	Solvent	Products (yield %) R, SPh, X, X	PhS, X, R, X	X
H	$MeCN \cdot Et_3N \cdot 3HF$	8[a]	—	F
	$MeOH \cdot Et_3N \cdot 3HF$	68	—	MeO
	HOAc–KOAc	39	—	AcO
Ph	$MeCN \cdot Et_3N \cdot 3HF$	72	—	F
	$MeOH \cdot Et_3N \cdot 3HF$	6	57	MeO
	HOAc–KOAc	20	50	AcO

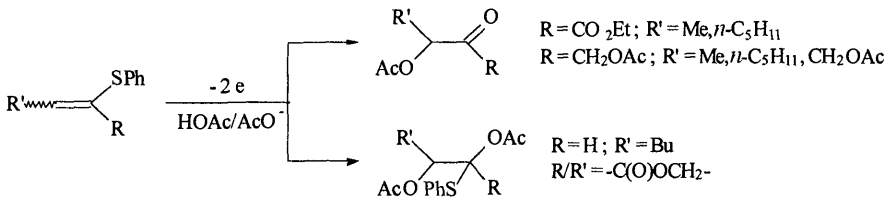
[a]Formation of an unstable, not characterized fluorinated dimer.

The best explanation for the varying ratios between the vicinal and geminal adducts (Table 3) changing the nucleophile (Nu) from F^- to MeO^- was to postulate an intermediate episulfonium ion in which the ring opening path is determined by the nature of Nu, as in Eq. (80).



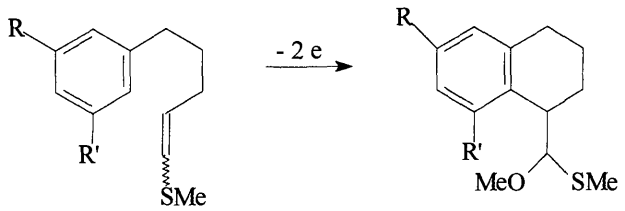
(80)

α, β-Unsaturated sulfides were transformed into α-acetoxy ketones or α, β-diacetoxy sulfides when electrolyzed in HOAc–NaOAc using an undivided cell and Pt electrodes [131].



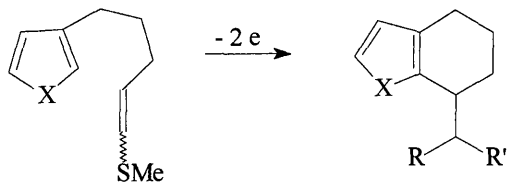
(81)

An intramolecular anodic cyclization using a vinyl sulfide moiety as initiator in the presence of an electron-rich phenyl, furan, or *N*-acylated pyrrole ring was described, as in Eqs. (82) and (83) [132].



(82)

R = OMe , R' = H 38 %
R = R' = OMe 72 %



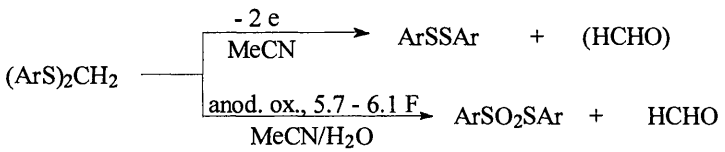
(83)

X = O, R = SMe, R' = OMe (54 %) + R = R' = OMe (17 %)
X = NCOBu-*t*, R = SMe, R' = OMe (66 %)

Conditions: reticulated vitreous C anode, 20% MeOH–CH_2Cl_2/$LiClO_4$ 0.4 mol L^{-1} 2,6-lutidine, constant current, undivided cell.

E. Thioacetals and Trithio-orthoesters

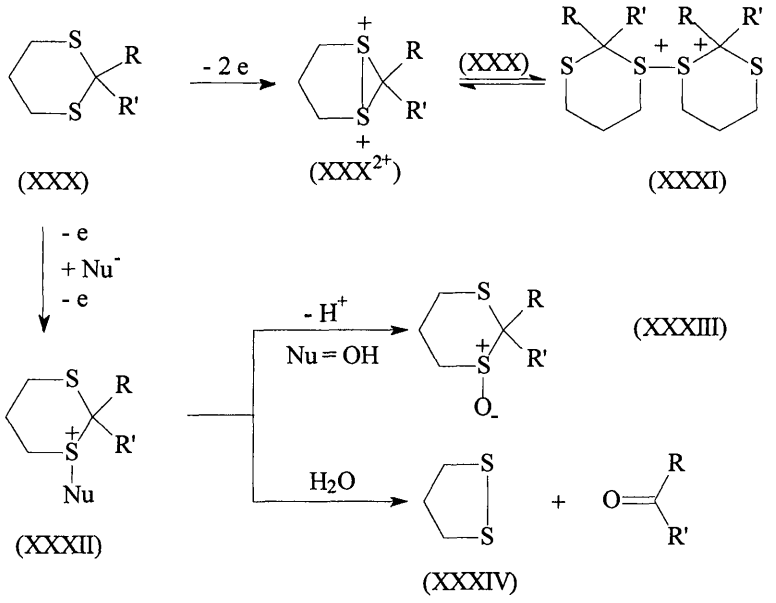
The anodic oxidation of 2,2-bis(ethylthio)propane producing acetone and an oxidation product of diethyl disulfide, claimed to be the corresponding disulfoxide, was reported many years ago [133]. A renewed interest in this reaction involving a C–S bond cleavage arose when bis(phenylthio)methane and some of its *p*-substituted ring derivatives were anodically oxidized in dry MeCN on Pt electrodes and afforded diaryl disulfides and formaldehyde, with the latter identified after aqueous workup [39, 134]. The same cleavage was observed when MeCN–H_2O (9:1 v/v) was the solvent, but aryl benzenethiosulfonates were the main products [39]:



(84)

Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$O_2NC_6H_4$

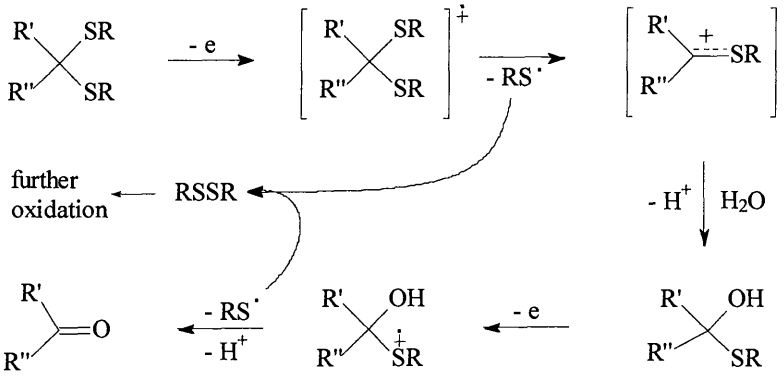
The mechanism of this transformation has been investigated [135, 136]. In the absence of nucleophiles and using carefully dried MeCN, the oxidation step of 1,3-dithiane derivatives corresponds to an EEC process involving one electron per molecule. To rationalize this process, the formation of a dication (**XXX**$^{2+}$) is suggested, which supposedly exists in equilibrium with a dimer (**XXXI**) originated by the reaction of **XXX**$^{2+}$ with the starting material (**XXX**) [Eq. (85)] [135].



(85)

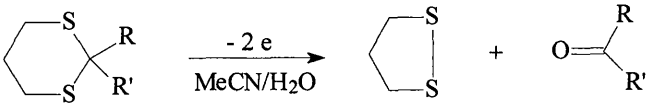
In the presence of nucleophiles like water, an ECE process involving two electrons per molecule seems to prevail, and formation of **XXXIII** or cleavage leading to **XXXIV** and the carbonyl compound are the follow-up reactions [Eq. (85)].

A different reaction scheme to account for all sulfur-containing products was proposed for the dialkyl thioacetals and is shown in a condensed form in Eq. (86) [136].



(86)

A convenient, electrochemically based procedure for regenerating aldehydes and ketones from their 1,3-dithiane derivatives was developed [137]:

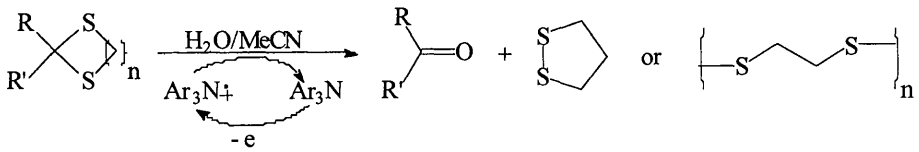


(87)

R = H or Me; R' = Ph, 4-$O_2NC_6H_4$

To avoid practical problems met within the direct electrochemical oxidation of 1,3-dithianes, and especially of 1,3-dithiolanes, a mild and effective removal of the protecting

groups using triarylamine cation radicals generated and regenerated in situ was developed [138]. Tris(4-methylphenyl)amine and tris(4-bromophenyl)amine as cation radical precursors were shown to be effective for 1,3-dithianes and 1,3-dithiolanes, respectively. A variety of starting materials was used, and good to excellent yields of the carbonyl compounds were obtained [Eq. (88)].



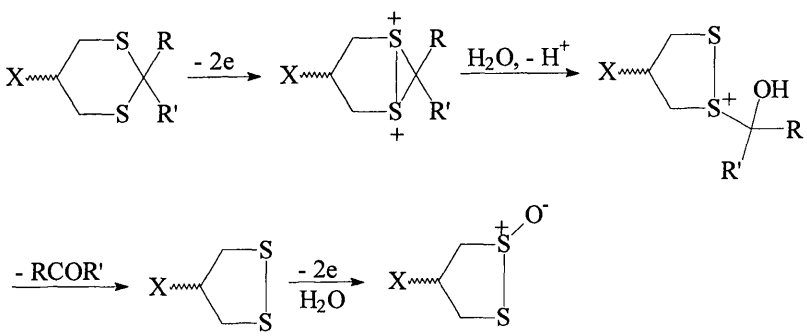
n=2 or 3

R = Me, R' = Ph; R/R' = -$(CH_2)_5$-; R = Et, R' = n-C_6H_{11}; R = H, R' = n-C_8H_{15}

n=2 74–84 %
n=3 85–97 %

(88)

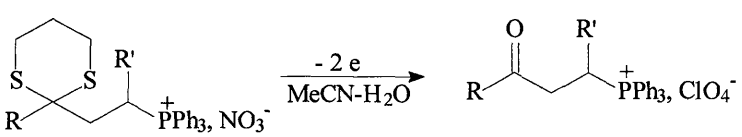
A series of 2- and 2,5-disubstituted 1,3-dithianes when oxidized in wet MeCN, using Pt electrodes in an undivided cell, provided 1,2-dithiolane-1-oxides selectively and in good yields, as in Eq. (89) [139]. These l-oxides had not been observed in previous studies, when divided cells were used.



(89)

X = OH, OMe, $OSiMe_3$, OSi(*t*-Bu)Me_2, -$O(CH_2)_2O$-; R = *t*-Bu; R' = H
X = H; R = H, Me, *t*-Bu, 4-$MeOC_6H_4$, Ph; R' = H

Nitrates of γ-thioacetalated phosphonium salts were conveniently transformed into their corresponding carbonyl compounds by anodic oxidation in MeCN–H_2O (9:1 v/v)–0.1 mol L^{-1} $LiClO_4$ on Pt or vitreous C anodes using a divided cell [Eq. (90)] [140]. These products are easily transformed into α, β-unsaturated carbonyl compounds.

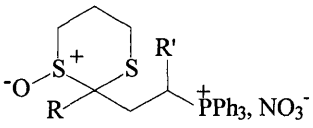


80–100%

(90)

R = Me, R' = H, Me, Bu, Ph; R = H, R' = Me, Ph; R / R' = -$(CH_2)_3$-

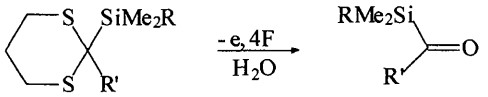
When Et_4NNO_3 was supporting electrolyte, monosulfoxides (**XXXV**) were produced [141].



(XXXV)

The electrochemical deprotection of carbonyl compounds proved to be a useful method; especially in cases where alternative chemical reactions are unsuccessful. α-Keto- and α-hydroxythioacetals, when oxidized in MeCN–H_2O (9:1 v/v) on a Pt anode, are transformed into the corresponding α-diones and α-ketols [142]. Diethyl dithioacetals of sugars were anodically oxidized in MeCN–H_2O (5% H_2O) on Pt electrode, and the substrates were successfully deprotected producing the correspondent carbohydrates in 65–85% yield [143]. It is noteworthy that protected hydroxy groups as esters or cyclic acetals were not affected. Selective deprotection to carbonyl compounds electrooxidizing mixtures of thioacetals, like a ketone and an aldehyde thioacetal, the former being preferentially deprotected, was described [144].

When 1,3-dithiane is substituted in the 2-position by alkyl or aryl groups, its electrochemical oxidation potential decreases from 1.18 V versus Ag/Ag^+ to 0.73–0.75 V [139]. The effect of trimethylsilyl and trimethylstannyl groups was evaluated [145], and it was shown that the decrease of the oxidation potentials caused by the latter is comparable to that of a 2-alkyl or aryl group, whereas in the case of the silyl group two of them must be linked to the 2-position for a similar effect to be observed. These neighboring effects are dependent upon the geometry of the molecules. The anodic oxidation of 2-alkyl-2-trialkylsilyl-1,3-dithianes performed in wet MeCN–$NaClO_4$ with a Pt anode produces saturated and α, β-insaturated acylsilanes [146]:



70 - 95 %

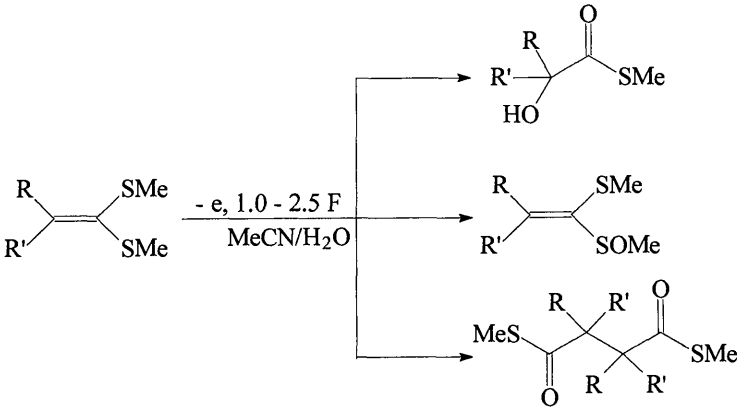
R = Me; R' = $Ph(CH_2)_2$, $Me(CH_2)_8$, Ph, $CH_2{=}CH(CH_2)_8$, $Me_2C{=}CH$, $Me(CH_2)_5CH{=}CH$ (*E*)
R = *t*-Bu; R' = Me

(91)

Conditions: controlled current, undivided cell.

The electrochemical behavior of dithioacetals under fluorination conditions (DME–$Et_3N \cdot 3HF$, divided cell, Pt electrodes) deserves attention. Anodic oxidation of 2,2-disubstituted 1,3-dithianes and thioacetals of ketones produced the corresponding geminal fluoro compounds, while thioacetals of aromatic and aliphatic aldehydes afforded geminal difluoro- and monofluoro thioethers, respectively [147] (see Chapter 26).

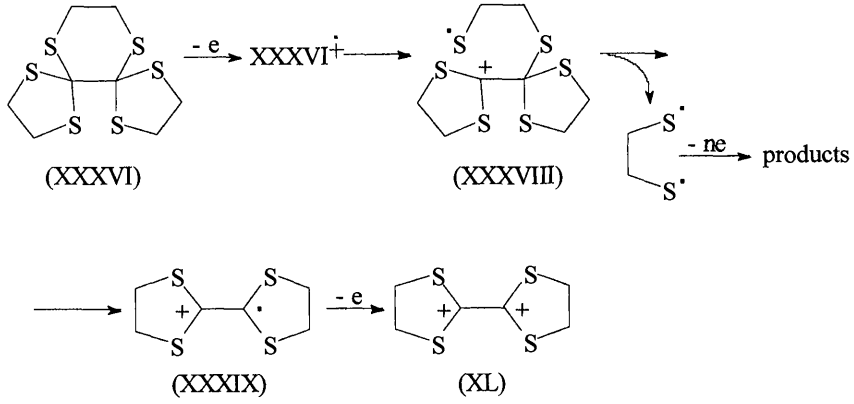
The anodic oxidation of several ketenedithioacetals, $RR'C{=}C(SMe)_2$, was investigated by cyclic voltammetry in dry MeCN and controlled-potential preparative electrolyses in MeCN–H_2O (10% H_2O) using Pt anodes and divided cells [148]. The main products were dimers for R = *n*-Pr or PhCO and R′ = H, and α-hydroxy thioesters and/or monosulfoxides for the substrates with tetrasubstituted C–C double bonds:



(92)

R = Pr, R' = H, Me; R/R' = -$(CH_2)_5$-
R = Ph, R' = H, Me, Ph; R = PhCO, R' = H, Me

The electrochemical behavior of trithio-orthoesters under oxidative conditions is far more complex from the mechanistic point of view than that of thioacetals. Examples, which may be considered as representatives of this class of compounds, are two types of thio oxalates, **XXXVI** and **XXXVII**. The oxidation of **XXXVI** in MeCN was shown to produce well-known tetrathioethylene derivatives, **XXXIX** and **XL** [Eq. (93)] [149].

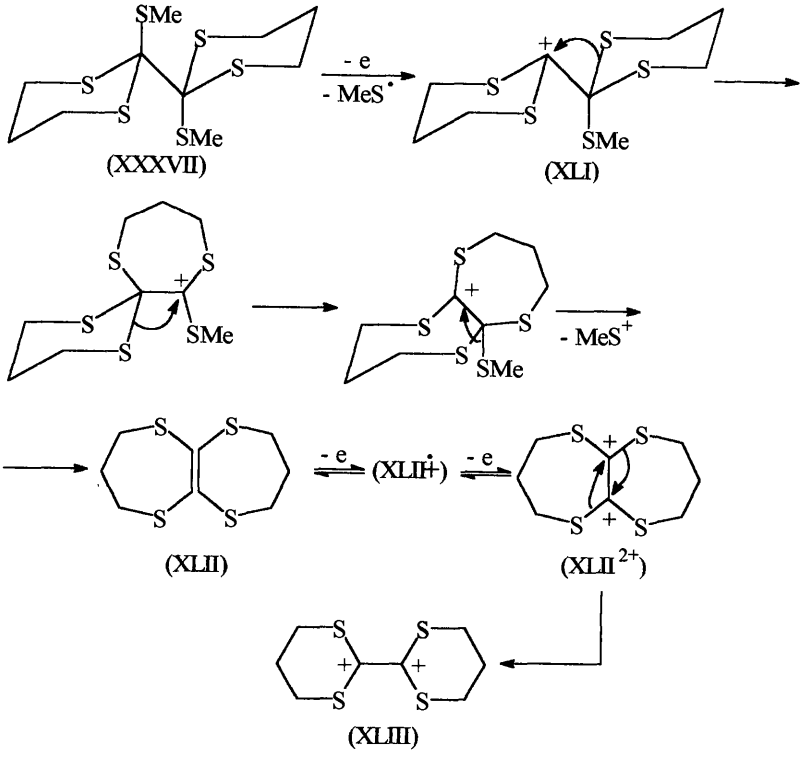


(93)

Two successive C–S bond cleavages at the cation radical stage are suggested, the result of the first one being supposedly structure **XXXVIII**, which is followed by a homolytic dissociation to produce cation radical **XXXIX**. This can be oxidized to form **XL**. Product **XXXIX** was identified by comparison of its cyclic voltammetric behavior with that of tetrathioethylene, and by electron spin resonance (ESR) spectroscopy.

The final product of the anodic oxidation of orthoester **XXXVII** is the same as in the case of **XXXVI**, but evidently a larger number of steps is involved, as in Eq. (94) [150].

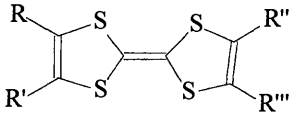
In the first step, an electron transfer and a homolytic cleavage at the cation radical stage of one of the C–S bonds to the methylthio group are proposed, leading to carbocation **XLI**, which in two successive 1,2-shifts followed by elimination of MeS^+ is transformed into the tetrathioethylene derivative (**XLII**). It was shown [150, 151] that compound **XLII**, after being oxidized in two reversible one-electron steps to the dication $\mathbf{XLII}^{2+}$, rearranges to the more stable dication **XLIII**. Reactions similar to those described have also been observed as result of nonelectrochemical oxidations [152].



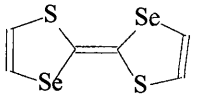
(94)

IV. OXIDATION OF TETRATHIOETHYLENES, TETRATHIAFULVALENES, AND DERIVATIVES

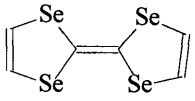
Organic π-donors based on tetrathiafulvalene (TFF) derivatives (**XLIV–XLVII**) and their cation radical salts (Bechgaard salts) [153] have been the subject of numerous studies, owing their ability to form charge-transfer compounds and their wide range of potential applicability as, for instance, molecular conductors [154–156], semiconducting Langmuir–Blodgett films [157], electroactive polymers [158] including low-bandgap materials [159], potential organic ferromagnets [160], molecular switches [161], and superconductors [162].



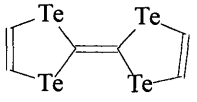
(XLIV)



(XLV)

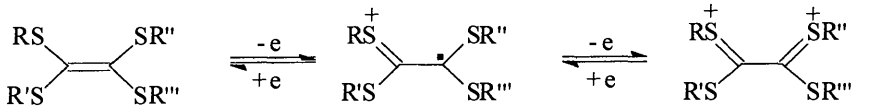


(XLVI)



(XLVII)

The oxidation of these compounds involves two successive reversible steps with formation of the radical cation (**XLVIII**) and the dication (**XLIX**), both quite stable, as shown for tetrathioethylenes (**L**):



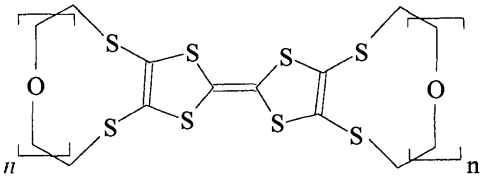
(L) (XLVIII) (XLIX) (95)

The half-wave potentials are dependent on the nature of the substituents (R^i) and of the heteroatom. Thus, electron-withdrawing groups or substituents that interfere with the coplanarity of the sulfur lone-pair electrons and the ethylene π system tend to increase [163, 164] while electron-donating groups decrease [163, 165, 166] these values. The potentials also become higher by exchanging the sulfur atoms of TTF by Se, while the opposite effect is observed for Te [167, 168] (see Tables 4 and 5).

The pH effect on the half-wave potentials is almost negligible, and the dependence on the solvent is not related to its polarity.

Anodic oxidation of TTF in the presence of halide ions leads to the formation of mixed-valence salts, $TTFX_{0.7}$, and the electrochemical behavior of these salts was studied by means of carbon paste electrodes [179].

Several TTF-crown ether derivatives, such as **LI**, have been prepared and investigated as potential metal ion sensor systems [180]. Cyclic voltammetry studies revealed in all cases two one-electron reversible oxidation steps with $E_{1/2(1)} = 0.48$ and $E_{1/2(2)} = 0.64$ V (vs. SCE), respectively. The addition of controlled amounts of metal ions such as Li^+, Na^+, K^+, and Ag^+ leads to shifts of $E_{1/2(1)}$ up to 80 mV toward more anodic potentials, as expected for a repulsive coulombic interaction. The magnitudes of the observed shifts are dependent on the hole size in the crown ether and on the concentration of the metal ion, up to a certain limit. The synthesis and spectroscopic and electrochemical studies of unsymmetrical annelated TTF-crown ethers bound to Na^+, Ag^+, and Ba^{2+} have been recently described [181].



$n = 1, 2, 3, 4$, or 5

(LI)

Table 4 Oxidation Potentials for Some Tetrathioethylenes (**L**) in MeCN

R = R″	R′ = R‴	E_1^a	E_2^a	Reference
C_6H_5	C_6H_5	1.2	1.4	169
CH_3	CH_3	0.89	—	169
CH_3CH_2	CH_3CH_2	0.93	—	169
$(CH_3)_2CH$	$(CH_3)_2CH$	0.97	—	169
	$CH_2CH_2CH_2$	0.70	0.84	170
	CH_2CH_2	0.68	1.12	170
	CH=CH	0.33	0.70	170

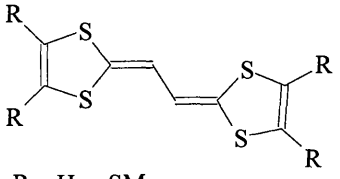
[a]Half-wave or formal potentials in V vs. SCE.

Table 5 Half-Wave Potentials for the Oxidation of Some Tetrathiafulvalenes and Related Compounds to the Corresponding Cation Radicals and Dications[a]

R	R′	R″	R‴	E_1^b	E_2^b	Solvent	Reference
H	H	H	H	0.33	0.70	MeCN	170
H	H	H	H	0.31	0.74	MeOH–benzene	171
CH_3	H	H	H	0.30[c]	0.67[c]	MeCN	163
CH_3	CH_3	CH_3	CH_3	0.21	0.59	MeCN	165
$CH_2CH_2CH_2$		$CH_2CH_2CH_2$		0.31	0.74	MeCN	166
$CO_2CH_2CH_3$	H	H	H	0.44[c]	0.80[c]	MeCN	167
CH_2OH	H	H	H	0.38[c]	0.76[c]	MeCN	167
CHO	H	H	H	0.50[c]	0.86[c]	MeCN	167
$COCH_3$	H	H	H	0.44[c]	0.80[c]	MeCN	167
$CO_2CH_2CH_3$	$CO_2CH_2CH_3$	$CO_2CH_2CH_3$	$CO_2CH_2CH_3$	0.80	1.07	MeCN	164
Ph	H	H	H	0.35	0.70	MeCN	165
Ph	H	Ph	H	0.39	0.78	MeCN	171
p-$CH_3OC_6H_4$	H	*p*-$CH_3OC_6H_4$	H	0.33	0.73	MeOH–benzene	171
p-ClC_6H_4	H	*p*-ClC_6H_4	H	0.43	0.79	MeOH–benzene	171
benzo		benzo		0.60[d]	0.94[d]	MeCN	172
SCH_2CH_2S		SCH_2CH_2S		0.37[e]	0.78[e]	CH_2Cl_2	154
SCH_2CH_2S		CH_3	CH_3	0.40	0.71	MeCN	173
2-thienyl	2-thienyl	2-thienyl	2-thienyl	0.78[d]	1.17[d]	CH_2Cl	174
3-thienyl	3-thienyl	3-thienyl	3-thienyl	0.84[d]	1.26[d]	CH_2Cl_2	175
[3,4]-furano		[3,4]-furano		0.72	1.03	MeCN	176
CO_2CH_3	CO_2CH_3	$S(CH_2)_2-C_6F_{13}$	$S(CH_2)_2-C_6F_{13}$	0.82	1.17	CH_2Cl_2	177
SCH_2CH_2S		$S(CH_2)_2-C_6F_{13}$	$S(CH_2)_2-C_6F_{13}$	0.65	1.00	CH_2Cl_2	177
XLV				0.40	0.72	MeCN	168
XLVI				0.48	0.76	MeCN	168
				0.62	0.90	CH_2CL_2	167
XLVII				0.59	0.84	CH_2Cl_2	167

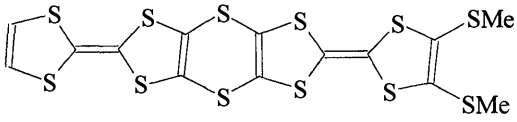
[a]The numbers of the substituents refer to structure **XLIV**. A more extended compilation of oxidation potentials may be found in Ref. 178.
[b]In V vs. SCE.
[c]Converted from peak potentials to half-wave potentials.
[d]Converted from V vs. Ag/Ag^+.
[e]Converted from V vs. Ag/AgCl.

Structural modifications of the TTF system by insertion of conjugated spacer groups between the two 1,3-dithiole rings, or extension of the π-system at the periphery of an intact TTF molecule, have been described [182], and some examples (**LII–LIV**) are shown.

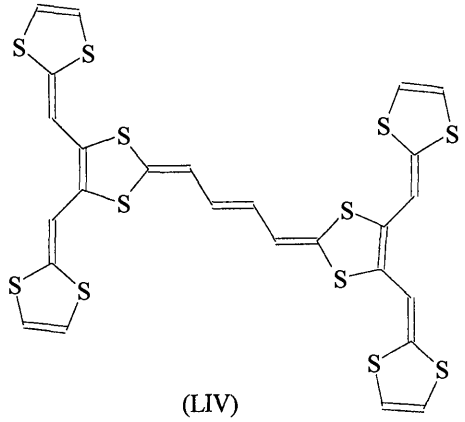


R = H or SMe

(LII)



(LIII)



(LIV)

Both the first and the second oxidation potentials of **LII** are lower than those observed for **XLIV** (R=R′=R″=R‴=H) and **XLIV** (R,R′=R″,R‴= SCH_2CH_2S), which suggests a reduced intramolecular repulsion in the dication of **LII**. The low oxidation potentials of compound **LIV** ($E_{1/2}$ = 0.12 and 0.47 V vs SCE) confirm this idea [183].

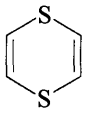
A comprehensive review on oligo-TTF has been published [184] covering electrochemical aspects especially of bis-TTF connected through one or two links. More than 100 oligomers are presented.

A TTF aspartic acid derivative and its corresponding di-, tri-, and tetrapeptides have been recently synthesized [185]. The voltammetry of the TTF amino acid showed similar behavior to that found for unsubstituted TTF, except that the redox potentials ($E_{p(1)}$ and $E_{p(2)}$) are shifted toward the anodic by 153 and 47 mV, respectively. In contrast, the voltammetry of the peptides showed broadening of the first redox wave but not of the second wave. Further experiments indicated that there are intramolecular, but no intermolecular, interactions between the TTF groups.

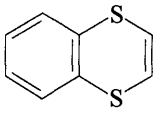
V. OXIDATION OF 1,4-DITHIINS AND RELATED COMPOUNDS

Similarly to tetrathioethylenes and tetrathiafulvalenes, 1,4-dithiin (**LV**) and its benzoderivatives (**LVI** and **LVII**) are electron-rich compounds that can be easily oxidized to their corresponding cation radicals and dications. There are several reviews [2, 3, 186, 187] on the chemistry of the radical cations of dibenzo-1,4-dithiin (**LVII**) and related compounds.

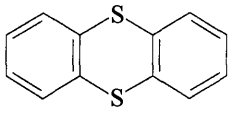
There is a relationship between the structure and the ease of oxidation. Thus, the oxidation potentials become higher when the double bonds become part of benzene rings, as in **LVI** and **LVII** [188]. Substitution by electron-donating groups lowers these potentials, as expected.



(LV)

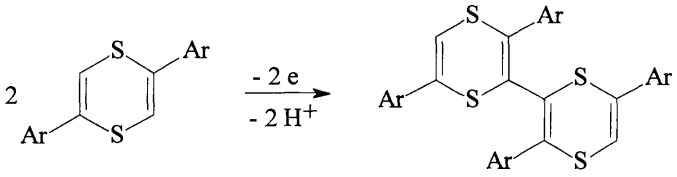


(LVI)



(LVII)

The anodic oxidation of a series of 2,5-diaryl-1,4-dithiins (**LVIII**), as in Eq. (96), has been studied in detail [189]. Cyclic voltammetry (CV) experiments showed that all compounds undergo two quasi-reversible one-electron transfers to form the radical cations and the dications. Linear correlations between $E^{o'}$ and σ were observed. Preparative electrolyses gave the corresponding 2,2′-dimers (**LIX**) as the major products in yields up to 20%. The low yields are due to workup difficulties and formation of polymeric materials of unknown composition.



(LVIII) (LIX) (96)

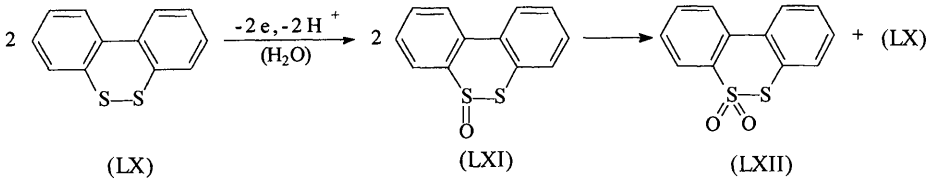
Ar = *p*-X-C_6H_4- (X = MeO, Me, H, Cl and NO_2)

The cation radical of thianthrene (**LVII**$^{+\cdot}$) has been subject of extensive investigation [3, 187]. Voltammetric experiments with thianthrene (**LVII**) when carried out in the presence of TFA and its anhydride or activated neutral alumina gave reversible oxidation potentials in a variety of solvents, and disproportionation equilibrium constants, K_{disp}, were calculated [190]. Accurate values of K_{disp} are important in the mechanistic evaluation for the reaction of **LVII**$^{+\cdot}$ with nucleophiles and have been used to rule out the disproportionation pathway, such as the reaction with water [191].

Reversible oxidation potentials for two consecutive one-electron transfers were also observed for alkoxy-substituted thianthrene [192, 193].

The reaction of **LVII**$^{+\cdot}$ and some related heterocycles with a large number of nucleophiles has been investigated thoroughly. Among the nucleophiles, which with few exceptions form sulfonium salts by their reaction with **LVII**$^{+}$, are water [194, 195], carboxylate ions [196, 197], pyridine [198], organometallic compounds like dialkylmercury and dialkylzinc [199], and Grignard reagents [200], alkenes and alkynes [201], and various aromatic compounds [202–204].

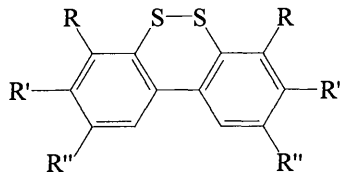
The electrochemical behavior of dibenzo-1,2-dithiin (**LX**), as in Eq. (97), was investigated in acetonitrile solution containing traces of water [205]. It undergoes three subsequent anodic oxidations. The first one-electron transfer forms the corresponding cation radical, which reacts with residual water to give the monoxide (**LXI**) via an ECE process. This unstable compound suffers a slow disproportionation to the dioxide (**LXII**), which is the sole isolated product. No product resulting from the cleavage of the disulfide bond was detected; neither conformational effects on the sulfur lone pairs nor ring strain plays a prevalent role during the abstraction of electrons.



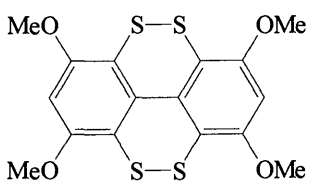
(LX) (LXI) (LXII)

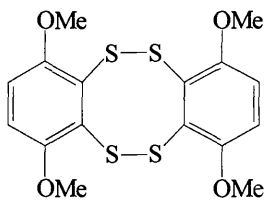
(97)

Ring-methoxylated biphenyls containing disulfide bridges (**LXIII–LXVI**) also were investigated to establish their electrochemical behavior under oxidative conditions, and it was shown that they are all oxidized in two one-electron steps [193].



(LXIII) R = H, R' = R'' = OMe
(LXIV) R = R'' = OMe, R' = H

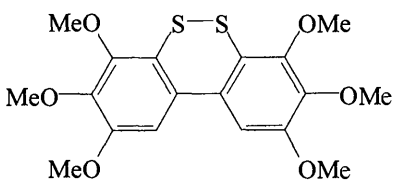




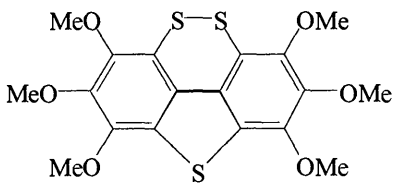
(LXV) (LXVI)

Compound **LXIII** was electrolyzed in CH_2Cl_2/Bu_4NClO_4 at −50°C and a blue cation radical perchlorate was formed (18.5% yield).

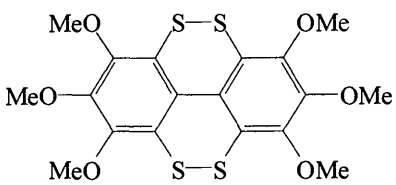
The anodic oxidation of some further sulfur-bridged hexamethoxybiphenyl compounds (**LXVII–LXIX**) was studied by cyclic voltammetry and controlled-potential electrolysis [206].



(LXVII)

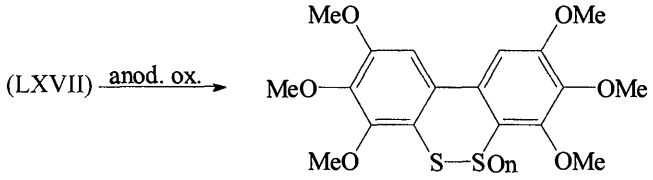


(LXVIII)



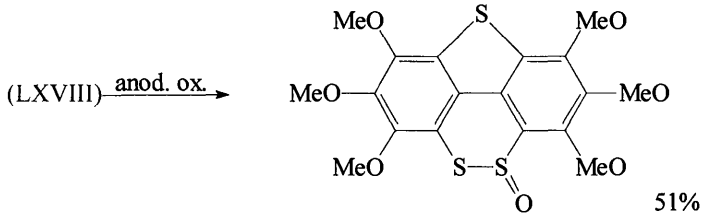
(LXIX)

Compound **LXVII** presents two reversible oxidation peaks, **LXVIII** one, and no signs of reversibility were observed with **LXIX**. Controlled-potential electrolysis in $MeCN/LiClO_4$ at a Pt anode of **LXVII** and **LXVIII** afforded, respectively, a sulfoxide–sulfone mixture and a sulfoxide [Eq. (98)].

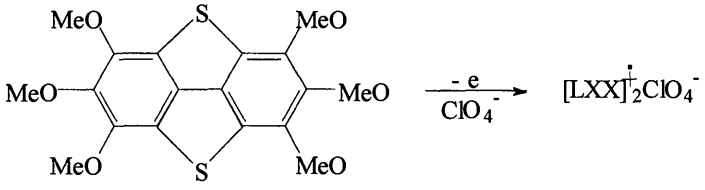


$n = 1$ 30%; $n = 2$ 35%

(98)



It is noteworthy that under the same experimental conditions, **LXX** produced a mixed valence salt in 94% yield, whereas **LXVII** gave a sulfoxide–sulfone mixture, although from its voltammetric behavior the formation of a similar salt was expected [Eq. (99)].



(LXX)

(99)

VI. OXIDATION OF THIOPHENES

The literature about the anodic oxidation of thiophenes and their derivatives is scarce because the usually favored reaction is the polymerization, and the electrochemically formed polymers often show high electrical conductance (see Chapter 33).

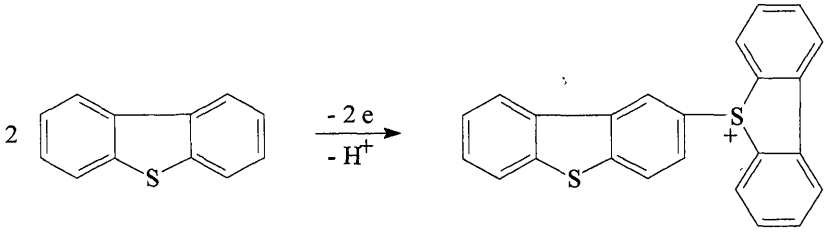
Electrochemical oxidation of thiophene derivatives in methanol at a Pt anode leads to different types of reactions depending upon the electrolytes used. With sodium methoxide, 2,5-dimethyl- and tetramethylthiophene [207] afforded 2,5-dimethoxy adducts as a mixture of *cis*/*trans* isomers together with side-chain oxidation products. However, in the presence of sodium acetate, the latter become the main products. In methanol/sulfuric acid solutions, at a carbon anode, thiophene and derivatives [208] oxidations resulted in a ring-opening reaction with loss of the sulfur atom, yielding γ-dicarbonyl compounds and their

acetals. In contrast, 2,2′-dithienylmethane under the same conditions was methoxylated on the methylene bridge [209].

Bromination of the thiophene ring was observed when the electrochemical oxidation was carried out in methanol/ammonium bromide solutions [209–211].

When benzothiophene and its derivatives are oxidized in methanol/KOH at a Pt anode, 2,3- and 4,7-methoxylated products are obtained [212, 213], and it was shown that their formation is temperature dependent [213]. The electrooxidation of benzothiophene and 2-methyl- and 3-methyl-benzo[*b*]thiophene in methanol containing NaCN leads to heterocyclic ring-substitution products [214].

The anodic oxidation of dibenzothiophene at Pt electrodes in aqueous H_2SO_4 or HCl solution affords as major product the corresponding 5-oxide or 5,5-dioxide, respectively, while in HBr solution ring-brominated products caused by electrogenerated bromine predominate [215]. The reaction mechanism appears to be the same as that for oxidation of diphenyl sulfides [88, 89]. When dibenzothiophene is electrolyzed in anhydrous MeCN/$NaClO_4$ [216] or MeCN/$LiClO_4$ in the presence of K_2CO_3 [217] at Pt electrodes, the isolated product is a sulfonium salt, as in Eq. (100), as was observed in the case of diphenyl sulfide [94].

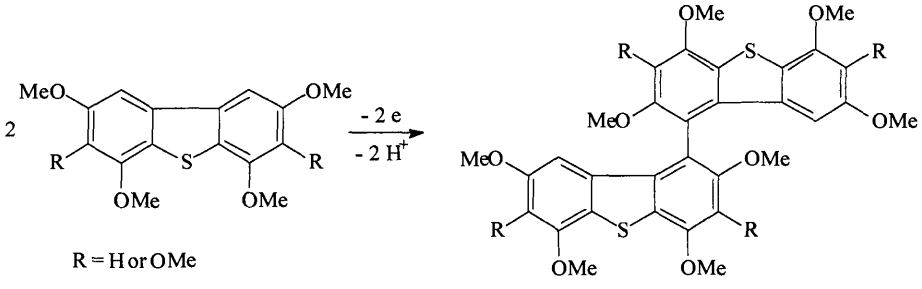


(100)

96% [220]

A sulfonium salt was also obtained (80%) when 2,8-bis(phenylsulfanyl) dibenzothiophene was oxidized in MeCN/CH_2Cl_2/$LiClO_4$ at Pt electrodes [206].

The electrooxidation of dibenzothiophene and its 2,8-dimethoxy derivative, performed at Pt electrodes in MeCN/$LiClO_4$, with or without lutidine, led to similar results. In the presence of lutidine the product was the corresponding 5-oxide (63%), whereas in the absence of base a sulfonium perchlorate was isolated (61%) [217]. However, the oxidation of 2,4,6,8-tetramethoxydibenzothiophene and 2,3,4,6,7,8-hexamethoxydibenzothiophene [Eq. (101)] under the same conditions resulted exclusively in a coupling product [217].

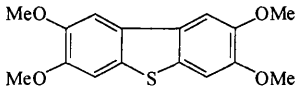


R = H or OMe

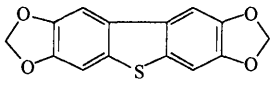
R = H 54%
R = OMe 73%

(101)

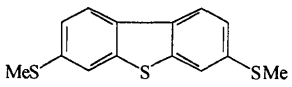
The electrooxidation of several dibenzothiophenes substituted with electron-donating groups such as methoxy (**LXXI**) [217], methylenedioxy (**LXXII**) [217], methylsulfanyl (**LXXIII**) [206], amino (**LXXIV**) [218], and dimethylamino (**LXXV**) [218] has been studied. All of them exhibited a reversible first oxidation peak in cyclic voltammetry, and, when electrolyzed at Pt anode in $MeCN/LiClO_4$ stable cation radical salts were isolated in 70–81% yield, except for **LXXIII**, whose salt was unstable in the air.



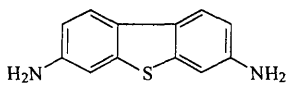
(LXXI)



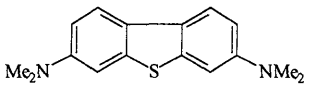
(LXXII)



(LXXIII)



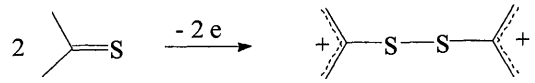
(LXXIV)



(LXXV)

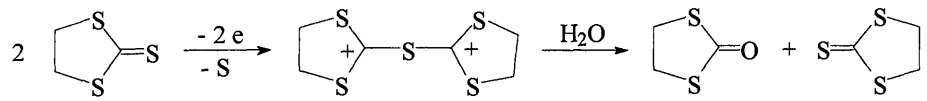
VII. MISCELLANEOUS

Several types of compounds containing the thiocarbonyl group, like trithiocarbonates [219], thioketones [219], and thioureas [219–221], undergo anodic oxidation to afford stable dimeric dications with a disulfide linkage:



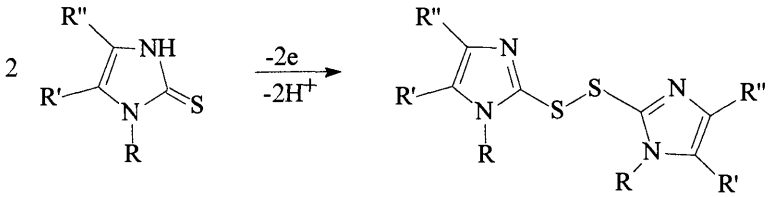
(102)

These dimeric cations are reactive species and frequently, under preparative oxidation conditions, different products are obtained. Cyclic trithiocarbonates, for example, in moist acetonitrile can eliminate sulfur and react with water, yielding the corresponding carbonyl compound [222]:



(103)

In the case of imidazole-2(3*H*)-thiones, the electrochemical oxidation, in EtOH/HCl solution at Pt electrode, is a convenient synthetic route to the corresponding disulfides [223]:

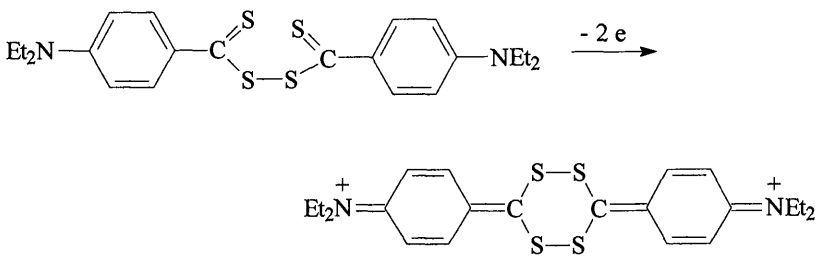


54 - 90 %

(104)

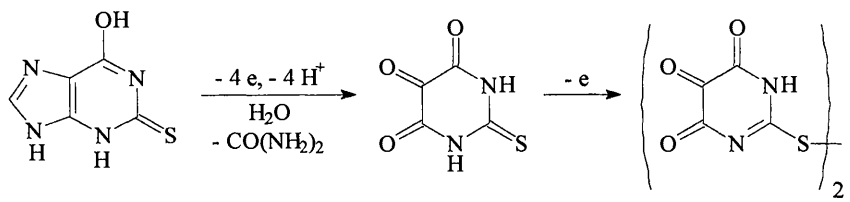
R = R' = R'' = H
R = H, R' = R'' = Ph
R = Me, R' = R'' = H
R = H, R'/R'' = -(CH=CH)$_2$-
R = H, R'/R'' = -CH=C(Me)CH=CH-

The disulfide formed during the oxidative electrodimerization of 4-dialkylamino-substituted benzenedithioacid (see Sec. II.A) is further oxidized to a stable dication containing a tetrathian ring [21, 224]:



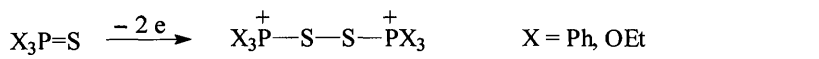
(105)

It is interesting to note that the electrochemical oxidation of 2-thioxantine also forms products containing the S–S linkage, but the oxidation of the purine ring precedes the oxidation of the mercapto group [225]:



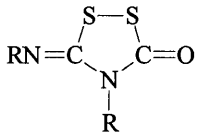
(106)

The electrooxidation of triphenylphosphine sulfide and *O,O,O*-triethylphosphorotioate at a Pt electrode in anhydrous MeCN/Bu_4NClO_4 [226] gives a dimeric dication [Eq. (107)], similar to the result for thiocarbonyl compounds [219].

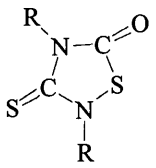


(107)

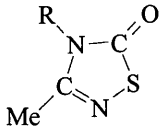
The anodic oxidation of alkyl isothiocyanates (RNCS) in MeCN is highly dependent on the nature of the alkyl group [227]. Primary RNCS afforded exclusively five-membered heterocyclic products **LXXVI–LXXVIII**, whereas secondary and tertiary RNCS involved formation of α-cleavage products ($RNHCOCH_3$) or isocyanates (RNCO) due to substitution of sulfur for oxygen processes.



(LXXVI)



(LXXVII)

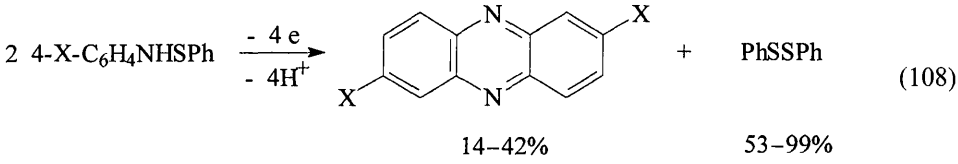


(LXXVIII)

However, the oxidation was found to be more selective when performed in CH_2Cl_2, yielding the heterocyclic products **LXXVI** and **LXXVII** only from primary and secondary RNCS. The tertiary alkyl isothiocyanates gave chlorinated products [228].

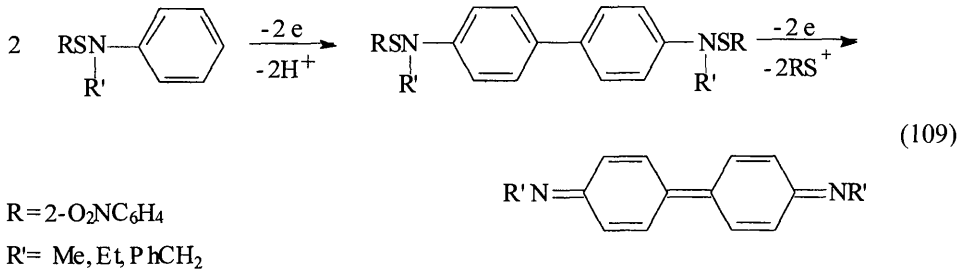
The anodic oxidation of sulfenamides has been the subject of a review in the literature [5].

Trialkylsulfenamides, R_2N-SR, can be oxidized reversibly to the corresponding cation radicals in MeCN, showing a one-electron oxidation wave at 0.7–1.0 V versus SCE [229]. Controlled-potential electrolysis of *p*-substituted benzenesulfenamides, 4-X-C_6H_4NHSPh (X = OMe, Me, Cl), in MeCN gives 2,7-disubstituted phenazines and diphenyl disulfide [230]:



14–42% 53–99% (108)

Aromatic sulfenamides give cation radicals that dimerize to biphenyl derivatives. The latter compound can suffer further oxidation, during which the N–S bond is cleaved, leading to a quinoid structure that can be oxidized to the corresponding cation radical [231]:



(109)

R = 2-$O_2NC_6H_4$

R' = Me, Et, $PhCH_2$

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18

Electrolysis of Heterocyclic Compounds

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I. INTRODUCTION

This chapter discusses some aspects of the electrolysis of heterocyclic compounds. The emphasis is on systems in which the electrochemical properties differ from those of the

corresponding carbocyclic compounds. The discussion is divided in three main sections: electrolytic formation of heterocyclic systems, electrolytic reactions of heterocyclic systems, and electrolytic reactions of substituted heterocyclic compounds.

Reviews on the electrolysis of heterocyclic compounds [1] discuss the literature in somewhat more detail than in the present chapter.

II. ELECTROLYTIC FORMATION OF HETEROCYCLIC SYSTEMS

The electrolytic reactions in which a heterocyclic system is formed are discussed in this section; the reactions are treated under the following headings:

Ring Closure Reactions
Ring Contractions
Ring Expansions

A. Ring Closure Reactions

In the electrolytic formation of heterocyclic systems the role of the current is to bring one or both of the reaction centers to a suitable oxidation state. These reactions may be classified in different ways; here they are treated according to the type of bond formed. Ring formation involving the creation of two bonds simultaneously (or nearly so) is discussed separately; when two bonds are formed in separate steps, the formation of the first bond determines the section in which it is discussed.

Ring closure reactions are intramolecular couplings; some of these are discussed in Chapters 21 and 22. The fundamental electrode reactions are discussed in Chapters 6 through 17.

A ring closure most often involves either the attack of an electrolytically formed nucleophile (alcohol, hydroxylamine, amine, or hydrazine) on an electrophilic center (existing or potential carbonyl group, cyano group, or nitro or nitroso group), a reaction between a nucleophile (e.g., hydroxyl or amino group or carboxylate ion) and an electrolytically generated electrophilic center (e.g., nitroso group or carbocation), a radical (including radical ion) coupling reaction, or a dipolar addition reaction.

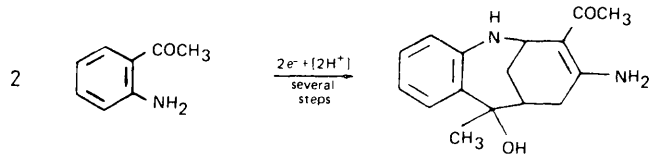
The formation of a nucleophilic center is most often the result of a reduction, whereas the creation of an electrophilic center in many cases is performed by an oxidation; radicals may be formed cathodically or anodically.

1. Formation of Carbon–Carbon Bonds

Electrolytic formation of carbon bonds during formation of heterocyclic compounds occurs in the reduction of ketones to pinacols, in the hydrodimerization reaction, in some radical coupling reactions, and in the oxidative coupling of activated aromatic systems.

An initial pinacol dimerization is responsible for the formation of 1,3,5,7-tetraphenyl-2,4,6-trioxatricyclo[3.3.0.1]nonane during the electrolysis of 1,3-diphenyl-1,3-propanedione in slightly acidic solution [2].

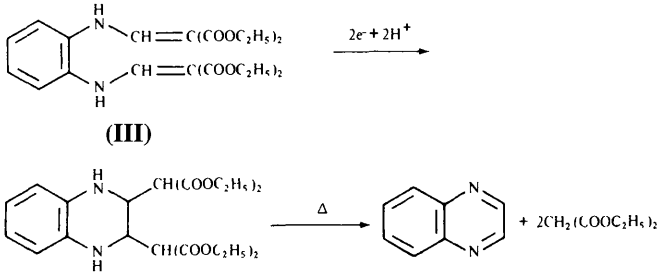
A "head-to-tail" dimerization of the initially formed radicals during the reduction *o*-aminoacetophenone (**I**) in alkaline solution leads to the formation of two stereoisomers of 3-acetyl-4-amino-7-hydroxy-7-methyl-2,6-methano-2,5,6,7-tetrahydro-1-(1*H*)-benzazonine (**II**) [3]:



(I) (II) (1)

Reduction of the semicarbazone of a phenacyl bromide in dimethylformamide (DMF) yields the bis-semicarbazone of 1,4-diaryl-1,4-butanedione, which in DMF forms 3,6-diarylpyridazine [4] or, after treatment with aqueous acid, 2,5-diaryl-furan [5]. Reduction of phenacyl bromide in DMF is reported to give 2,4-diarylfuran [6].

The hydrodimerization is also a useful method in the preparation of heterocycles [7,8]. *o*-Bis(*β*-bicarbethoxyvinylamino)benzene (**III**) thus yields by intramolecular reductive coupling 2,3-bis(dicarbethoxymethyl)-1,2,3,4-tetrahydroquinoxaline (**IV**), which on heating gives quinoxaline [7], as in Eq. (2). Compound IV may be anodically oxidized to the substituted quinoxaline [9].



(III) (IV) (2)

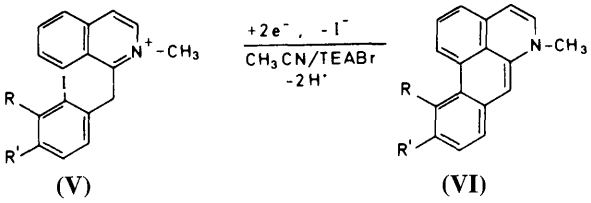
Attempts to hydrodimerize aliphatic bis-enaminones to pyrazines were less successful, as the hexahydropyrazines formed catalyze the hydrogen evolution, which then becomes the major cathodic reaction [8]; however, reduction at a lead cathode of aromatic diimines in DMF containing methanesulfonic acid gives stereoselectively *N,N′*-unsubstituted 2,3-diarylpiperazines [10].

Reductive formation of a carbanion, either by reduction of a C-halogen bond or by removal of a proton by an electrogenerated base, followed by an intermolecular nucleophilic substitution, has been used in the synthesis of substituted lactams [11]. A similar reaction is used for the formation of quinolizidine and indolizidine derivatives from 1-(4- and 1-(3-oxoalkyl)pyridinium salts [12].

On reduction of aryl halides the initially formed ion radical decomposes to halide ion and aryl radical [13–16]. In appropriate substituted compounds the radical may in an intramolecular attack effect a ring closure. This is exemplified in the reductive cyclization of 5-(2-chlorophenyl)-1-phenylpyrazole to pyrazolo[1,5-*f*]phenanthridine [13] and *N*-allyl-2-chloroacetanilides to *N*-acetyl-2,3-dihydroindoles [15].

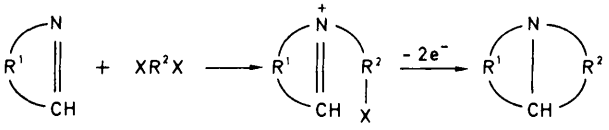
A somewhat similar reaction is found in the reduction of the 1-(2-iodobenzyl)isoquinolinium methiodide (**V**) to aporphine (**VI**) in MeCN/TEABr [Eq. (3)] [16]. The reaction, however, is suggested to involve a loss of two hydrogen atoms rather than that assumed for the reactions discussed earlier.

Pyrrolidines can be obtained by a mixed Kolbe electrolysis of a *β*-allyl-aminoalkanoate with a coacid. The reaction is discussed in Chapter 14.



(V) (VI) (3)

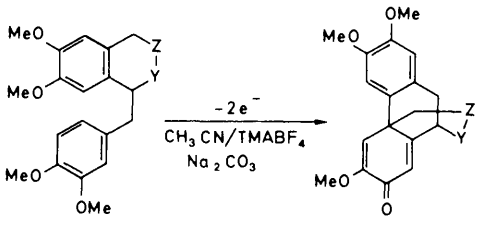
Reductive alkylation of immonium salts has been used in the synthesis of heterocyclic compounds, including different types of alkaloids [17]:



(4)

Electroreduction of 2-methyl-3,4-dihydro-6,7-dimethoxyisoquinolinium salt in the presence of 3-bromomeconine, for example, thus yields cordrastine.

The oxidative coupling of aromatic nuclei activated by alkoxy groups has been explored for the formation of natural products. Thus, laudanosine (**VII**), $Y = NCH_3$, $Z = CH_2$, has been oxidized [18–22] at a platinum anode in MeCN-TMABF$_4$ to *O*-methylflavinantine (**VIII**), and other benzyltetrahydroisoquinolines react similarly on anodic oxidation in good to excellent yield:



(VII) (VIII) (5)

An anodic oxidation of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (**VII**, Y = CO, Z = O) in MeCN–$NaClO_4$ containing sodium carbonate [23] resulted in a similar ring closure reaction, whereas 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (**VII**, Y = O, Z = CO) on a similar oxidation gave 6,12-dioxo-2,3,7-trimethoxy-6,8*a*,9,10-tetrahydro-9,8*a*-epoxyethanophenanthrene as main product rather than the expected compound with the aporphine skeleton [24]. The solvent may influence the course of such couplings [25]. Sometimes blocking of certain reactive sites is necessary to promote the desired coupling.

A number of related couplings have been reported during the synthesis of alkaloids, such as oxocrinine and cryptoplurine [26], the intramolecular coupling of diarylamines to dibenzazepine, and dibenzazocine structures [27], synthesis of galanthamine [28] and phenanthropyrrolidines [29], and the intramolecular arylation of enamines [30].

The anodic dimerization of enamine ketones or esters in MeCN–$NaClO_4$ at a graphite anode is followed by an elimination of 1 mol of amine, which results in the formation of pyrroles [31].

Anodic oxidation in DMF of the open-chain tetrapyrrole, 1′,8′-dimethyl-*a*,*c*-biladiene, yielded porphyrin; one methyl group is lost from a cyclic intermediate with four conjugated pyrrole subunits by attack of a nucleophile [32].

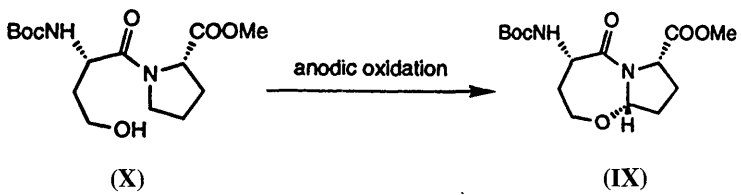
Formation of a cation radical of the diene may catalyze Diels–Alder reactions with certain dienophiles; thus oxidation of substituted vinylindoles to the cation radical in the presence of a push-pull dienophile may form different heterocyclic compounds by the Diels–Alder reaction, for instance pyrido[1,2*a*]indoles from vinylindoles and β-enaminoesters [33]. Similarly, anodic oxidation in MeCN of certain oxazolidines in presence of vinyl ether leads to derivatives of oxazepines in a catalytic reaction in which the ring-opened radical cation of the oxazolidine adds to the vinyl ether and the radical cation of the resulting oxazepine oxidizes the oxazolidine [34].

2. Formation of Carbon–Oxygen Bonds

a. Hydroxyl Group as Nucleophile. An electrolytically formed alcohol group participating in a ring closure is found in the reduction of some phthalic acid derivatives to phthalides and of *o*-carboxyphenyl ketones to substituted phthalides; the latter reaction is exemplified in the reduction [35] of *o*-benzoyl-*N*,*N*-diethylbenzamide to 3-phenylphthalide and its C-3 dimer.

An intramolecular substitution reaction similar to the well-known anodic alkoxylation of derivatives of saturated *N*-heterocycles (Chapter 24) was described early for the oxidation of *N*-benzyl-*N*-methylethanolamine in alkaline methanol; among the three main products were 3-methyl-2-phenyloxazolidine and 3-benzyloxazolidine. The reaction is initiated by a loss of an electron from nitrogen [36].

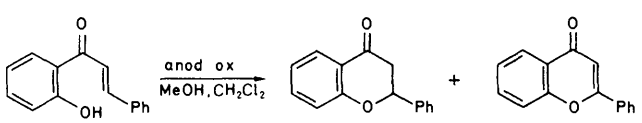
A similar reaction has been used for the synthesis in 50% yield of 1-aza-6-oxa-2-oxobicyclo[5.3.0]decane ring skeleton (**IX**) in a one-step electrochemical cyclization from the dipeptide Boc-L-homoserine-L-proline-OMe (**X**). The reaction is highly diastereoselective, generating a new chirale center having an *S* configuration [37].



(X) (IX) (6)

An amide oxygen also acts as a nucleophile in the anodic oxidation of $RCON(Me)C_6H_4OR'$ in MeOH to *N*-methylbenzoxazolium perchlorate. A metastable intermediate, detected by spectroscopy, may be a quinone imine derivative [38] and the reaction analogous to the anodic substitution of hydroquinone with certain nucleophiles, such as pyridine [35]. A somewhat similar reaction is found in the anodic oxidation of 4-methoxyacetic acid to a dioxaspiro compound [39].

Anodic addition of an oxygen function to a C=N or C=C double bond may be exemplified by the oxidative cyclization of aryl semicarbazones to 1,3,4-oxadiazoles in acetonitrile–acetic acid containing H_2SO_4 or, under strictly anhydrous conditions (in the presence of acetic anhydride), to triazolinones [40]. Other examples are the anodic oxidation of benzaldehyde-2-hydroxyanil to 2-phenyl-1,3-benzoxazole derivatives [41] and the indirect oxidation of 2-hydroxychalcones to flavonoids using tris(4-bromophenyl)amine in $MeOH–CH_2Cl_2$ as mediator [42]:

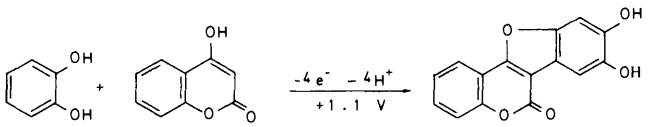


(7)

Of the same type is the oxidation of (*S*)-2-acetamido-2-(3,4-dimethoxybenzyl)propionitrile to (4*R*, 5*S*)- and (4*R*, 5*R*)-4-cyano-5-(3,4-dimethoxyphenyl)-2,4-dimethyl-2-oxazoline [43] and the oxidation of *N*-acylhydrazones of aldehydes and ketones to 1,3,4-oxadiazolines and 1,3,4-oxadiazoles [44].

Aromatic ketones *ortho*-substituted with an imino ether group and having a methylene group α to the carbonyl group form on reduction in MeCN at a low current density 2-alkoxyquinolines under influence of the electrogenerated base (EGB), which deprotonates the methylene group; the carbanion attacks the azomethine group. Higher current densities result in a mixture of the quinoline and a benzoxazine by attack of the alcoholate on the azomethine group. In DMF the main product is the benzoxazine, as the deprotonation by the EGB is slower [45].

The ring closure by phenolic coupling is illustrated by the anodic coupling of catechol with 4-hydroxycourmarin **(XI)** to 11,12-dihydroxycoumestan **(XII)** in 95% yield in an undivided cell at a graphite anode [46]:



(XI) (XII) (8)

The oxidation of some 1,5-diketones to pyrylium salts has been reported [47]; this reaction is discussed in Chapter 16.

b. Hydroxylamino Group as Nucleophile. A ring closure of this type has been reported only in the reduction of *o*-nitrocarbonyl compounds to anthranils. Larger rings cannot be obtained by this method as an attack by the nitrogen atom of the intermediate hydroxylamine is the preferred mode.

o-Nitroacetophenone is reduced to methyl anthranil in sulfuric acid [48] and acetate buffer; in the latter medium the yield is quantitative. *o*-Nitrobenzaldehyde [46,124] is reduced similarly, and such a reduction may be expected in general from *o*-nitrocarbonyl compounds. The reduction of *o*-nitrobenzophenone [49] has, however, been reported to yield the dihydroanthranil. This is surprising because a reduction of an intermediate anthranil is expected to result in a hydrogenation of the nitrogen–oxygen bond rather than in saturation of the double bond, but the reduction potentials may be quite close.

In a similar reaction, α-cyano-β-nitrostyrene and α-acyl-β-nitrostilbene form isoxazoles on cathodic reduction [50].

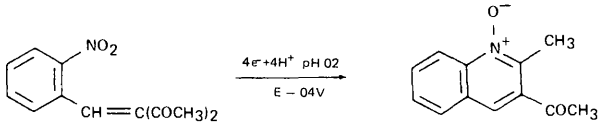
3. Formation of Carbon–Nitrogen Bonds

Aromatic nitro compounds may generally be reduced in a four-electron reduction to hydroxylamines, which in acid solution at a more negative potential can be reduced further to amines. By choosing a suitable cathode potential it is thus possible to avoid the further reduction of the hydroxylamine to the amine. When a hydroxyl or amino group is *ortho* or *para* to the nitro group, it is not feasible to isolate the hydroxylamino compound, as it is too easily dehydrated to the reducible quinone mono- or diimine. It may, however, be possible to trap the intermediate.

a. Reaction With Carbonyl Groups. A hydroxylamino group has two nucleophilic centers, the nitrogen and the oxygen atom. Whenever attack of the nitrogen atom on a carbonyl group would result in the formation of a ring having five or more members,

this mode is preferred to attack by oxygen. The reaction results in a cyclic nitrone (*N*-oxide) or hydroxamic acid.

The reduction of *o*-nitrobenzalacetylacetone (**XIII**) in acid solution at the potential of the first polarographic wave gives the hydroxylamine, which cyclizes to the cyclic *N*-oxide (**XIV**) [51, 52]; the isolated yield is 70–75%, but polarographic determination of the product in the reduced solution showed a somewhat higher yield. Compound XIV may at a more negative potential be reduced further, but the reduction potentials of the *N*-oxide and the carbonyl group are rather close in acid solution, making a selective reduction of the *N*-oxide difficult:



(9)

(XIII) **(XIV)**

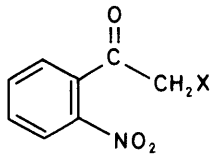
o-Nitrobenzalmalonic acid derivatives can be reduced in a four-electron reduction [51], and the resulting cyclic hydroxamic acid is, like many hydroxamic acids [51], further reducible in acid solution to the amine, the carbostyril.

In compounds of the type o-$NO_2C_6H_4CH{=}CYY'$ (Y, Y′ = CN, COOR, COPh) the ring closure usually involves the group *cis* to the phnenyl ring, but isomerization during the reduction has been observed [53].

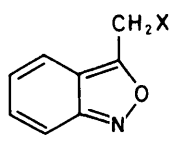
Reductions at the potential of the first wave of 1-acetamino-2-nitronaphthalene, 2-acetamino-3-nitronaphthalene, and 8-acetamino-1-nitronaphthalene yield cyclic *N*-oxides, for two former naphthimidazole-*N*-oxides, and the latter 2-methylperimidine-1-oxide [54].

Several examples have been reported of similar ring closures with the formation of heterocyclic *N*-oxides, *N*-hydroxy compounds, or hydroxamic acids [55–58]. For the ring closure of 2-(2-nitrophenylthio)-acetic acid to 4-hydroxy-2*H*-1,4-benzothiazine-3(4*H*)-one the reduction in an ammonical buffer is preferable [59].

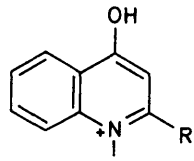
If the intermediate hydroxylamino group has a choice of attacking a carbonyl group with the oxygen atom to form a benzisoxazole (XVI) or reacting with a keto (**XVa**), ester (**XVb**), or cyano group (**XVc**) through its nitrogen atom to a quinoline derivative (**XVII**) in such compounds as **XV**, **XVa** is reduced in acid solution to a quionoline *N*-oxide, **XVb** predominantly to a *N*-hydroxyquinolone with minor amounts of **XVIb**, whereas **XVc** gives mostly **XVIc** [60]. In ammonia buffer, however, **XVc** yields **XVIIc**.



XV a X = $COCH_3$
b X = $COOCH_3$
c X = CN



XVI a X = $COCH_3$
b X = $COOCH_3$
c X = CN



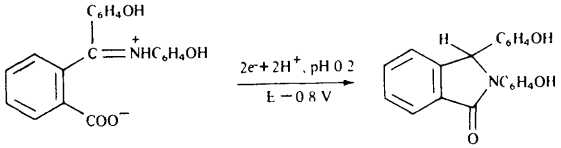
XVII a R = CH_3
c R = NH_2

In the aliphatic series, pyrroline *N*-oxides [61], *N*-hydroxypyrrolidinones, and isoxazolones [61] may be obtained by reduction of γ-nitroketones, γ-nitroesters, and β-nitroamides, respectively.

Deprotonation by electrogenerated bases, from the probase ethyl 2-bromo-2-methylpropanoate, of β-bromoamides or β-bromohydroxamic esters has been used to form β-lactams through $N-C_4$ bond formation [62].

A somewhat similar ring closure in which a nitrogen anion attacks a halogenated carbon center is obtained in the anodic oxidation of dimethyl α-(ω-tosylaminoalkyl) malonates in methanol containing KI in an undivided cell. Aziridines, azetidines, and pyrrolidines may be formed in good yield [63].

Reduction of an azomethine group to an amine and ring closure occurs in the reduction of "phenolphthalein oxime" (**XVIII**) and similar very stable anils [64]:



(10)

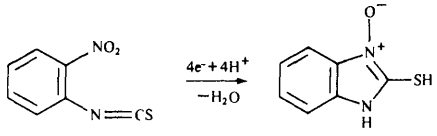
(**XVIII**)

The reductions of *o*-nitroacetanilide [65, 66] to 2-methylbenzimidazole, acylated nitronaphthylamines to naphthimidazoles [54], 2-nitrophenylthiocyanate [65] to 2-aminobenzothiazole, and 2,2′-dicarboxy-6,6′-dinitrobiphenyl to 4,9-diaza-5,10-dioxo-4,5,9,10-tetrahydropyrene [67] have been reported.

Sometimes a "cathodic substitution" reaction takes place during the reduction of *o*-substituted nitrobenzenes; thus, the reduction of 2-nitrophenoxyacetic acid [52] in 2 *N* hydrochloric acid (50% ethanol) yielded 5-chloro-2*H*-1,4-benzoxazin-3(4H)-one rather than the expected cyclic hydroxamic acid [52]. In the presence of another nucleophile Y^- (e.g., thiocyanate), a ring substitution with this reagent occurs.

Oxidation of the methyl group in *o*-toluenesulfonamide at a nickel oxide electrode in aqueous carbonate leads to saccharin in 40% yield [68].

b. Reaction With Potential Carbonyl Groups. In principle, condensations similar to those described for carbonyl groups are possible for the corresponding azomethine compounds. An example of this kind is the reduction of 2-nitrophenylisothiocyanate (**XIX**) in ethanolic hydrochloric acid, which in a four-electron reduction forms 2-mercaptobenzimidazole-*N*-oxide (**XX**) [52]:



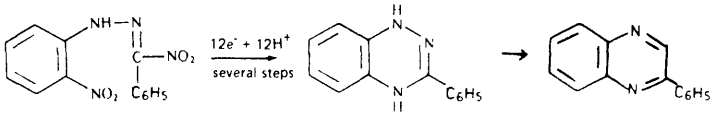
(11)

(**XIX**) (**XX**)

2-Nitro-2′-isothiocynanatobiphenyl is in a similar manner converted to a dibenzodiazepine *N*-oxide [69], and 2-nitrophenyl dithiopivalinoate to 2-*t*-butylbenzothiazol [70].

c. Reaction With Azomethine Groups. A useful synthesis of 3-phenylbenzo-1,2,4-triazine and other benzotriazines is exemplified by the reductive ring closure of *o*-nitrophenylazophenylnitromethane (**XXI**) [71]. This compound is converted in an acetate buffer by a four-electron reduction to *o*-nitrophenylbenzhydrazidoxime, which at a more negative potential is reduced to *o*-nitrophenylbenzamidrazone and further to *o*-aminophenylbenzamidrazone. Ring closure follows to give 1,4-dihydro-3-phenylbenzo-1,2,4-triazine (**XXII**), which may be oxidized to **XXIII** by air or anodically. A high yield

(85–96%) of this compound may be obtained in hydrochloric acid solution or acetate buffer containing DMF by reduction at the potential of the second wave:



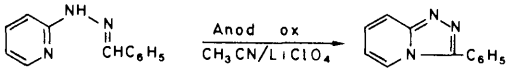
(12)

(XXI) **(XXII)** **(XXIII)**

Other leaving groups may be used [71]; thus, thiobenz-(*o*-nitrophenyl)hydrazine gives a good yield of **XXII** on reduction, but benz-(*o*-nitrophenyl)-hydrazine does not. This is probably because the hydroxyl group is a poorer leaving group than the protonated amino or sulfhydryl group. The ring-closed intermediate does not lose water but opens to *o*-hydrazinobenzanilide, which forms a benzimidazole on ring closure.

2-Nitrophenylhydrazides (2-NO_2-C_6H_4N-NHCOR) are in aqueous medium reduced the phenylhydroxylamine, which disproportionates. In basic medium the disproportionation reaction competes with a ring closure to the 1,2,4-benzotriazine. In acid solution the disproportionation is faster and the resulting amine forms a dihydrobenzotriazine when R = H or Me; the dihydrocompound may be oxidized anodically to the 1,2,4-benzotriazine; with R = Ph, only a low yield of benzotriazine is obtained [72].

Anodic oxidation of substituted hydrazones may induce ring closure. Oxidation of *para*-substituted phenylhydrazones of 2-oxophenylacetonitrile yields derivatives of 1-phenyl-3-cyano-1*H*-indazoles [73]; *p*-nitrobenzylidene-*o*-phenylenediamine is oxidized in MeCN-$LiClO_4$ to 2-(*p*nitrophenyl)benzimidazole [74], chalchone phenylhydrazone in MeCN-C_5H_5N-$LiClO_4$ to 1,3,5-triphenylpyrazol [74], and benzylidene 2-pyridylhydrazone (**XXIV**) to 3-phenyl-*s*-triazolo[4,3-a]pyridine (**XXV**); oxazoles and imidazoles may be prepared similarly [74]:



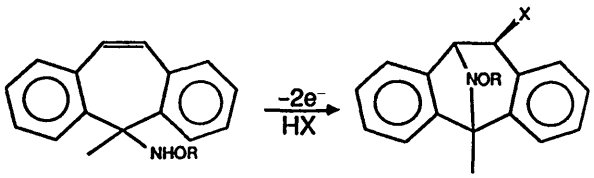
(13)

(XXIV) **(XXV)**

The initial attack in the anodic oxidation of papaverine [75] probably involves a similar attack; further oxidation and dimerization leads to the isolated product, 12,12′-bis-(2,3,9,10-tetramethoxyindolo[2,1-*a*]isoquinolyl). An analogous reaction is the electrooxidation of a tetramethoxy-substituted 2-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinoline to a dibenzoquinolizinium derivative [76] and the oxidation of *N*,*N*′-triphenyl-*o*-phenylenediamine to 9,10-diphenylphenazine [77]. Intramolecular Michel addition of nitrogen in a tetrahydroquinoline derivative to an *o*-quinone moity have resulted in the formation of a 5,6-dihydrodibenz[*b*,*d*]indolizine derivative [78]. A similar ring closure occurs during the oxidation of various catecholamines [79] and similar compounds [79] to indoles. Cyclic α-carbonylazo compounds, generated by anodic oxidation of the hydrazines, may be trapped by reaction with dienes to the expected heterocycles [80].

Recently examples of ring closure by addition of nitrogen centered radicals to alkenes have been explored; thus anodic oxidation of the Li salt of substituted δ-alkenylamines in THF/HMPA (30:1) gave stereoselectively *cis*-2,5-substituted-1-methylpyrrolidines by aminyl radical addition to the double bond [81]. A somewhat similar ring closure with addition of a nitrogen-centered radical is observed in the anodic oxidation in aqueous THF of a methoxyamine-substituted dibenzo[*a*,*d*]cycloheptene (**XXVI**) to (**XXVII**); the

radical of the ring-closed intermediate is oxidized to a cation which adds a nucleophile. Besides **XXVII**, a C-11 stereoisomer and a rearranged compound are found as minor products [82].



(14)

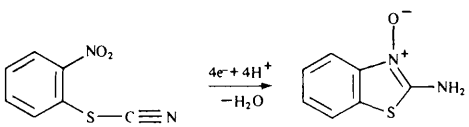
(XXVI) **(XXVII)**

Oxidation of benzoylacetanilide in MeCN gives a good yield of 2,4-dioxo-1-phenyl-1,2,3,4-tetrahydroquinoline. The reaction is reported to be an intramolecular coupling between an amidyl radical and the radical cation of the benzoyl group [83], but an electrophilic aromatic substitution by the amidyl cation or an addition of the amidyl radical to the phenyl ring (followed by an oxidation) could also be considered.

Cyclic secondary amines (C_7–C_9) can be oxidized to bicyclic tertiary amines at a graphite anode in aqueous MeCN with LiBr as electrolyte. It is proposed that a positive species ("Br^+") is formed and is essential for the reaction [84].

Indirect oxidation using I^- as mediator (I^+) of aliphatic ketoximes affords 2,2-dialkyl-2,5-dihydro-1*H*-imidazoles, probably through a nitrenium ion or an azirine as intermediate. The intermediate attacks the ketimine to the product [85].

d. Reaction With Cyano Groups. These reactions are similar to those already described; the following example, the reduction of *o*-nitrophenylthiocyanate (**XXVIII**) [52], may illustrate this:



(15)

(XXVIII)

In strongly acidic solution, *o*-nitrobenzyl thiocyanate forms 2-aminobenzo-4*H*-3,1-thiazine-1-oxide, whereas at higher pH the reaction involves a reductive loss of SCN^- and formation of different products, including 11,12-dihydrodibenzo[*c*,*g*]diazocine and its *N*-oxide [86].

A similar reaction is found in the formation of 5-amino-1-cyano-2,4-dimethyl-3,10*b*-dihydrobenzo[*c*][2,7]naphthyridine by reduction of 3,5-dicyano-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine [87] and tetrahydroquino[2,1-*c*]benzodiazepines from 2-cyano-1-(2-nitrobenzyl)-1,2,3,4-tetrahydroquinoline [88]. When the hydroxylamino group has a choice between a nitrile or an ester group, as in 3-ethoxycarbonyl-5-cyano-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine, it condenses with the nitrile in acidic solution and with the ester in basic media [89].

Another type is observed in the reduction of 2-cyano-3-(2-pyridyl)methylacrylates in MeCN containing chlorotrimethylsilane to indolizines. The dihydropyridine anion attacks the cyano group with ring closure [90].

Nitroso Groups as Electrophilic Centers. Nitroso derivatives may be formed as intermediates in the reduction of nitro compounds, but as the nitroso group generally is more easily reducible than the nitro group, the lifetime of the nitroso stage is rather

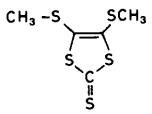
short. Alternatively, the nitroso compound may be prepared by anodic oxidation of a hydroxylamine at a suitable pH.

By this method *N*-hydroxyindoles may be prepared from derivatives of *o*-nitrostyrenes [91].

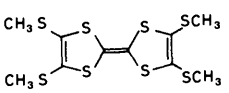
Activated methyl groups may react with an intermediate nitroso group in acid solution. Thus, *o*-nitrodimethylaniline yields on reduction in 2 *N* HCl a mixture of *N*-methylbenzimidazole and *o*-aminodimethylaniline [91].

4. Formation of Carbon–Sulfur Bonds

Carbon–sulfur bonds are formed during the reduction of carbon disulfide in aprotic medium; methylation of the product yields 4,5-bis(methylthio)-1,3-dithiole-2-thione (**XXIX**) [92]; if this compound is ethylated with Meerwein's reagent, followed by electrochemical reduction and thermal elimination, tetrathiomethoxy tetrathiofulvalene (**XXX**) is produced [93]. The mechanism of the formation of **XXIX** has been discussed [94, 95], and it has been shown that carbon sulfide (CS) is not involved in the formation of **XXIX** [96].



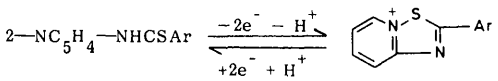
(XXIX)



(XXX)

A special reaction is the reduction of certain acetylenes to thiophenes [97a] and dimeric isothiazoles from sulfonyl-substituted 2-alkenenitriles [97b] at a compact sulfur/graphite electrode [98].

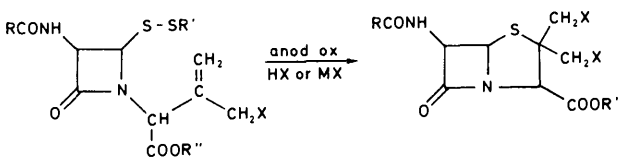
Thiobenzanilide, on anodic oxidation in CH_3CN-TEAP at a platinum electrode, yields 2-phenylbenzothiazole; other aromatic thiobenzamides react similarly [41]. Analogously, oxidation of *N*-(2-pyridyl)-thiobenzamide at controlled potential gives 2-phenyl-1,2,4-thiadiazolo[2,3-*a*-] pyridinium perchlorate (**XXXI**) in 80% yield [41]:



(16)

(XXXI)

Anodic oxidation of disulfides usually gives the equivalent of RS^+, which may add to double bonds [99]; oxidation of (**XXXII**) in the presence of HX (X = halogen) gives (**XXXIII**) [100]; it is interesting that a five-membered, rather than a six-membered ring is formed, as in Eq. (17); the reaction is proposed to pass through an episulfonium ion [100].



(17)

(XXXII) **(XXXIII)**

The formation of sulfur heterocycles using a sacrificial sulfur electrode is discussed in Chapter 29.

5. Formation of Nitrogen–Nitrogen Bonds

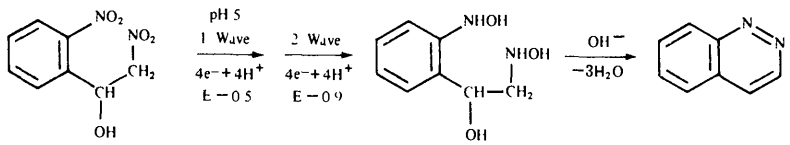
This type of ring closure is achieved mostly either by reaction between a hydroxylamino and a nitroso group or between a hydrazine or amine derivative and a nitro or nitroso group.

A reductive coupling is possible whenever two aromatically bonded nitro groups are in such a position that a six- or seven-membered ring may be formed. The coupling probably occurs between a hydroxylamino group and an intermediate nitroso group with the formation of a cyclic azoxy derivative, a heterocyclic *N*-oxide, possibly through a radical–radical coupling (Chapter 9).

2,2′-Dinitrobiphenyl [101–104] is thus in alkaline solution at a suitable potential, reducible to benzo[*c*]cinnoline-*N*-oxide; in acid solution the reduction proceeds to 4,5-dihydrobenzo[*c*]cinnoline, which is very easily (e.g., by air) oxidized to benzo[*c*]cinnoline. A similar ring closure during the reduction of 2,2′,6,6′-tetranitrobiphenyl yields *N*-oxides of 4,5,9,10-tetraazapyrene [105–107]. Reduction of 2,2′-dinitrodiphenylsulfide yields via 2,2′-(bishydroxylamino)diphenylsulfide in strongly acidic or in alkaline solution dibenzo[*b*,*f*]-1,4,5-thiadiazepine and its *N*-oxide [108]; under slightly different conditions the formation of 3-hydroxyphenothiazine has been reported [109].

1,8-Dinitronaphthalene could be expected from the coulometric data [110] to undergo ring closure on reduction, but suitable conditions have not been found yet. The diamine [111] and 8-amino-5-hydroxy-1,4-naphthoquinone-1-imine [112] have been reported as products.

When one of the nitro groups is aliphatically bonded, a coupling may take place, although the yield is often lower. 2-Nitro-1-(2′-nitrophenyl)-ethanol (**XXXIV**) can in acetate buffer be reduced in two, four-electron steps. The dihydroxylamino compound (**XXXV**) is transformed to cinnoline (**XXXVI**) by alkali and a trace of oxygen [113]:

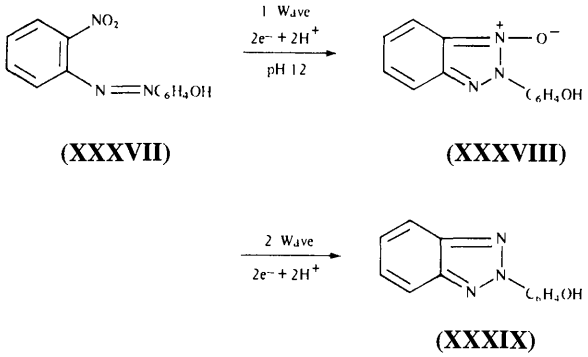


(18)

(**XXXIV**) (**XXXV**) (**XXXVI**)

Indazoles may be obtained by reduction of *o*-nitrobenzylamines followed by reoxidation of the hydroxylamine to a nitroso group; ring closure occurs by addition of the amino group to the nitroso group followed by elimination of water [114].

Reduction of an azo compound to a hydrazine may lead to a ring closure when a nitro group is suitably situated. Thus, the reduction of 4-hydroxy-2′-nitroazobenzene (**XXXVII**) in alkaline solution follows Eq. (19) [115–117]:



(XXXVII) **(XXXVIII)** (19)

(XXXIX)

By controlling the electrode potential it is possible to prepare the *N*-oxide (**XXXVIII**) in good yield [116], whereas the "classic" procedure yields the benzotriazole (**XXXIX**) [115]. In DMF 2-nitroazobenzene is reduced to 1,3-dihydroxy-2-phenylbenzotriazole [118].

Derivatives of hydrazine may also condense with a nitroso group, formed on oxidation of a hydroxylamino group; thus *o*-nitrobenzhydrazide forms, on reduction followed by reoxidation, benzo-1,2,3-triazinone-4 [119].

Anodic oxidation of formazanes in MeCN-TEAP at a platinum anode produces tetrazolium salts in good yield [120, 121]. The ring closure probably takes place through the dication. A similar anodic coupling is the oxidation of 2-acetylpyridine phenylhydrazone to 3-methyl-1-phenyl-8-azaindazolium perchlorate [41], of benzilmonoxime phenylhydrazone to 2,4,5-triphenyl-1,2,3-triazole-1-oxide, and of 3-hydroxyiminomethyleneamino-6-chloropyridazine to 6-chloro-*s*-triazole[1,5-*b*]pyridazine-3-oxide [74, 122].

Indirect oxidation with tris-(4-bromophenyl)amine or 2,3-dihydro-2,2-dimethylphenothiazine-6(1*H*)-one transforms formazane to tetrazolium, semicarbazones to 2-amino-1,3,4-oxadiazoles, benzaldehyde 2-pyridylhydrazones to *s*-triazolo[4,3-*a*]pyridinium compounds, and phenyl 2-pyridyl ketone phenylhydrazone to 1*H*-1,2,3-triazolo[3,4-*a*]-pyridinium compounds [123].

6. Formation of Oxygen–Nitrogen Bonds

Anodic oxidation of vicinal dioximes in MeCN–TEAP gives formazanes in fair to good yield [122, 125]; in dioximes of arylglyoxal, electron-donating substituents in the aryl group direct toward the formation of 4-arylfuroxanes whereas electron-attracting substituents favor the formation of 3-arylfuroxanes.

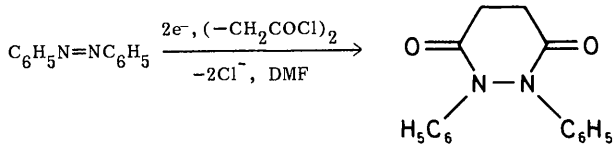
Benzofuroxanes may be prepared by anodic oxidation of *o*-nitroaniline in MeCN containing iodide [126].

7. Intermolecular Coupling Reactions

Reductive and oxidative couplings are treated in more detail in Chapters 21 and 22, respectively. Here are briefly mentioned some reactions that have been used in heterocyclic chemistry.

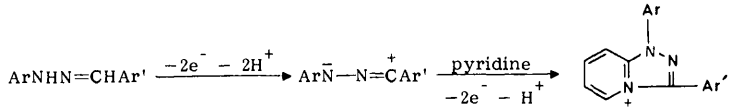
Electrochemical alkylation and acylation are well-established reactions and have been employed for the formation of heterocyclic compounds. The reduction of azobenzene [127] or azomethine compounds [128] in the presence of α,ω-dibromoalkanes leads to cyclic hydrazines, piperazines, or pyrrolidines. Similarly, reduction of nitrobenzene in the presence of 1,5-dibromopentane yields *N*-phenylperhydro-1,2-oxazepine [129].

Electrochemical reduction of azobenzenes in DMF in the presence of succinyl chloride gives pyridazinediones in fair yield [128]; a similar reaction with azomethine or nitroso compounds gave low or no yield of heterocyclic compounds. The reactions require dry media and unreactive solvent systems; the reaction type may be illustrated by Eq. (20):



(20)

Anodic oxidation of benzylidenephenylhydrazine gives diarylnitrileimine, which may react with suitable dienophiles in a 1,3-dipolar addition reaction. Pyridine [130], some alkenes, and *N*-heterocycles [131] may act as dienophiles with formation of substituted 1,2,4-triazoles (**XL**) or pyrazolines:



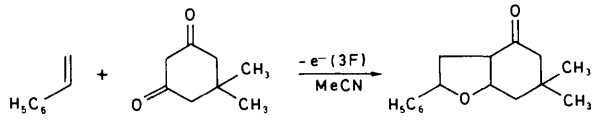
(21)

(XL)

Oxidation of a 1,1-disubstituted hydrazine in MeCN containing $HClO_4$ [132–134] or anhydrous HBF_4 [135] forms a diazenium cation that may react with alkenes in a cycloaddition reaction to a tetrahydrocinnoline. If both substituents on nitrogen are aryl, an oxidative coupling between them may compete with the dipolar reaction [135].

Another type of oxidative (formal) cycloaddition is exemplified by the oxidation of 1,3-diketones in MeCN in the presence of an olefin to di- or tetrahydrofuran derivatives [136]; similar products may be obtained by reduction of 2,2-dibromo-1,3-diketones in the presence of an alkene [136].

Thus constant current oxidation of 5,5-dimethyl-1,3-cyclohexadione and styrene in MeCN (3 F/mol) yielded 2-phenyl-4-oxo-6,6-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (**XLI**) in 97% yield [136]:



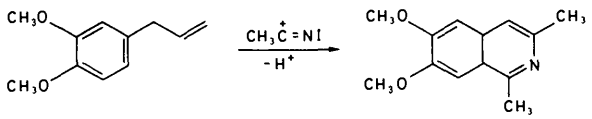
(22)

(XLI)

Pyrrolizidines and indolizidines may be prepared by reaction between the electrogenerated anion of methyl dichloroacetate and acylated α-aminoaldehydes, obtained from amino acids. High diastereoselectivity (> 99%) was observed in the reaction of some cyclic α-aminoaldehydes [137].

Acetonitrile is widely used as solvent in electrochemistry but is not always an inert solvent. In the nitrile group the nitrogen is sufficiently basic to react with carbocations and some other positively charged atoms, and the carbon may react with a nucleophilic center.

Anodic oxidation of 3,4-dimethoxyallylbenzene and iodine in MeCN containing $LiClO_4$ yielded 1,3-dimethyl-6,7-dimethoxyisoquinoline (**XLII**). The iodinated MeCN, $CH_3C^+{=}NI$, probably reacts in an aromatic, electrophilic substitution, followed by addition to the allyic double bond with ring closure [138]:



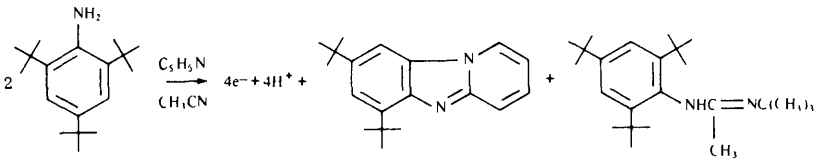
(23)

(XLII)

In MeCN, anodic oxidation of *o*-toluenesulfonamides yields 3-methyl-4,5-dihydro-1,2,4-benzothiadiazepine-1,1-dioxides, probably by an initial Ritter reaction followed by ring closure [138].

Oxidation of conjugated dienes in MeCN–$NaClO_4$ in the presence of 1,3-dimethylurea gives a mixture of the possible 4,5-disubstituted-1,3-dimethylimidazolidin-2-ones in about 40% yield [139].

Many aromatic compounds yield carbocations on oxidation at a platinum electrode in a nonaqueous solvent like acetonitrile. 2,4,6-Tri-*t*-butylaniline yields, on anodic oxidation in acetonitrile containing pyridine, the following compounds [140]:



(24)

(XLIII) (XLIV)

The reaction starts with a loss of two electrons from the aromatic amine and is stabilized by loss of a *t*-butyl carbenium ion, which reacts with acetonitrile in a Ritter-type reaction, and by attack by the nucleophile pyridine. The second loss of two electrons may occur before or after the ring closure. A somewhat similar reaction is the anodic oxidation in acetonitrile of 2,6-di-*t*-butylphenols leading to 7-*t*-butylbenzoxazoles [141].

On anodic oxidation of 3,6-diisobutylpiperazine-2,5-dione in acetonitrile a compound was obtained that was suggested to be 1,6-diisopropyl-3,8-dimethyl-5*H*,10*H*-diimidazo[1,5-*a*:1′5′-*d*]pyrazine-5,10-dione, formed by 1,3-cycloaddition of the primary oxidation product to solvent [142]. Another example of inclusion of MeCN during the formation of heterocycles is the electrolysis of acetylenes in MeCN in the presence of a Co complex to pyridines [143].

Electrolysis of alkyl arenedithioates in MeCN with benzyltriethylammonium chloride as electrolyte yields 5-aryl-4-cyano-3-methylisothiazoles. It is suggested that the dithioester is chlorinated at the anode and reacts with 3-iminobutyronitrile, which is formed from MeCN by the cathodically generated base, to the isothiazole [144].

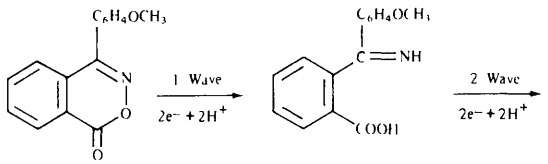
DMF may also participate in ring formation. Reduction of *N*-phenyl-2-bromoisobutyramide in DMF gave, besides debrominated and dehydrobrominated products, 5,5-dimethyl-2-dimethylamino-3-phenyl-4-oxazolidone [145].

B. Ring Contractions

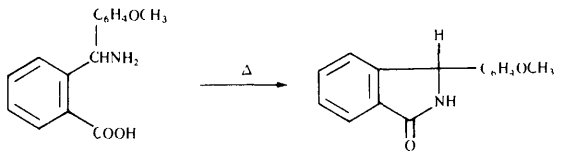
In ring contractions occurring during electrolysis of nitrogen-containing heterocyclic compounds, a hydrogenolysis of a single bond takes place at some step, which is then followed by a ring closure. These reactions may be classified according to the single bond cleaved in the reduction. Examples of hydrogenolysis of oxygen–nitrogen, nitrogen–nitrogen, and nitrogen–carbon bonds are discussed.

1. Hydrogenolysis of an Oxygen–Nitrogen Bond

The initial step in the reduction of protonated oximes has been shown [146] to be a hydrogenolysis of the oxygen-nitrogen bond; in cyclic derivatives of oximes the same occurs. In 4-(4′-methoxyphenyl)-2,3-benzoxazin-1-one (**XLV**) the reduction proceeds in two steps, and it is possible to isolate the rather stable intermediate ketimine [146]:



(XLV) (25)

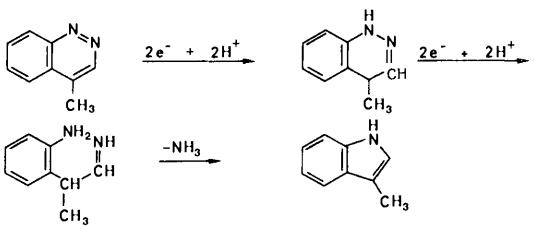


2. Hydrogenolysis of a Nitrogen–Nitrogen Bond

A ring contraction involving this reaction has been found in cyclic hydrazones, hydrazines, and triazines.

The initial step in the reduction in acid solution of azines, hydrazones, and substituted hydrazones has been suggested to be a hydrogenolysis of the nitrogen–nitrogen bond [146]; the ald- and ketimine thus formed are mostly, but not always, reduced further at the potential necessary for the reductive cleavage; this depends on the nature of the substituents. This type of reduction is discussed in Chapter 11.

In acid solution cinnolines are reduced to dihydrocinnolines; a 1,4-dihydrocinnoline may be regarded as derived from a phenylhydrazone, which is reduced with cleavage of the nitrogen–nitrogen bond [101, 147]:



(26)

Similar ring contractions in which the nitrogen–nitrogen bond is cleaved are found in the reductive ring contractions of pyridazines to pyrroles [148, 149], phthalazines to isoindoles [150], 5,6-diphenyl-1,2,4-triazinones to imidazolones [151], benzo-1,2,4-triazines to benzimidazoles [71], benzo-1,2,3-triazinone to indazolone [1a, 152], benzo-1,2,3-triazin-3-oxide to indazole [1a], benzo-2,3-diazepines to isoquinolines [153], benzo-1-pyrano-[4,3-*e*]-as-triazin-3-one to benzopyranoimidazolone [154], and 2-methyl-4,5-dihydropyridazin-3-ones to pyrrolin-2-ones [155].

The reduction of phthalazinones [156] and 4,5-dihydropyridazin-3-ones [155] are examples of a reduction of a protonated compound containing > C=N–N in which the C=N double bond has been proved to be more easily reducible than the N–N bond. Reduction at the potential of the second wave of phthalazinones results in cleavage

of the N–N bond and ring contraction. 4-Methylphthalazinone is thus reduced to 1-methylphthalimidine [156].

3. Hydrogenolysis of a Nitrogen–Carbon Bond

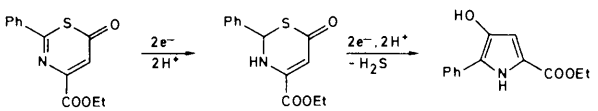
An electrolytic cleavage of such a bond in a convenient potential interval occurs only when the bond is activated, for example, by an adjacent carbonyl or azomethine group.

A ring contraction occurs during the reduction of 7-chloro-2-methylamino-5-phenyl-3*H*-4,5-dihydro-1,4-benzodiazepine to 6-chloro-2-methyl-4-phenyl-3,4-dihydroquinazoline [157]. It has been suggested [51] that the cleavage occurs between C-3 and N-4, although another interpretation has also been offered [157].

The reductive ring contraction of 2-phenylpyrimidines to 2-phenylpyrroles involves a cleavage of a carbon-nitrogen bond, followed by attack by a carbanion on an azomethine group [158].

4. Hydrogenolysis of a Carbon-Sulfur Bond

Reduction of 4-carbethoxy-2-phenyl-1,3-thiazinone-6 (**XLVI**) in aqueous alcoholic media yields 2-carbethoxy-4-hydroxy-5-phenylpyrrole (**XLVII**) in a 4e-process. The first step in the reduction is suggested to be the saturation of the C=N double bond; the mechanism of the reductive loss of H_2S and C–C bond formation is not yet established [159]:



(27)

(XLVI) **(XLVII)**

C. Ring Expansions

Only a few types of ring expansions involving electrolysis have been reported so far. In the preparation of ψ-phthalazinones from *N*-anilinophthalimides [160], the phthalimide derivative is reduced to a derivative of phthaldehydic acid, *N*-anilinohydroxyphthalimidine. It has been suggested [160, 161] that this compound undergoes a ring opening to a hydrazide of phthalaldehydic acid. On ring closure, the more nucleophilic nitrogen of the hydrazide attacks the aldehyde group with formation of a six-membered ring, a ψ-phthalazinone. In strongly acid solution the ψ-phthalazinone ring may be opened again, and then some of the hydroxyphthalimidine forms a phenylhydrazone of phthalaldehydic acid. The phenylhydrazone would on ring closure yield 2-phenylphthalazinone; this Rowe rearrangement [161] can thus be explained by assuming that the ψ-phthalazinone is the kinetically controlled product, whereas the 2-arylphthalazinone is the thermodynamically controlled product.

A special type of ring enlargement is found in the electrolytic reduction of bicyclic α-amino ketones at a lead cathode in 30% sulfuric acid at 60°C to monocyclic products [162]. Thus, 1-ketoquinolizidine under these conditions gave 59% 5-hydroxyazacyclodecane and 4.5% 1-azabicyclo[5.3.0] decane. The initial cleavage of the carbon–nitrogen bond is analogous to that found in the reduction of derivatives of 2-aminoacetophenone [163].

The "abnormal" Reimer–Tiemann reaction involves a ring expansion, in the classical case from a pyrrole to a 3-chloropyridine, resulting from an attack of dichlorocarbene on a double bond. An electrochemical equivalent can be made by electrolysis in a chloroform solution, where the electrogenerated base produces dichlorocarbene. By using this method, 2,3-dimethylindole could be transformed to 3-chloro-2,4-dimethylquinoline in fair yield; some of the "normal" Reimer–Tiemann product, 3-dichloromethyl-2,3-dimethyl-3*H*-indole, was also formed [164].

A somewhat similar ring expansion is found in the oxidation of tetraphenylpyrrole in nitromethane to tetraphenylpyridine [165], which is discussed in Sec. III.C.

III. ELECTROLYTIC REACTIONS OF HETEROCYCLIC SYSTEMS

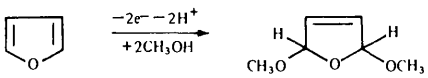
In this section the electrode reactions of heterocyclic compounds in which the nucleus undergoes a reduction or oxidation are discussed. Substituted compounds are included in this section only if the substituent does not become reduced or oxidized.

One advantage of using electrolytic methods in heterocyclic systems is the possibility of preparing partly reduced systems, in most cases from π-electron-deficient compounds, and it is probably the most general method for doing so.

Another useful method is the electrolytic substitution of heterocyclic compounds, which are π-electron rich or substituted with electron-donating groups.

A. Compounds with One Oxygen Atom

Furan is, as a π-electron rich compound, easily oxidized electrolytically. In acetonitrile the oxidation potential of furan is comparable to that of anisole [35]. In methanol the oxidation is an ECEC mechanism in which 2,5-dihydro-2,5-dimethoxyfuran is formed [166] in the Clauson–Kaas reaction:



(28)

The reaction may be performed in the presence of an excess of ammonium bromide, where the bromide ions are oxidized to bromine, which in turn oxidizes furan. The dimethoxydihydrofuran is a valuable intermediate for the preparation of various heterocyclic compounds, such as pyridines [167] and pyridazines [168–170]. The oxidation of a furan to a dimethoxydihydrofuran is thus a key step in a synthesis of pyridoxine [177].

The stereochemistry of the anodic cyanomethoxylation of 2,5-dimethylfuran [172] depends, at a platinum electrode, on the concentration of substrate and of additives; the *cis–trans* ratio changes from 2.89:1 to 1.46:1 on increasing the concentration of substrate from 0.01 to 0.2 M. At a carbon anode a ratio close to the equilibrium mixture 1.42:1 is obtained.

Anodic acetoxylation of furan can be done in acetic acid containing acetate [173, 174] and benzoyloxylation in DMF containing benzoic acid and lithium chloride [175]. A mixture of *cis*- and *trans*-benzoyloxylated product is formed. Cyanomethoxylation of 2,5-dimethylfuran gives a mixture of *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrofuran [176–178].

Anodic oxidation of 5-alkyl-2-furoic acid in aqueous methanol yielded mainly [179] 1-butenolides and γ-keto esters, whereas oxidation of 5-acetylfuroates in methanol leads to ring-opened diesters besides the 2,5-dimethoxylated dihydrofuroates [180].

Pyrylium [181–183] and *isobenzopyrylium* [184] salts have been shown to be polarographically reducible in a one-electron reduction. In cyclic voltammetry in aprotic solvents, 2,4,6-trisubstituted pyrylium salts show two peaks; the shape of the peak depends on the rate of dimerization. This process occurs more rapidly at C-4 than at C-2 (C-6) [182, 183], and the dimerization takes place spontaneously for 4-unsubstituted pyrylium salts. The equilibrium between radicals and dimer is displaced in favor of the radicals on introduction of electron-withdrawing substituents; such groups enhance the aromatic character of the radical [185]. If the reduction of pyrylium salts is made in the presence of an alkyl iodide a fair yield of the 4-alkylated 4*H*-pyrane is isolated with the dimer [182].

Anodic oxidation of chromone in aqueous methanol containing a halide gives 3-halo-2-methoxychromanone in a reaction that is a variant of the Clauson–Kaas reaction [186].

Electrochemical reduction of coumarin [187] affords the meso and (±) forms of a product hydrodimerized (at C-4) like many other α,β-unsaturated acid derivatives. In the presence of tertiary amines, which are not destroyed during the process but catalyze the evolution of hydrogen, a transfer of hydrogen takes place from the amine radical to the coumarin radical with formation of 3,4-dihydrocoumarin. Asymmetric amines cause asymmetric induction during the reduction of 4-methylcoumarin, as in Chapter 26 [188].

Voltammetric studies in DMF [189] of aryl-substituted isobenzofurans like 1,3,4,7-tetraphenylisobenzofuran show that it gives two, one-electron reduction waves and one, one-electron oxidation wave. By cyclic voltammetry (CV) it was shown that the first reduction product was stable, whereas the first oxidation product and the second reduction product were unstable.

B. Nuclei Containing One Sulfur Atom

1. Thiophene

Anodic oxidation in methanol of thiophene and substituted thiophenes at low temperatures (−20 to −30°C) results in methoxylation and ring opening with loss of sulfur as SO_2 [190]. From thiophene is isolated butenedialdehyde tetramethylacetal, some methoxysuccinic dialdehyde tetramethylacetal, and a small amount of methyl β-formylpropionate. In general, oxidation of thiophenes results in the formation of derivatives of α,β-unsaturated γ-dicarbonyl compounds or γ-keto esters. Cyanomethoxylation of 2,5-dimethylthiophene yields mainly *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrothiophene and 3-cyano-2,5-dimethylthiophene [191].

Thiophene is not reducible by direct electroreduction, but by indirect reduction (Chapter 29) in DMF using biphenyl radical anion as electron transfer agent it is possible to reduce thiophene to 2,5-dihydrothiophene and tetrahydrothiophene in high yield [192]; thiophenes substituted at C-2 with carboxyl, however, may be reduced by direct electrolysis to the 2,5-dihydro derivatives [193].

Dibenzo[*b*,*e*]thiepinones are reductively ring opened at the "benzylic" C-S bond [194]; anthrone and anthraquinone are among the products. The cleavage and ring closure are akin to those observed in the reduction of 2-phenyl-1,3-thiazin-6-ones to 3-hydroxypyrroles [195].

Benzothiophene and its alkylated derivatives afford the corresponding 2,3-dimethoxy-2,3-dihydrobenzothiophenes in the Clauson–Kaas reaction, whereas others, such as the methyl 3-methylbenzothiophene-2-carboxylates, do not [196].

The reduction of benzothiophene by "ammonium amalgams" is discussed in Chapter 28.

Benzothiophen-1,1-dioxide is polarographically reducible at about -1.3 V at pH > 2 [197]. In alkaline solution the polarographic behavior is complicated by the addition of nucleophiles to the 2,3-double bond. Controlled potential reduction in acetate buffer produced 2,3-dihydrobenzothiophen-1,1-dioxide [198].

2,4,6-Triphenylthiopyrylium salts and some other trisubstituted thiopyrylium compounds show two reversible redox systems [185]; the anion from the second reduction has been used as electron transfer agent in indirect reduction of and coupling with alkyl halides [199].

C. Nuclei Containing One Nitrogen Atom

1. Aziridine Derivatives

Aziridinium salts are easily reducible, both in aqueous and nonaqueous solvents; usually, from alkylaziridinium salts, a mixture of products is obtained as a result of subsequent chemical reactions of the primary products [200]. Electroanalytical data point to a one-electron reduction followed by ring opening of the radical.

Arylaziridinium salts show a "reverse" structural effect on the polarographic half-wave potential, as electron-donating substituents make the reduction in aqueous solution easier and electron-attracting groups have the opposite effect [201]. A tetramerization of 1-benzylaziridine to a tetra-azacyclododecane may be induced anodically [202].

2. Pyrroles and Benzopyrroles

Pyrrole is not polarographically reducible but can be reduced at a lead cathode in dilute sulfuric acid to pyrroline and further to pyrrolidine [203]. Under similar conditions 1,2-dimethylpyrroline [204] is also reduced to the pyrrolidine and indoles [205–207] to indolines or dimerized products [208]. 1-Methylindole can be reduced to 2,3-dihydro-1-methylindole in aqeuous THF at very negative potentials using TBAOH as electrolyte [209]. Pyrrole may also be oxidized anodically; oxidation of pyrrole may result in the formation of polypyrrole useful for preparation of conducting polymers (Chapter 32).

In acetonitrile, pentaphenylpyrrole is oxidized to a rather stable cation radical [210], and tetrasubstituted pyrroles react similarly [211]; in methanolic solution 1-methylpyrrole forms 1-methyl-2,2,5,5-tetramethoxypyrroline [212].

2,3,4,5-Tetraphenylpyrrole is in nitromethane oxidized in two, one-electron steps, the first reversible. Oxidation at the potential of the first wave at low temperatures gives $n = 2$, indicating a disproportionation of the initially formed radical cation. The dication thus formed reacts with the residual water to give a hydroxylated compound that on heating rearranges to a pyrrolone. At higher temperatures the radical cation reacts with nitromethane, forming nitrite ion and a tetraphenylpyridine, reported to be 2,3,4,6-tetraphenylpyridine [165, 213].

In methanolic cyanide solution *N*-substituted pyrroles [165, 213] are substituted in the 2-position by a nitrile group; when both 2- and 5-positions carry a methyl group, cyanation initially [215] takes place in the 2- and 5-positions, but these compounds are unstable and the final substitution occurs in the side chain [214, 215]. *N*-substituted indoles

are likewise cyanated in good yield; substitution in the 2-position dominates, although some 3-substitution takes place [214].

N-Substituted pyrrolidines (and piperidines) are, similarly to other tertiary aliphatic amines, anodically cyanated α to the nitrogen in aqueous methanolic solution containing sodium cyanide [216].

2,3-Diphenylindole forms, on anodic oxidation, a cation radical that dimerizes; the dimer is probably of the indole–indolenine type [217, 218], dimerized at C3–C6′ [219] rather than at C3–C5 [220, 221]. The reaction is similar to the oxidation of 1,2,3,4-tetrahydrocarbazole [222].

N-Methyl-1,2,3,4,7-tetraphenylisoindole has been investigated by CV in DMF. Contrary to the isobenzofurans already discussed, it forms a stable cation radical but unstable anions [189].

Carbazoles are oxidized at controlled potential at a platinum anode in acetonitrile to cation radicals that are stable when the 3-, 6-, and 9-positions are blocked [223]. The radical cation from carbazole dimerizes predominantly at the 3-position to 3,3-dicarbazyl, which is further oxidizable to the quinoidal dication at the potential used. In the presence of pyridine, which may cause a rapid deprotonation of the N–H proton 9,9′-dicarbazyl is the isolated product.

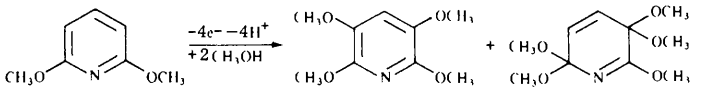
3. Pyridine Derivatives

Pyridine is not polarographically reducible in aqueous media; in MeCN catalytic hydrogen evolution is the main reaction of protonated pyridine at the cathode [224]. Pyridine can, however, be reduced to piperidine at a lead cathode in 10% H_2SO_4 [225]; the yield is very dependent on the purity of the lead and other components. Side products are α,α-, α,γ-, and γ,γ-dipiperidyl. Pyridine may be reduced to a dimer in liquid ammonia [226]. In MeCN pyridine is reduced in a two-electron wave; dihydropyridine and cyanomethylated tetrahydropyridine are formed, the latter by attack of $(CH_2CN)^-$ on the dihydropyridine [227]. Electrochemical synthesis involving pyridine and its derivatives has been reviewed [1c].

The potential-limiting anodic reaction in pyridine with perchlorate as supporting electrolyte is presumably the oxidation of pyridine to an onium ion, which with excess of pyridine forms *N*-(2-pyridyl)pyridinium perchlorate [228].

Substituents may render the nucleus more easily reducible or oxidizable; electron-attracting substituents such as carbethoxy groups facilitate the reduction, whereas methoxy groups, for example, make the oxidation easier. Thus most derivatives of pyridinedicarboxylic acids are reduced in the nucleus rather than in the carboxyl group [229]. A positive charge on the nitrogen atom also facilitates the reduction of the nucleus, but the charged pyridine ring also makes the electron-attracting substituent more easily reducible. In some cases the electron reaction changes with pH; in several such instances it is found that the substituent is reduced in acid solution and the ring in alkaline medium. Polymerization may also occur, especially if C-4 is unsubstituted.

The presence of two methoxy groups on the pyridine ring makes it susceptible to anodic oxidation. In alkaline methanol the main products [212] from 2,6-dimethoxypyridine are 2,3,5,6-tetramethoxypyridine and an azaquinone, probably with the structure (**XLVIII**) as in Eq. (29).



(29)

(XLVIII)

Alkyl-substituted (or arylakyl-substituted) pyridines may be oxidized to the corresponding acids in high yield in acid solution on a PbO_2 anode in a divided cell; a continuous removal of the products is an advantage [230].

The anodic oxidation of 4,4-disubstituted 1,4-dihydropyridines in MeCN gives a relatively stable cation radical, which catalyzes the oxidation of MeCN; some of the cation radicals lose a 4-substituent as a radical, and the nucleus is oxidized further [231].

Electrochemical oxidation of dihydropyridines [231–233] has mostly been formulated as a loss of $2e^-$ and $2H^+$, but a loss of $1e^-$, $1H^+$ and a hydrogen atom has also been described [234].

Pyridinium salts are generally polarographically reducible in neutral and alkaline solution, and dimerized dihydropyridine derivatives have been postulated as products [235–237]. The bimolecular dimerization rate constant has been found to be $1 \times 10^7\ M^{-1}\ s^{-1}$ [238]. Further reduction produces the 1,4-dihydro derivative. In a few cases the structures of the dimers have been established; thus, reduction of 1,2,6-trimethyl-3,5-dicarbethoxypyridinium cation yields a mixture of isomers. The less stable isomer, the 2,4′-dimer, undergoes rearrangement through two pyridil radicals into the thermally more stable 4,4′-dimer [239]. Anodic oxidation of the dimerized products, tetrahydrobipyridines, gives a mixture of alkylpyridinium salts and the dication of 1,1′-dialkyl-4,4′-bipyridine [240]. The reductive dimerization of 1-alkylpyridinium salts followed by oxidation has been used for the synthesis of the herbicide paraquat [241].

The rate of cleavage of the *N*-substituent of the radical obtained by a one-electron reduction of 1-substituted 2,4,6-triphenylpyridinium has been measured in DMF; benzyl and allyl substituents cleave fast, whereas the radicals with 1-phenyl and 1-methyl are more stable [242].

1-Alkyl-4-carbomethoxypyridinium salts are reduced in protic and aprotic media [243, 244] to a rather stable radical; in DMF this radical is reduced in a reversible reaction to an anion that acts as a good electron-donating reagent [245]. The radicals from the 2- and 3-isomers are less stable and dimerize readily [243].

N-Methylpyridinium or *N*-methylquinolinium salts [246] may be oxidized to the *N*-methyl-2-pyridone or *N*-methyl-2-quinolone, respectively, in alkaline medium containing some potassium hexacyanoferrate (III). The reaction is probably an indirect electrolysis in which the hexacyanoferrate oxidizes the pseudobase and is, in turn, reoxidized at the anode.

The reduction of quaternary derivatives of nicotinic amide as model compounds for the phosphopyridine nucleotides has been subject to many polarographic [235, 247–255] and electrolytic investigations. At pH 4–7 a one-electron wave is found, whereas in alkaline solution two, one-electron waves are seen. Controlled potential reduction in a phosphate buffer at the potential (−1.2 V) of the first wave of 1-methyl-3-carbamoyl or 1-benzyl-3-carbamoylpyridinium ions produces a mixture of dimers, including diastereomers of 6,6′- [248] and 4,4′- [253], in addition to unsymmetrical dimers [254].

Reduction at the potential of the second wave (−1.80 V) of NAD^+ analogs substituted at N-1 with benzyl or methyl gives primarily the 1,6-dihydro compound, which was shown by nuclear magnetic resonance (NMR) spectroscopy and deuterium experiments;

the 1,6-dihydro compounds are rather easily isomerized to the 1,4-dihydro compounds. 1-Phenyl-NAD^+ analogs are reduced to the 1,4-dihydro compounds [254].

Analogous results have been obtained in the electrolysis of the pyridine nucleotides [256–261]. The dimer has, however, been suggested to be 4,4′-dimers. The coenzyme activity of the reduction product varies with the experimental conditions. Some reductions yielded totally inactive products; others produced partly or fully active material. The highest activity was obtained by an indirect electrolytic reduction of TPN (Chapter 29) [261]; electrochemical reduction of methyl viologen in the presence of ferridoxin-TPN reductase caused a reduction of triphosphopyridine nucleotide (TPN) to a biochemically active product.

Electrochemical oxidation of the reduced form (NADH) of nicotinamide adenine dinucleotide and its analogs has been investigated [262]; best results are obtained using a carbon felt electrode. The results are consistent with an ECE mechanism yielding the pyridinium salt. Indirect oxidation of NADH (and reduction of NAD^+) is treated in Chapters 27 and 29.

4. Quinoline, Isoquinoline, and Acridine

Quinoline and isoquinoline derivatives are polarographically reducible in a way similar to the pyridine compounds, but the reduction potentials required are generally less negative.

The reduction of quinoline at different electrodes in sulfuric acid to dihydro- and tetrahydroquinoline has been studied using constant current [263]. The reaction proceeds with high current efficiency at electrodes with high hydrogen overvoltage (e.g., lead), but not at platinum, which has a low hydrogen overvoltage.

At neutral pH, quinoline derivatives may be dimerized in aqueous methanolic solution [264]. It is suggested that a radical–radical reaction occurs at low substrate concentration and a radical–substrate coupling at higher concentrations.

Quinolines, isoquinolines, and other heterocyclic compounds may be electrochemically carboxylated by reduction in aprotic medium in the presence of CO_2. The carboxylation is in many cases faster than the loss of chlorine from a chlorinated heterocycle, so such compounds may be, especially at low temperature, carboxylated without loss of chlorine [265].

Reduction of quinoline and and isoquinoline in NH_3 [266] or DMF [267] in the presence of alkyl halides yields alkylated products.

It is of interest that a dihydroisoquinoline like 3,4-dihydropapaverine is more easily reducible than the parent compound [268]; the electrode reaction is saturation of the azomethine bond. 3,4-Dihydro-2-alkylisoquinolinium salts may be reductively benzylated at C-1 [17] in aprotic media.

Anodic oxidation of quinoline at a platinum anode in 75% sulfuric acid yields quinolinic acid (77%) [269]; other quinolines bearing substituents in the hetero ring in the 3-position may do similarly, whereas some 2- and 4-substituted derivatives form tar [261].

Acridine is polarographically reducible both in acid and alkaline solutions [270]. In strongly acid solution a single one-electron wave is found, and from a preparative reduction compounds dimerized at C-9 [35] were isolated. In less acid and in alkaline solutions, two one-electron waves are found.

Anodic oxidation of 9,9-substituted 9,10-dihydroacridines in MeCN–TBAP at a Pt electrode gives a cation radical that dimerizes to a 2,2′-biacridane system; such a dimer is further oxidizable to a quinonoid system [271].

The acridizinium and phenanthridizinium systems are reducible [272] in a manner similar to acridine.

D. Compounds With One Oxygen and One Nitrogen Atom

1. Oxaziridines

Oxaziridines are very easily reducible compounds, and their polarographic wave [273, 274] begins at the dissolution wave of the mercury. In the reduction there is formed a *gem*-amino alcohol that at low pH loses water with the formation of a Schiff base and at higher pH loses an amine to a carbonyl compound. The Schiff base or the carbonyl compound may be further reducible.

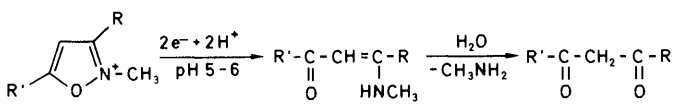
2. Oxazoles and Isoxazoles

Aryl-substituted oxazoles are reducible [275] at rather negative potentials [−1.0 to −2.1 V (SCE)], and the electrode reaction consumes in most cases six electrons; 2-(1-naphthyl)-5-phenyloxazole, however, consumes two electrons.

In DMF diphenyloxazole is reduced in two one-electron reductions, the first resulting in a relatively stable radical anion, the second presumably in a dihydro derivative [276]. In MeCN, 3-phenyl-substituted isoxazoles are reduced to a monoimine that is hydrolized to the diketone [277].

Reduction of oxazolinium salts in DMF yields the anion of the tetrahydro-oxazole, which may be used as an acyl anion equivalent [278].

N-Alkylisoxazolium compounds may be reduced in neutral solution to 3-alkylamino-2-butenones (Eq. (30)] [277, 279] and *N*-alkyl-4,5-dihydroisoxazolium salts to 4-hydroxy-2-butanones [277].



(30)

3. Anthranils

These compounds give in acid solution two polarographic waves, and a reduction at a potential corresponding to the foot of the first wave of 3-methylanthranil yields *o*-aminoacetophenone in good yield [51]. The second wave represents the reduction of this compound. In alkaline medium a single three-electron wave is found, and the reaction mixture contains several dimerized compounds [3].

4. Oxazines

N-Formylated 1,4-oxazines, including morpholine, can be oxidized anodically in methanolic solution to 3-methoxy derivatives, which under acidic conditions lose methanol to *N*-acylenamines; these are of potential synthetic interest [280]. Other acylated secondary amines, such as those from pyrrolidine, piperidine, and tetrahydroisoquinoline, behave similarly (Chapter 24) [281].

E. Compounds With One Sulfur and One Nitrogen Atom

1. Thiazole Derivatives

Thiazole and its simple alkyl or aryl derivatives are not polarographically reducible. Substitution in the thiazole ring with electron-attracting groups may render the nucleus reducible. Derivatives of thiazole-2-carboxylic acid are reducible in alkaline solution, and the reduction is assumed to take place in the nucleus [282].

Many thiazolium salts are polarographically reducible [283, 284]; 3-methylbenzothiazolium iodide [283] is reduced in a single wave; a preparative reduction gave n between 1 and 2, and a mixture of dimer and monomer 2,3-dihydro-3-methylbenzothiazole was found. Aryl groups in the 2-position hinder dimerization [283]. With TEAP as supporting electrolyte 2-methyl-3-ethylbenzothiazolium ion gives two, one-electron waves [284].

The reduction of thiamine hydrochloride in neutral buffer is reported to involve a cleavage between the pyrimidine ring and the thiazolium ring and a ring opening of the latter; further chemical steps lead to a substituted thiourea [285].

On electrochemical reduction of bis(2-ethylthio-1,3-thiazolium) salts dithiadiazafulvalenes are obtained. Such diaza analogues have very high π-electron donating properties compared to the tetrathiafulvalenes [286].

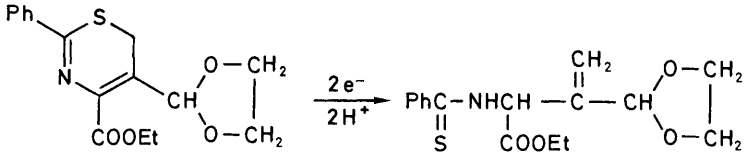
2. Isothiazole Derivatives

Substituted benzenesulfonamides bearing strongly electron-attracting substituents can be reduced in slightly alkaline solution at the dropping mercury electrode to ammonia, sulfur dioxide, and a substituted benzene (Chapter 23). Saccharin is a compound of this type, and the primary electrode reaction is a cleavage of the carbon–sulfur bond; chemical reactions follow the initial cleavage.

In acid solution the reduction follows a route similar to that of phthalimide with a primary reduction of the carbonyl group [287].

3. Thiazines

2-Phenyl-1,3-[6H]-thiazines substituted at C-5 with an electron-withdrawing group (EWG) are reduced first at the C=N double bond and at the C=C bond at a more negative potential; if both C-4 and C-5 carry an EWG the C=C bond is reduced prior to the C=N bond [288]. If C-4 carries an EWG and C-5 an electronically "neutral" group, a cleavage of the allylic C6–S bond occurs with formation of a substituted benzthiamide as in Eq. (31) [288]. The reduction of 2-benzylthio-5,6-dihydro-4*H*-1,3-thiazine depends on the electrode material; at an Hg cathode a reductive loss of benzylthiol occurs, whereas at carbon the benzyl group is lost as toluene with formation of a thiazinethione [289].



(31)

Several derivatives of phenothiazine have been found to be oxidizable at a gold anode in dilute sulfuric acid [290]. The product proved to be the sulfoxide rather than the *N*-oxide.

In acetonitrile phenothiazine is oxidized in two, one-electron waves; the radical cation obtained in the first oxidation loses a proton and is oxidized to the phenazothionium ion and isolated as the perchlorate [291] or dimerizes at nitrogen or at C-3 [292].

Reduction of 1,3-thiazinium salts in acetonitrile yield 6,6′-bi-1,3-thiazinyls; the 6,6′-bi-1,3-thiazinyls are oxidized to thiazinium salts at a platinum electrode, whereas dehydrogenation by chloranil affords 6,6′-bi-1,3-thiazinylidene [293].

F. Compounds With Two Oxygen or Two Sulfur Atoms

Ethylene trithiocarbonate is reduced in DMF to the radical anion, which loses ethylene [294]; the reaction is akin to other reductive elimination reactions. The sulfur-containing part reacts with another anion radical to a bis(trithiocarbonate) dianion.

Electrochemical reduction of 4,5-alkylthio-1,3-dithiol-2-ones in aprotic medium, followed by alkylation, gives tetraalkylthioethylenes in almost quantitative yield; the same products are formed, albeit in lower yields, on the reduction of 4,5-alkylthio-1,3-dithiol-2-thiones [295].

Voltammetric oxidation of 1,4-dioxins and 1,4-dithiins in acetonitrile containing perchlorate yields a radical cation in the first one-electron oxidation and a dication in the second one-electron oxidation. Both compounds are typical π-electron-rich heterocycles, whereas the dication contains six π-electrons, and the relatively high stability of the dication is connected with this "aromaticity" [296].

The monocation radical of dibenzodioxine can be prepared electrochemically and isolated as a stable perchlorate [297]; if the medium is not dry, hydroxylated and further oxidized products are obtained.

G. Compounds With Two Nitrogen Atoms

1. Diazirines

Diazirines are polarographically reducible in acid solution in a four-electron reduction to a *gem*-diamine, which is hydrolyzed to a carbonyl compound, and in alkaline medium in a two-electron reaction [298] to a diaziridine. Diaziridines are reducible only in acid solution [299] with cleavage of the N–N bond, in alkaline solution they can be oxidized anodically to diazirines [298].

The protonated diaziridine is more easily reducible than the diazirine, which has too weakly basic properties to be protonated in aqueous solution. In alkaline medium in which both are unprotonated, the diazirine is the more easily reducible. This explains why it has been difficult to obtain good yields of diaziridine by chemical and catalytic reduction of a diazirine; if such a reduction is to result in a high yield of diaziridine, it must be performed in an alkaline medium.

Di-*tert*-butyldiaziridinone is reduced in DMF–TEABr to *N*,*N*′-di-*tert*-butylurea with cleavage of the nitrogen–nitrogen bond; the presence of the electron-attracting carbonyl group makes it possible for the reductive cleavage of the unprotonated compound [300] to take place.

2. Pyrazoles

Pyrazolines have been investigated polarographically in a 2:2:1 mixture of DMF, benzene, and methanol with tetraethylammonium iodide as electrolyte. The polarographic data

indicate a two-electron reduction of the carbon–nitrogen double bond [301]. In DMF suitably substituted pyrazoles may be reduced to Δ^4-pyrazolines [302].

The anodic oxidation of 1-arylpyrazolines has received considerable attention. In acetonitrile, without added base, the primarily formed cation radical dimerizes at C-3 to bis-(1-phenylpyrazolinyl-3) if this carbon is unsubstituted; otherwise the dimerization takes place at the *p*-carbon of the 1-phenyl group, if this is unsubstituted, to bis(pyrazolinyl-1)-biphenyl derivatives, which are further oxidized. In the presence of base, such as pyridine, a 1-phenylpyrazole is obtained [303–305].

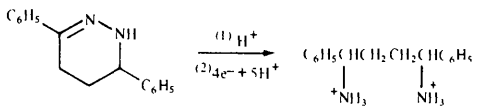
3. Pyridazines

Pyridazines are polarographically reducible [306, 307], often stepwise. The first reduction generally yields a dihydropyridazine, which can exist in different tautomeric forms, the most stable forms usually being the 1,4- and 4,5-dihydropyridazines [306]. The further reduction is complicated by the fact that the different tautomeric forms may be reduced differently and at different potentials and that the rate of transformation of a given tautomer to the most easily reducible one may or may not be fast compared to the further reduction.

The product isolated [306] from the two-electron reduction of 1-methyl-3,6-diphenylpyridazinium iodide in acid solution after extraction from neutral solution was 1,4-dihydro-1-methyl-3,6-diphenylpyridazine, but as it was found that 1,4-dihydro-3,6-diphenylpyridazine in trifluoroacetic acid was transformed to the 4,5-dihydro derivative [148], this may be the predominant tautomer in the acid solution.

The reduction in acid solution of di- and tetrahydropyridazines and pyridazinones is often best understood when their resemblance to hydrazones is considered. The reduction of such compounds has been discussed (Chapter 11), and the primary step is a hydrogenolysis of the nitrogen–nitrogen bond. The reduction of 1,4-dihydro-1-methyl-5-*t*-butyl-3,6-diphenylpyridazine to pyrroles has been described [148, 149]; at more negative potentials, pyrrolines and pyrrolidines may be obtained from pyridazines.

3,6-Diphenyl-2,3,4,5-tetrahydropyridazine (**XLIX**) is structurally similar to a benzylhydrazone of propiophenone, and accordingly, a four-eletron polarographic wave is observed in acid solution with formation of **L** [306]. The electrode reaction is as follows:



(32)

(XLIX) **(L)**

Reduction in acetate buffer at the potential of the first wave of 3-phenyl-6-dimethylaminopyridazine yields the 4,5-dihydro derivative in high yield [306].

In a similar way, other pyridazines [306], such as 3-phenyl-6-methoxypyridazine and 3-methyl-6-chloropyridazine, are reduced, but the dihydropyridazines are in these cases rather unstable and may lose methanol or hydrogen chloride, forming the corresponding 4,5-dihydropyridazinone, which being an acylated hydrazone is cleaved with ring opening and reduction or hydrolysis of the ketimine (Chapter 11).

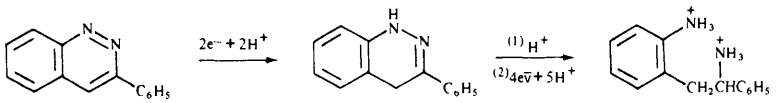
In alkaline solution 3,6-diphenylpyridazine gives a two-electron polarographic wave that in strongly alkaline solution is followed closely by a smaller wave. A preparative reduction at the potential of the second wave yields 3,6-diphenyl-2,3,4,5-tetrahydropyr-

idazine. It has been suggested [148] that the primary reduction product is a 1,2-dihydropyridazine that tautomerizes to the 4,5-dihydro derivative; this compound is then reduced further, analogously to the reduction of benzalazine [146]. In DMF 3,6-diphenylpyridazine may be reductively acetylated [308] or carboxylated [265].

4. Cinnolines

Cinnolines are generally reducible [101] in two or more steps. The first step in the reduction of aryl- or alkyl-substituted cinnolines is the formation of 1,4-dihydrocinnolines. This reduction is not reversible. Only in the case of benzo[*c*]cinnoline is the reduction, a saturation of the nitrogen–nitrogen double bond; the reaction resembles the reduction of azobenzene to hydrazobenzene and, like this system, is nearly polarographically reversible.

1,4-Dihydrocinnolines may be regarded as cyclic phenylhydrazones, and their reduction is in accordance with the concept that only the protonated compounds are reducible, and the first two-electron step produces an amine and an imine. If the imine is reducible at the potential necessary for the hydrogenolysis of the nitrogen-nitrogen bond (Chapter 23), the imine is reduced to an amine; if not, a ring closure to an indole takes place, unless the potential is kept so negative that the further reduction of the imine can compete with the ring closure. The ring contraction to indoles has been discussed. The reduction of 1,4-dihydro-3-phenylcinnoline proceeds by a four-electron reaction:

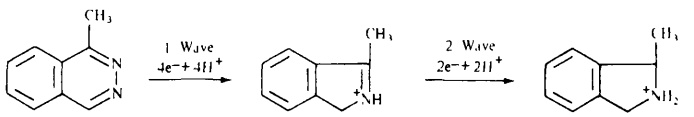


(33)

Derivatives of 1,2-dihydrocinnoline may be prepared by reductive acylation of cinnoline in DMF [308].

5. Phthalazines

These compounds are reduced in acid solution somewhat differently from cinnolines. Phthalazine is reduced polarographically in acid solution in a six-electron wave [309], presumably to *o*-xylene-α,α'-diamine, but 6 *N* hydrochloric acid [150] is required as medium if the diamine is the desired product. 1-Methylphthalazine is reduced as follows:



(34)

(LI)

By reducing at −0.65 V (SCE) it is possible to prepare 1-methylisoindole (**LI**).

4-Dimethylamino-1-phenylphthalazine can in acid solution be reduced in a four-electron reaction to 2-(1′-amino-1′-phenylmethyl)-*N*,*N*-dimethylbenzamidine [310], which at higher pH forms 1-phenyl-3-iminoisoindoline, which can be reduced to 1-phenylisoindoline (**LII**) in a four-electron reduction. From the reduction corresponding to the first wave of 4-methoxy-1-phenylphthalazine, the cyclic imidic ester 3-methoxy-1-phenylisoindole can be isolated; it may be further reduced to **LII**.

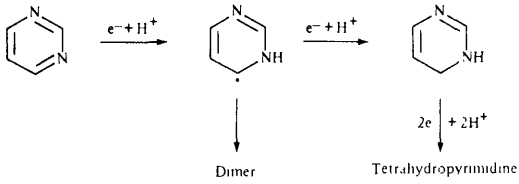
In alkaline solution phthalazine is reduced polarographically in a two-electron reduction, but in a preparative reduction it is possible to isolate mostly dimerized products, resulting from a one-electron reduction, or 1,2-dihydrophthalazine (**LIII**), depending on the conditions; **LIII** is reducible at a more negative potential to 1,2,3,4-

tetrahydrophthalazine, which may be oxidized anodically to **LIII**. Thus the electrolytic method is advantageous for the preparation of **LIII** [150, 311]. The dimerized products from the reduction of 2-methylphthalazinium iodide have been shown to have coupled at carbon rather than at nitrogen [150].

The reduction course of substituted phthalazines depends on the substituents; thus 1-methylphthalazine is reduced in alkaline solution to 1-methyl-3,4-dihydrophthalazine, whereas 1-phenyl-4-dimethylaminophthalazine is reduced to 1,2-dihydro-1-phenyl-4-dimethylaminophthalazine.

6. Pyrimidines

In acid solution, pyrimidine [312–316] is reduced polarographically in two one-electron waves; two two-electron waves are observed in neutral medium, whereas a four-electron reduction occurs in alkaline solution. These findings have been interpreted in the following way:



(35)

The dimer from 4-methylpyrimidine is the 6,6′-dimer [158].

The structure of the tetrahydropyrimidine has not been proved. 2-Aminopyrimidine is reduced similarly, but the dihydropyrimidine is not further reducible.

2-Phenylpyrimidines are reduced differently; they are reduced in acid solution in a four-electron reaction to 2-phenylpyrroles and ammonia [158].

7. Quinazolines

The polarographic behavior of quinazoline (**LIV**) [317, 318] is complicated by the hydration of the quinazolinium ion. The hydrated cation is not reducible, and in the acid region the wave height is partly determined by the rate of its dehydration; this has been used to find the rate of its dehydration at different pH values [317].

The reduction of **LIV** resembles that of pyrimidine. In alkaline solution it is reduced stepwise to the 1,2,3,4-tetrahydroquinazoline. 4-Hydroxyquinazoline [306, 319, 320] is reducible in weakly alkaline and neutral solution. The reduction is analogous to the reduction of dihydroquinazoline to tetrahydroquinazoline. At higher concentrations a product dimerized at C-2 was also isolated [319–321].

8. Pyrazines, Quinoxalines, and Phenazines

Pyrazine and its reduction product 1,4-dihydropyrazine form a system that at a mercury electrode behaves nearly reversibly [322, 323]. In acid solution, two one-electron waves are found, indicating a certain stability of the semiquinone-type one-electron reduction product. In substituted pyrazines, the initially formed reduction product, the 1,4-dihydropyrazine, may tautomerize into the less easily oxidizable 1,2- or 1,6-dihydropyrazine; the rate of tautomerization is pH dependent [324].

The electrochemical reduction of 2,3-disubstituted 5,6-dihydropyrazines yields the 1,4,5,6-tetrahydropyrazines [325]. Thus, the diimine–enediamine system is analogous to

the dione-enedion system. It is of interest that the 5,6-dihydropyrazines are somewhat more easily reducible than the pyrazines.

Quinoxaline (**LV**) [325–330] is reduced to 1,4-dihydroquinoxaline, which may be reversibly reoxidized to **LV**. 2-Methylquinoxaline is reduced to 3,4-dihydro-2-methylquinoxaline [328], whereas 2-phenylquinoxaline forms 1,2-dihydro-2-phenylquinoxaline. The 1,4-dihydroquinoxalines may be formed primarily but then tautomerize to the more stable dihydroquinoxaline. 2,3-Diphenylquinoxaline is reduced to *cis*-1,2,3,4-tetrahydro-2,3-diphenylquinoxaline; the 1,4-dihydro compound is transformed to the 1,2-dihydro derivative, which is further reducible [328]. 1,2-Dihydro-2,3-dimethylquinoxaline is reduced in acid solution with ring opening to an imine of 2-butanone, which is hydrolyzed to *o*-phenylenediamine and 2-butanone [329].

A number of condensed pyrazines (furopyrazines, thienopyrazines, furoquinoxalines, and thienoquinoxalines) have been reduced in protic and aprotic media; in all cases the primary reduction took place in the pyrazine ring [331].

In the two-step reduction of *N*,*N*′-dialkylpyrazinium and quinoxalinium salts, the first one-electron reduction leads to a cation radical, which is the most persistent oxidation state [332].

Reduction of quinoxaline in DMF in the presence of acetic anhydride [308] produces 1,4-diacetyl-1,4-dihydroquinoxaline; reoxidation of this compound in MeCN at a Pt electrode regenerates quinoxaline with formation of acetylium ions [333]. Similarly, phenazine may be reductively alkylated to 5,10-dialkyl-5,10-dihydrophenazine and pyrazine acylated to a 1,4-dihydro derivative [334].

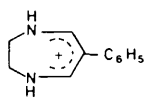
5,10-Dihydro-5,10-dimethylphenazine (**LVI**) exhibits two successive reversible one-electron oxidation steps in acetonitrile. When **LVI** is oxidized in a more nucleophilic solvent or in the presence of a nucleophile, the initially formed dication acts as a methylating agent toward the nucleophile [335] with formation of 5-methylphenazinium cation.

9. Naphthyridines

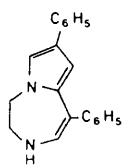
1,5-Naphthyridine is polarographically reducible at all pH values [336–338]. Macroscale reductions consume approximately one electron per molecule and point to a dimerization. The structure of the reduction products has not been established. The diquaternary salt of 1,5-naphthyridine is polarographically reducible [336]; 1,6-. 1,7-, 1.8-, 2,6-, and 2,7-naphthyridine behave similarly [337, 338].

10. Diazepines and Pyridopyrimidines

Electrochemical reduction in DMF–TPAP of 6-phenyl-2,3-dihydrodiazepinium salt (**LVII**) gives a pyrrolodiazepine (**LVIII**) with consumption of 1 F/mol. A plausible explanation of the formation of **LVIII** involves dimerization of an initially formed radical followed by intramolecular displacement of ethylenediamine [339].



(LVII)



(LVIII)

Both 1,4- [340–342] and 1,5-benzodiazepines [343] are polarographically reducible; the latter is somewhat unstable in aqueous solution, which complicates the investigations. 1,4-Benzodiazepines like 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-diazepine-4-oxide are reducible in acid solution in three steps. The first two steps, the reduction of the *N*-oxide and the saturation of the benzophenone imine, are straightforward. The mechanism of the third step, a reductive ring contraction to 6-chloro-2-methyl-4-phenyl-3,4-dihydroquinazoline, is more controversial [51, 157].

In acetonitrile some 1,5-benzodiazepine derivatives, prepared by condensation of *o*-phenylenediamine with 4,6-dimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione, have been reductively acetylated to substituted barbaralanes [344].

4-Alkyl-1-aryl-5H-2,3-benzodiazepines (**LIX**) are reduced in acidic solution in a four-electron reduction [153, 345]; in dilute hydrochloric acid 1-aryl-3-alkylisoquinoline is formed [153]. In DMF, **LIX** is reduced with 2 F/mol to its 1,2-dihydro derivative.

Pyrido[1,2-*a*]pyrimidines are reduced in acid solution with 1 F/mol to a product dimerized at C-8 and in alkaline medium in a two-electron reaction to an 8,9-dihydro derivative [346].

H. Compounds With One Oxygen and Two Nitrogen Atoms

1. Oxadiazoles

Aryloxadiazoles [275, 347] are reducible at rather negative potentials; both four- and six-electron reactions are found, sometimes as two-step reductions. The four-electron reduction of symmetrical diaryloxadiazoles has been suggested to produce the oxadiazolidines.

2. Benzofurazan

This compound is polarographically reducible in the whole pH region in a six-electron reaction [348], and the product is supposedly *o*-phenylenediamine. At a macroelectrode some condensation reactions may be expected to occur in acid solution as side reactions just as in the case of *o*-dinitrobenzene reduction [349].

3. Sydnones

3-Phenylsydnones are polarographically reducible both in acid and in alkaline medium. In the former case six electrons are consumed per molecule, whereas at high pH, $n = 4$ [350]. In acid solution an α-amino acid is formed, whereas an α-hydrazino acid is the product in alkaline solution.

I. Compounds With One Sulfur and Two Nitrogen Atoms

1. 1,3,4-Thiadiazoles

Many thiadiazoles are polarographically reducible [148, 351]; not many of them have been investigated by controlled potential electrolysis. The wave height of 2,5-diphenyl-1,3,4-thiadiazole (**LX**) corresponds in acid solution to a two-electron reduction to a dihydro derivative, which is probably hydrolyzed to benzaldehyde thiobenzoylhydrazone. This compound is reducible at the reduction potential of **LX** and will thus be reduced further similarly to other acylated hydrazones (Chapter 11).

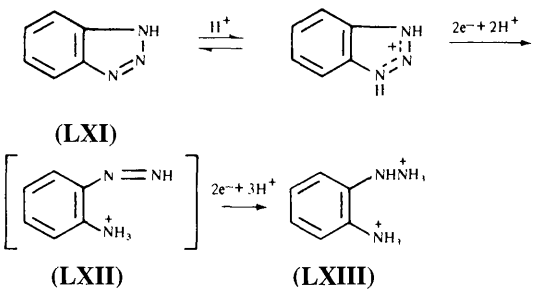
2. Benzo-2,1,3-thiadiazoles

These compounds and the corresponding selenodiazoles are reduced [352, 353] like the furazanes in a six-electron reduction; *o*-phenylenediamine and hydrogen sulfide and hydrogen selenide, respectively, are formed.

J. Compounds With Three Nitrogen Atoms

1. Benzotriazoles

Benzotriazoles (**LXI**) are reducible in acid solution, but only 2-substituted derivatives have been found to be reducible in alkaline solution. In acid solution the following scheme has been proposed [116]:



(LXI) (LXII) (LXIII) (36)

The *o*-aminophenyldiimide (**LXII**) cannot be isolated as it is more easily reducible than the benzotriazole, but a small concentration of it can be detected polarographically during the electrolytic reduction. *o*-Aminophenylhydrazine (**LXXIII**) has three nucleophilic centers, and it may be a useful intermediate in the preparation of some heterocyclic compounds [116, 354].

In alkaline solution, 2-methylbenzotriazole is reduced to the 1,3-dihydro derivative, which may be reoxidized anodically to the starting material [116]. In acid solution the dihydrobenzotriazole forms a phenyldiimide; this compound does not cyclize in alkaline solution.

In DMF, 1-phenylbenzotriazole is reduced to a 1:1 mixture of carbazole and diphenylamine; in the presence of acetic anhydride, benzotriazole is reduced in DMF to 1,2,3-triacetyldihydrobenzotriazole [355].

2. Triazines, Triazepines, and Triazanaphthalenes

1,2,4-Triazines are in the first step reduced to dihydro derivatives; thus 3-(2-pyridyl)-5,6-diphenyl-1,2,4-triazine is in DMF in the presence of EtBr reduced to a mixture of diethylated products of 1,2- and 2,5-dihydro-1,2,4-triazine [356]. On reduction in MeCN, 1,3,5-triazine dimerizes to 4,4′-dihydrobitriazyl; this is hydrolyzed to tetraformamidoethane [357]. Benzo- 1,2,4-triazines and dihydrobenzotriazines form a redox system that polarographically behaves nearly reversibly [71, 150]. The further reduction of the dihydrobenzotriazines was discussed in Sec. II.B; 3-alkylsubstituted dihydrobenzotriazines are generally not further polarographically reducible, but the unsubstituted and 3-phenyl-substituted derivatives are.

2-Amino-7-chloro-5-phenyl-1,3,4-benzotriazepine is reduced in acidic solution with four electrons to 2-amino-6-chloro-4-phenyl-1,2-dihydroquinazoline. The reduction does probably not go through the tetrahydrobenzotriazepine as suggested [358], but rather through a reductive ring opening, attack by a nitrogen on the azomethine group with

ring contraction, elimination of ammonia, and reduction of the quinazoline derivative to the product.

Pyrido[2,3-*b*]pyrazines [359] form on reduction in aprotic medium primarily a 1,4-dihydro derivative, which may tautomerize into the 1,2- or 5,8-dihydro derivative; in the presence of acetic anhydride, a 5-acetyl-5,8-dihydro derivative is isolated.

Other triazanaphthalenes are expected to be reducible, and the positions of the nitrogen atoms are the most critical factors for influencing the reduction potential.

K. Compounds With Four Nitrogen Atoms

The more nitrogen atoms inserted in an aromatic nucleus, the more easily reducible the system becomes. When a heteroaromatic system has two (or more) nitrogen atoms in a six-membered ring, the compound is reducible, at least in acid solution, and if two nitrogen atoms occupy *para* positions in such a ring, the redox system approaches reversibility.

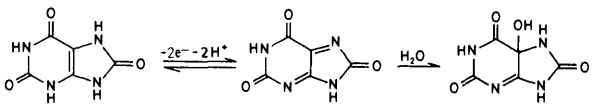
1. Tetrazolium Salts

Tetrazolium salts are generally reduced in a four-electron reduction [360]; the first step is probably a cleavage of the nitrogen–nitrogen bond, which is followed by the reduction of a nitrogen–nitrogen double bond. Depending on the substituents, the four-electron product may be further reduced. In alkaline solution, formazanes may be formed.

2. Purine and Pteridine

The electrolytic reduction of purine, which has been reviewed [313, 314, 361], takes place only in acid solution and thus differs from that of pyrimidine and quinazoline. The reduction proceeds in acid solution in two two-electron steps, the first resulting in a 3,4-dihydro derivative, whereas the tetrahydro compound formed in the second step is hydrolyzed to formaldehyde and an imidazole derivative.

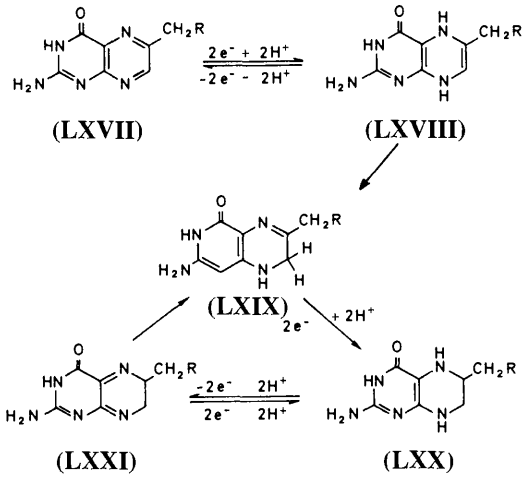
Oxidation of uric acid (**LXIV**) and its *N*-methylated derivatives at a graphite anode produces a quinonoid product (**LXV**), which adds water or another nucleophile across a C=N double bond to an unstable intermediate (**LXVI**), which reacts to products. From the oxidation of uric acid can be isolated, depending on pH, allantoin, 5-hydroxyhydantoin, alloxan, and urea [362, 363]:



(37)

(LXIV) **(LXV)** **(LXVI)**

Pteridines behave electrochemically akin to quinoxaline [364], with the pyrazine ring being reduced; the 3,4-double bond may be hydrated akin to quinazoline [314, 364]. In the first, reversible step of 6-methyl-2-amino-4(3*H*)-pteridone (**LXVII**; R = H), a 5,8-dihydro derivative (**LXVIII**) is formed, which in a pH-dependent reaction tautomerizes into the more stable 7,8-dihydro compound (**LXIX**); **LXIX** is reduced in acidic and neutral solution to the 5,6,7,8-tetrahydro derivative (**LXX**), which may be oxidized to a quinonoid dihydro compound (**LXXI**); **LXIX** is formed on tautomerization of **LXXI** [365, 366]:



(38)

Pteridone redox couples have been used as mediators in electron transfer reactions to large biologic molecules [367].

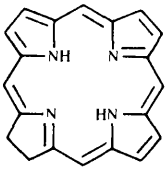
Folic acid [**LXVII**; R = $NHC_6H_4CONHCH(COOH)(CH_2)_2COOH$] is in the first step reduced as **LXVII** (R = H); in acidic solution 7,8-dihydrofolic acid is reduced with cleavage of the C-9/N-10 bond to **LXIX** (R = H) [365]. Besides the electrochemical cleavage, a nonelectrochemical cleavage with loss of the 4-aminobenzoylglutamate side chain from the 5,8-dihydrofolic acid has been observed [368]. In neutral medium with low buffer capacity, it is possible to reduce 7,8-dihydrofolic acid to the 5,6,7,8-tetrahydrofolic acid [369].

3. Pyrazinopyrazines

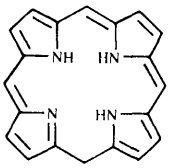
Pyrazino[2,3-*b*]pyrazines are reduced in aqueous alcoholic solution to the 1,4-(5,8)-dihydro derivatives [359]; in acidic medium the two-electron wave is followed by a four-electron reduction to a hexahydro derivative. The benzo and dibenzo derivatives are similarly reduced primarily in a reversible two-electron reduction [370]; the further reduction of 5,12-dihydroquinoxalino[2,3-*b*]quinoxaline yields 2-(*o*-aminoanilinomethyl)benzimidazole [371].

4. Porphines

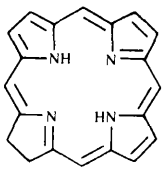
The polarographic and controlled potential reduction of porphines (**LXXII**) has been investigated, and it was shown that porphine was reduced polarographically in two two-electron steps [372]. Reduction of *meso*-porphyhyrinedimethyl ester yielded a product that was easily reoxidized by oxygen. From the UV spectrum of the reduced solution, which was reduced in deuterium oxide, it could be shown that the reduction yielded a phlorine (**LXXIII**) rather than a chlorine (**LXXIV**). Reduction of a chlorine yielded a "chlorine/phlorine."



(LXXII)



(LXXIII)



(LXXIV)

In dimethylformamide, porphines are reduced in three or four one-electron steps, which results in the formation of mono-, di-, tri-, or tetranegative ions [373].

Anodic oxidation of porphine in alkylnitriles at a platinum electrode takes place in two, one-electron steps [374]. The loss of electrons occurs from the lone pairs on the nitrogen atoms.

Electrochemical oxidation in DMF of Zn-octaethylporphyrin in the presence of cyanide at 0.45 V (SCE) gives a quantitative yield of cyanooctaethylporphyrin; at more positive potentials di-, tri, and tetracyanooctaethylporphyrin may be obtained [375].

IV. ELECTROLYTIC REACTIONS OF SUBSTITUTED HETEROCYCLIC COMPOUNDS

This section treats the electrolysis of substituted heterocyclic compounds *if the electrode reaction involves the substituent directly and if the electrode reaction in some way is different from what would be expected from the carbocyclic series.*

A. Alkyl and Alkenyl Substituents

Alkyl derivatives of π-electron-deficient heterocyclic compounds may be oxidized anodically to carboxylic acids; alkyl and arylalkyl pyridines can be oxidized to the corresponding acids in good yields at a lead dioxide anode in aqueous sulfuric acid [229, 230, 376–378].

Methylpyridines and methylpyridine-*N*-oxides react with superoxide ions, generated electrochemically in DMF, to the carboxylic acids; the *N*-oxides react better than the parent compounds [379].

Hydrodimerization of activated *alkenes* is a well-established process. π–Electron-deficient heteroaromatic compounds activate a double bond similarly to a cyano or carbethoxy group, and in accordance with that analogy vinylpyridines can be hydrodimerized. 4-Vinylpyridine [380] forms 1,4-bis-(4-pyridyl)butane in 82% yield on electrolysis in a mildly alkaline solution containing methyltriethylammonium *p*-toluenesulfonate and some DMF. The mechanism is discussed in Chapter 21.

If the nucleus contains more than one nitrogen atom, the nucleus is reduced at a less negative potential than the double bond. The two-electron reduction of 1,2-di(4-pyridyl)ethylene leads to a quinodal form which rearranges to 1,2-di(4-pyridyl)ethane at a pH-dependent rate [381].

Ethynylpyridines are reducible polarographically [382] in a medium containing tetraethylammonium iodide, 2-ethynylpyridine at -1.72 V, and 2-methyl-5-ethynylpyridine at -2.06 V (SCE). The reduction potentials of the ethynylpyridines are very close to those of the corresponding vinyl compounds [382]. Similar results have been found for benzene

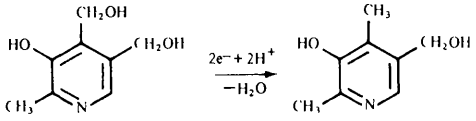
derivatives [383]. The electrode reaction is thus expected to be a four-electron reduction of the ethynyl group to an ethyl group.

B. Hydroxyl Derivatives

Heterocyclic hydroxyl derivatives can be divided into two groups according to whether the hydroxyl group is exocyclic. Heterocyclic compounds having a hydroxyl substituent at the ring have the possibility of existing in different tautomeric forms [384], the hydroxy or the oxo form, and in many cases the oxo form is predominant. Nevertheless, regardless of the position of the prototopic equilibria, the compounds are treated here as "hydroxyl compounds." Phenolic compounds, for example the oxidative dimerization of 1,2,3,4-tetrahydroisoquinoline phenols [385], are not discussed.

1. Compounds With Hydroxyl Groups Attached to a Substituent

Hydroxyl groups are reducible when they are activated by an electron-attracting group, such as the phenacyl group [386, 387]. A pyridine ring activates its substituents, but largely in the 2- and 4-positions. This is illustrated by the reduction of pyridoxol, which is reducible in an ammoniacal buffer (pH 8.5–10) according to Eq. (39) [388]:



(39)

Indirect reductive removal of hydroxyl groups in furan derivatives in hydrochloric acid containing iodide [389] is discussed in Chapter 29.

The reductive loss of the acetoxy function from the C-3 substituent in cephalosporin C derivatives [390, 391] is another example of an electrochemical removal of an activated hydroxyl function, which seems rather general [392].

2. Compounds With Hydroxyl Groups Attached to the Ring

Such compounds are treated as "hydroxyl compounds" even if their dominant tautomeric form is the "keto tautomer." Reduction usually takes place either in the nucleus or at the carbonyl group. Simple examples of the first type are maleic imide [393, 394] and hydrazide [395]; in many other examples a second reduction leads to a ring contraction. Reduction of the keto group leads to a hydroxyl group; in many cases water is eliminated and a further reduction takes place. An example of this is the reduction of *N*-methylsuccinimide to *N*-methylpyrrolidone [396]. Oxidation of hydroxy-substituted dihydroheterocycles may introduce a double bond; an example is the oxidation of 1,2-dihydro-3-methoxycarbonyl-4-hydroxyquinoline in AcOH/*t*-BuOH to 1,4-dihydro-4-oxo-3-methoxycarbonylquinoline [397]. The use of pyrrolidone as a probase is discussed in Chapter 30 [398].

a. Pyridazin-3-ones. The reduction of pyridazin-3-ones takes place with saturation of the 4,5-double bond [1a]; the further reduction differs according to the substitution at N-2. N-Unsubstituted dihydropyridazinones are reduced to *N*-aminopyrrolidin-2-ones through the tetrahydropyridazinone, whereas 2-methyl-4,5-dihydropyridazinones form pyrrolin-2-ones after cleavage of the N–N bond [155].

b. Pyrimidones. Pyrimidone-2 is reduced in a single, linearly pH-dependent one-electron wave; the radical formed dimerizes at position 6 to 6,6′-bis-(3,6-dihydropyrimi-

done-2) [399]. In nonaqueous solution the radical anion abstracts a proton from the parent compound and the radical dimerizes; the parent anion may be oxidized at the mercury electrode with formation of a mercury salt [400].

The electrophor of derivatives of 2-aryl-5,6-dihydro-4-pyrimidone is similar to that of benzamidine and the reduction of the azomethine group is observed. The product, a geminal amine, may be hydrolyzed with loss of an arylaldehyde [401].

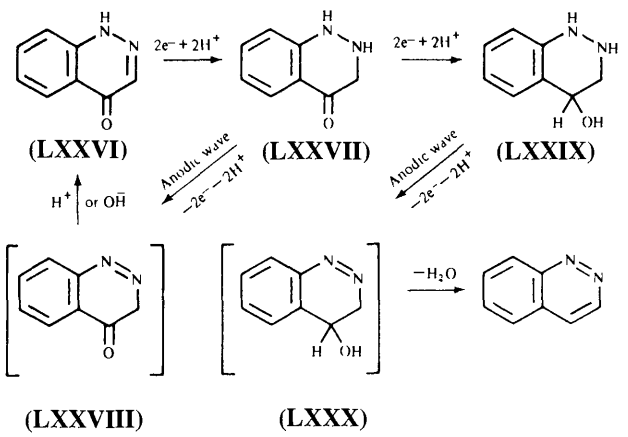
c. Derivatives of Isoindole. Phthalimide in acid solution is reduced polarographically [402, 403] by a two-electron reduction, whereas two one-electron waves are found in slightly alkaline medium. The two-electron reduction product [404] hydroxyphthalimidine (**LXXV**), a derivative of phthalaldehydic acid, reacts with any nucleophile HY present. In ethanolic solution ethoxyphthalimidine is formed, and in the presence of isoindoline, 1-*N*-isoindolino-3-oxoisoindoline [404].

In strongly acid solution, **LXXV** dehydrates to the easily reducible 3-oxoisoindole, which is reduced to phthalimidine; a further reduction to isoindoline may take place under conditions similar to those used for the reduction of benzamides [405–407].

d. Derivatives of Cinnoline. 3-Hydroxycinnoline [101] is reduced in a two-electron wave from pH 0 to 11. In strongly acid solution the main product is 1-aminooxindole, which is also obtained on reduction with zinc and sulfuric acid [408]. Reduction of an emulsion in aqueous phosphate buffer (pH 6.5) and *n*-butanol produced a nearly quantitative yield of 3-keto-1,2,3,4-tetrahydrocinnoline; this compound was easily reoxidized to 3-hydroxycinnoline [101]. By choosing a pH for the reduction at which the product is stable, the preparation of this labile compound could be accomplished.

4-Hydroxycinnoline (**LXXVI**) [101] in acid solution is reducible in two, two-electron steps. The product from the first two-electron reduction is 4-keto-1,2,3,4-tetrahydrocinnoline (**LXXVII**). This compound is a derivative of phenylhydrazine and can thus be oxidized anodically in alkaline solution to an azo compound (**LXXVIII**), which then tautomerizes to **LXXVI**. The carbonyl group of **LXXVII** is activated by the phenyl ring and—in contrast to 3-keto-1,2,3,4-tetrahydrocinnoline—is thus further reducible; the reduction yields 4-hydroxy-1,2,3,4-tetrahydrocinnoline (**LXXIX**). On standing, this compound loses water with the formation of 1,4-dihydrocinnoline. If, however, the compound is oxidized in alkaline solution, the product (**LXXX**) loses water and forms cinnoline.

As 4-hydroxycinnoline is one of the more easily accessible derivatives of cinnoline, this reaction may be the method of choice for the preparation of cinnoline [101]. The reactions are formulated in Eq. (40):



(LXXVI) (LXXVII) (LXXIX)

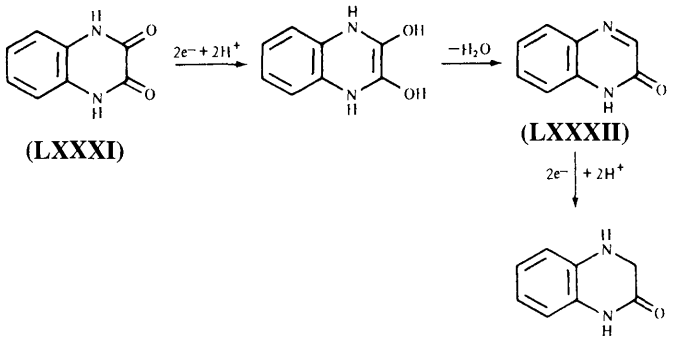
(LXXVIII) (LXXX)

(40)

e. Derivatives of Phthalazine. Dihydroxyphthalazines [156] like 2,3-dihydro-2,3-dimethyl-1,4-phthalazinedione are at low pH reduced to a phthalimidine in a six-electron reduction. In alkaline solution, 4-hydroxy-3,4-dihydro-2,3-dimethyl-1-phthalazinone is formed in a two-electron reaction; in this medium it is not further reducible, but in acid solution it loses water to the reducible phthalazinonium compound. The product from this reaction is 3,4-dihydro-2,3-dimethyl-1-phthalazinone, which at low pH can be reduced to *N*-methylphthalimidine and its precursor *N*-methyl-2-(methylaminomethyl)benzamide.

f. Derivatives of Quinazoline. 4-Methoxyquinazoline is in acid solution reduced to the 3,4-dihydro derivative, which eliminates methanol; the quinazoline thus formed is reduced to 3,4-dihydroquinazoline. In alkaline solution there is formed, besides quinazoline, some biquinazolyl in a reaction analogous to the benzoin condensation [409].

g. Derivatives of Quinoxaline. Both 2-hydroxy- and 2,3-dihydroxyquinoxaline are polarographically reducible, the former by a two-electron and the latter in acid solution by a four-electron reduction [410, 411]. The former is more easily reducible than the latter, which is understandable since 2-hydroxyquinoxaline (**LXXXII**) may be regarded as a derivative of glyoxalic acid, whereas 2,3-dihydroxyquinoxaline (**LXXXI**) is a derivative of oxalic acid. Derivatives of aldehydes are easier to reduce than the corresponding acid derivatives:



(**LXXXI**) (**LXXXII**) (41)

h. Derivatives of Triazine. The electrochemical reduction of *as*-triazin-3-ones, such as 5,6-diphenyl-*as*-triazin-3-one [412], produces a 1,4-dihydroderivative, which tautomerizes into a 4,5-dihydro compound, a kind of cyclic semicarbazone. This compound is in acid solution (pH 1) reduced in a two-electron reaction to a mixture of the ring-contracted product 4,5-diphenylimidazol-2-one and the *trans*-1,4,5,6-tetrahydro-5,6-diphenyl-*as*-triazin-3-one; in neutral solution the *cis* derivative is obtained [412]. However, the herbicide 1,2,4-traizinone derivative Metamitron (4-amino-3-methyl-6-phenyl-1,2,3-triazin-5(4*H*)-one) is reduced in two steps, the first one being reduction of the C6–N1 double bond, the second one probably saturation of the N2–C3 double bond [413].

3. *N*-Oxides and *N*-Hydroxy Compounds

N-Oxides of heteroaromatic compounds are generally electrolytically reducible in acid solution [414–426]. The most studied compounds of this type are the pyridine-*N*-oxides [414, 417–420]. At low pH, pyridine-*N*-oxide gives a two-electron polarographic wave, but at pH > 4 the wave height diminishes, as the preprotonation step becomes too slow:

$$C_5H_5\overset{+}{N}-O^- \overset{+H^+}{\rightleftharpoons} C_5H_5\overset{+}{N}-OH \xrightarrow{2e^- + 2H^+} C_5H_5\overset{+}{N}H + H_2O \qquad (42)$$

The assumption that it is the O-protonated *N*-oxide that is reduced is substantiated by the similarity in reduction potential between pyridine *N*-oxide and *N*-methoxypyridinium ion in acid solution; the latter is also reducible in alkaline solution [148].

A number of different *N*-oxides have been investigated polarographically, such as *N*-oxides of quinoline [421], acridine [422], pyrazine [423], benzimidazole [424], quinoxaline [415], phenazine [416], and adenine [425], and the influence of substituents was discussed.

When the heterocyclic ring contains more than one nitrogen atom, the initial reduction of the *N*-oxide may take place in the nucleus or the reduction of the nucleus and the *N*-oxide function occur simultaneously; the reduction of quinazoline-3-oxide [317], 3-methoxy-2,5-dimethylpyrazine-1-oxide [414], and cinnoline mono- and dioxide [426] is reported to take this route.

At pH < 1.5, however, *N*-oxides like cinnoline-*N*-oxide [101], 3,6-diphenylpyridazine-*N*-oxide [148], or pyrazine-*N*-oxide [423] give a two-electron polarographic wave followed by the reduction waves of the parent compounds.

Derivatives of 1-hydroxy-2,2,6,6-tetramethylpiperidine have been widely investigated electrochemically, mainly due to the interest in the nitroxyl radicals derived from them [427]. The application of TEMPO and that of *N*-hydroxyphthalimide [428] as agents for indirect oxidations are discussed in Chapter 29.

4. *S*-Oxides

Both phenothiazine-*S*-oxide and *S*-dioxide are polarographically [429] reducible at rather negative values in a medium containing tetramethylammonium chloride. The electrode reaction is not known. In acid solution, only the *S*-oxide is reducible; the reduction is probably preceded by a loss of water to the phenothiazonium salt.

C. Aldehydes, Ketones, and Their Derivatives

π-Electron-deficient heterocyclic rings facilitate the addition of nucleophilic reagents to a carbonyl group in conjugation with the ring; protonation of a ring nitrogen enhances this effect. Protonated or quaternized formylpyridines [430–435] are to a high degree hydrated in aqueous solution. This influences their polarographic behavior since the hydrated form, a *gem*-diol, is not reducible at the dropping mercury electrode. The wave height of such hydrated aldehydes is thus determined at a given pH by the equilibrium constant for the hydration and the rate of the dehydration reaction. Since only the protonated form is appreciably hydrated, the pK_a of the compound is also of importance for interpreting the polarographic data. The dehydration reaction is both acid and base catalyzed, the latter being of importance for the quaternized aldehydes. The acid-catalyzed dehydration reaction has been shown to follow this path:

$$\overset{+}{R}NC_5H_4CH(OH)_2 \overset{H^+}{\rightleftharpoons} \left[\overset{+}{R}NC_5H_4CH(OH)\overset{+}{O}H_2\right] \underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}} \left[\overset{+}{R}NC_5H_4\overset{+}{C}H-OH\right]$$

$$-H^+ \uparrow\downarrow +H^+$$

$$\overset{+}{R}NC_5H_4CHO$$

The hydration is most pronounced when the formyl group is in a position strongly activated toward nucleophilic attack; thus 2- and 4-formylpyridine are hydrated more than the 3-isomer, and 2-formylimidazole [436] and 2-formylthiazole [437] more than the 4- and 5-isomers. The quaternary derivatives are hydrated at least as strongly as the protonated parent compounds and in a broader pH region.

In strongly acid solution the diprotonated pyridinecarboxaldehydes are reduced in a two-electron reaction, whereas between pH 2 and 12, 2- and 4-formylpyridine are reduced in two steps; reduction at the potential of the first wave gives pinacols [434]. In alkaline solution, pinacols and some polymeric material are formed. The stereochemistry of the reduction of acetopyridines is discussed in Chapter 26.

The electrochemistry of the azomethine derivatives, such as oximes, Schiff bases, and hydrazones is mostly similar to that of the analogous carbocyclic compounds; however, the base produced during the reduction of pyridine-4-aldoxime in DMF deprotonates the oxime [435] rather than produce the nitrile as is found for benzaldoxime, Chapter 11. Possibly the higher acidity of pyridine-4-aldoxime compared to benzaldoxime can explain the difference.

D. Carboxylic Acids and Derivatives

Carboxylic acids and most of their derivatives are difficult to reduce, and a polarographic reduction of a carboxyl group requires activation by a strongly electron-attracting group. The addition of electrons may take place either to the carboxyl group or to the activating group, often depending on pH.

π-Electron deficient heterocyclic nuclei may activate a carboxyl group sufficiently to render it polarogrraphically reducible [436, 438–446]. An aldehyde is always more easily reducible than the corresponding carboxylic acid, so it is generally not possible to isolate aldehydes from a reduction of carboxylic acids. The electron-attracting groups that activate a carboxyl group toward reduction also activate the aldehyde toward nucleophilic addition reactions, and these aldehydes are in a certain pH region hydrated to a certain degree. It is thus possible in some cases to trap the easily reducible aldehyde formed during the reduction of a carboxylic acid as the nonreducible aldehyde hydrate. As some of the free, reducible aldehyde is always present in equilibrium with the hydrate, a reduction of an acid to an aldehyde must be performed at a suitable pH and at a low temperature, at which the rate of the dehydration reaction is low. The reduction must not be allowed to proceed to completion but must be stopped after the consumption of about 2 F/mol. Some dimerization and polymerization are usually observed, and in some cases these may be the dominant reactions.

The 4-pyridinecarboxylic acids [440, 441], 2-carboxythiazoles [445] and 2-carboxyimidazoles [436, 446], and their esters amides, and thiamides [392, 447–450] are reduced in this way. The corresponding hydrazides [451] and hydroxamic acids [51] are reduced to the amides in the first step and then further reduced. When the activating group in pyridine is in the 3-position the reduction may take place in the nucleus, depending on pH.

The four-electron reduction of derivatives of 3-methoxypicolinic acid may follow different routes, depending on the substitution in the ester or amide. Amides may, after uptake of two electrons, lose an amino or a hydroxyl group, and then be further reduced to a pyridinemethanol or an aminomethylpyridine, or the compound may be reduced in the pyridine ring; steric crowding favors the formation of aminomethylpyridines or tetrahydropyridines [452].

Although pyridine carboxamides are reduced to the carbinol at a lead cathode, in aqueous sulfuric acid the addition of titanium salts results in the aminomethylpyridine as the main product [453].

1. Anodic Reactions

Kolbe reactions of heterocyclic compounds have been studied in only a few cases. Anodic oxidation of 1-azabicyclo[2.2.2]octane-2-carboxylic acid under "Kolbe conditions" produced 2-methoxy-1-azabicyclo[2.2.2]octane [454]. The primary radical, formed by loss of an electron from the carboxylate ion, decarboxylates and is oxidized further to a carbocation, which is attacked by a methoxide ion. A similar pseudo-Kolbe reaction is found in the anodic decarboxylation of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid derivatives to 3,4-dihydroisoquinolines [455].

If two vicinal carboxyl groups are present, the Kolbe electrolysis may result in the introduction of a double bond; this has been used in the transformation of 2-aza-3-oxo-bicyclo[2.2.2]oct-7-en-5,5-dicarboxylic acid to 2-aza-bicyclo[2.2.2]octa-5,7-dien-3-one [456].

2. Nitriles

The reduction of cyanopyridines exhibits special features. In acid solution the protonated species is reduced in a four-electron reaction [457–461] to the pyridylmethylamine, but in alkaline medium the carbon–carbon bond is cleaved with formation of pyridine and cyanide ion [447, 462] (Chapter 23). 3-Cyanoquinoline is reduced to the 1,4-dihydro derivative [463] in slightly alkaline solution.

For the reduction of cyanopyridines to the aminomethylpyridines, a lead cathode in dilute sulfuric acid containing $FeSO_4$ has been recommended [460].

E. Nitrogen-Containing Substituents

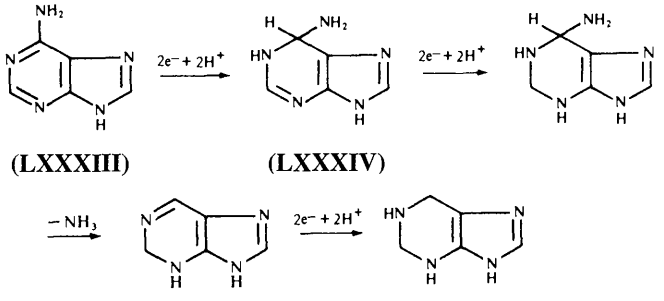
The reduction of heterocyclic C- and N-nitro and nitroso compounds exhibits generally no special features and is not discussed here; compare Chapter 9.

N-Aminopyridinium iodide in acid solution is reduced to pyridine; similar *N*-amino heteroaromatics are probably reduced in the same way [148, 464].

Activated amino groups as found in 4-pyridylmethylamines [465] or 2-pyridyltrimethylammonium iodide [148] are reductively removed in acid solution. The reduction of the latter requires protonation of the ring to obtain sufficient activation.

Anodic oxidation of 3- and 4-aminopyridine between pH 2 and 11 results in the formation of the *trans*-azopyridines [466].

Elimination of an amino group is sometimes found as a chemical step between the transfer of electrons. The reduction of adenine (**LXXXIII**) illustrates this [467, 468]:



An elimination of ammonia from **LXXXIV** to purine followed by reduction of the latter may also be possible [468]; such a reduction route is analogous to that of 4-aminoquinazoline in acid solution [409], in which quinazoline can be detected as an intermediate during the reduction. A similar reaction, a reduction followed by elimination of an amine and further reduction is found for the herbizide hexazinone (3-cyclohexyl-6-(dimethylamino)-1-methyl-1.3.5-triazine-2,4(1H,3H)-dione [469].

Adenine gives in aqueous solution a single well-defined anodic voltammetric wave at the pyrolytic graphite electrode [470]; it is oxidized first to 2-hydroxyadenine and then to 2,8-dihydroxyadenine. Further oxidation results in several products [470].

Electrochemical oxidation of 2-aminobenzothiazole in aqueous solutions at a pH between 3 and 11 consumes 2 F/mol, and 2,2′-azobisbenzothiazole is reported as the product [471].

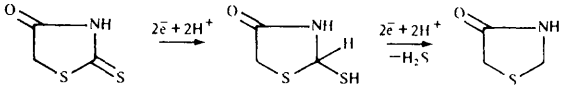
F. Sulfur-Containing Substituents

Reduction of heterocyclic disulfides and anodic reactions of sulfhydryl compounds show no special features. Elimination of a sulfhydryl group may be the slow step in some reactions.

4-Mercaptocinnoline [101] gives a two-electron polarographic wave, but a preparative reduction consumed four electrons per molecule and produced 1,4-dihydrocinnoline. The reaction must thus involve a slow step after the first two-electron reduction, which is assumed to be loss of H_2S with formation of cinnoline; this is further reduced to the product.

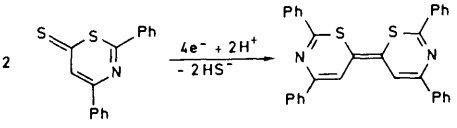
A similar reaction takes place in 4-mercaptoquinazoline [409] and 2,6-dimercaptopurine [472].

2-Mercapto-4-hydroxythiazole (rhodanone) is reducible in two two-electron steps [473] the second step being found at rather negative potentials. The reduction takes place at the exocyclic sulfur and has been formulated as follows:



(44)

1,3-Thiazine-6-thione [474] is in DMF reduced stepwise to the dianion, which forms the bithiazinylidene (**LXXXV**) with loss of hydrogen sulfide in a reaction resembling that of dithio esters:



(45)

(LXXXV)

In thiouracil and other 2-pyrimidinethiones the reduction takes place in the hetero ring rather than at the thione [475].

Cyclic voltammetric data at a pyrolytic graphite electrode of 2,6-dimercaptopurine show three anodic peaks. The first and second correspond to a disulfide formation from the 6- and 2-mercapto groups, respectively, whereas the third peak is due to an oxidation to purine-2,6-disulfonic acid. Some disulfinic acid was obtained on preparative oxidation [476]. Oxidation of 6-thioguanine gives at low potential the disulfide, whereas oxidation at more positive potentials involves both the sulfur group and the purine ring [477].

G. Halogen Derivatives

The electrode reactions of heterocyclic halogen compounds exhibit generally no special features, but some may be of preparative value. Anodic halogenation may be advantageous in fluorination and iodination reactions and in halogenations in which a low, easily measured concentration of halogen is desirable.

Large-scale reductive removal of the halogens is sometimes of preparative value; thus it is convenient to remove chlorine from 4-chloroquinazoline [317], halogen from 2-halothiazoles [478, 479] and iodine from 4-iodophthalazines [306] by reduction at a mercury cathode, and chlorine from 2-amino-4-chloropyrimidine at a spongy cadmium electrode [480].

Reduction of pentafluoropyridine in DMF at a mercury cathode gives perfluoro-4,4′-bipyridyl; in the presence of hydroquinone 2,3,5,6-tetrafluoropyridine is obtained. Pentachloropyridine gives very little bipyridyl derivative, but tetrachloropyridine and bis(tetrachloropyridyl) mercury in the absence of a proton donor [481].

In a mixture of THF and H_2O (1:1) pentachloropyridine is reduced at a silver cathode to 2,3,5,6-tetrachloropyridine and further to 2,3,5-trichloropyridine [482]. 3,4,5,6-Tetrachloro-2-picolinic acid may similarly be stepwise reduced [483] and chlorine reductively removed from 3-chlorobenzothiophene [484].

In DMF containing a few percent water, 4-chloro-6-(trichloromethyl)-2-phenylpyrimidine can be reduced nearly quantitatively to 4-chloro-6-(dichloromethyl)-2-phenylpyrimidine [158]. Dihalo-β-lactams may be reductively dehalogenated in DMF containing a proton donor [485].

A special reaction of a halogen derivative is the 2F/mol reduction of 1,4-dichlorophthalazine which leads to phthalonitrile and involves the cleavage of the two C-Cl bonds and the N-N bond; 1-chloro-4-methoxyphthalazine is reduced similarly [486].

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19

Electrosynthesis of Bioactive Materials

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References

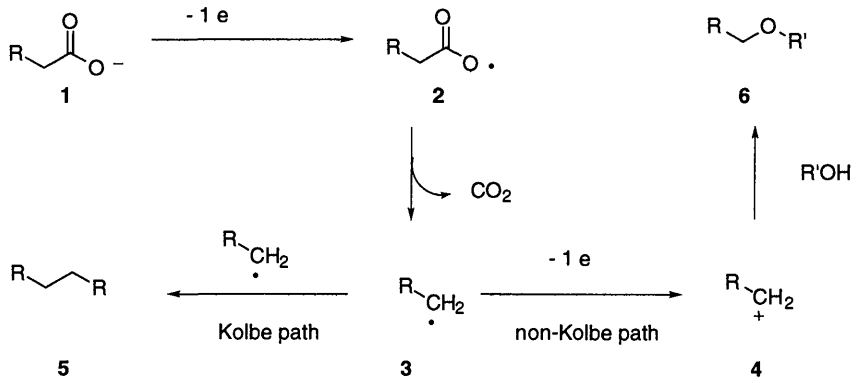
I. INTRODUCTORY REMARKS

Organic chemists commonly think of redox processes as those involving changes in the oxidation state of a functional group—the conversion of a ketone to a secondary alcohol, or the reverse transformation, for example. Electrochemistry provides a variety of solutions to problems of this nature. One also associates the term "redox" with the more fundamental processes of adding or removing an electron. Exciting opportunities are revealed when one thinks in this manner, because in so doing, one quickly realizes that reactive intermediates are formed. Often they display reactivity patterns opposite to that of the starting material. The β-carbon of the radical anion derived from an α,β-unsaturated ester, for example, displays nucleophilic rather than electrophilic character. Similarly, the cation radical derived via oxidation of an enol ether displays electrophilic behavior. Beyond this, and in a point that we believe is sometimes not recognized by nonelectrochemists, is the fact that electrochemistry provides the opportunity to make the carbon–carbon bond, or bonds between carbon and heteroatoms. That is, it provides the chemist with alternative and sometimes unique ways to build molecules. The chemistry described in this chapter provides an overview of some of the creative ways researchers have elected to use electrochemistry to synthesize naturally occurring molecules, ranging from structurally simple, to those of much complexity.

II. KOLBE CHEMISTRY

A. Introduction

A thorough discussion of the well-known Kolbe oxidation is found in Chapter 16 of this book [1–3]. Typically a one electron oxidation is carried out on the salt of a carboxylic acid to give the corresponding carboxyl radical **2** (see Scheme 1). Loss of carbon dioxide affords alkyl radical **3**. In addition to dimerization to afford **5**, **3** may undergo a second oxidation leading to carbocation **4**. The cation is typically intercepted by the alcoholic solvent to give rise to the so-called non-Kolbe product **6**. The latter pathway is favored by low current density, the use of graphite electrodes, salt additives, and an alkaline medium [1]. Conversely, high current density, the use of platinum electrodes, an acidic media, and electron releasing groups favor the Kolbe pathway [11].

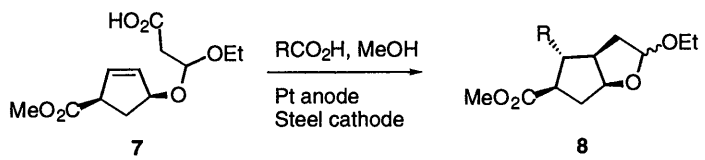


Scheme 1

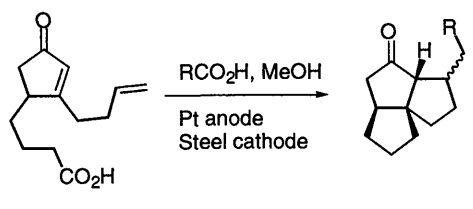
The chain length of the carboxylic acid is another factor that is related to the Kolbe versus non-Kolbe product distribution (**5/6**) [4]. As the length of the chain increases, so does the preference for Kolbe dimer. This is believed to arise as a result of the packing of the substrates at the electrode surface; the carboxylates tend to stack perpendicular to the electrode surface in a monolayer. The resulting close packing of the carboxylates leads to a high local concentration of radicals, thus favoring the Kolbe dimers. An excellent paper describing the fundamental concepts of the Kolbe and non-Kolbe pathways has been written by Schäfer and coworkers [1].

The radicals may dimerize, participate in mixed coupling between two different radicals, or undergo cyclization. Each of these avenues is illustrated by the examples discussed next. Simple dimerization allows retrosynthetic disconnections to be made at any symmetrical carbon–carbon bond in a target molecule, and has been used in, for example, the synthesis of onocerin (**13**) [5], α- and β-oconceradiene (**14** and **15**) [6], and pentacyclosqualene (**16**) [6,7]. The use of a mixed Kolbe oxidation allows disconnections to be made at nonsymmetrically substituted sites. A host of natural products have been generated using the latter protocol including, for example, brevicomin (**21**) [8], looplure (**29**) [9], and disparlure (**35**) [10] [note Scheme 2, Eq. (6), and Scheme 3].

Intramolecular radical cyclizations are exceptionally useful and have found widespread use in organic synthesis [11,12]. Kolbe chemistry has been exploited in this manner providing access to the prostaglandin precursor **8** [13], and to ring systems (**10**) that are common to the angularly fused triquinane natural products [14].



(1)

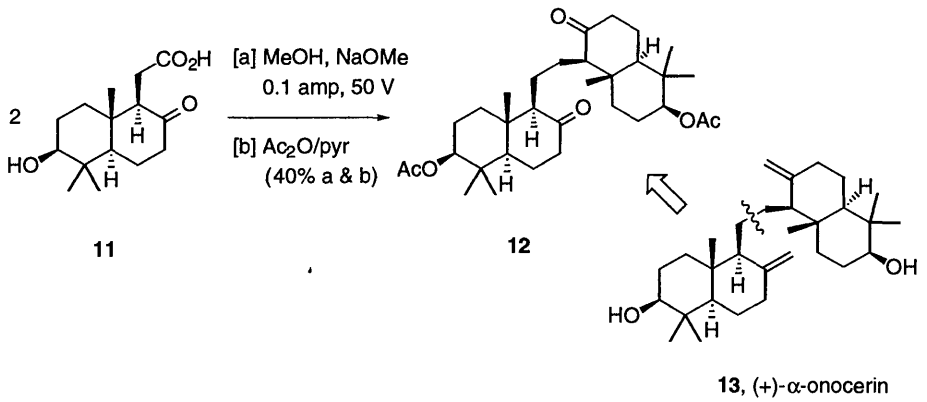


(2)

B. Simple Kolbe Oxidation: (+)-α-Onocerin (13) [5-] α-Onoceradiene (14) [6], β-Onceradiene (15) [6], and (+)-Pentacyclosqualene (16) [6,7]

Kolbe dimerization may be carried out with minimal electrochemical equipment. A typical experiment involves the constant current electrolysis of an alkaline alcoholic solution (5–10% neutralized carboxylic acid) between platinum electrodes in an undivided cell.

A good example of the simplicity of the operation is provided by Stork's total synthesis of the complex triterpene (+)-α-onocerin (**13**) [5]. In this instance, the (+)-hydroxy keto acid **11** was oxidized in a methanol solution containing a trace of sodium methoxide at 0.1 A and 50 V, at a temperature of 50°C. Following acetylation with acetic anhydride/pyridine and chromatography, the (+)-diacetoxydione **12** was isolated in a 40% yield.



(3)

Another example of a Kolbe dimerization reaction is found in Corey's synthesis of α-onoceradiene (**14**), β-onceradiene (**15**) and (+)-pentacyclosqualene (**16**); each is derived from either the ammonium salt **18**, or the acetoxy ammonium salt derived in situ from **20** in the manner portrayed in Eqs. (4) and (5) [6,7].

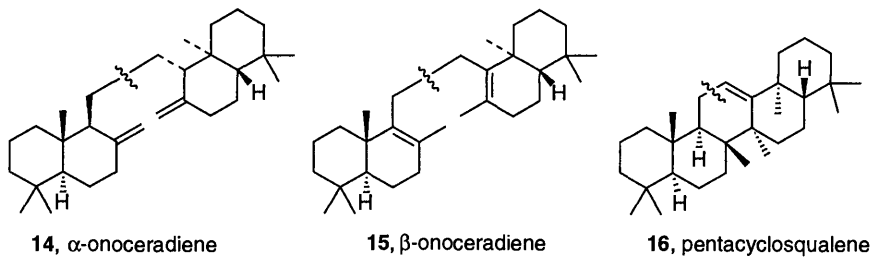
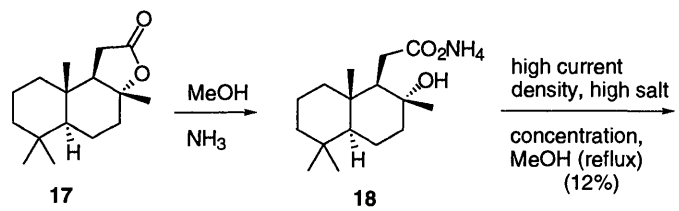
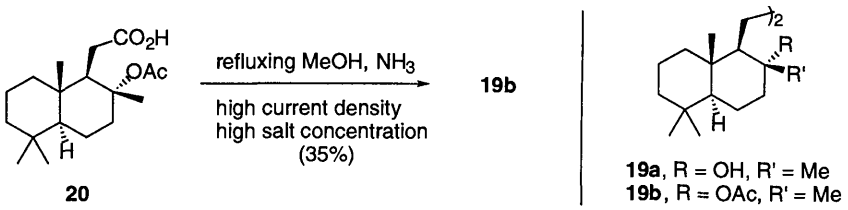


Figure 1. Onoceradienes (**14** and **15**) and pentacyclosqualene (**16**).



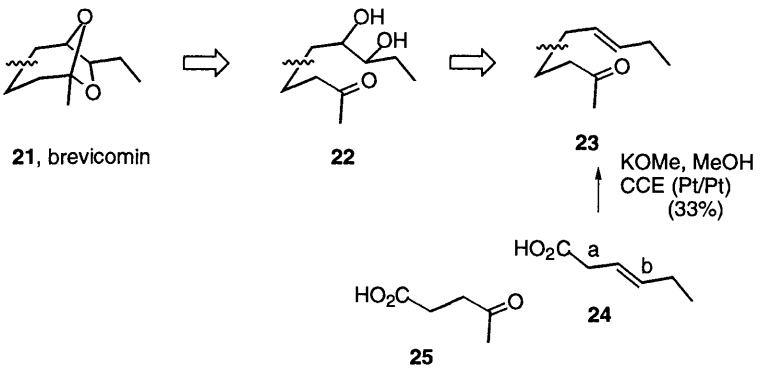
(4)



(5)

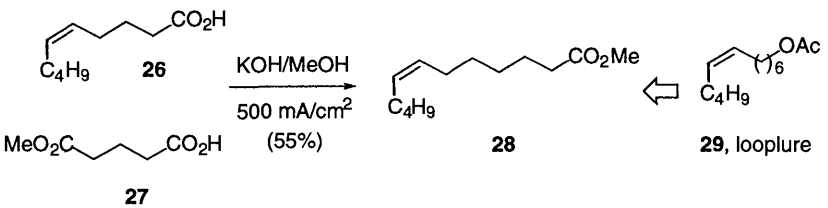
C. Heterocoupling—Mixed Kolbe Oxidation: Brevicomin (21) [8], Looplure (29) [9], Disparlure (35) [10], C-Glycosides [15]

Nonsymmetrical coupling reactions have been used extensively by Schäfer and coworkers to generate a variety of natural products [1,8–10, 13–17]. A typical procedure calls for the use of a large excess (5–10 equivalents) of one of the acids. In conjunction with a total synthesis of the pheromone brevicomin [8] (**21**), compounds **24** and **25** (ratio of 5:1) were co-oxidized in methanolic potassium hydroxide to afford ketone **23** in 33% yield. The heterocoupling was complicated by the allylic nature of the radical derived from **24**; the undesired coupling isomer constituted 12% of the product. Subsequent treatment of the desired isomer **23** with osmium tetroxide formed diol **22**. Acid-catalyzed intramolecular ketalization led to brevicomin (**21**) in a 42% yield.



Scheme 2

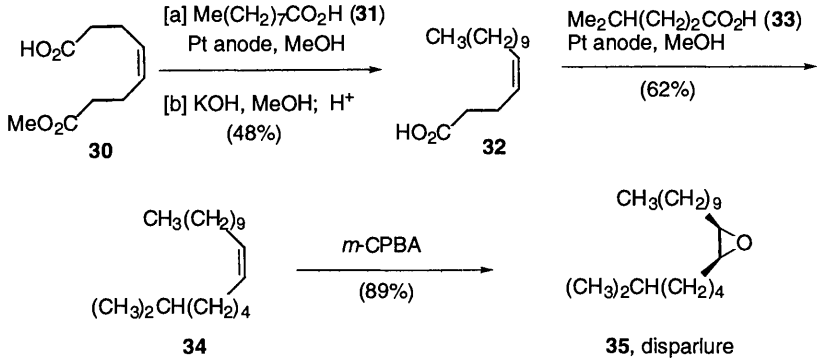
The insect pheromone looplure (**29**) was synthesized by using the mixed coupling illustrated in Eq. (6) [9]. Electrolysis of **26** and **27** (1:2 ratio) provided only moderate yields of the desired coupling product (26–35%), but the use of a 10-fold excess of monomethyl glutarate **27** increased the yield of **28** to 55%.



(6)

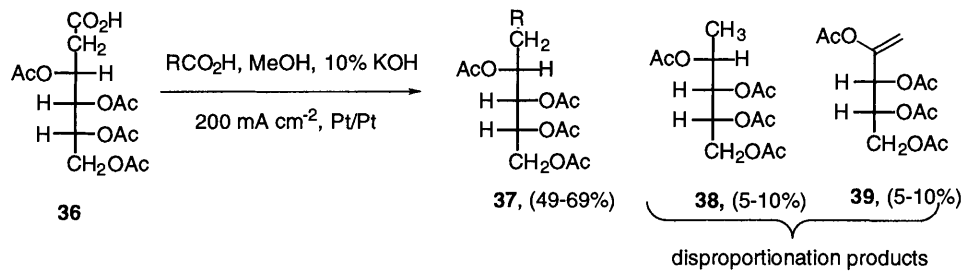
Of interest is the fact that one of the coupling partners in the looplure synthesis was the half acid, half ester **27**. Since the ester unit is untouched in the coelectrolysis, it could potentially function as a site for a second Kolbe oxidation and subsequent coupling

reaction. Such a strategy was utilized in the synthesis of disparlure (**35**) that is illustrated in Scheme 3 [10]. In this instance a mixed coupling between the half acid-ester **30** and **31** (1:10 ratio) proceeded smoothly to afford **32**. Saponification unmasked a second carboxylic acid unit that served nicely in a second heterocoupling reaction (1:10 **32/33**), thereby providing rapid and efficient (62%) access to **34**; epoxidation afforded the insect pheromone disparlure (**35**).



Scheme 3

Radical disproportionation can be encountered as a side reaction of the Kolbe electrolysis. For example, disproportionation by-products **38** and **39** [Eq. (7)]; and **42** plus **43** [Eq. (8)] were isolated during the synthesis of C-glycosides **37** and **41** [15]. The desired heterocoupling products **37** and **41** were isolated in 40–69% yield with the disproportionation products being formed in 5–10% yield (see Tables 1 and 2).



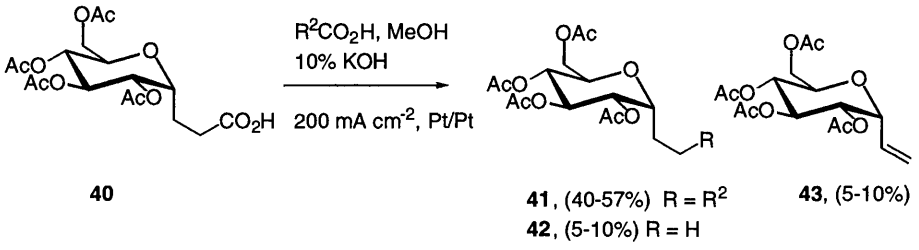
(7)

Table 1 Yield From Eq. (7)

Entry	R	Yield **37** (%)	Yield **38** (%)	Yield **39** (%)
1	C_5H_{11}	69	5–10	5–10
2	C_7H_{15}	54	5–10	5–10
3	$(CH_2)_7CO_2Me$	49	5–10	5–10

Table 2 Yield From Eq. (8)

Entry	R	Yield **41** (%)	Yield **42** (%)	Yield **43** (%)
1	C_5H_{11}	40	5–10	5–10
2	C_7H_{15}	57	5–10	5–10
3	$(CH_2)_5CO_2Me$	43	5–10	5–10
4	$(CH_2)_7CO_2Me$	46	5–10	5–10



40

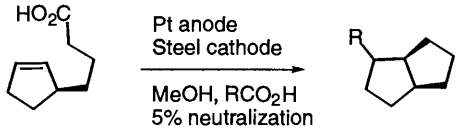
41, (40-57%) R = R^2
42, (5-10%) R = H

43, (5-10%)

(8)

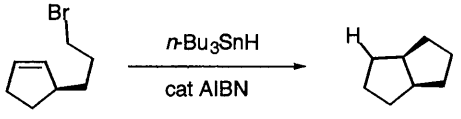
D. Kolbe Cyclizations: Prostaglandin Precursors

The radical produced after oxidative decarboxylation may be trapped intramolecularly by an olefin to form five- or six-membered rings. This methodology avoids the use of the toxic organotin reagents that are commonly used in the generation of radicals. Moreover, when R_3SnH/AIBN is used, a C–H bond is formed in the radical termination step. Kolbe reaction protocol, on the other hand, allows the radical formed after cyclization to be captured by a different radical, rather than being reduced (cf. **45** and **47**).



44 **45**

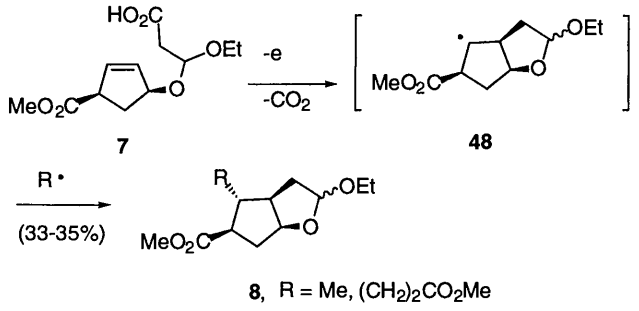
(9)



46 **47**

(10)

Schäfer has exploited this mode of cyclization in the construction of prostaglandin precursor **8** in modest yield (33–35%) [13]. The termination step occurred when the cyclized intermediate **48** was intercepted by an alkyl radical, R$^{\cdot}$ (generated by cooxidation using a fourfold excess of the desired co-acid), to afford **8**.

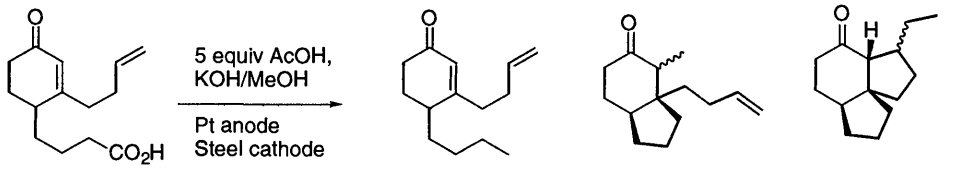


7 48

8, R = Me, $(CH_2)_2CO_2Me$ (11)

E. Tandem Cyclizations: Angularly Fused Triquinanes

Tandem cyclizations have also been achieved. For example, the mixed Kolbe oxidation of the functionalized enone **49a** in the presence of a fivefold excess of acetic acid afforded tricyclic adduct **52** in yields ranging from 25 to 42% [14]; Table 3 shows that low current density favored its formation. However, use of a current density below 25 mA cm^{-2} resulted in oxidation of the solvent, rather than oxidation of the substrate.

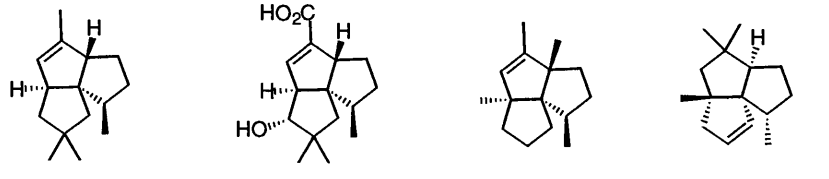


49a **50a** (8-20%) **51** (5-24%) **52** (25-42%)

(12)

In principle, substrates could be designed to allow an application of the tandem sequence to the synthesis of a variety of natural products, particularly the angularly fused triquinanes **53–56** illustrated in Figure 2.

While both five- and six-membered rings can be generated, the yield of product produced by intercepting the first radical formed prior to cyclization (**50a** from **49a**, and **50b** from **49b**) increases significantly when the first ring to be formed is of size six [14]. Compare entry 5 of Table 3, for example, with the reaction portrayed in Eq. (13). Notice the increase in noncyclized product from 8% of **50a** to 40% of **50b**, while the sum of the yields of the cyclized materials remains comparable.

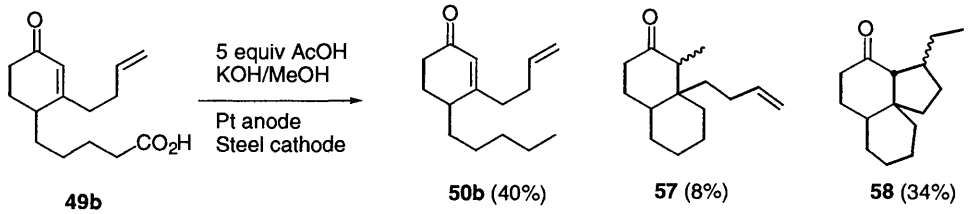


53, pentalenene **54**, pentalenic acid **55**, isocomene **56**, silphinene

Figure 2.

Table 3. Yield From Eq. (12)

Entry	mA cm^{-2}	Yield **50a** (%)	Yield **51** (%)	Yield **52** (%)
1	200	20	24	25
2	100	17	21	33
3	50	12	17	34
4	40	10	16	34
5	25	8	5	42



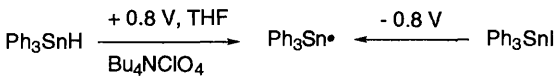
49b **50b** (40%) **57** (8%) **58** (34%)

(13)

The preceding sections illustrate the utility of electrochemistry as a means of producing carbon-centered radicals. As described later, it can also be used to form tin and sulfur-centered radicals, thereby expanding the range of product structures that can be constructed.

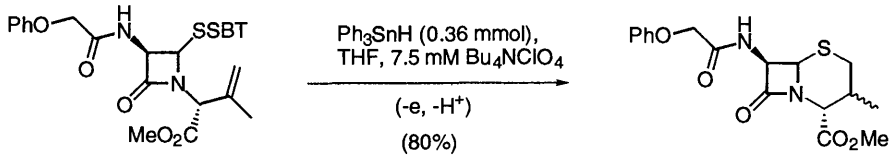
III. ELECTROGENERATED TRIPHENYLTIN: ACCESS TO THIYL RADICALS AND CEPHALOSPORIN ANALOGS

The electrochemical oxidation of triphenyltin hydride (+0.8 V vs. SCE) or the electrochemical reduction of triphenyltin iodide (−0.8 V vs. SCE) provides a convenient source of the triphenyl tin radical **60** [18,19].



59 **60** **61**

CV studies indicate that Ph_3SnY, where Y = Cl, OTf, OCHO, $SnPh_3$, do *not* serve as a source of the triphenyltin radical because in these instances the radical is generated at potentials where it is either oxidized or reduced [19]. Reaction of the triphenyltin radical with an alkyl halide or a disulfide produces a carbon- or a sulfur-centered radical, respectively. Use of the latter transformation in conjunction with a subsequent intramolecular cyclization onto an alkene is nicely illustrated by the conversion of β-lactam **62** to the cephalosporin analog **63**.



62

BT = 2-benzothiazolyl

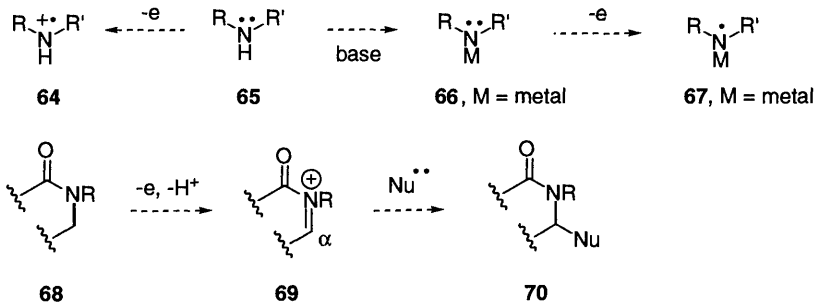
63

(14)

IV. OXIDATION AT NITROGEN

A. Introduction

As anticipated, and illustrated in Scheme 4, the electrochemistry of amines and amides involves oxidation at nitrogen (for greater detail, see Chapter 15). Neutral amines **65** can be oxidized to afford a cation radical **64**. Deprotonation of a secondary amine, followed by electrooxidation of the resulting anion leads to an aminyl radical **67**, one capable of participating in carbon–nitrogen bond-forming reactions with remotely tethered alkenes [Equation (15)]. Amides (carbamates) **68** are susceptible to oxidation at an alkyl center adjacent to nitrogen. The resulting acyl imminium ion **69** can be intercepted by a variety of nucleophiles in a process (**69** to **70**) that sets the stage for subsequent carbon–carbon bond formation. Each of these avenues is illustrated by the examples discussed next.

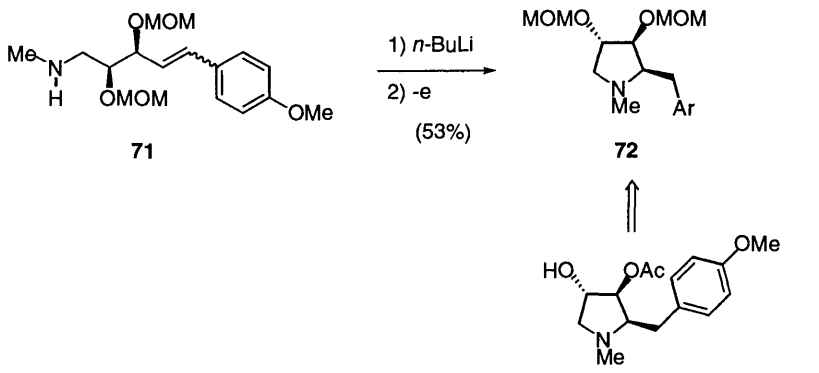


Scheme 4

B. Applications

1. (−)-Anisomycin (73)

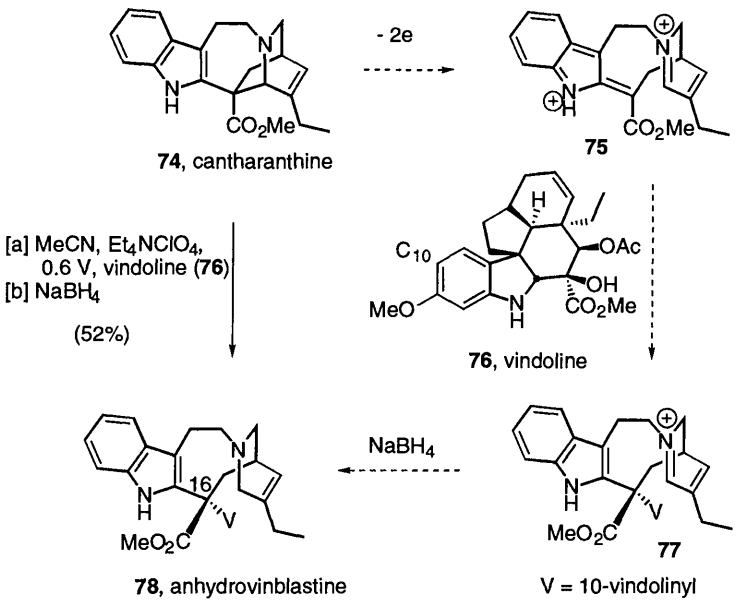
Illustrative of the chemistry of the aminyl radical is a synthesis of the *N*-methyl derivative of the antibiotic (−)-anisomycin (**73**) [20]. It was obtained by treating (*E*)-δ-alkenylamine **71** with *n*-butyllithium at −78°C, followed by anodic oxidation at a constant current (17.5 mA/cm^2) in a 100:1 mixture of tetrahydrofuran (THF) and hexamethyl-phosphorous-triamide (HMPA) containing 0.25 *M* lithium perchlorate at −10°C. A 5-exo,trig cyclization of the metalated aminyl radical afforded pyrrolidine **72** as a single isomer in a 53% yield. A routine series of transformations converted **72** to the target structure **73**.



(15)

2. Anhydrovinblastine (78)

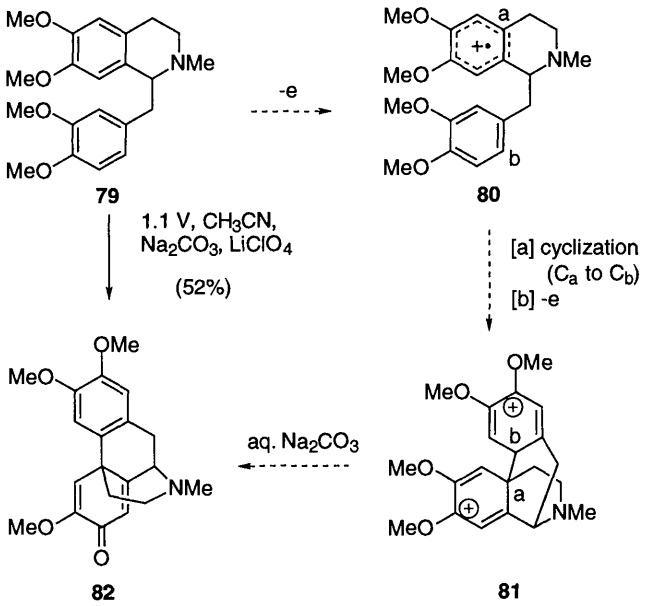
The vinblastine alkaloids are important chemotherapeutic materials, and are well known for their antitumor properties. A two-electron electrooxidation of alkaloid cantharanthine (**74**), followed by nucleophilic capture of the resulting imminium ion **75** by C_{10} of vindoline (**76**), affords **77** and provides access to this important class of materials [21]. Oxidation of cantharanthine (**74**) was carried out in the presence of vindoline (**76**) at a potential that allowed the selective oxidation of the former. Oxidation was shown to occur in a stepwise manner with vindoline (**76**) serving to intercept the putative dication **75**, and leading to the production of **77**. Reduction of the latter with sodium borohydride afforded anhydrovinblastine (**78**) in a 52% yield accompanied by 12% of the material epimeric at C_{16}.



Scheme 5

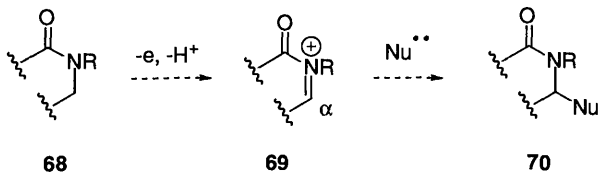
3. O-Methylflavinantine (82)

The power and utility of the anode as a selective oxidant are highlighted nicely in the electrooxidative cyclization of 1-benzyltetrahydroisoquinolines [22]. These substrates possess several oxidizable sites. Racemic laudanosine (**79**), for example, could be oxidized at nitrogen or in one or both of the electron rich aromatic rings. In fact, it displays five voltametric peak potentials at 0.63, 0.81, 1.13, 1.30, and 1.47 V ($Ag/AgNO_3$). Yet, using potential control, it is a simple matter to oxidize a dialkoxyaryl unit in the presence of the *N*-methylamine subunit. Thus, the preparative scale oxidation of laudanosine (**79**) at +1.1 V in acetonitrile containing sodium carbonate, at 0°C with either Me_4NBF_4 or $LiClO_4$ as the supporting electrolyte, led to the isolation of a 52% yield of *O*-methylflavinantine (**82**) [22, 23]. The mechanism illustrated in Scheme 6 has been suggested to account for this result.



Scheme 6

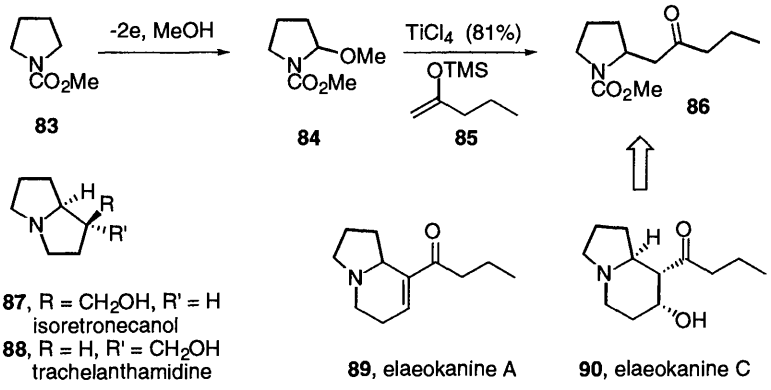
As indicated previously, amides (carbamates) **68** are susceptible to oxidation at an alkyl center adjacent to nitrogen (C_α in **69**). The resulting acyl imminium ion intermediate **69** can be intercepted by a variety of nucleophiles in a process that sets the stage for subsequent carbon–carbon bond formation. As the following discussion illustrates, the creative utilization of this protocol provides an exceptionally useful entry to a host of alkaloidal systems.



(16)

4. Elaeokanine A and C (89, 90), Isoretronecanol (87), Trachelanthamidine (88)

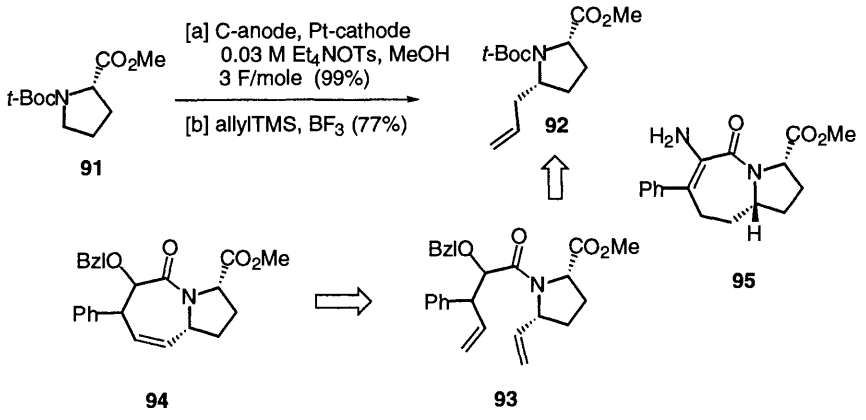
Both pyrrolizidine and indolizidine alkaloids can be synthesized by taking advantage of the anodic α-alkoxylation of *N*-alkoxycarbonylpyrrolidines (e.g., **83** to **84**). The method, first developed by Ross, Finkelstein, and Petersen, and later explored by Ban and co-workers [24, 25], has been utilized by Shono's group to synthesize isoretronecanol (**87**), trachelanthamidine (**88**), elaeokanine A (**89**), and elaeokanine C (**90**) [26] (Scheme 7). Once the α-methoxy group has been installed via electrooxidation and nucleophilic capture of the intermediate by methanol, the product **84** is treated with enol ether **85** and titanium tetrachloride to affect C–C bond formation adjacent to nitrogen and afford **86**. The latter served nicely in syntheses of both indolizidine alkaloids elaeokanine A (**89**) and C (**90**).



Scheme 7

5. Peptide Mimetics

Moeller and coworkers have made extensive use of the anodic α-alkoxylation of amides [27–31]. Much of their work has focused upon the synthesis of conformationally restricted peptide mimetics in an effort to ascertain the relationship between the bioactivity of the parent peptide and a specific conformer of it. The example illustrated in Scheme 8 portrays an exceptionally clever synthesis of **94**, a key substance en route to the Phe-Pro building block **95** [28]. Both the electrooxidation and ring-forming metathesis (**93** to **94**) reactions are of special note.

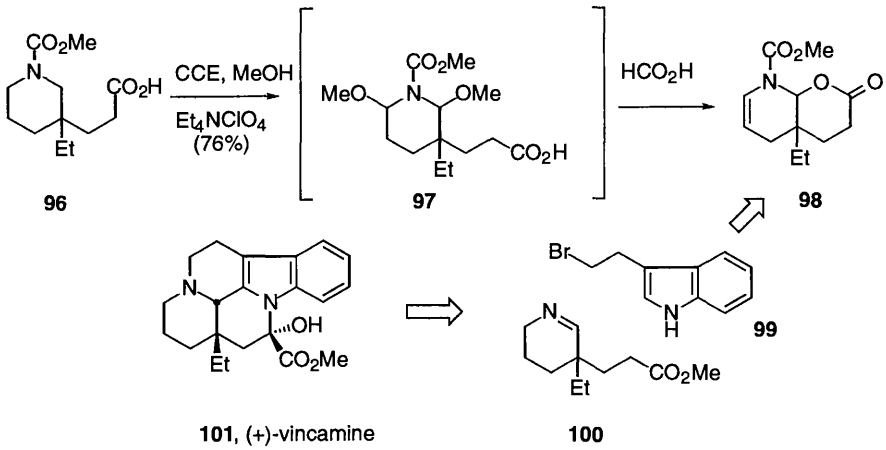


Scheme 8

6. Vincamine (101)

Ban and coworkers completed a formal total synthesis of vincamine (**101**) by capitalizing upon the electrochemical oxidation of the piperidine carboxylic acid ester **96** [24]. Thus, when oxidized at a constant current (CCE; 30 mA) in methanol at room temperature (Et_4NClO_4; 8.2 F/mol), **96** was converted to **97**, a material that, when treated with formic acid, afforded lactone **98** in a 76% yield after chromatography. Hydrogenation, hydro-

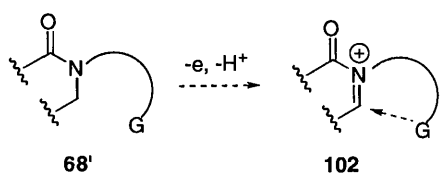
lysis, and esterification afforded ester **100**. The latter served as a key coupling partner with tryptophyl bromide **99** en route to the assembly of vincamine (**101**) (Scheme 9).



Scheme 9

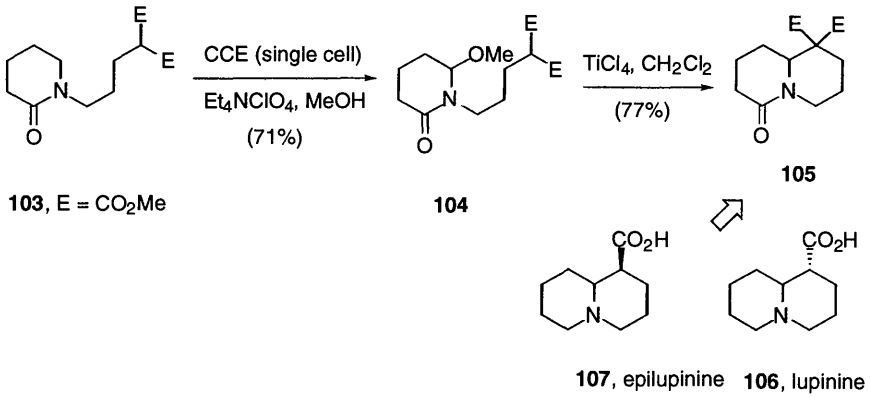
7. Lupinine (106) and Epilupinine (107)

Another effective route to alkaloids involves the electrochemical oxidation of lactams **68′** bearing useful functionality on nitrogen that is ultimately to be used to annelate a second ring.



(17)

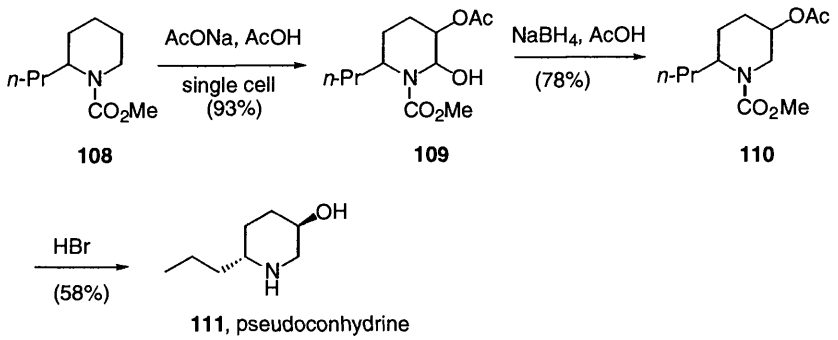
The synthesis of alkaloids lupinine (**106**) and epilupinine (**107**) (Scheme 10) nicely illustrates the methodology [25]. Thus, electrochemical oxidation of lactam **103** (constant current, 50 mA; Pt/Pt, Et_4NClO_4) in methanol at room temperature afforded a 71% yield of ether **104** after the passage of 2.8 F/mol. Subsequent treatment with titanium tetrachloride affected cyclization to the [4.4.0] bicyclic adduct **105**. Krapcho decarbomethoxylation followed by hydride reduction of both the amide and ester units of the resulting epimeric esters provided the natural products **106** and **107**.



Scheme 10

8. Pseudoconhydrine (111)

A convenient method to affect the oxidation beta to nitrogen in piperidines is based upon the anodic oxidation of *N*-carboalkoxy piperidines. For example, the electrochemical oxidation of piperidine **108** in the presence of acetic acid and potassium acetate afforded a mixture of isomeric 2-hydroxy-3-acetoxypiperidines **109** in a combined yield of 93%, following an aqueous workup [32]. Reduction with sodium borohydride severed the C–OH bond. Treatment of the resulting acetate **110** with HBr followed by NaOH completed a straightforward synthesis of pseudoconhydrine (**111**) (Scheme 11).



Scheme 11

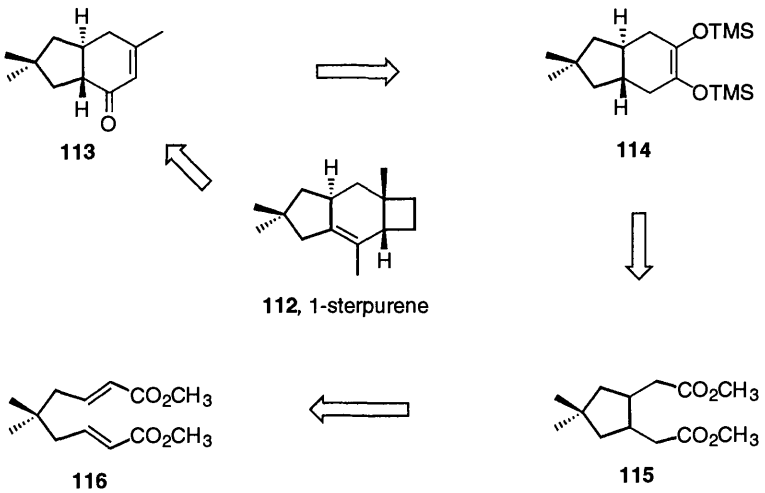
V. ELECTROREDUCTIVE CYCLIZATION

The reduction of an electron-deficient alkene renders a formally electropositive carbon center nucleophilic. The β-carbon of the radical anion derived from an α,β-unsaturated ester, for example, displays nucleophilic rather than electrophilic character. Realization of this factor uncovered a very rich and fertile territory for the development of new reactions, the exploration of mechanism, and the application of the methodology to the synthesis of materials. The fields of electrohydrodimerization and electrohydrocylization are clear and direct consequences of this realization. In the sections to follow, we describe a variety of

cyclization processes that are initiated by electroreduction, and the application of them to natural product synthesis.

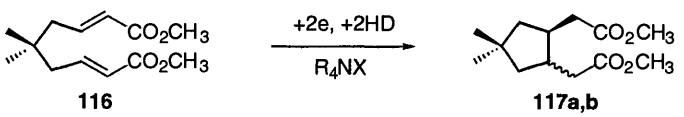
A. Sterpurene (112)

The tricyclic sesquiterpene 1-sterpurene (**112**) is thought to be the causative agent of the so-called "silver leaf disease" that effects certain species of scrubs and trees [33]. Its synthesis focused upon three key steps: (a) electrochemical cyclization of the bis unsaturated ester **116** to produce the five-membered ring of **115**, (b) a Ruhlman-modified acyloin condensation to provide the six-membered ring (**115** to **114**), and (c) a photo[2 + 2] cycloaddition to generate the four-membered ring that is found in the natural product (Scheme 12).



Scheme 12

The electrohydrocyclization of **116** was investigated under a number of different conditions. As noted in Table 4, both the yield and stereoselectivity varied in response to changes in electrode and proton donor. Environmental factors clearly make the use of a glassy carbon electrode preferable to other electrodes. Yields range from 58 to 87%, and stereoselectivity from a low of 2.6:1 *trans/cis* (**117a/117b**) to as high as 14.8:1, with the latter occurring when the reaction was conducted in the presence of cerium(III) chloride (see last entry of Table 4). In each instance the *trans* isomer **117a** was preferred. The influence of cerium chloride, while interesting and significant in terms of its effect, is not clearly understood.



(18)

B. Perhydrophenanthrene Skeleton

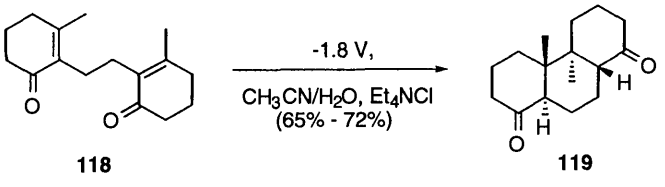
The utility of the electrohydrocyclization reaction in the assembly of natural products remains essentially untapped. The reason for this observation is not entirely clear.

Table 4 Effect of Proton Donor and Electrode Material

Electrode	Proton source	Trans/cis ratio[a]	Yield (%)	Additive[b]
Hg	AcOH, H_2O	2.6:1	82–87	None
Hg	$CH_2(CO_2Et)_2$	7.5:1	66	None
glassy carbon	$CH_2(CO_2Et)_2$	7.1:1	73	None
Cu	$CH_2(CO_2Et)_2$	11.6:1	58	None
Hg	$CH_2(CO_2Et)_2$	14.8:1	73	1.3 equiv. $CeCl_3$

[a]Compounds **117a, 117b.**
[b]Suspension in acetonitrile.

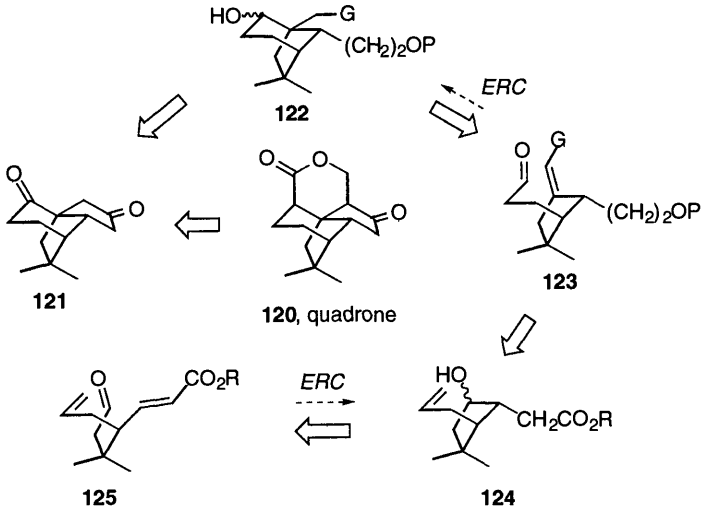
Consider, for example, the rapid and efficient construction of the perhydrophenanthrene skeleton **119** as exemplified by the conversion illustrated next [34]. The reaction is stereospecific, leading to the *trans*–anti-*trans* ring fused adduct in a 65% to 72% yield. Furthermore, C–C bond formation occurred despite the fact that in so doing, a very crowded environment consisting of vicinal quaternary carbon centers, is produced. There are very few methods that provide such scope. It takes little thought to imagine the application of this powerful transformation to the synthesis of steroids. Yet, the opportunity to apply the methodology to natural product synthesis has not been realized.



118 **119** (19)

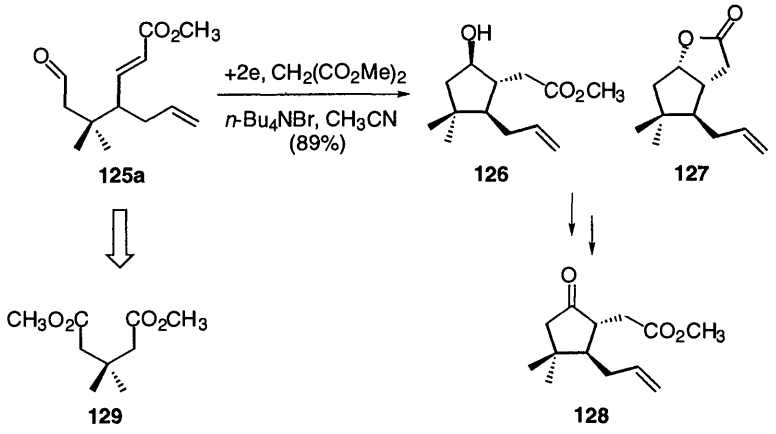
C. Quadrone (120)

The utility of electroreductive cyclization (ERC) reaction is demonstrated by the formal total synthesis of the antitumor agent quadrone (**120**) that is outlined in Scheme 13 [35]. The reaction serves to link the β-carbon of an electron deficient alkene to the carbonyl carbon of an aldehyde or ketone tethered to it. The transformation plays a pivotal role in the key carbon–carbon bond forming events leading to **124** and **122**, and en route to quadrone (**120**).



Scheme 13

The formal total synthesis began with a controlled potential reduction of **125a** in the presence of dimethyl malonate as a proton donor. This afforded a mixture of two products, the γ-hydroxy ester **126** and lactone **127**, in a combined yield of 89%; each was converted to a common intermediate, **128**.



(20)

The selective formation of products where the ester and allyl units are *trans* to one another can be attributed to the preference for the allyl unit of **125a** to occupy a pseudoequatorial, rather than a pseudoaxial orientation in the product determining transition state **130** (cf. **131** Fig. 3). This stereochemical outcome is fortunate, as later in the sequence, it is necessary for the aldehyde unit to move across the top face of the cyclopentyl ring system during the conversion of **132** to **133**. Were the substituents *cis* to one another, this would not be possible.

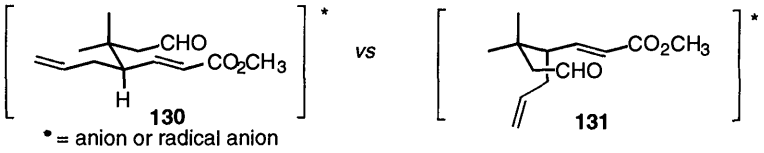
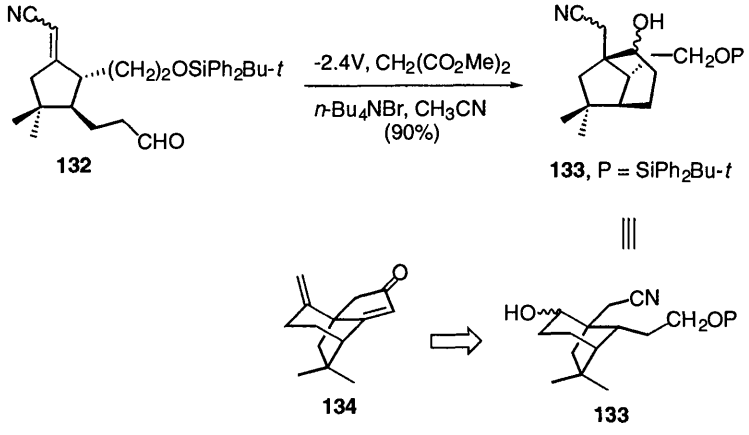


Figure 3

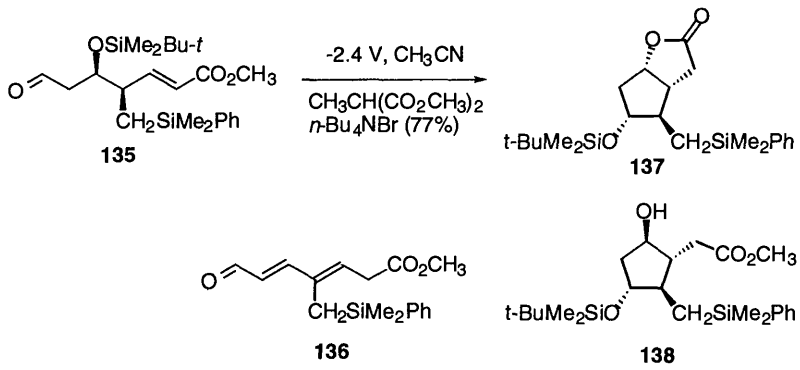
Keto ester **128** was converted to the unsaturated nitrile **132** in a routine manner. Concern that the significant steric demands associated with the formation of a sigma bond to the fully substituted β-carbon of the unsaturated nitrile would prevent the electroreductive cyclization reaction from occurring were allayed by the discovery that the controlled potential reduction of **132** at -2.4 V, in the presence of dimethyl malonate as the proton donor, afforded a 90% isolated yield of the requisite [3.2.1] adduct **133**. This material was subsequently converted to enone **134** [36], a convergent point with an existing synthesis of quadrone (**120**).



(21)

D. Corey Lactone (137)

A case where acid–base chemistry competes with cyclization is found in efforts to construct an analog of the Corey lactone, a substance that has often served as a prostaglandin precursor [37]. The enantiomerically pure unsaturated ester **135** was assembled and subjected to the conditions indicated in Scheme 14. Dimethyl α-methylmalonate was used as the proton donor to avoid the competitive 1,4-addition of the conjugate base to **135** that occurs when the less hindered dimethyl malonate is used as the proton source.

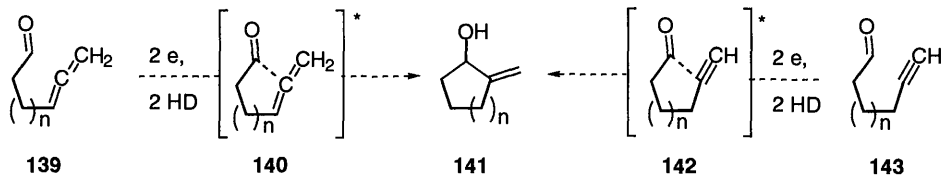


Scheme 14

Cyclization afforded a combined 77% isolated yield of the lactone **137** and the γ-hydroxy ester **138**; the hydroxy ester could be converted to the lactone in a straightforward manner, thus allowing it to be used to throughput additional material to the target structure. Unfortunately, these materials were accompanied by the formation of the conjugated diene **136**, a substance that undoubtedly arises via the intervention of acid–base chemistry, leading to β-elimination of the silyloxy unit from **135**.

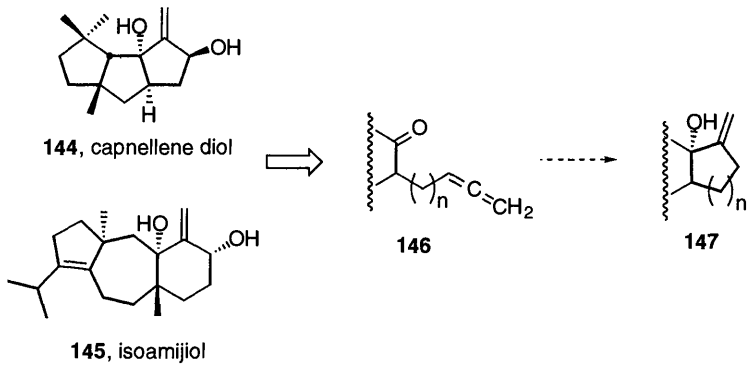
E. Capnellene Diol (144), Isoamijiol (145)

An interesting and useful variation on the electroreductive cyclization theme calls for the use of substrates wherein an allene or alkyne is tethered to an aldehyde or ketone [38]. As exemplified by the conversion of **139** or **143** to **141**, the reductive cyclizations lead to an allylic alcohol. This functionality, of course, is exceptionally useful, offering the opportunity for a host of followup reactions to be employed.



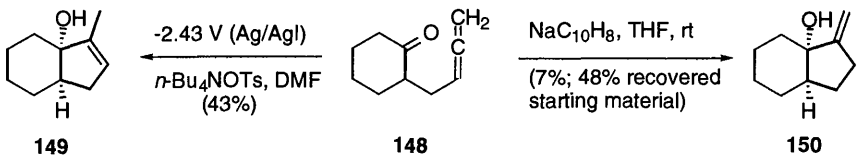
(22)

Two marine natural products, capnellene diol (**144**) and isoamijiol (**145**), were viewed as ideal candidates upon which to explore these transformations [39]. Both of these materials incorporate a bridgehead hydroxyl group and an exocyclic carbon–carbon π-bond, subunits that are produced as a natural consequence of the methodology (Scheme 15).

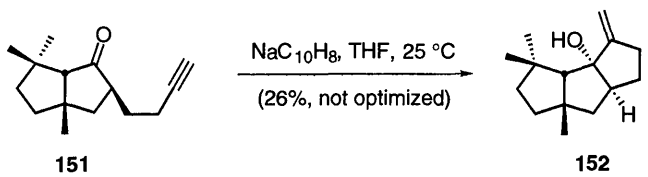


Scheme 15

Unfortunately, efforts to synthesize the natural products were thwarted by the formation of the endocyclic alkene **149**. In the cases illustrated in Eqs. (23) and (24), the use of sodium naphthalide afforded the desired adducts, **150** and **152**, though the yield in both of the cases was poor.



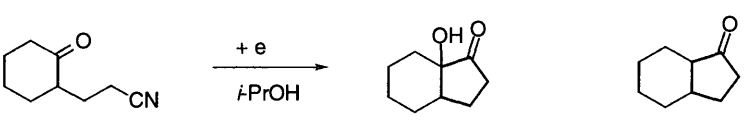
(23)



(24)

F. Guaiazulene (163), Dihydrojasmone (165), Rosaprostol (170), Valeranone (174), Hirsutene (77), $\Delta^{9(12)}$-Capnellene (182)

Keto nitriles, such as **153**, function admirably as substrates in reductive cyclizations [40, 41]. Two product types are obtained, one the simple ketone **155**, the other **154**, incorporating the α-hydroxy ketone (ketol) functionality that is present in many natural products. Both controlled-potential and constant-current conditions have been utilized. Of the electrodes examined (Ag, Cd, Pb, Zn, C-fiber, and Sn), tin generally proved most effective. Using tin, the controlled potential reduction of **153** in *i*-PrOH at -2.8 V versus SCE (divided cell, ceramic diaphragm) afforded a 76% yield of ketol **154** accompanied by 2% of ketone **155**. As illustrated in Table 5, the preference for ketol formation drops when the transformation is carried out at constant current or without using a diaphragm.

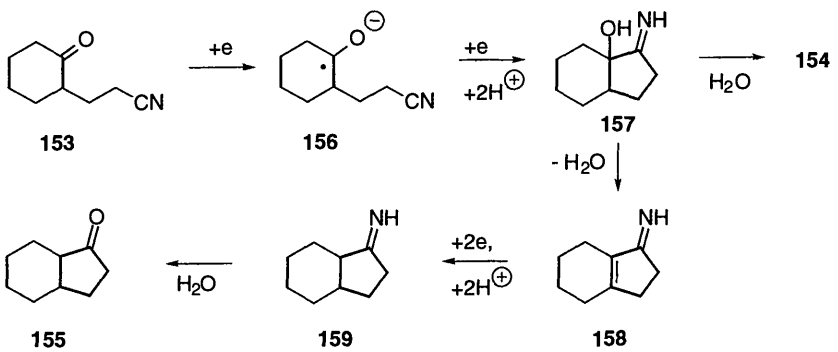


(25)

Table 5 Reduction of Keto Nitriles

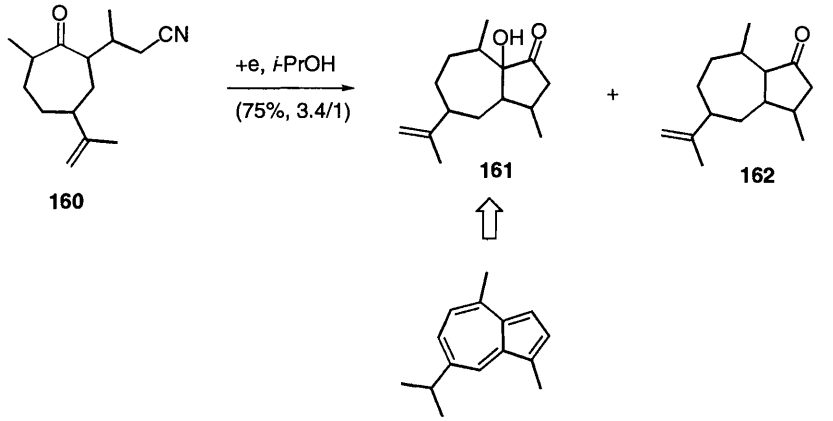
Conditions	F/mol	Yield (% **154**, % **155**)
i-PrOH, 25°C, −2.8 V (SCE; Sn) divided cell, ceramic diaphragm	3	76, 2
i-PrOH, 25°C, constant current of 0.2 A, divided cell, ceramic diaphragm	3.5	63, 16
i-PrOH, 25°C, −2.8 V (SCE; Sn) divided cell, no diaphragm	4	65, 11

The reaction is assumed to occur via the formation and cyclization of a ketyl, **156**, followed by the addition of a second electron and two protons, leading to an unstable α-hydroxyimine **157**. Hydrolysis affords the ketol **154**, while elimination of water, followed by a second reduction of the resulting α,β-unsaturated imine and hydrolysis, leads to the ketone **155** (Scheme 16).



Scheme 16

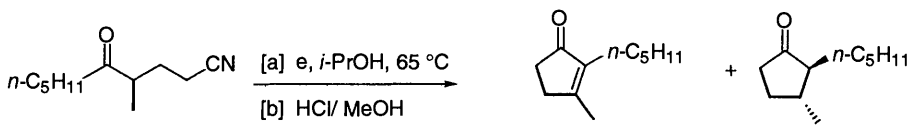
The transformation has been employed extensively in the preparation of precursors to a number of natural products [note Eqs. (26)–(32)], including, guaiazulene (**163**), dihydrojasmone (**165**), rosaprostol (**170**), and convergent synthesis of (−)-valeranone (**174**), hirsutene (**177**), and $\Delta^{9(12)}$-capnellene (**182**) [41]. The key cathodic cyclization step is illustrated for each natural product.



160 **161** **162**

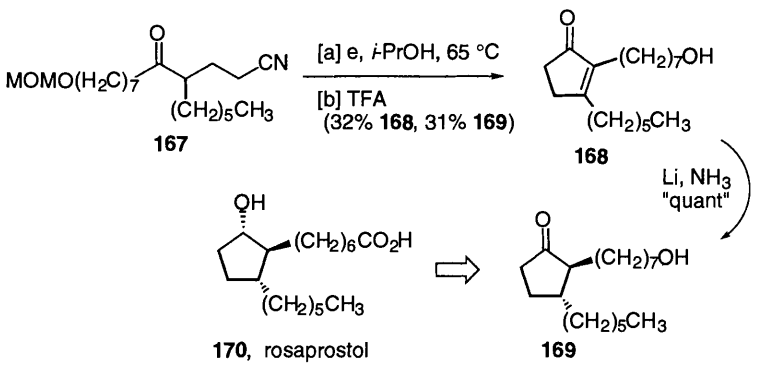
163, guaiazulene

(26)



164 **165**, dihydrojasmone (64%) **166** (13%)

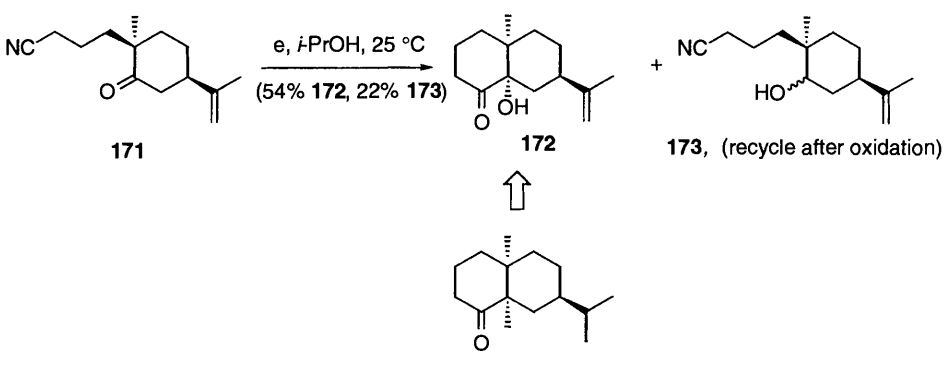
(27)



167 **168**

170, rosaprostol **169**

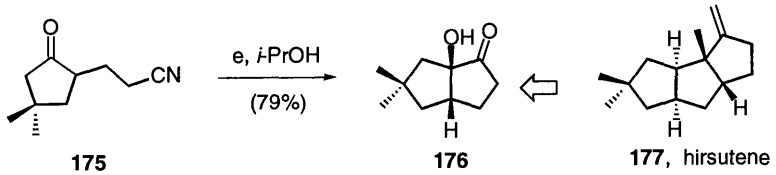
(28)



171 **172** **173**, (recycle after oxidation)

174, (-)-valeranone

(29)



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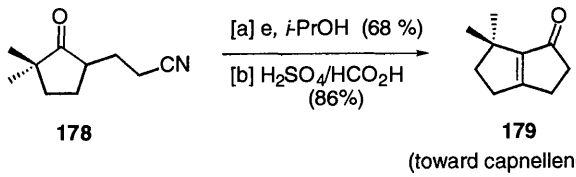

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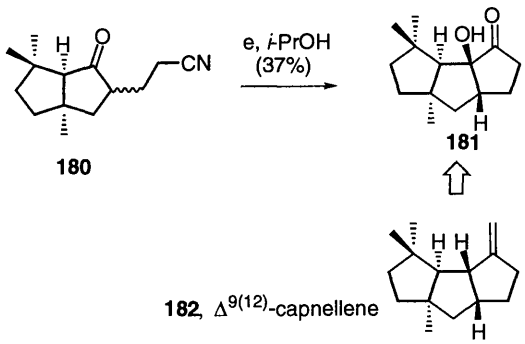
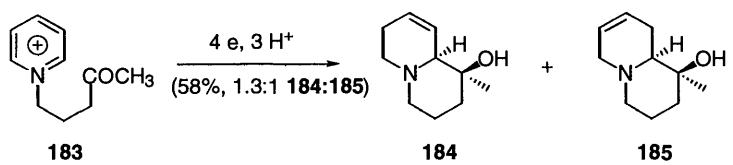


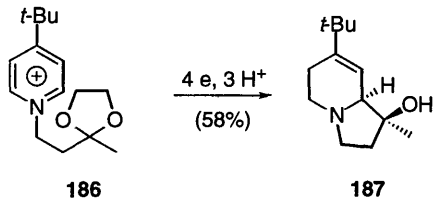
(32)

VI. REDUCTION OF PYRIDINIUM SALTS—QUINOLIZIDINE AND INDOLIZIDINE DERIVATIVES

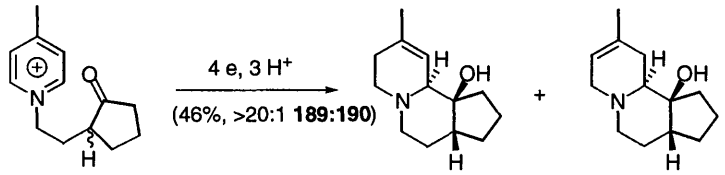
Pyridinium salts tethered to ketones also undergo cathodic cyclization [42]. The reaction provides a convenient diastereoselective route to quinolizidine derivatives such as **184**, **185**, **189**, and **190**, as well as to indolizidine derivatives (e.g., **187**). The transformation appears to hold significant promise as a route to alkaloids. Optimal reaction conditions are listed below the equations. In each instance, the product corresponds to that diastereomer wherein the hydroxyl group and ring junction hydrogen are trans to one another. A mercury cathode is preferred, as passivation occurs when lead is used, and the reaction does not occur using either graphite or glassy carbon electrodes.



(33)



186 187 (34)



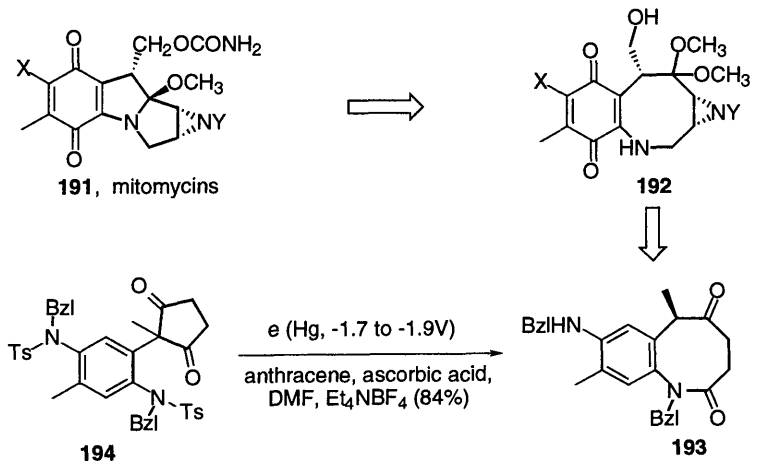
188 189 190 (35)

Hg (constant current of 4.2 mA cm^{-2}, charge 8 F mol^{-1}), 10% H_2SO_4, 0.2 M in pyridinium salt, 20 °C

VII. MEDIATED PROCESSES

A. Mitomycins (191)

The mitomycins (**191**) have attracted much attention as a result of their interesting structure and potent anticancer properties [43]. One approach to these materials is illustrated in Eq. 36 [44]. A key intermediate in the implementation of this plan is azocinone (**193**), a substance that proved accessible in high yield via the novel mediated *N*-tosyl group cleavage–cyclization–fragmentation of **194**. Here, ascorbic acid behaves as a proton donor and a reductant in combination with anthracene (Scheme 17).

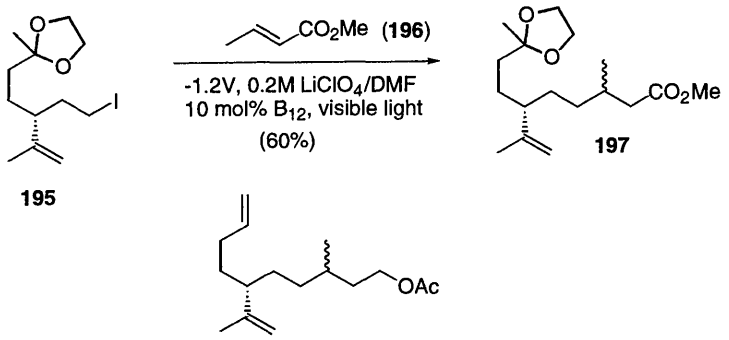


(36)

Scheme 17

B. Vitamin B_{12}-Mediated Cyclizations: California Red Scale Pheromone (198), $PGF_{2\alpha}$ Precursor (201)

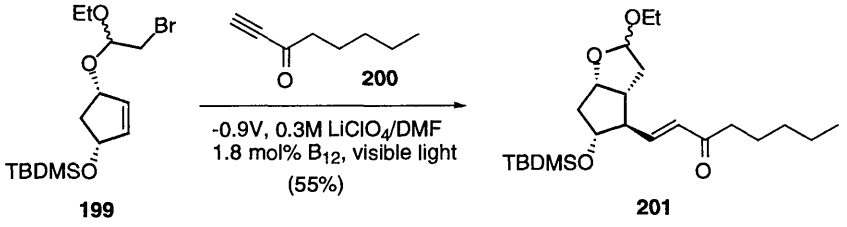
Vitamin B_{12} reacts with alkyl halides to form a cobalt(III) alkyl intermediate. Irradiation of it with visible light leads to the expulsion of a carbon-centered radical and a cobalt(II) species. The latter is easily reduced electrochemically at −0.8 V to reconvert it to a cobalt(I) species that reenters the catalytic cycle by reacting with a second molecule of the halide [45]. The radical is capable of undergoing a variety of interesting transformations, including conjugate addition to a Michael acceptor (e.g., **196**), as is illustrated in Eq. (37), leading to the synthesis of the California red scale pheromone (**198**).



(37)

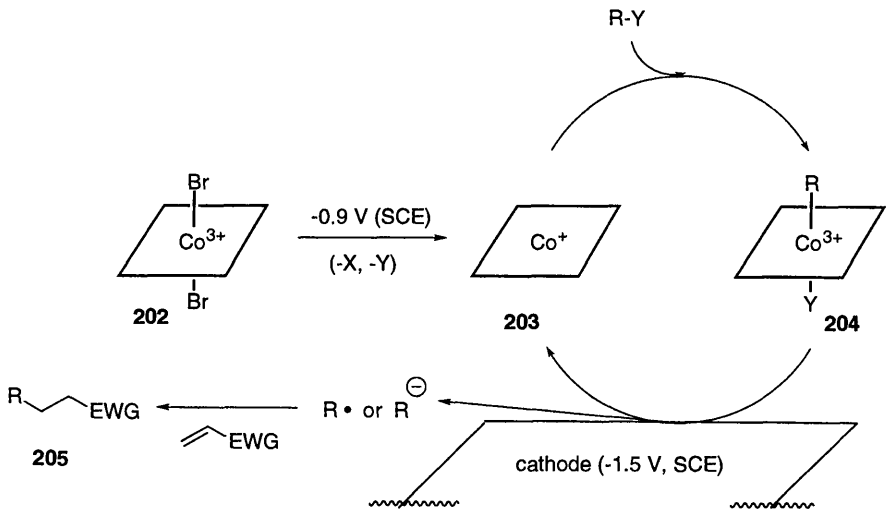
198, California red scale pheremone

Another illustration of the power of this methodology to construct natural products is illustrated by Scheffold's synthesis of $PGF_{2\alpha}$ in the manner portrayed in Eq. (38) [46]. Here the initially formed radical undergoes a 5-exo,trig cyclization with the simple alkene found in **199**. The resulting radical, when intercepted by ynone **200**, affords enone **201**; the latter is an advanced stage intermediate en route to $PGF_{2\alpha}$.



(38)

The chemistry takes place via an initial reduction of vitamin B_{12} or a similar cobalt(III) species **202**, in a process that sees the conversion of cobalt from the +3 to the +1 oxidation state, and the opening of two sites of unsaturation, to afford **203** [47]. This very reactive, highly nucleophilic intermediate reacts rapidly with the alkyl halide to form the octahedral complex **204**, and reestablish a +3 oxidation state on cobalt. A catalytic cycle is secured when this material undergoes reaction with a typical Michael acceptor leading to the formation of product, **205** (Scheme 18).



Scheme 18

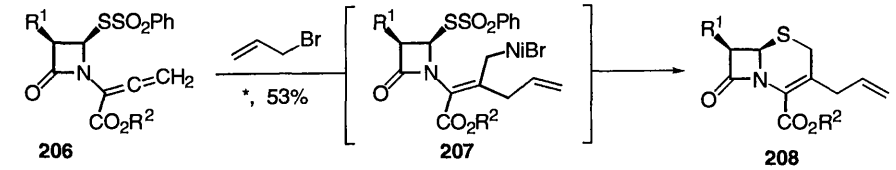
Control experiments establish that the initial process converting the dibromide **202** to **203** takes place in two steps with $E_{1/2}$ for extrusion of the first and second axial ligands occurring at −0.36 and −1.08 V, respectively [48]. After reaction with the alkyl halide, the resulting octahedral complex **204** is further reduced in the range of −1.4 to −1.7 V to form a cobalt (II) complex, which decays via the addition of an additional electron, cleavage of the C–Co and Co–Y bonds, and reaction with the Michael acceptor.

Typically, the reactions are carried out under controlled-potential conditions, with the potential being set within the range of −1.4 to −1.9 V (Ag/Ag^+). This is much less than that needed to reduce either the enone or alkyl halide. Only 1–20 mol% of the mediator is needed, in a medium consisting of $LiClO_4$ as the supporting electrolyte, DMF as solvent, and NH_4Br as the proton donor.

VIII. ORGANOMETALLICS

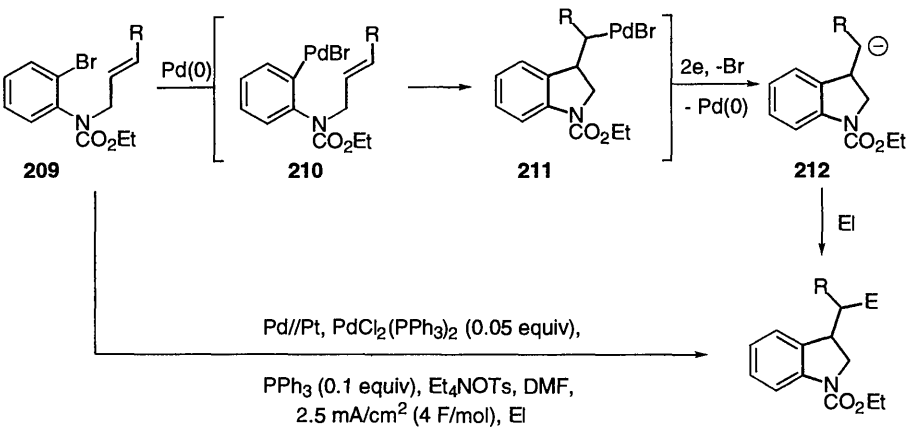
A. Cephalosporin Derivative (208)

Allylic and aryl halides, in the presence of an appropriate metal, serve as convenient sources of electrogenerated organometallics [49]. The example illustrated by Eq. (39) portrays a novel route to the cephalosporin derivative **208** [50,51], with it being formed through the intermediary of the allyl nickel species **207**. The presence of catalytic amounts of $NiCl_2(bpy)$ and $PbBr_2$ is essential for the formation of product [49]. The second example [Eq. (40)] is reminiscent of a Stille coupling [52]. The putative carbanion **212** undergoes reaction with electrophiles, El (e.g., **212** → **213**), in this case carbon dioxide or a proton source, to provide a convenient route to indoles.



R^1 = NHCOCH$_2$Ph
R^2 = CH$_2$C$_6$H$_4$OMe-*p* * $NiCl_2$(bpy) (0.1 equiv), $PbBr_2$ (0.05 equiv), Pt-Al, CC (6.7 mA/cm^2, 3.23 F/mol)

(39)

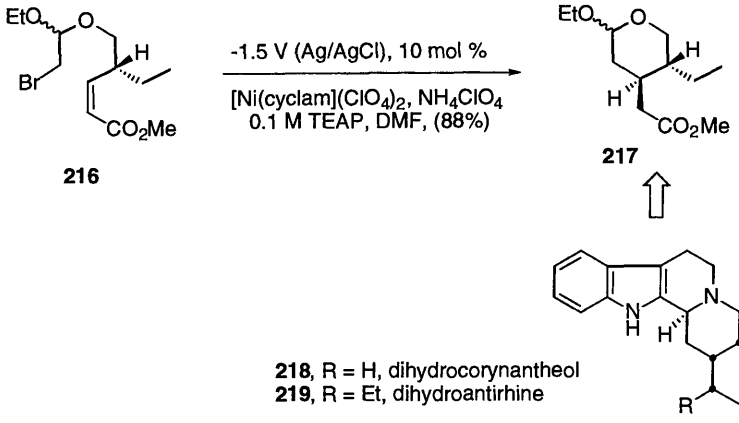


213, E = CO_2H, R = H, 81%
214, E = H, R = Me, 33%
215, E = CO_2H, R = Ph, 67%

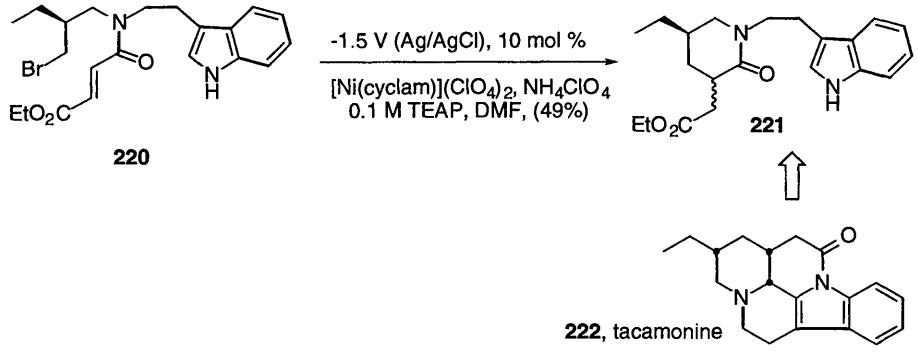
(40)

B. Dihydrocoryantheol (218), Dihydroantirhine (219), and Tacamonine (222)

β-Bromoacetals and *β*-bromoacetates readily undergo nickel(II) catalyzed cathodic cyclization onto alkenes [53]. The process has its obvious counterpart in free-radical-initiated chemistry using an organostannane, organomercury reagent, or an organosilane, and in electroreductive cyclizations as well as in their vitamin B_{12}-mediated counterparts. The use of [Ni(cyclam)]$(ClO_4)_2$ as a mediator avoids high dilution that is often required of organotin-promoted radical cyclizations, and allows the process to take place in the presence of only 10 mol% of the cyclam. Cyclization is most effective when an electron-deficient alkene is utilized. Of particular note is the fact that the product of the first reaction, **217**, is an intermediate in the synthesis of Ipecac and Corynanthe alkaloids **218** and **219**, while the lactam, **226**, is a synthetic precursor of the alkaloid tacamonine (**222**).



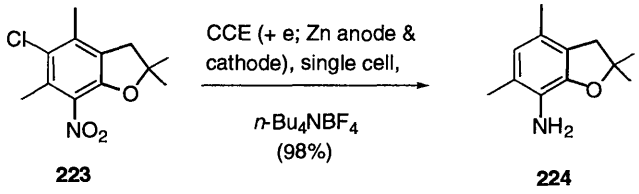
(41)



(42)

IX. REDUCTION OF ARYL CHLORIDES: ACYL-COA CHOLESTEROL ACYLTRANSFERASE-INHIBITORY SUBSTANCES

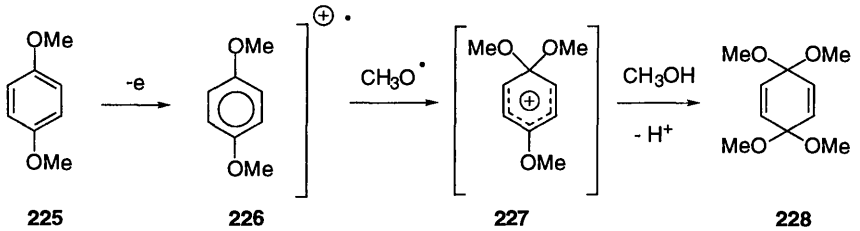
Benzofuran (**224**), a key intermediate in the synthesis of acyl-CoA cholesterol acyltransferase-inhibitory substances, has been generated in a one-pot reduction protocol wherein the aryl nitro group of **223** is reduced while simultaneously reducing the aryl chloride [54]. This one-step process is of particular significance as aryl nitro groups are typically reduced in acidic media, whereas aryl halides require neutral conditions. By careful control of the electrolysis conditions (solvent, electrolyte, and electrode composition), the aryl nitro group was reduced under neutral conditions.



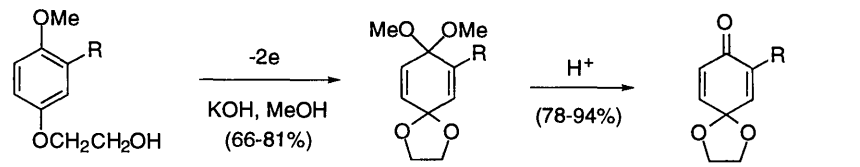
(43)

X. ARENE OXIDATIONS

Swenton and coworkers have devised and achieved an exceptionally elegant synthesis of anthracyclinone aglycons. Key to the successful outcome is the ability to intercept the intermediate radical cation **226** formed in the oxidation of aromatic ethers, either inter- or intramolecularly, with the alkoxy radical, $CH_3O^{\cdot}$, which is also formed electrooxidatively [55,56]. As illustrated, the methodology leads to the facile assembly of substituted quinone mono- or bisketals, **230** and **231**.



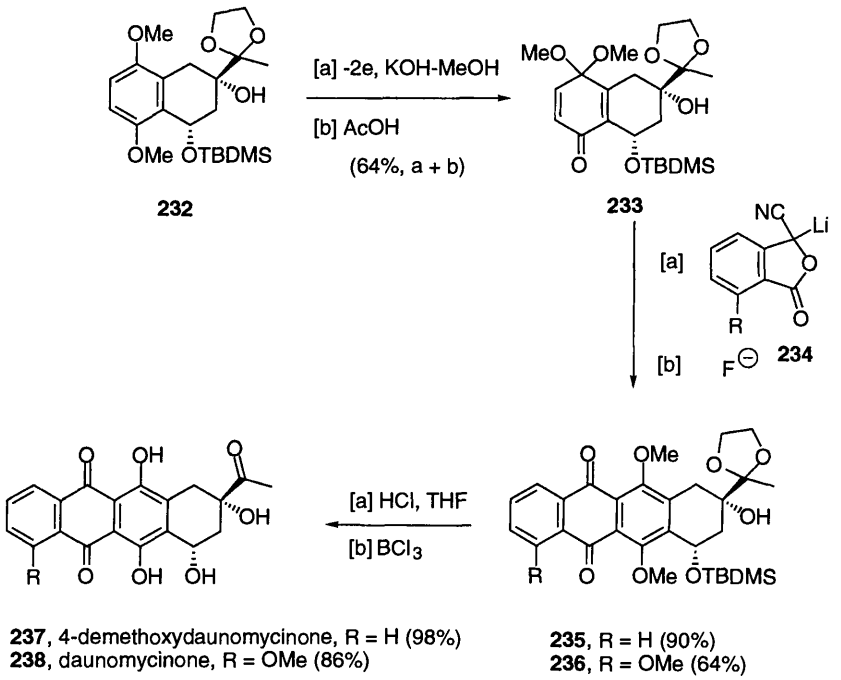
225 **226** **227** **228** (44)



229a-c, R = H, Br, Me **230** **231** (45)

A. Anthracyclinone Aglycons: (+)-4-Demothoxydaunomycinone (237) and (+)- Daunomycinone (238)

Substituted quinone ketals serve nicely in annelation strategies. The methodology has been skillfully applied to the total synthesis of several natural products, including (+)-4-demethoxydaunomycinone (**237**) and (+)-daunomycinone (**238**) [57–59]. One annelation strategy calls for a Michael addition of **234** to quinone ketal **233** followed by capture of the intermediate enolate, and leads to annelated product **235** when R = H, and to **236** when R = OMe. These materials were converted to the natural products **237** and **238** in the manner shown in Scheme 19 [59].



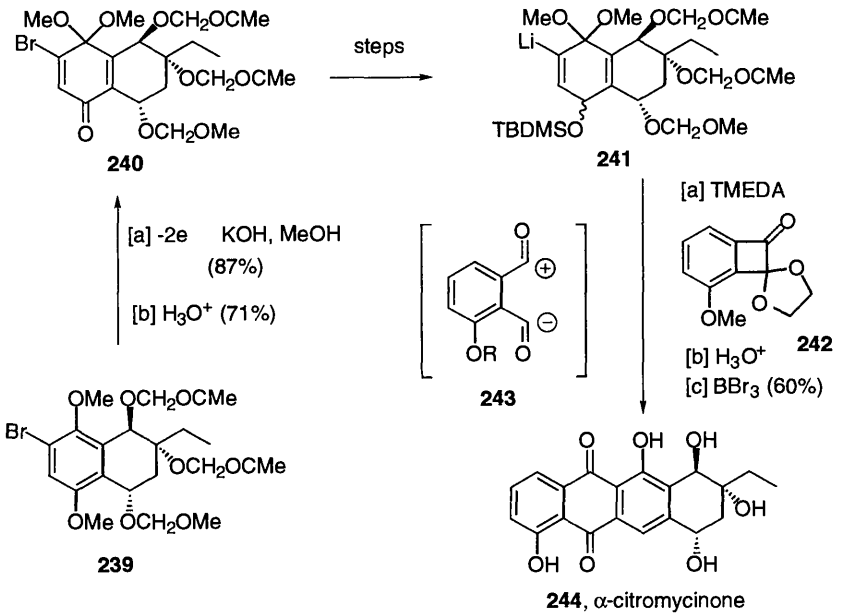
237, 4-demethoxydaunomycinone, R = H (98%)
238, daunomycinone, R = OMe (86%)

235, R = H (90%)
236, R = OMe (64%)

Scheme 19

1. α-Citromycinone (244)

Another approach to the anthracycline antibiotics is exemplified by the synthesis of α-citromycinone (**244**); see Scheme 20 [57,58]. In this instance the electrochemically generated brominated quinone monoketal **240** was converted to the lithiated species **241**. Its reaction with ketal **242**, a rather remarkable synthon for the 1,4-dipole **243** [60,61], proceeded smoothly to afford, after sequential treatment with aqueous acid and boron tribromide, a 60% yield of α-citromycinone (**244**).

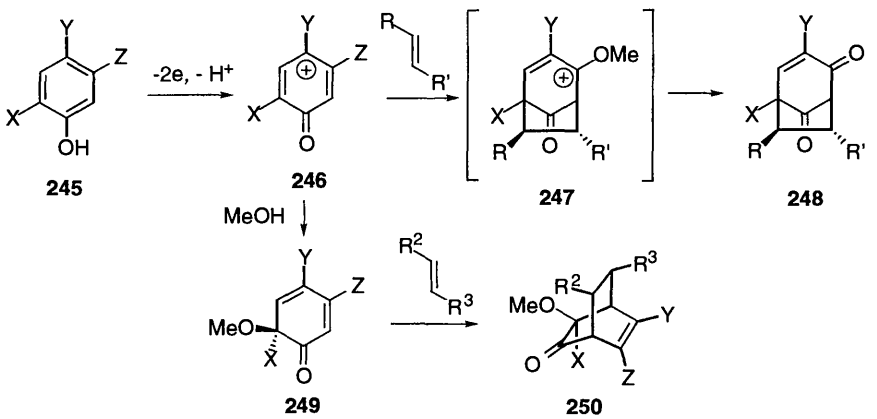


(20)

Scheme 20

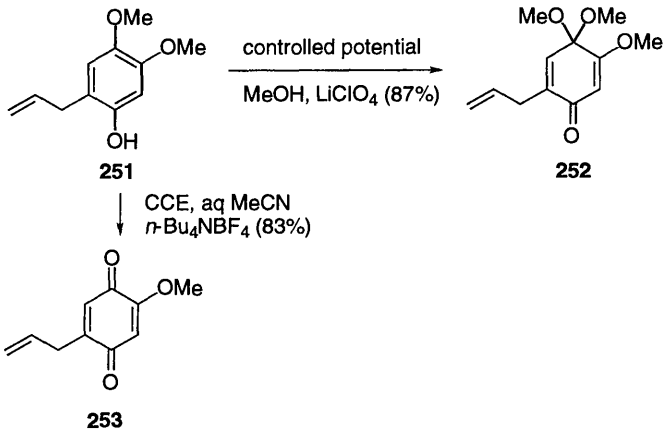
B. [5 + 2]-Cycloaddition

Yamamura and coworkers have made elegant and varied use of the oxidative chemistry of phenols [62,63]. The key intermediate in much of this work, cation **246**, is like that of Swenton's work [55,56]. As expected, **246** can be intercepted by alkenes in a [5 + 2]-cycloaddition (**246** to **247**), or by a nucleophilic solvent such as methanol, leading to a conjugated diene **249** that is capable of serving as a Diels–Alder cycloaddition partner (**249** to **250**) (Scheme 21).



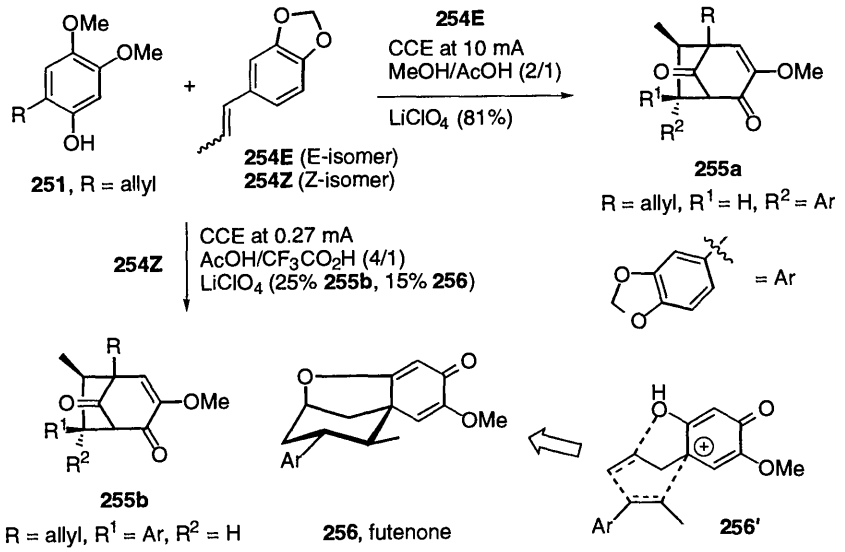
Scheme 21

Both inter- and intramolecular cycloaddition modes have been explored and utilized in the synthesis of natural products. Successful intermolecular cycloaddition depends upon making an appropriate selection of solvent, supporting electrolyte, oxidation potential, and current density. This is nicely illustrated in the equations portrayed in Schemes 22 and 23. For example, in methanol the controlled-potential oxidation of phenol **251** affords a high yield (87%) of **252**, the adduct wherein methanol has intercepted the reactive intermediate [62]. In contrast, another constant-current electrolysis afforded an 83% yield of quinone **253** when the reaction was conducted in acetonitrile, rather than in methanol.



Scheme 22

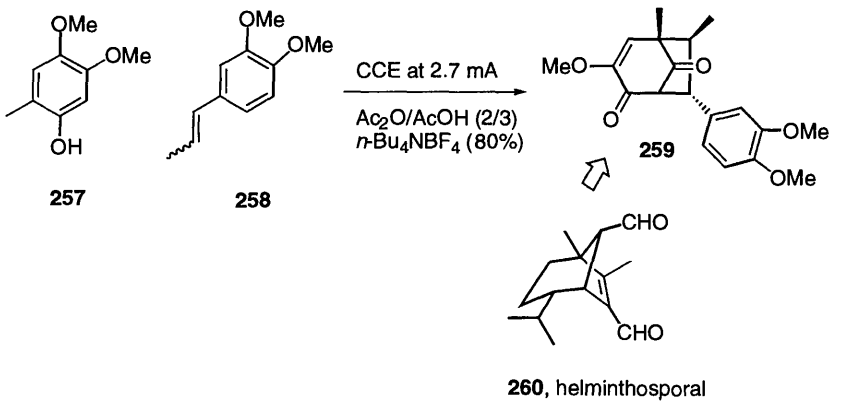
As the examples portrayed in Scheme 23 illustrate [62], cycloaddition occurs by using mixed solvent combinations consisting of either methanol/acetic acid (2:1) or acetic acid/trifluoroacetic acid (4:1) with lithium perchlorate as supporting electrolyte. Notice the different current densities that are associated with these transformations. Often, the success of the cycloadditions depends upon finding the optimal current density. Cycloaddition between **251** and **254E** leads to the aniba neolignan **255a** in high yield. Notice that the olefin stereochemistry is maintained in this process. When the *Z*-isomer (**254Z**) is used, the chemistry is not nearly as efficient. Two products, **255b** and **256** (futenone), are produced in a yield of 25 and 15%, respectively. It is interesting to speculate concerning the origin of **256**. That **254Z** is incorporated into **256** with a loss of olefin stereochemistry certainly implies a stepwise process. Drawing **256′** illustrates the key bond connections leading to **256** and is not meant to imply mechanistic detail.



Scheme 23

1. Helminthosporal (260)

The reaction of **251** with **254E** illustrates the ease with which the aniba neolignan **255a** can be synthesized by using Yamamura's methodology [62]. In the case of **255a**, the aromatic ring of the styryl cycloaddition partner **254E** constitutes an integral part of the structure of the target structure and does not require substantial modification to reach the target. This is in contrast to a total synthesis of the sesquiterpene helminthosporal (**260**) [63]. Here, the electrochemically initiated cycloaddition proceeds efficiently, affording **259** in 80% yield. However, its transformation to the natural product required that the aromatic ring be converted to an aldehyde, a requirement of some proportion.

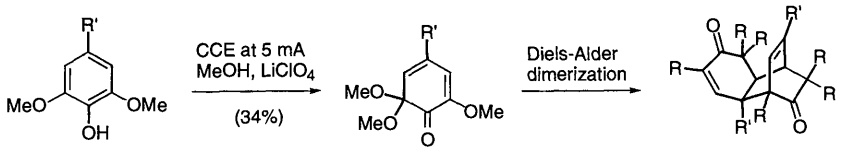


(46)

2. Asatone (263)

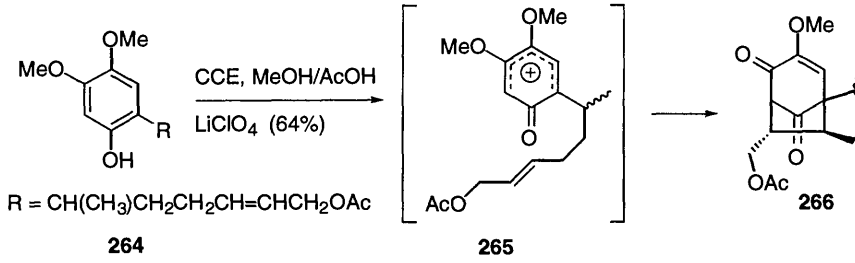
Asatone (**263**), a neolignan, was elegantly assembled by capitalizing upon the ability of a nucleophilic solvent to intercept the intermediate cation formed upon the electrooxidation

of **261** [62]. By starting with a 2,6-dimethoxyphenol, the conjugated 1,3-diene **262** is produced (cf. the oxidation of 4,5-dimethyoxyphenol **251** where the nonconjugated 1,4-diene is generated). Diene **262** served admirably as both the diene and dienophile in an intermolecular Diels–Alder reaction leading to asatone (**263**).

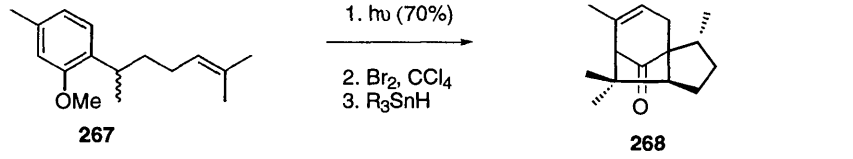


261, R' = allyl **262** **263**, R = OMe, R' = allyl asatone (47)

Yamamura has extensively explored the intramolecular [5 + 2]-cycloaddition mode. This chemistry bears a remarkable similarity to the so-called arene olefin meta-photocycloaddition [64] reaction (e.g., **267** to **268**) that has frequently been used in the synthesis of complex bioactive natural products. While different intermediates are involved, the photo- and electrochemical reactions provide access to many of the same basic ring systems. This is nicely demonstrated by comparing key steps and the outcome of an electrochemical approach to the total synthesis of pentalene (**53**) [65] and a photochemical pathway that ultimately led to cedrene (compare equations 48 and 49).



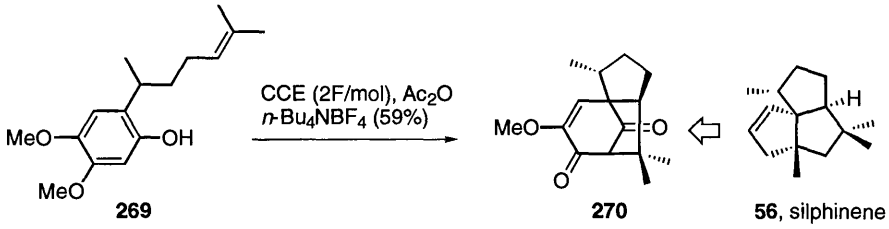
R = $CH(CH_3)CH_2CH_2CH{=}CHCH_2OAc$ **264** **265** **266** (48)



267 **268** (49)

3. Silphinene (56)

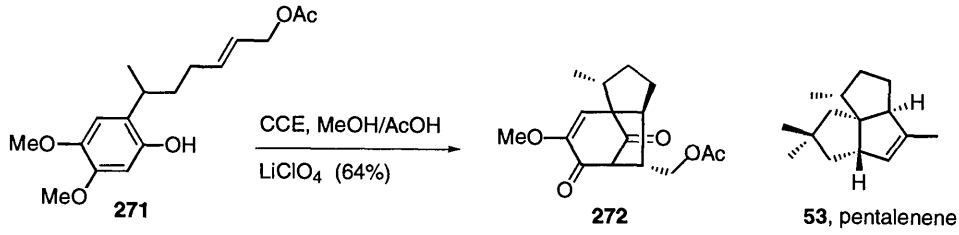
Silphinene (**56**) is a member of the angularly fused triquinane class of natural products, and has been the focus of many synthetic endeavours [66]. Yamamura and coworkers made excellent use of their intramolecular electrooxidative phenol cycloaddition chemistry as a key step in the assembly of this material [63,67]. It is noteworthy that the conversion of **269** to **270** is not thwarted by the fact that cycloaddition must occur with a sterically demanding trisubstituted double bond.



(50)

4. Pentalenene (53)

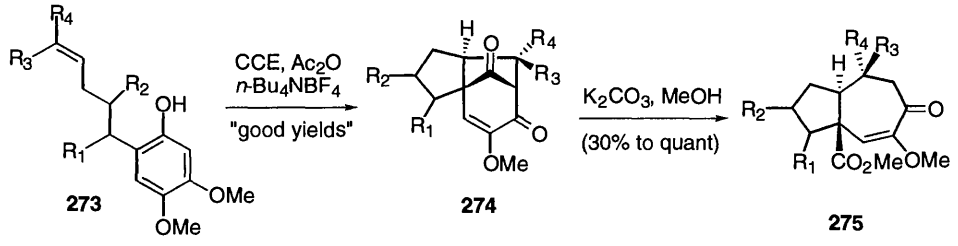
Similar methodology was used in a total synthesis of the angularly fused triquinane pentalenene (**53**) [65]. The known phenol **271** was used as the starting material. In this and the previous instance (viz. with **269**) constant-current electrolyses were performed, this time converting **271** to a mixture of the desired adduct **272** (64%) as well as a material epimeric at the CH_2OAc-bearing carbon (16%). The major adduct corresponds to one wherein the original olefin stereochemistry has been maintained. Conversion of **272** to the natural product followed chemistry similar to that used in the synthesis of silphinene (**56**).



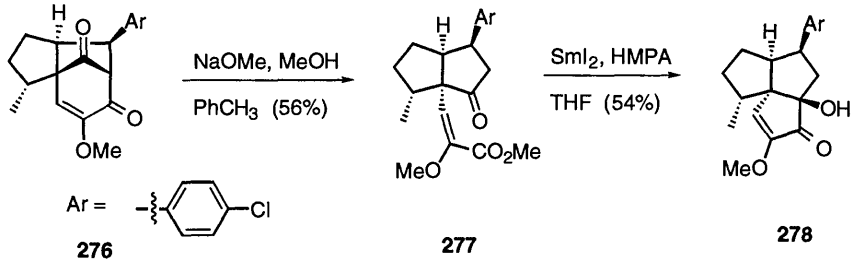
(51)

5. Hydroazulene Skeleton

The hydroazulene skeleton **275** that is common to a host of natural products is readily accessible via a base-catalyzed fragmentation of tricyclic [5 + 2]-cycloadducts such as **274** [68]. The trans ring junction stereochemistry between the bridgehead hydrogen and the carbomethoxy unit in the hydroazulene **275** is determined by the stereochemical relationship between the one carbon bridge and the five-membered ring that is syn to it in **274**. Interestingly [69], when the keto unit found on one carbon bridge is severely hindered by both the five membered ring and an aromatic ring as is the case with **276**, then the enone carbonyl is attacked preferentially to afford **277**, a direct precursor to the angularly fused triquinane skeleton **278**.



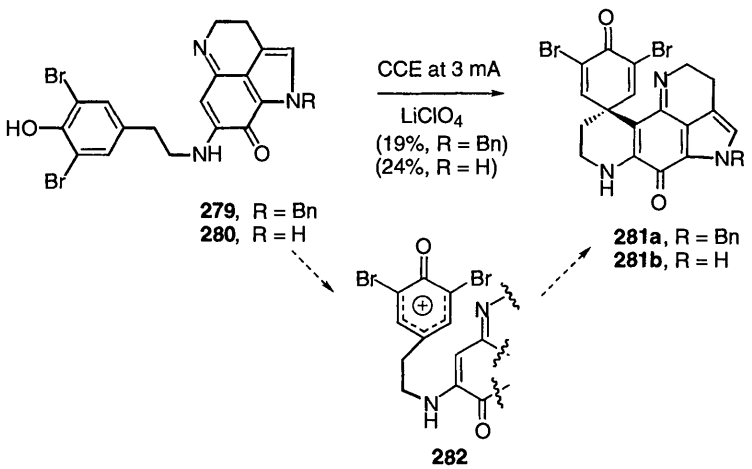
(52)



(53)

C. Pyrroloquinoline Alkaloids: Discorhabdin C (281)

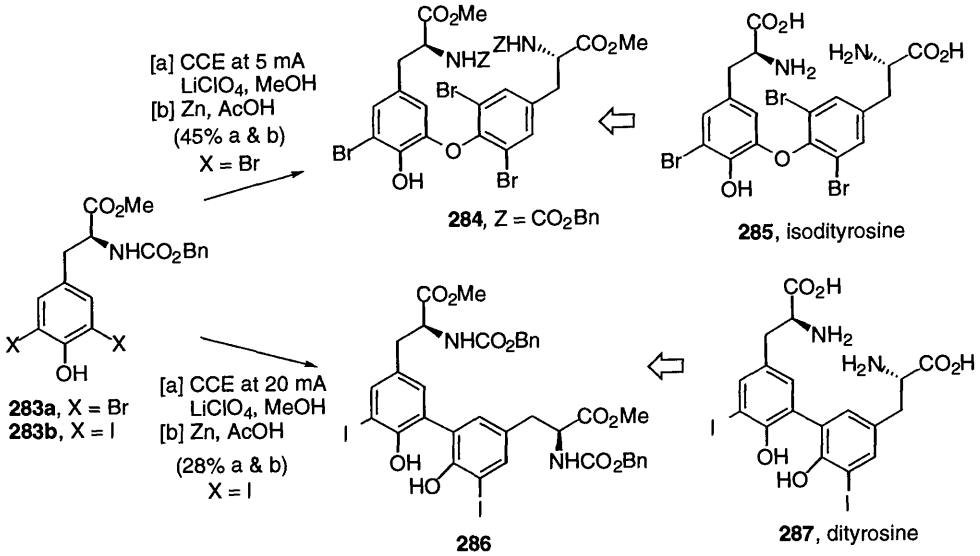
The pyrroloquinoline alkaloid family of bioactive marine natural products has been assembled by exploiting a biomimetic strategy. In the case of the *N*-benzyl derivative of discorhabdin C (**281a**), for example, the cation **282** that is formed upon electrooxidation of dibromophenol **279** was intercepted intramolecularly to afford **281a** in modest 19% yield [70]. Unfortunately, all attempts to remove the benzyl group failed. Consequently, the approach to the natural product was modified to affect debenzylation earlier in the scheme. Electrochemical oxidation of the free amine **280** did lead to discorhabdin C (**281b**), albeit in a low yield (24%).



(54)

D. Vancomycin Model Studies

Model studies directed toward the total synthesis of the potent antitumor agent vancomycin have focused upon the oxidative coupling of 2,6-dibromo- or 2,6-diiodophenols such as **283a** and **283b**. Of particular interest is the fact the bromo and iodo phenols **283a** and **283b** undergo different modes of coupling (Scheme 24), with bromide **283a** affording the diaryl ether **284**, while the iodide **283b** affords the biaryl **286** [71]. Fortunately, both of these substructures are common to the exceptionally complex vancomycin. Further modification of **284** led to isodityrosine (**285**), while **286** was converted to dityrosine (**287**).



Scheme 24

XI. CLOSING REMARKS

As the preceding examples illustrate, electrochemistry provides access to a rich assortment of complex structures and natural products. There is much to be appreciated in the research of the many who have contributed to this field. It is hoped that some day the methodology will be embraced by *all* practicing organic chemists, and that it will be properly recognized as a routine tool that is available to assist them in solving problems of both the mechanistic and synthetic varieties.

ACKNOWLEDGMENTS

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20
Organoelemental Compounds

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I. INTRODUCTION

The organoelemental compounds such as group 1, 2, 13, and 14 organometallic compounds have played a major role in organic synthesis and enjoy widespread use in both laboratories and industry. Some organometallic compounds such as organosilicon compounds are also utilized as materials.

This chapter provides a brief outline of electrochemical synthesis and reactions of organoelemental compounds. The electrochemistry of organoelemental compounds has a long history, and enormous advances have been made in the study of this field so far. The scope of this subject is, therefore, too extensive to be covered completely in a single chapter. There are excellent review articles on general electrochemistry of organoelemental compounds [1–6] and specific topics [7–9] in this field. Thus, the approach here is to present those fundamental aspects of electrochemical synthesis and reactions of organoelemental compounds with special emphasis on recent developments. This chapter is not an exhaustive compilation of all known reactions, but rather a sampling of sufficient variety to illustrate the fascinating chemistry of electrochemical synthesis and reactions of organoelemental compounds.

II. ELECTROCHEMICAL SYNTHESIS OF ORGANOELEMENTAL COMPOUNDS

Electrochemical reactions serve as efficient and convenient methods for the synthesis of organoelemental compounds. There are four major methods for the formation of element (metal)–carbon bonds. The first method utilizes the anodic oxidation of organometallic compounds using reactive metal anodes. In the second method, the organic compounds are reduced using reactive metal cathodes. The third method involves the cathodic reduction of organic compounds in the presence of metal halides. The fourth one utilizes both the cathodic and the anodic processes.

A. Oxidative Formation of Metal–Carbon Bonds

1. Oxidation of Organometallic Compounds Using Reactive Metal Anodes

Organometallic compounds can be synthesized by so-called "anodic transmetallation." This reaction proceeds by the initial oxidation of the starting organometallic compounds (RM^1) to generate an organic radical ($R^{\cdot}$), which reacts with a reactive anode (M^2) to form the desired organometallic product (RM^2) [Eq. (1)]. In some cases, a mechanism involving the ionic reaction of the cation of M^2 formed at the anode surface with RM^1 is suggested.

$$\text{R-M}^1 \xrightarrow{-e} \text{R}^{\bullet} + \text{M}^{1\,+} \qquad \text{R}^{\bullet} \xrightarrow{\text{M}^2\ (\text{anode})} \text{R-M}^2 \tag{1}$$

The anodic oxidation of Grignard reagents using reactive metal anodes such as Al [10,11], Zn [10,12], Mn [12], Cd [10,12], Bi [12], and B [13] is known to give the corresponding organometallic compounds [Eq. (2)]. This reaction has been used for the synthesis of tetraalkyllead on an industrial scale (NALCO process) [14,15].

$$\text{RMgX} + \text{M (anode)} \xrightarrow{-e} \text{R}_n\text{M} \tag{2}$$

$$\text{M} = \text{Al, Zn, Mn, Cd, Bi, B, Pb (NALCO process)}$$

The anodic oxidation of "-ate complexes" such as $Na[ZnR_3]$, $Na[AlR_4]$, and $Na[BR_4]$ also leads to the formation of the metal–carbon bonds [Eq. (3)]. Mg [16], Zn [17,18], Cd [18], Hg [18–20], Sn [18,19,21], Pb [18–20,22,23], Sb [18–20], and Bi [18,20] are effective as reactive metal anodes.

$$\text{Na}[\text{M}^1\text{R}_n] + \text{M}^2\ (\text{anode}) \xrightarrow{-e} \text{R}_n\text{M}^2 \tag{3}$$

$$\text{M}^1 = \text{Zn, Al, B}$$
$$\text{M}^2 = \text{Mg, Zn, Cd, Hg, Sn, Pb, Sb, Bi}$$

B. Reductive Formation of Metal–Carbon Bonds

1. Reduction of Organic Compounds Using Reactive Metal Cathodes

Reduction of some organic compounds at reactive metal cathodes leads to the formation of organometallic compounds as shown in Eq. (4). This reaction seems to proceed by one-

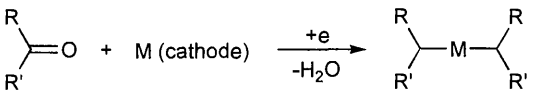
electron reduction to form radical intermediates, which react with metals to form the metal–carbon bonds.

$$\text{organic substrate} \xrightarrow{+e} R^{\cdot} \xrightarrow{M\ (\text{cathode})} R\text{–}M \tag{4}$$

Organic halides serve as effective precursors of organic radicals, and the reduction of organic halides with reactive metal cathodes leads to the formation of organometallic compounds [Eq. (5)]. For example, the reduction of alkyl halides with a Pb cathode results in the formation of R_4Pb [24–28]. The reduction at a Hg cathode results in the formation of R_2Hg [29–32]. Sn is also effective as a reactive cathode to give R_4Sn [33–35].

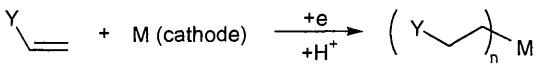
$$R\text{–}X + M\ (\text{cathode}) \xrightarrow{+e} R\text{–}M \qquad M = Pb, Hg, Sn \tag{5}$$

Carbonyl compounds are also used as starting materials for the reductive synthesis of organometallic compounds. The electrochemical reduction of carbonyl compounds such as ketones and aldehydes using reactive metal cathodes gives the deoxygenated organometallic compounds, although yields and selectivites are generally not high [Eq. (6)]. Ge [36], Pb [37,38], Sn [39], Hg [38,40], and Zn [41] are known to be effective as reactive metal cathodes. A mechanism involving an α-hydroxy carbon radical is suggested [42].



(6)

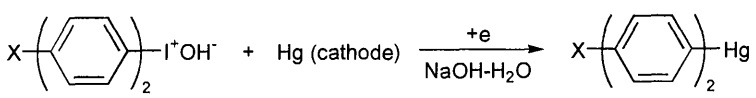
Activated olefins such as acrylonitrile and methyl vinyl ketone are also effective as precursors of organometallic compounds. The electrochemical reduction of activated olefins using Sn [43,44], Bi [45], Se [46], Te [46], and Hg [47] cathodes gives the corresponding hydrometallated compounds as shown in Eq. (7).



Y = CN, COMe, COOH
M = Sn, Bi, Se, Te, Hg

(7)

Diaryliodonium ions are also reducible, and their cathodic reduction using an Hg cathode affords Ar_2Hg [Eq. (8)] [48]. Benzylsulfonium ion is also effective as a substrate [49].



(8)

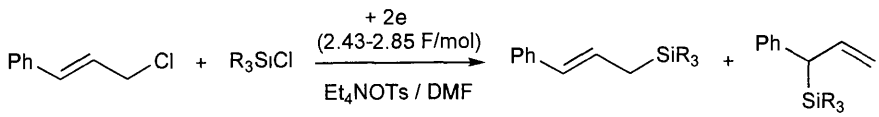
2. Reduction of Organic Compounds in the Presence of Metal Halides

The combination of organic halides and metal halides is also effective for the reductive formation of the metal-carbon bond. This type of reaction proceeds by a mechanism involving the cathodic reduction of organic halides [Eq. (9)] because reduction potentials

of organic halides are usually less negative than those of metal halides. The carbanion intermediate is usually responsible for the formation of organometallic compounds.

$$R\text{–}X \xrightarrow{+2e} R^- \xrightarrow{M\text{–}X} R\text{–}M \tag{9}$$

Several examples have been reported for the synthesis of organosilicon compounds. The reduction of organic halides such as allyl, benzyl, aryl, and alkenyl halides in the presence of chlorosilanes in a divided cell gives the corresponding organosilicon compounds [Eq. (10)] [50–52]. It is interesting that the regioselectivity of the reaction of allyl halides depends on the nature of the silylating agent. Trimethylsilyl and dimethylphenylsilyl groups are introduced to the less substituted end of the allyl group, whereas the dimethylsilyl group is introduced to both ends of the allyl group.



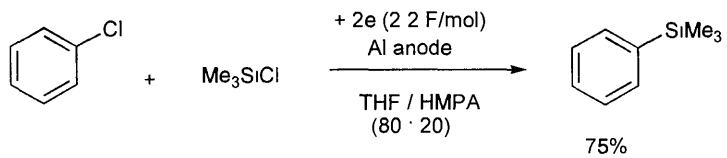
(10)

R_3Si	ratio	yield
Me_3Si	100 : 0	98
$PhMe_2Si$	100 : 0	66
HMe_2Si	50 : 50	84

Palladium-catalyzed reductive silylation has also been reported. The cathodic reduction of allylic acetates in the presence of silylating agents and a catalytic amount of $(Ph_3P)_4Pd$ [53] gives the corresponding allylsilanes. The initially formed π-allylpalladium(II) complex seems to be reduced at the cathode to generate the allyl anion intermediate, which reacts with chlorosilane to give the final product.

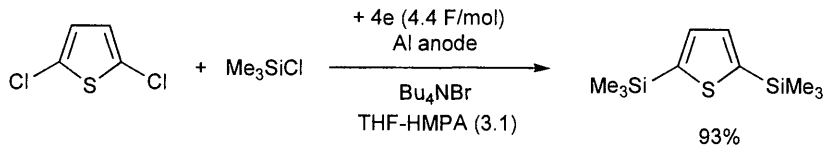
The Al-promoted alkylation of $SiCl_4$ with organic halides followed by the electrochemical regeneration of metallic Al is also noteworthy [54]. This reaction serves as an effective method for the synthesis of the tetraalkylsilanes from the corresponding alkyl halides on a large scale.

Reductive silylation of organic halides is effectively accomplished using a sacrificial Al or Mg anode and HMPA as a cosolvent, as shown in Eq. (11) [55–58]. It is advantageous that this reaction can be carried out in an undivided cell. It is also worth noting that aryl chlorides, which are less easily reduced than corresponding bromides and iodides, can be used as organic halides.



(11)

Reductive silylation of mono- and polyhalothiophens has also been achieved using an Al sacrificial anode [Eq. (12)] [59–61]. This reaction provides a convenient method for the preparation of 2,5-bis(trimethylsilyl)thiophene, which serves as a good precursor of polythiophene. The sacrificial Mg and Al anode technique was also successfully applied to the reductive silylation of bromopyrroles [62].



(12)

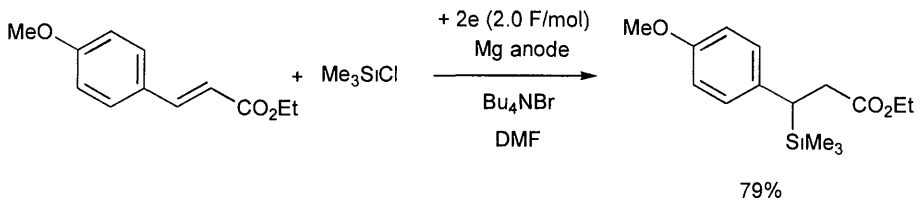
Selective mono- and disilylation of polychloromethanes such as carbon tetrachloride and chloroform has been achieved using Zn and Mg sacrificial anodes [Eqs. (13) and (14)] [63]. The product selectivity seems to depend on the electrode material. The application of this method for the reduction of $ClCH_2SiMe_2Cl$ leads to the formation of polycarbosilanes [64].

$$CCl_4 + Me_3SiCl \xrightarrow[Et_4NBF_4/DMF]{\text{+2e (2.2 F/mol)}\ \text{Zn anode}} \underset{94\%}{Me_3SiCCl_3} + \underset{66\%}{(Me_3Si)_2CCl_2} \tag{13}$$

$$CCl_4 + Me_3SiCl \xrightarrow[Et_4NBF_4/DMF]{\text{+4e (4.4 F/mol)}\ \text{Mg anode}} \underset{68\%}{(Me_3Si)_2CCl_2} \tag{14}$$

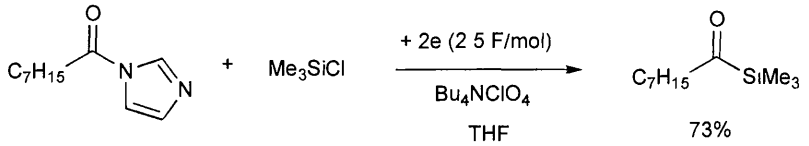
Fluorine-substituted alkenyl bromides and chlorides were also found to be effective as organic halides [65]. Fluorovinylsilanes were obtained by the electrochemical reduction of the corresponding fluoro-substituted alkenyl chlorides and bromides in the presence of Me_3SiCl using a sacrificial Al or Zn anode.

Activated olefins are also effective for the reductive metal–carbon bond formation. The electrochemical reduction of α,β-unsaturated esters, nitriles, and ketones in the presence of Me_3SiCl using a sacrificial Mg, Nz, or Al anode affords the corresponding silylated compounds [Eq. (15)] [66].



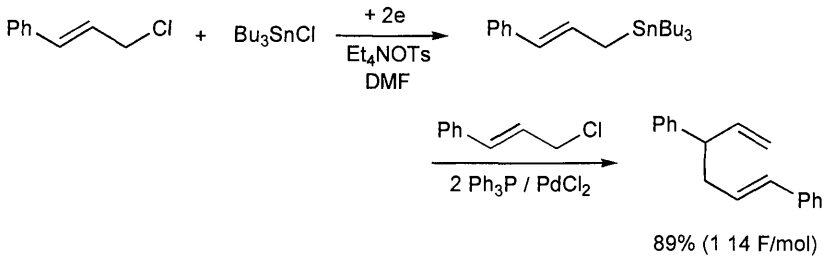
(15)

The acyl metals are also synthesized electrochemically. The cathodic reduction of acylimidazoles in the presence of Me_3SiCl using a Pt cathode and a Pt anode gives the corresponding acylsilanes [Eq. (16)] [67]. A mechanism involving the intial *N*-silylation of the imidazole moiety with Me_3SiCl, which decreases the reduction potential of the amide group, is suggested. The reductive silylation of acylsilane thus produced also takes place under appropriate conditions to give the silyl ether of the α,α-disilyl alcohol. Acid anhydrides are also effective for the reductive silylation. The cathodic reduction of aromatic acid anhydrides in the presence of Me_3SiCl gives the acylsilanes together with the simply reduced alcohols [68].



(16)

Organotin compounds may be synthesized by the cathodic reduction of organic compounds in the presence of tin halides. For example, the reduction of allylic halides in the presence of chlorostannanes gives the corresponding allylstannanes in good yields [69]. Combination of this reaction with in situ palladium-catalyzed reaction with allylic halides leads to effective formation of the head-to-tail homo coupling products as shown in Eq. (17).



(17)

3. Reduction of Organic Compounds Using Reactive Metal Anodes

The combination of the cathodic reduction of organic halides and the reactive metal anode is also effective for the synthesis of organometallic compounds [Eq. (18)]. Examples using Al [70], In [71], and Sn [72–74] as the anode to give the corresponding $RAlX_2$, $RInX_2$, and R_2SnX_2 respectively, have been reported. The reactions are suggested to proceed by the reduction of RX to generate X^-, which is oxidized at the metal anode to give MX. Organic sulfates can be used for this purpose. For example, the electrolysis of diethylsulfate using an Sn anode in the presence of CH_3CH_2I gives $(CH_3CH_2)_4Sn$ [75].

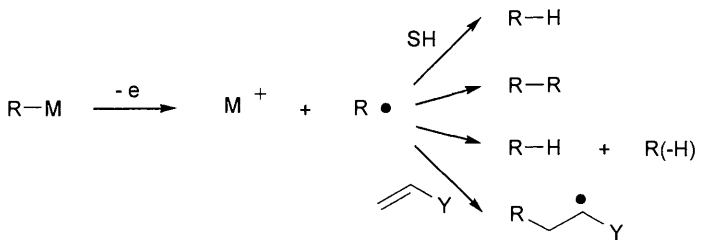
$$RX + M\ (anode) \xrightarrow{\text{electrolysis}} R_mMX_n \tag{18}$$

It is worth noting that this method is also effective to produce dinuclear compounds. Organodialuminum compounds such as $Cl_2AlCH_2AlCl_2$ were synthesized from CH_2Cl_2 [76].

III. ELECTROCHEMICAL OXIDATION OF ORGANOELEMENTAL COMPOUNDS

A. Electrochemical Oxidation of Group 1 and 2 Organometallic Compounds

Electrochemical oxidation of group 1 and 2 organometallic compounds generally leads to the formation of organic radicals. When a reactive metal anode is used, the radical reacts with the anode to give the corresponding organometallic compounds (see Sec. II.A). When an inert anode is used, the radical undergoes coupling, hydrogen abstraction, addition, and disproportionation depending on the conditions, as shown in Eq. (19).

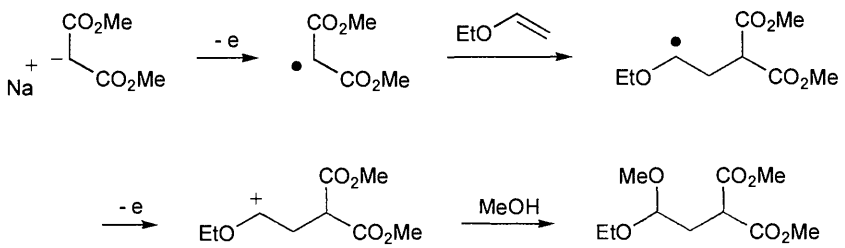


(19)

The electrochemical oxidation of RLi using an Hg anode results in the formation of homo coupling products R–R [77,78]. The electrochemical oxidation of Grignard reagents has been studied extensively [79–86]. The anodic oxidation of RMgX also gives the homo coupling product R–R. This process competes with hydrogen abstraction and disproportionation. The addition of the R radical to the carbon–carbon double bond takes place when the reaction is carried out in the presence of olefinic compounds such as styrene and butadiene [87].

The electrochemical oxidation of enolates and related compounds has also been studied. For example, the anodic oxidation of Li enolates of esters at low temperature gives the corresponding coupling products [88].

The anodic oxidation of Na malonates in the presence of olefinic compounds such as vinyl ethers in methanol gives the addition product [Eq. (20)] [89]. The following mechanism is proposed. The one-electron oxidation gives the radical of malonic ester, which adds to the carbon–carbon double bond. The resulting radical is further oxidized to give the cation, which is trapped by methanol to give the final product.



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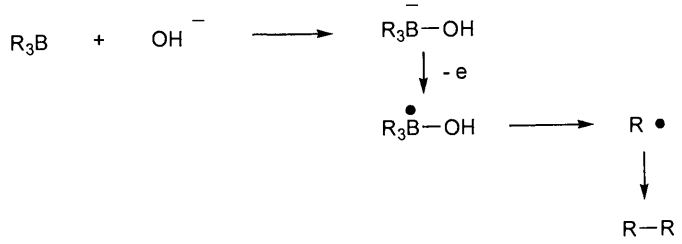
B. Electrochemical Oxidation of Group 13 Organometallic Compounds

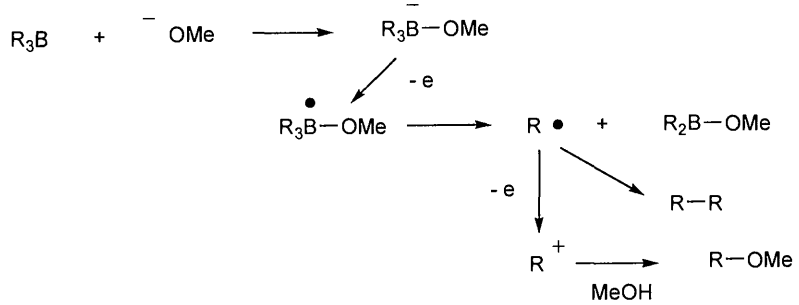
This section focuses on a rich variety of synthetic applications of electrochemical oxidation of organoboron compounds, because the electrochemical oxidation of other group 13 organometallic compounds such as organoaluminum compounds have been studied less extensively. There is a comprehensive review on the electrochemistry of organoboron compounds [90]. In general, the oxidation of triorganoborane (R_3B) needs activation by a nucleophile to form an ate complex. This negatively charged electron-rich ate complex then undergoes the electron transfer.

R_3B compounds are readily oxidized at a Pt electrode in methanol containing KOH as a nucleophile to give the homo coupling products (R–R) [91]. Three R groups on B may react, although yields are not very high. A mechanism involving the initial formation of the borate, which is subjected to one-electron oxidation to form the R radical, is proposed [Eq. (21)]. This mechanism is consistent with the cross-coupling experiment, which gave a nearly statistical distribution of three possible coupling products. The R radical formed by the anodic oxidation of R_4B anion was detected by the spin-trapping experiment [92].



(21)

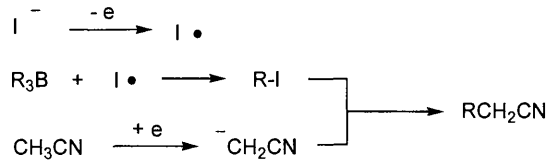
The use of a graphite anode, however, gives rise to the formation of different products. The anodic oxidation of R_3B using a graphite anode in methanol containing MeONa and $NaClO_4$ gives ROMe as a major product together with the homo coupling product R–R [93]. In this case, the R radical intermediate undergoes further oxidation at the anode to give the R cation, which is trapped by methanol to give ROMe [Eq. (22)]. Similarly, the anodic oxidation in acetic acid in the presence of NaOAc leads to the formation of ROAc. The R cation also undergoes the elimination reaction to give a regioisomeric mixture of olefins [94,95].



(22)

The anodic oxidation of $NaBPh_4$ is also reported to give the coupling product Ph–Ph, but this reaction does not seem to proceed by the radical coupling. A mechanism involving the intramolecular carbon–carbon bond formation is proposed [96–98].

Several synthetically useful carbon–carbon bond-forming reactions using anodic oxidation of organoboron compounds have been reported. For example, the anodic oxidation of R_3B in the presence of butadiene resulted in the transfer of R to butadiene [99]. A mechanism involving the intitial formation of R_3BOMe^-, which undergoes anodic oxidation to generate the R radical, has been proposed. The anodic oxidation of R_3B in the presence of terminal acetylenes to give the coupling products is also interesting [100]. The reaction of R_3B with CH_3CN is interesting from both a mechanistic and a synthetic point of view. The electrolysis of R_3B in acetonitrile using Bu_4NIX (X = Br, I) in an undivided cell gives RCH_2CN [101]. This reaction is suggested to proceed by a nucleophilic attack of cathodically generated $^-CH_2CN$ on the anodically generated RI as shown in Eq. (23). RI seems to be produced by the reaction of R_3B and electrogenerated I radical. The electrolysis of R_3B in CH_3NO_2 also seems to proceed in a similar fashion to give RCH_2NO_2 [102]. Some other electrochemical reactions of R_3B have also been reported in the literature [103,104].



(23)

It is notable that BH_4^- also undergoes one-electron oxidation to produce H_2 and BH_3 (B_2H_6). The BH_3 thus formed can be utilized for in situ hydroboration of olefins [105,106].

C. Electrochemical Oxidation of Group 14 Organometallic Compounds

Group 14 organometallic compounds, especially organosilicon and -tin compounds, have received significant research interest from the view point of electronic structures, reaction mechanism, organic synthesis, and material science. Since the oxidation potentials of tetraorganometals, especially tetraorganosilanes, are very positive, some activation is needed for the anodic oxidation. Although there are several methods for activation, the use of orbital interactions to raise the HOMO level is common for this purpose [107], and various anodic oxidation reactions of organosilicon and -tin compounds have been developed based on this concept.

1. Electrochemical Oxidation of Tetraorganometals

a. Unactivated Tetraorganometals. The oxidation potential of group 14 tetraorganometals increases in the order of Pb < Sn < Ge < Si (Table 1) [108]. This order is the same as that of the ionization potentials. Since the steric effect of the alkyl group is very small, the electron transfer is suggested as proceeding by an outer-sphere process. In the case of tetraorganosilanes, their oxidation potentials are very positive and outside of the electrochemical window of the usual supporting electrolyte/solvent systems. Therefore, it is rather difficult to oxidize unactivated tetraorganosilanes electrochemically in a practical sense. Thus, several methods for the activation of tetraorganosilanes toward electrochemical oxidation have been developed (vide infra).

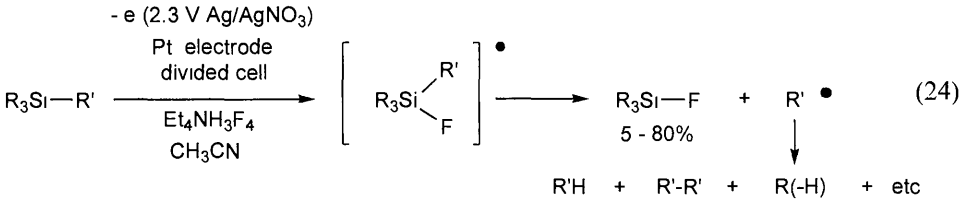
b. Activation by Fluoride. Fluoride ion is known to decrease the oxidation potential of tetraorganosilanes [109]. For example, the oxidation potential of $PhSiMe_3$ in the presence of $Et_4NH_3F_4$ (2.3 V vs. $Ag/AgNO_3$) is less positive than that in the absence of the fluoride source (2.6 V). The preparative anodic oxidation of tetraorganosilanes in the presence of $Et_4NH_3F_4$ results in the cleavage of the C–Si bond, to give the corre-

Table 1 Oxidation Potentials and Ionization Potentials of Tetraalkylmetals [108]

R_4M	E_p (V vs. SCE)	I_D(eV)
Et_4Si	2.56	9.78
Et_4Ge	2.24	9.41
Et_4Sn	1.76	8.93
Et_4Pb	1.26	8.13

Note: E_p, peak potential determined by cyclic voltammetry using a Pt anode in Et_4NClO_4/CH_3CN.

sponding fluorosilanes [Eq. (24)]. The eliminated organic group R′ can react in several ways, and the product selectivity is thus not high.

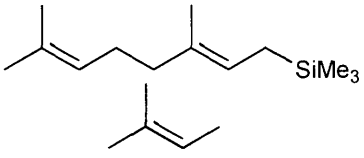


(24)

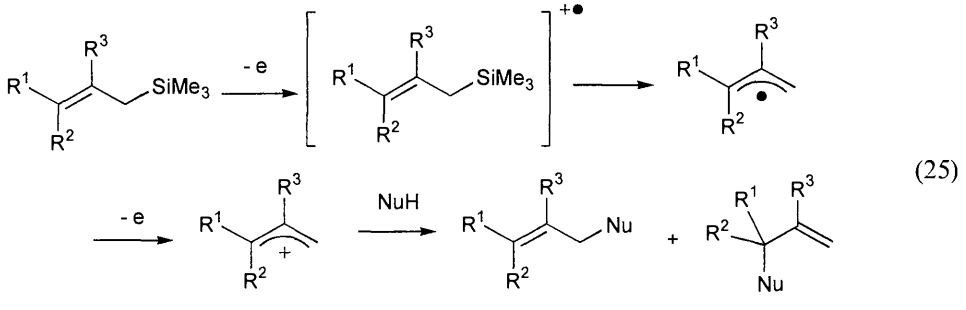
c. Activation by σ–π Interaction. The C–Si σ orbital interacts effectively with a neighbouring π orbital (σ–π interaction) because there is a good energy match between these orbitals. This orbital interaction causes significant increase of the HOMO level, which in turn favors the electron transfer. Thus, the oxidation potentials of allylsilanes are less positive than those of the corresponding simple alkenes and tetraorganosilanes (Table 2) [110–113].

The preparative electrochemical oxidation of allylsilanes proceeds smoothly and the C–Si bond is cleaved selectively without affecting other allylic C–H bonds [110–113]. This selectivity is ascribed to the selective cleavage of the C–Si bond in the cation radical intermediate. The resulting allyl radical intermediate is further oxidized to give the allyl cation intermediate, which is trapped by nucleophiles such as alcohols, water, carbamates, and tosylamides to give the corresponding allylic substitution products as shown in Eq. (25). Usually, the nucleophiles are introduced to both ends of the allyl cation, and therefore a mixture of two regioisomeric products is formed.

Table 2 Oxidation Potentials of Allylsilanes and Related Compounds

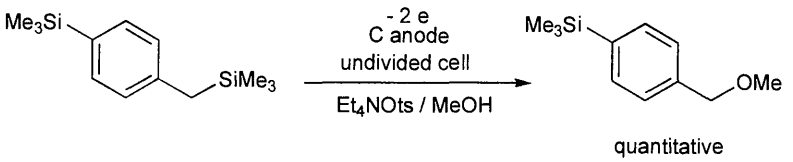
Compound	E_p (V vs. Ag/AgCl)
	1.30
	1.85
Me_4Si	> 2.5

Note. E_p, Peak potentials determined by cyclic voltammetry using a Pt anode in $LiClO_4/CH_3CN$.



(25)

The oxidation potentials of benzylsilanes are also less positive than those of the corresponding aromatic hydrocarbons and tetraorganosilanes owing to the σ–π interaction. The preparative electrochemical oxidation of benzylsilanes results in the cleavage of the C–Si bond and the introduction of a nucleophile on the carbon [110]. The following example demonstrates that the benzylic C–Si bond is cleaved selectively without affecting the aromatic C–Si bond:



(26)

d. Activation by σ–n Interaction. The C–Si σ orbital interacts with a neighbouring nonbonding *p* orbital of heteroatoms such as oxygen, nitrogen, sulfur, and phosphorous (σ–n interaction). Because of the σ–n interaction, the oxidation potentials of α-heteroatom-substituted tetraorganosilanes are less positive than those of the corresponding simple heteroatom compounds and tetraorganosilanes [114,115]. Table 3 demonstrates that the oxidation potentials of α-heteroatom-substituted organosilicon compounds exhibit less positive oxidation potentials than β-heteroatom-substituted organosilicon compounds, indicating the importance of σ–n interaction.

Since the orbital interaction plays a major role, the oxidation potentials of α-heteroatom-substituted organosilicon compounds depend on the geometry. As a matter of fact, the oxidation potentials of α-alkoxysilanes in which the rotation around the C–O bond is restricted vary dramatically with the torsion angle of Si–C–O–C (Table 4) [115].

It is also interesting that the introduction of an additional silyl group on the same carbon causes a further decrease of the oxidation potential, probably because of the increase in the population of the favorable conformers.

The oxidation potential also depends on the nature of the substituent on silicon (Table 5). For example, the introduction of F on silicon causes an anodic shift of the oxidation wave, although the introduction of H on silicon results in a very little anodic shift [116].

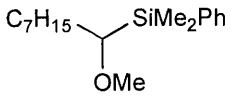
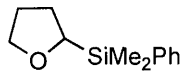
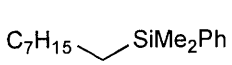
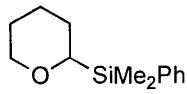
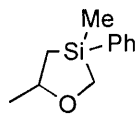
The preparative electrochemical oxidation of α-heteroatom-substituted tetraorganosilanes gives rise to cleavage of the C–Si bond and the introduction of a nucleophile such as methanol on the carbon [Eq. (27)]. Various reactions of this type have been reported for compounds containing oxygen [117–119], nitrogen [121], sulfur [116,119,120,122,123], and selenium [123].

Table 3 Oxidation Potentials of Nitrogen, Sulfur, and Phosphorus-Substituted Organosilicon Compounds [114]

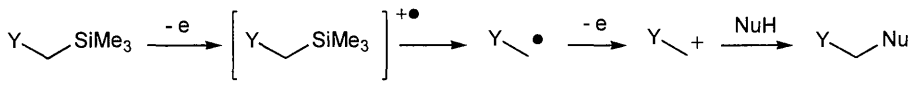
Compound	$E_{p/2}$ (V vs. SCE)	Compound	$E_{p/2}$ (V vs. SCE)
Me_3SiCH_2NHPh	0.44	$Me_3SiCH_2PPh_2$	0.63
$Me_3SicH_2CH_2NHPh$	0.60	$Me_3SiCH_2CH_2PPh_2$	0.88
Me_3SiCH_2SPh	1.15		
$Me_3SiCH_2CH_2SPh$	1.26		

Note. $E_{p/2}$, Half-wave potentials determined by single-sweep voltammetry using a Pt working electrode in Me_4NClO_4/CH_3CN.

Table 4 Oxidation Potentials of α-Alkoxysilanes [115]

Compound	E_d (V vs. Ag/AgCl)	Compound	E_d (V vs. Ag/AgCl)
	1.33		1.39
	1.95		1.54
			1.64

Note. E_d, Decomposition potentials determined by rotating-disk electrode using a glassy carbon anode in $LiClO_4$/CH_3CN.



(27)

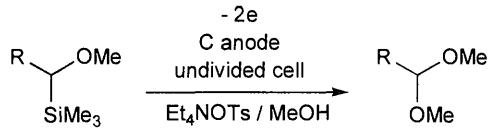
Several synthetic applications of the electrochemical oxidation of α-heteroatom-substituted organosilicon compounds have been developed. Since the anodic oxidation of α-alkoxysilanes in alcohols lead to the formation of acetals [Eq. (28)], which are readily hydrolyzed to carbonyl compounds such as aldehydes and ketones, α-alkoxysilanes serve as synthons of carbonyl groups [118,119]. A general iterative method for the synthesis of optically active polyols was developed based on this concept [124]. The anodic oxidation of α-phenylthiosilanes in alcohols results in the formation of the corresponding S,O-acetals, which undergo further electrochemical oxidation to give the corresponding acetals [Eq. (29)]. Therefore, α-phenylthiosilanes also serve as synthons of carbonyl compounds [122]. The anodic oxidation of α-nitrogen-substituted organosilanes is also useful in organic synthesis [121]. For example, the anodic oxidation of α-silyl carbamates gives α-

Table 5 Oxidation Potentials of Sila-Functional α-Heteroatom-Substituted Organosilicon Compounds [116]

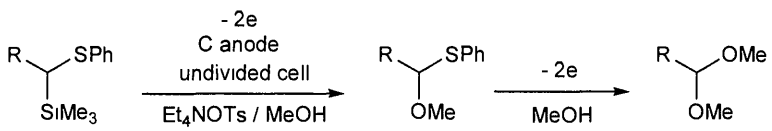
Compound	E_d (V Ag/AgCl)	Compound	E_d (V Ag/AgCl)
MenthylO SiMe3	1.65	PhS SiMe3	1.17
MenthylO SiMe2H	1.73	PhS SiMe2H	1.17
MenthylO SiMe2F	1.81	PhS SiMe2F	1.27

Note. E_d, Decomposition potentials determined by rotating-disk-electrode voltammetry using a glassy carbon anode in $LiClO_4/CH_3CN$.

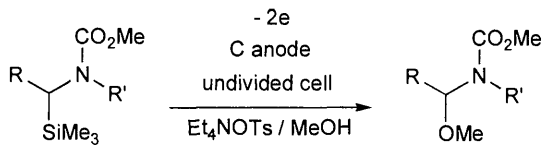
methoxycarbamates regioselectively [Eq. (30)]. The decrease of the oxidation potential is also advantageous. This chemistry was successfully applied for the regioselective functionalization of β-lactams [125,126].



(28)

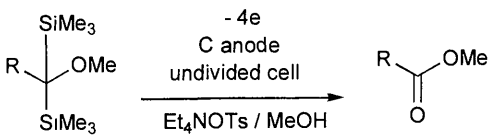


(29)



(30)

The anodic oxidation in methanol of sulifides and esters having two silyl groups leads to the formation of the corresponding methyl esters [Eq. (31)]. Since (phenylthio)-bis(trimethylsilyl)methane and methoxybis(trimethylsilyl)methane can be easily deprotonated and alkylated, these compounds serve as effective synthons of the anion of the methoxycarbonyl group [118,119,122].



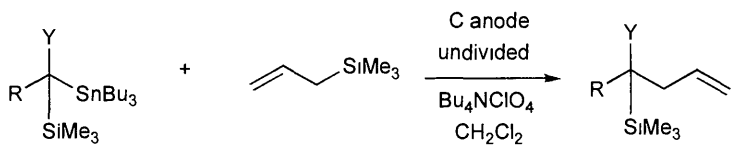
(31)

The activation by σ–n interaction is also effective for other organometallics. For example, the oxidation potentials of α-heteroatom-substituted tetraorganogermanes are less positive than those of the corresponding organosilicon compounds [127]. It is interesting that the anodic oxidation of ethers having a silyl group and a germyl group on the same α-carbon results in a selective cleavage of the C–Ge bond. In the cation radical intermediate, the C–Ge bond seems to be more susceptible toward cleavage than the C–Si bond.

The C–Sn σ orbital also interacts with a neighboring nonbonding p orbital of heteroatoms, and this interaction decreases the oxidation potential significantly [128,129]. It should be noted that the oxidation potentials of α-heteroatom-substituted tetraorganostannanes are less positive than those of carbon nucleophiles such as allylsilanes and enol sily ethers. Consequently, such carbon nucleophiles can be used for the electrochemical oxidation of α-heteroatom-substituted tetraorganostannanes to achieve the carbon–carbon bond formation. In fact, various intermolecular carbon–carbon bond formation reactions have been developed using α-heteroatom-substituted tetraorganostannanes [130–132].

The anodic oxidation of heteroatom compounds having a silyl group and a stannyl group on the same α-carbon has been examined [133]. The anodic oxidation in the presence of the allylsilane led to the selective cleavage of the C–Sn bond and the introduction of the allyl group on the carbon [Eq, (32)]. Probably the C–Sn σ orbital interacts more

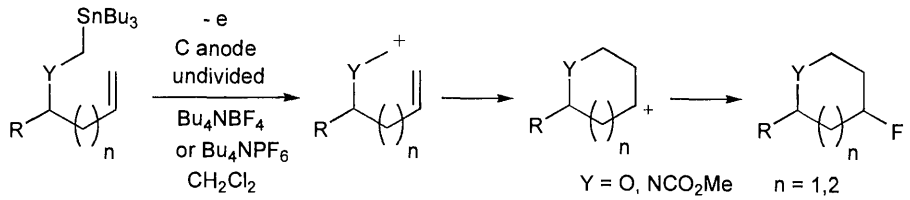
effectively with the p orbital of the heteroatom than the C–Si σ orbital in the radical cation intermediate.



(32)

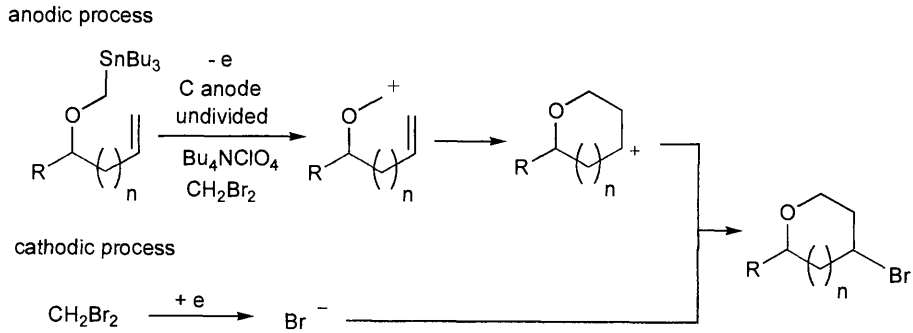
Y = R'O, R'S

This type of reaction is also effective for the intramolecular carbon–carbon bond formation. The electrochemical oxidation of α-heteroatom-substituted tetraorganostannanes having a carbon–carbon double bond in an appropriate position gives rise to effective cyclization [Eq. (33)]. The fluoride ion derived from the supporting electrolyte (Bu_4NBF_4 or Bu_4NBF_6) is introduced to the cyclized carbocation intermediate [134]. The reaction is generally applicable to the formation of six- and seven-membered ring and provides an efficient route to fluorine-containing compounds via the carbon–carbon bond formation.



(33)

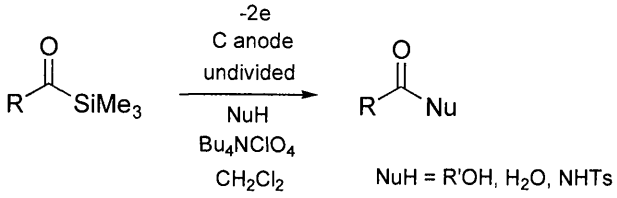
The bromide ion can also be introduced using cathodically generated Br^- as a nucleophile. The use of Br^- as the supporting electrolyte results in the selective oxidation of Br^- without affecting the substrate. Thus, the anodic oxidation using Bu_4NClO_4 as a supporting electrolyte in CH_2Br_2 leads to the formation of the cyclized bromides [135]. Since this reaction does not proceed in a divided cell, the cathodic reduction seems to play an important role. A mechanism has been suggested involving the reduction of CH_2Br_2 to generate Br^-, which reacts with the anodically generated cyclized cation [Eq. (34)].



(34)

The activation by σ–n interacation is also applicable for the acyl metal compounds such as acylsilanes. The oxidation potentials of acylsilanes are less positive than those of aldehydes and ketones because the nonbonding p orbital of the carbonyl oxygen atom

interacts effectively with the C–Si σ orbital [136,137]. This effect seems to be small in the case of aromatic acylsilanes [138]. The anodic oxidation of acylsilanes results in cleavage of the C–Si bond. Various nucleophiles including water, alchols, and tosyl amides are introduced to the carbonyl carbon [Eq. (35)] [136,137].

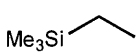
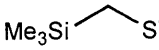
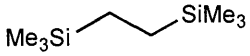
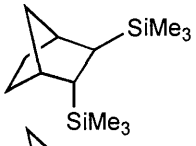
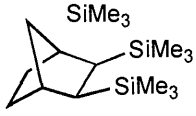
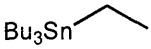
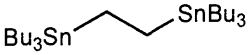
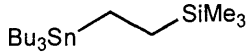


(35)

The acylsilane toxylhydrazones exhibit slightly less positive oxidation potentials than the corresponding tosylhydrazones of aldehydes [137]. The preparative anodic oxidation of acylsilane tosylhydrazones in a divided cell gave the corresponding nitriles. This reaction seems to be promoted by the electrogenerated acid.

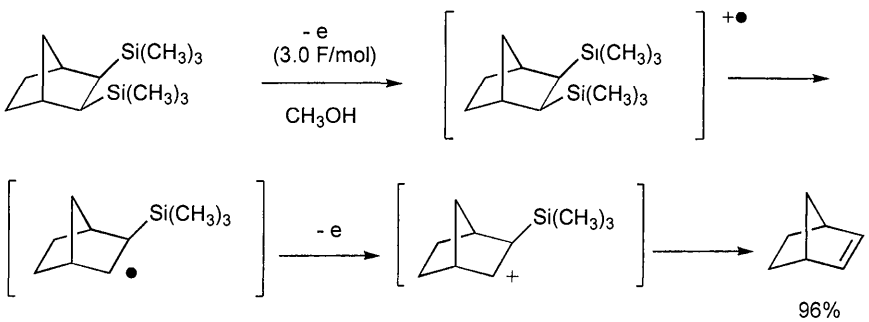
e. Activation by σ–σ Interaction The tetraorganometals are also activated toward electron transfer by the interaction of a carbon–metal σ orbital with a neighboring carbon–metal σ orbital. For example, the oxidation potential of 1,2-bis(trimethylsilyl) ethane is much less positive than those of trimethylsilylethane, 1,1-bis(trimethyl) methane, and 1,3-bis(trimethylsilyl)propane (Table 6) [9,139]. The interaction between two neighboring C–Si σ orbitals is responsible for this phenomenon. The geometric requirement of the interaction is important. The oxidation potential of *cis(exo,exo)*-1,2-bis(trimethylsilyl)norbornane is less positive than that of the *trans* isomer, because in the former case two C–Si bonds are in the same plane whereas in the latter case they are in almost perpendicular orientation. The preparative electrochemical oxidation of

Table 6 Oxidation Potentials of 1,2-Disilyl- and 1,2-Distannyl-Substituted Ethanes and Related Compounds [9,139]

Compound	E_d (V vs. Ag/AgCl)	Compound	E_d (V vs. Ag/AgCl)
	2.19		>2.5
	2.20		
	1.74		1.65
	2.02		1.41
	1.45		0.66
	1.22		

Note. E_d, Decomposition potentials determined with rotating-disk-electrode voltammetry in $LiClO_4/CH_3CN$ using a glassy carbon working electrode.

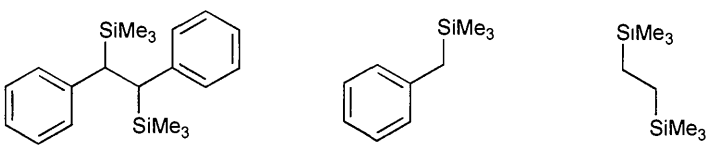
cis(exo,exo)-1,2-bis(trimethylsilyl)norbornane resulted in the cleavage of two C–Si bonds to form norbornene [Eq. (36)].



(36)

The σ–σ interaction is also effective for organotin compounds (Table 6) [9,139]. The oxidation potential of 1,2-bis(tributylstannyl)ethane is much less positive than that of tributylstannylethane, indicating a significant interaction between two neighboring C–Sn σ orbitals. The interaction between the C–Si σ orbital and the C–Sn σ orbital is, however, less effective, as demonstrated by 1-trimethylsilyl-2-tributylstannylethane. This is probably because the energy match between the two orbitals is not good.

It is interesting that the σ–σ interaction system further interacts with a neighboring π system [140,141]. For example, the oxidation potential of 1,2-diphenyl-1,2-bis(trimethylsilyl)ethane is less positive than those of benzyltrimethylsilane and 1,2-bis(trimethylsilyl)ethane. Such interactions seem to provide an important concept for the development of new electronic systems.



meso· Ed = 1.23 V

dl· Ed = 1.32 V

Ed = 1.39 V

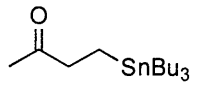
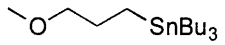
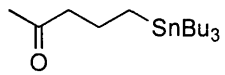
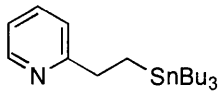
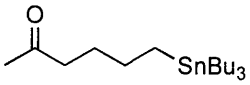
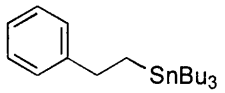
Ed = 1.74 V

f. Activation by Dynamic Coordination. As a method for the activation of tetraorganometals toward electron transfer, dynamic coordination has recently received significant research interest because it does not utilize orbital interactions. The utility of this concept is demonstrated by the following example: The oxidation potential of (3-oxobutyl)tributylstannane is less positive than that of tetrabutylstannane (Table 7) [142].

Since spectroscopic studies did not indicate the coordination of the carbonyl group in the neutral molecule, the electron transfer must be facilitated by the coordination in the radical cation intermediate. In fact, such dynamic coordination is suggested by ab initio molecular orbital calculations. It is particularly interesting that the effect of the carbonyl group depends on its position. The dynamic coordination to form a five-membered ring seems to be the most effective. The coordination to form a six- and seven-membered ring is less effective. The ether group, the pyridyl group, and the phenyl group are also effective as a coordinating group. The effect of the pyridyl group is especially remarkable.

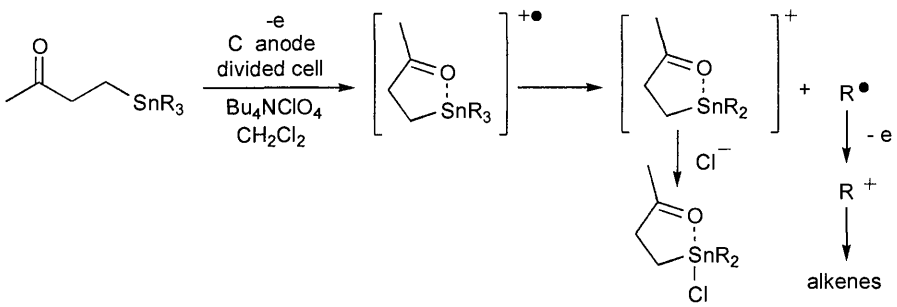
The preparative electrochemical oxidation followed by treatment with aqueous NaCl results in cleavage of the Sn–C bond and the introduction of Cl on Sn to give the five-

Table 7 Oxidation Potentials of Heteroatom-Substituted Tetraorganostannanes [142]

Compound	E_d (V vs. Ag/AgCl)	Compound	E_d (V vs. Ag/AgCl)
	1.41		1.42
	1.55		1.14
	1.61		1.50
Bu_4Sn	1.67		

Note. E_d, Decomposition potentials determined by rotating-disk-electrode voltammetry in Bu_4NClO_4/CH_2Cl_2 using a glassy carbon electrode.

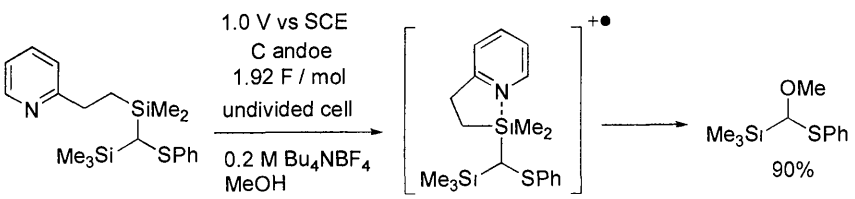
coordinated organotin compound [Eq. (37)]. In the radical cation intermediate, the C–Sn bond is cleaved to produce a tin cation stabilized by the coordination and the alkyl radical. The tin cation is trapped by Cl^- upon workup to give tin chloride. The alkyl radical is further oxidized to give the cation, which undergoes an elimination reaction via isomerization to yield a regioisomeric mixture of alkenes.



(37)

The dynamic coordination is also effective for the activation of α-heteroatom-substituted tetraorganosilanes [143]. The oxidation potentials of the 2-pyridylethyl (2-Pye)-substituted compounds are less positive than those of the corresponding parent compounds. The decrease of the oxidation potential can be explained in terms of the coordination of the pyridyl group to silicon in the cation radical intermediate (Table 8).

The dynamic coordination also facilitates selective bond cleavage. In fact, the preparative electrochemical oxidation of a compound having both a (2-Pye)Me_2Si group and an Me_3Si group resulted in selective cleavage of the C–(2-Pye)Me_2Si bond [Eq. (38)].



(38)

Table 8 Oxidation Potentials of the Heteroatom Compounds Having 2-Pyridylethyltrimethylsilyl Group [143]

Compound	E_d (V vs. SCE)	Compound	E_d (V vs. SCE)
2-PyeMe$_2$SiCH$_2$OMe	1.36	2-PyeMe$_2$SiCHOMe SiMe$_3$	1.19
Me$_3$SiCH$_2$OMe	1.58	Me$_3$SiCHOMe SiMe$_3$	1.25
2-PyeMe$_2$SiCH$_2$SPh	0.93	2-PyeMe$_2$SiCHSPh SiMe$_3$	0.85
Me$_3$SiCH$_2$SPh	1.12	Me$_3$SiCHSPh SiMe$_3$	1.05

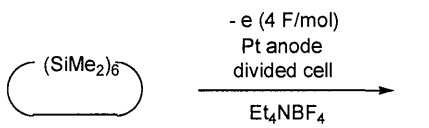
Note. E_d, Decomposition potentials determined with rotating-disk-electrode voltammetry using a glassy carbon anode in $LiClO_4/CH_3CN$.

2. Electrochemical Oxidation of Dimetals (R_3M–MR_3)

The group 14 organometallic compounds having metal–metal bonds are rather easily oxidized in comparison with simple organometallic compounds. This can be understood in terms of the high-energy metal–metal σ orbital [144].

The oxidation potentials of compounds having Si–Si bonds, the disilanes and polysilanes, are interesting (Table 9). The oxidation potentials decrease with increasing chain length [145]. Decrease of the HOMO level with chain length seems to be responsible for this phenomena. The oxidation potentials of polysilanes also depend on the nature of the organic group on silicon [146].

The preparative electrochemical oxidation of hexamethyldisilane resulted in cleavage of the Si–Si bond, although the product was not fully characterized [145]. The anodic oxidation of cyclic polysilanes using Et_4NBF_4 as supporting electrolyte gave rise to ring opening to form α,ω-difluoroilsanes [Eq. (39)] [147,148].



(39)

n	1	2	3	4	5	6
% yield	5 5	27	12	49.5	1.5	0.5

Table 9 Oxidation Potentials of Permethylpolysilanes [145]

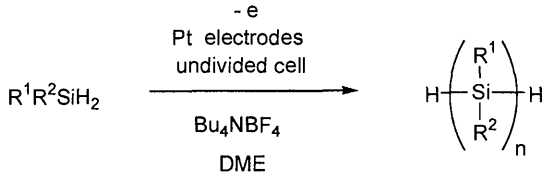
Polysilane	Oxidation Potential (V vs. SCE)
Me(SiMe$_2$)$_2$Me	1.88
Me(SiMe$_2$)$_3$Me	1.52
Me(SiMe$_2$)$_4$Me	1.33
Me(SiMe$_2$)$_5$Me	1.18
Me(SiMe$_2$)$_6$Me	1.08

Note. Determined by AC polarography.

The oxidation potentials of other group 14 dimetals are shown in Table 10 [149]. The oxidation potentials decreased in the order: Si–Si > Si–Ge > Ge–Ge > Si–Sn > Ge–Sn > Sn–Sn, probably reflecting the relative energy level of the metal–metal σ orbital.

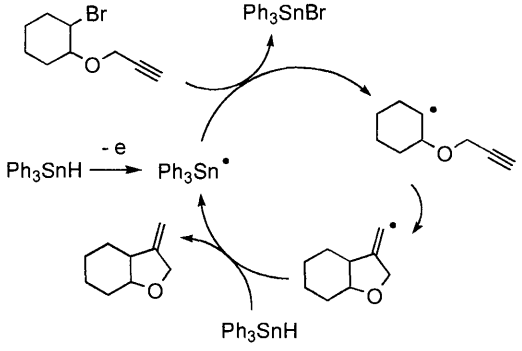
3. Electrochemical Oxidation of Metal Hydrides (R_3MH)

The metal hybrides are susceptible to oxidation in the absence of activation. For example, the electrochemical oxidation of $PhMe_2SiH$ in the presence of CuCl leads to the formation of $PhMe_2SiCl$ [150]. The use of R_2SiH_2 in the absence of CuCl results in the formation of oligosilanes as shown in Eq. (40) [151,152].



(40)

The anodic oxidation of tin hydrides has also been studied. The anodic oxidation of Ph_3SnH leads to the formation of the corresponding tin radical (+0.80 V vs. SCE) [153,154]. The tin radical dimerizes to form $Ph_3SnSnPh_3$. The tin radical can also be utilized for the initiation of a radical chain reaction promoted by tin hydride as demonstrated by Eq. (41). At more positive potential potential (+1.15 V), Ph_3SnH is reported to be oxidized to tin cation.



(41)

Table 10 Oxidation Potentials of Group 14 Dimetals [149]

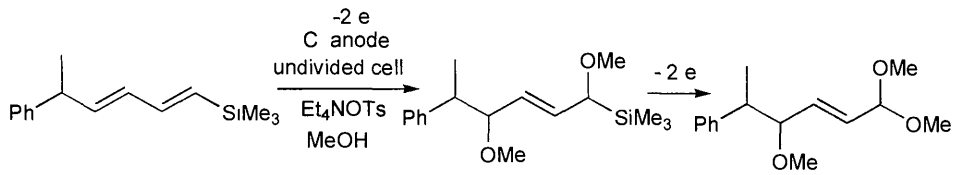
Dimetal	E_p (V vs. Ag/AgCl)	Dimetal	E_p (V vs. Ag/AgCl)
$Me_3SiSiMe_3$	1.76	$Me_3SiSnMe_3$	1.60
$Me_3SiGeMe_3$	1.76	$Me_3GeSnMe_3$	1.44
$Me_3GeGeMe_3$	1.70	$Me_3SnSnMe_3$	1.28

Note. E_p, Peak potentials determined by cyclic voltammetry in Et_4NClO_4/CH_3CN with a glassy carbon anode.

4. Electrochemical Oxidation of Other Types of Group 14 Organometallic Compounds

This section concerns cases where the initial electrochemical reaction does occur at a functional group other than the organometallic part in the substrate and the subsequent chemical or electrochemical process takes place at the organometallic part. In other words, the organometallic part plays a major role in follow-up processes.

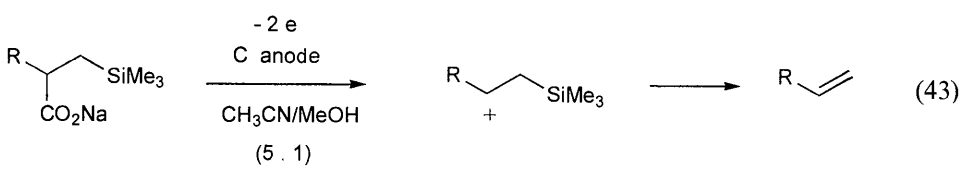
The first example of this category is the anodic oxidation of 1-trimethylsilyl-1,3-dienes [155]. The initial oxidation of 1,3-diene part in methanol generates the 1,4-dimethoxylated intermediate, just like simple 1,3-dienes [Eq. (42)]. The electronic effect of an α-silyl group on the π-system is not as large as far as the oxidation is concerned, although the α-silyl group slightly lowers the LUMO of the π-system (see Sec. IV). The 1,4-dimethoxylated intermediate can also been seen as an allylsilane, and therefore undergoes electrochemical oxidation in a fashion similar to simple allylsilanes. The C–Si bond is cleaved and a methoxy group is introduced on the carbon. In this case, the methoxy group is introduced selectively at one of the allyl terminals bearing the methoxy group that is introduced by the first oxidation. This selectivity is explained in terms of the cation-stabilizing effect of the methoxy group. Consequently, the overall reaction leads to the formation of 1,1,4-trimethoxyl-2-butene derivatives, and this reaction provides a useful transformation in organic synthesis.



(42)

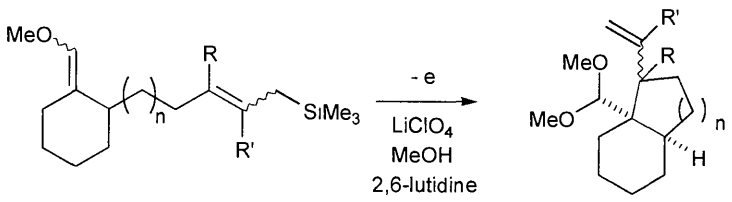
Another example of the anodic oxidation of π-systems having a silyl group at the α-position is the electrochemical oxidation of 2,5-bis(trimethylsilyl)thiophene, resulting in the elimination of the trimethylsilyl group to produce polythiophene. Polythiophenes obtained by this method have high conductivity [156].

The anodic oxidation of β-silyl carboxylic acids is fascinating. The reaction results in the elimination of the carboxylate group and the silyl group to form olefinic products [Eq. (43)] [157,158]. A plausible mechanism involves the initial electrochemical oxidation to eliminate CO_2, followed by facile β-elimination of the silyl group from the generated carbocation to form the carbon–carbon double bond.



(43)

Facile β-elimination of the silyl group is also utilized in the intramolecular anodic olefin coupling reactions [159–161]. For example, the intramolecular anodic coupling of enol ether with allylsilane group has been reported [Eq. (44)]. This reaction seems to be quite useful for the construction of functionalized cyclic compounds because it leads to the regioselective formation of olefinic product via a facile β-silyl elimination.



(44)

IV. ELECTROCHEMICAL REDUCTION OF ORGANOELEMENTAL COMPOUNDS

In general, it is rather difficult to reduce main-group organometallic compounds, especially group 1 and 2 organometallics. Group 14 metal halides, however, are electrochemically reducible under suitable conditions, like organic halides. Another interesting aspect of electrochemical reduction of organoelemental compounds is that group 14 metals such as silicon behave as electron-withdrawing groups to neighboring π-systems by virtue of so called d_π–p_π integration. Such systems are susceptible toward electrochemical reduction, and metals play roles of both activating and controlling groups. Therefore, this section focuses on the electrochemical reduction of group 14 organometallic compounds.

A. Electrochemical Reduction of Group 14 Organometal Halides

1. Reduction Potentials and General Reaction Patterns of Group 14 Organometal Halides

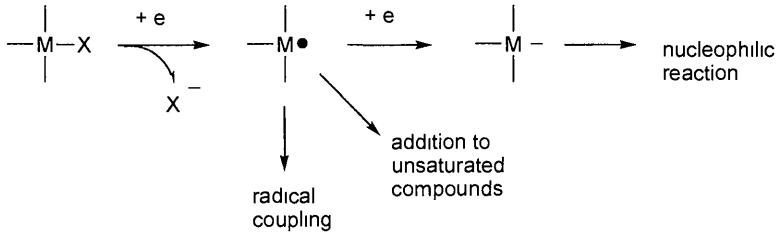
It is rather difficult to determine the reduction potentials of halosilanes because they are very easily hydrolyzed. Hydrogen halides produced by the hydrolysis exhibit a less negative reduction potential, and this may cause some difficulty in measurement [163,163]. Careful measurements in anhydrous solvents, however, revealed that reduction potentials of halosilanes are generally more negative than the corresponding organic halides (Table 11) [164,165]. The reduction potentials of other group 14 metal halides have also been determined [164,165]. As to the nature of the metal, it is notable that the reduction becomes more facile in the order of Si < Ge < Sn < Pb [166]. It should also be kept in mind that the reduction potential becomes less negative as one progresses along the series, F, Cl, and Br.

The general reaction pattern for the reduction of group 14 organometal halides is shown in Eq. (45) [166]. The one-electron reduction of metal halides leads to the formation of the metal centered radicals. The metal radicals may undergo radical coupling to produce metal–metal bonds or addition to unsaturated compounds. The metal radical may also be reduced electrochemically under some conditions to give the metal anions, which react with electrophiles.

Table 11 Polarographic Reduction Potentials of Halosilanes and Halogermanes [165]

Compound	$E_{1/2}$ (V)	Compound	$E_{1/2}$ (V)
Ph_3SiF	−2.15	Ph_3GeF	−1.85
Ph_3SiCl	−1.95	Ph_3GeCl	−1.75
Ph_3SiBr	−1.93	Ph_3GeBr	−1.60

Note. $E_{1/2}$ values were measured vs. Bu_3NI sat. AgI/Ag reference electrode.

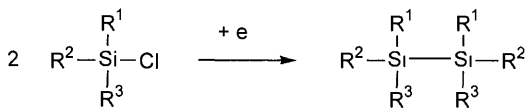


(45)

2. Reductive Formation of Metal–Metal Bonds

The electrochemical reduction of group 14 metal halides to form metal–metal bonds is rather common. This type of reaction proceeds either via radical coupling or via nucleophile attack of metal anions on metal halides, depending on the reaction conditions such as cathode potentials.

The electrochemical reduction of chlorosilanes has received significant research interest because this reaction provides an efficient route to disilanes and polysilanes having Si–Si bonds [Eq. (46) [162, 166–176]. The electrode material and the supporting electrolyte seem to be important factors for the effective homo coupling. The sacrificial metal anodes have been found to be quite effective for the reductive coupling of chlorosilanes, and extensive work has been devoted to this field. In fact, various sacrificial anodes such as Hg [167,171], Mg [172], Cu [173,174], Ag [171], and Al [174–176] were found to be effective for the reductive coupling of chlorosilanes to form disilanes. The application of this method to dichlorosilanes gives rise to the formation of polysilanes [Eq. (47)].



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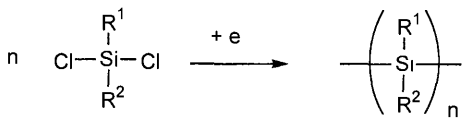
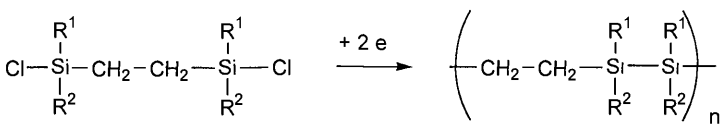


(47)

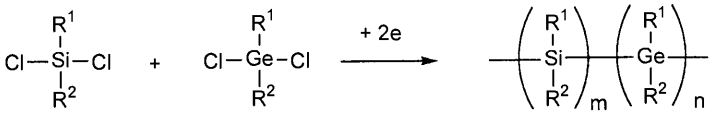
Copolymerization of two different dichlorosilanes can also be achieved by the reduction using a sacrificial anode [177,178]. It is interesting that copolymerization of sila-functional dichlorosilanes with simple dichlorosilanes took place smoothly to provide an elegant route to functionalized polysilanes [178]. As to the synthesis of sila-functional polysilanes, the electrochemical reduction of perfluoroalkyl-substituted trichlorosilane to give perfluoroalkyl-substituted polysilane is interesting [179].

The sequence-ordered polysilanes was prepared by the electrochemical reduction of dichlorooligosilanes using an Mg sacrificial anode [180]. The reductive coupling of monomers having two chlorosilyl groups leads to the formation of polymers containing Si–Si bonds as shown in the following scheme [181,182]:



(48)

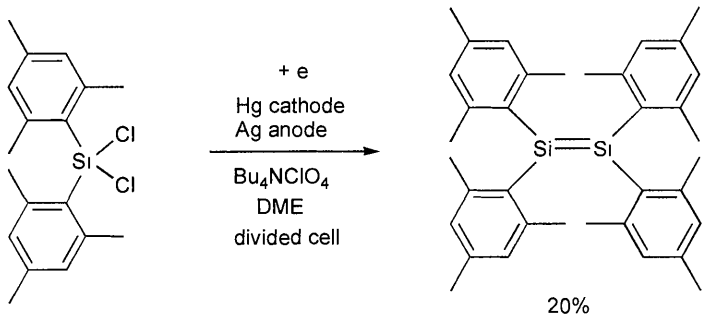
A magnesium sacrificial anode is also effective for the synthesis of Si–Ge and Ge–Ge bonds. This method is quite successful for the preparation of polygermanes and germane–silane copolymers [Eq. (49)] [183]. Polygermanes were also prepared by conventional electrochemical reduction of dihalogermanes using a Pt cathode and an Ag anode [184].



(49)

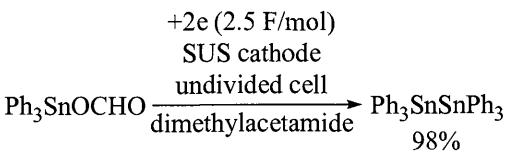
The use of sacrificial metal anodes inevitably leads to the formation of metal halides as by-products. This problem can be solved by the use of a silicon carbide electrode. The homo coupling takes place smoothly in an undivided cell without formation of metal halides [185]. A hydrogen electrode is also effective for this purpose [185].

Under suitable conditions, the electrochemical reduction of R_2SiCl_2 resulted in the formation of an Si–Si double bond rather than polymerization. The cathodic reduction of dichlorodimesitylsilane with an Hg pool cathode and a Pt anode in dimethoxyethane (DME) gave tetramesityldisilene [Eq. (50)] [186]. The bulky substituents on the silicon atom seems to be responsible for the retardation of the polymerization and the protection of the highly reactive Si–Si double bond.



(50)

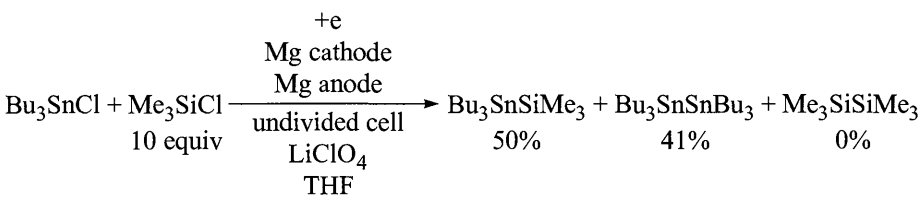
The cathodic reduction is also useful for the formation of Sn–Sn bonds [166]. For example, Ph_3SnCl exhibits two major reduction peak (Hg cathode, −1.40 V and −2.60 V vs.) in cyclic voltammetry [187,188]. At lower potential, Ph_3SnCl undergoes a one-electron reduction to give the tin radical that dimerizes to give $Ph_3SnSnPh_3$. At a more negative potential a two-electron reduction process takes place to give the tin anion that reacts with Ph_3SnCl to produce $Ph_3SnSnPh_3$. Some modifications have been reported for the electrochemical dimerization of R_3SnCl [189,190]. In a similar fashion, tin formates ($R_3SnOCHO$) also undergoes cathodic reduction to give the corresponding homo coupling products [Eq. (51)] [191].



(51)

The electrochemical reduction of a mixture of a R_3SnCl and R'_3SiCl using Mg electrodes under ultrasonic irradiation was reported to give the corresponding cross-coupling product together with the distannane [Eq. (52)] [192]. The disilane was not formed. The fact that the reduction potential of R_3SnCl is less negative than that of

R'_3SiCl implies that the reaction proceeds by the initial reduction of the R_3SnCl. The product distribution is also consistent with this mechanism.

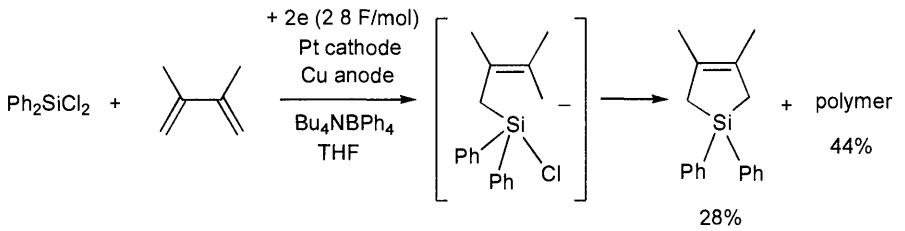


(52)

3. Reductive Formation of Metal–Carbon Bonds

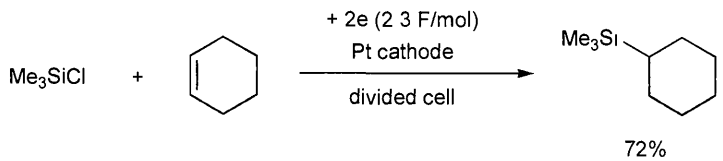
The reduction of group 14 halides in the presence of organic compounds of more negative reduction potentials leads to the formation of the metal–carbon bond. This type of reaction also provides a method for the synthesis of organometallic compounds, although there are only a few examples. A mechanism involving the initial formation of the metal anion intermediate followed by the nucleophilic reaction with organic substrates is proposed. Another possibility to be considered is the formation of a metal-centered radical intermediate, which reacts with organic substrates.

The electrochemical reduction of R_2SiCl_2 in the presence of 2,3-dimethylbutadiene proceeds smoothly to give the sila-cyclopentene derivatives [Eq. (53)] [193]. Probably the initial reduction of R_2SiCl_2 produces an silyl anion, which adds to the 1,3-diene. The intramolecular displacement reaction of the resulting allylic carbanion with the chlorosilane moiety gives the cyclized product.



(53)

The following reaction also provides an example of the reactions of cathodically generated silyl species with organic compounds. The electrochemical reduction of R_3SiCl in the presence of unsaturated compounds such as phenylacetylene, styrene, and cyclohexene gives the corresponding formal hydrosilylation products [Eq. (54)] [194,195]. In this case, a mechanism involving a silyl radical seems to be more plausible because the addition of a silyl anion to cyclohexene is quite unlikely. The hydrogen that was added to the other formal acetylenic or olefinic carbon seems to come from the solvent via radical abstraction reaction. The disilane is also effective as a source of the silyl group.



(54)

The tin anion generated by the cathodic reduction can also be utilized for carbon–metal bond formation. The electrochemical reduction of mixtures of R_3SnCl in the presence of organic chlorides gives the corresponding coupling products [Eq. (55)]. Since the reduction potentials of R_3SnCl are less negative than those of organic chlorides, the reaction seems to proceed by the initial reduction of R_3SnCl to generate the nucleophilic stannyl anion, which attacks the organic chlorides to give the final product [192].

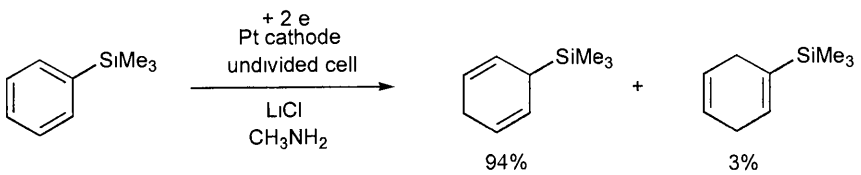
$$\underset{5\text{ equiv}}{Bu_3SnCl + BuCl} \xrightarrow[\text{undivided cell}]{\substack{+2e \\ \text{Mg cathode} \\ \text{Mg anode} \\ LiClO_4/THF}} \underset{76\%}{Bu_3Sn{-}Bu} + \underset{20\%}{Bu_3SnSnBu_3} + \underset{\text{trace}}{Bu{-}Bu} \qquad (55)$$

B. Electrochemical Reduction of Group 14 Organometallic Compounds Containing Reducible π- and σ-Systems

It is known that group 14 metals facilitate the electron transfer from the neighboring π-system by virtue of so called d_π–p_π interaction [196]. The LUMO level is decreased by such interaction, which in turn favors the reduction of the system. The silyl group also stabilizes the anion radical intermediate formed by a one-electron reduction [197,198]. These effects can also be explained in terms of the orbital interaction with a low-lying σ^* orbital of the sily group instead of the vacant d orbital.

Arylsilanes serve as a typical example of this system. The reduction potentials of arylsilanes are slightly less negative than those of the parent aromatic hydrocarbons [199–203]. This seems to be attributed to the d_π–p_π interaction between the aromatic ring and the silicon atom. The electrochemical behavior of silyl-substituted cyclooctatetraene is interesting [204]. The second reduction potential becomes less negative by the silyl substitution. The stabilization of the dianion (aromatic 10 π-system) by d_π–p_π interaction seems to be responsible for this phenomenon.

Preparative electrochemical reduction of arylsilanes in methylamine gives Birch-type products [Eq. (56)] [198]. The hydrogen atom is introduced preferentially on the carbon adjacent to the silyl group, and this regioselectivity is explained in terms of the stabilization of the radical anion by the neighboring silyl group.



(56)

Reduction of α-halo organometallic compounds (R_3MCH_2X) also seems to be assisted by a similar orbital interaction. The negative charge formed by the reduction of the carbon–halogen bond should be stabilized by the interaction with group 14 metals. As a matter of fact, the reduction potentials of halomethylsilanes are less negative than those of simple alkyl halides [205,206]. The electrochemical reduction of halomethylstannanes has also been reported [207].

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21
Reductive Coupling

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References

I. INTRODUCTION

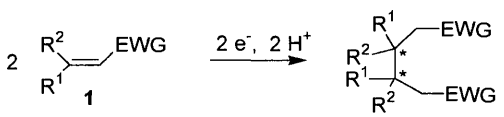
Electroreductive coupling reactions constitute an important class of carbon–carbon bond-forming reactions involving a multitude of compound types as starting materials. Not all types of coupling reactions are covered in this chapter, and in a number of cases more details can be found in other chapters covering the electrochemistry of specific classes of compounds. The focus in this chapter is on reductive couplings involving alkenes and other carbon–carbon multiple bonds as a substrate, either in dimerization reactions or in cross-coupling reactions with other compounds. In the last section, carbon–carbon bond forming reactions initiated by reduction of aromatic systems are discussed.

It is beyond the scope of this chapter to cover the industrial applications of electroreductive coupling reactions, and the reader is referred to Chapter 31 and references found in that chapter. However, the industrial importance of electrohydrodimerizations has initiated an impressive amount of work on this particular type of reductive coupling since the early finding by M. M. Baizer that the use of tetraalkylammonium *p*-toluensulfonates as supporting electrolyte greatly improved the yield of adiponitrile in the electrochemical reduction of acrylonitrile in partially aqueous media [1]. Further reports from M. M. Baizer and coworkers at Monsanto in the 1960s demonstrated the possibility of electroreductive coupling of a great variety of α,β-unsaturated carboxylic acid derivatives (nitriles, esters, amides) [2–4]. Much recent preparative work has focused on improvements in yields, on regio- and stereoselectivity of reductive coupling reactions—in a number of cases by application of transition-metal catalysts and templating cations—and on intramolecular reductive couplings.

Kinetic and mechanistic studies on reductive couplings have accumulated in the last decades, and particularly electrohydrodimerizations and dimerization of aromatic systems have been much studied. The level of the mechanistic discussions in this chapter reflects the somewhat uneven level of knowledge accumulated for the different types of coupling reactions. In some cases where little mechanistic work has been done, the mechanistic rationalizations presented are based on evaluations made by the present authors. No attempts have been made to bring reduction potentials on a common scale since differences in solvent, supporting electrolytes, added acids, electrode material, etc. may lead to considerable differences in the measured potentials. This is particularly so when it comes to values of reduction peak potentials measured under conditions where the electrogenerated intermediate is consumed in a fast follow-up reaction. In some cases, however, the relative values may be of interest in a mechanistic discussion. Unless stated otherwise the cited potentials have been measured versus SCE.

II. HOMOCOUPLING BY ELECTROHYDRODIMERIZATION (EHD)

This section concerns the classical hydrodimerization of alkenes activated by electron-withdrawing substituents, as in Eq. (1). The literature in this area is extensive and this chapter cannot be exhaustive. The focus will be on typical reactions and general conclusions, which may serve as guidelines for further work. Special emphasis will be put on the effect of reaction conditions on the mechanisms, product selectivity, and stereochemistry. Section II.A deals with the monoactivated alkenes, that is, structures of the type **1** where R^1 and R^2 are H, alkyl, or aryl; Sec. II.B deals with intramolecular coupling reactions where two identically activated alkenes are linked together within the same molecule. The reactions of alkenes activated by two electron-withdrawing groups either in α, α- or in α,β-positions, are treated in Sec. II.C.

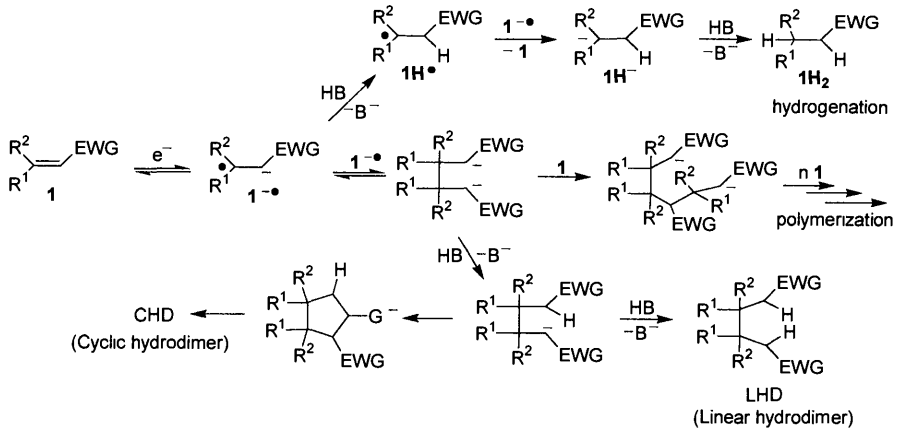


(1)

A. Intermolecular Hydrodimerizations

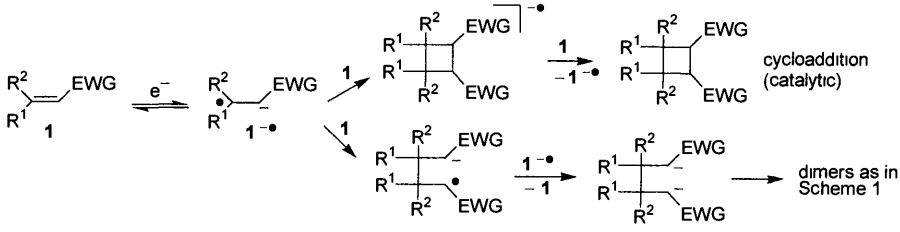
1. General Mechanistic Considerations

The reactions of monoactivated alkenes upon one-electron reduction may in most cases be rationalized within the general mechanism outlined in Scheme 1.



Scheme 1

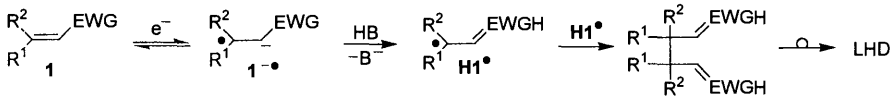
Two major side reactions compete with the coupling reaction: protonation of the radical anion followed by further reduction and protonation leading to the saturated dihydro product, and polymerization induced by the basic dianion formed by coupling of two radical anions. Other, less typical reaction pathways include reaction between a radical anion and a molecule of substrate, Scheme 2, dimerization of two radicals formed by protonation of the initial radical anion, Scheme 3, or, infrequently, cleavage of the radical anion followed by coupling. However, for radical anions derived from monoactivated alkenes, the pathway in Scheme 2 has only been unequivocally established as a major pathway in a few cases in which the final zero-electron product is a cyclobutane, that is, a cycloaddition product.



Scheme 2

The pathway in Scheme 3 relates mainly to alkenes activated by keto or aldehyde groups, for reduction in hydroxylic solvents. Under these conditions, radical anions derived from carbonyl compounds are protonated at oxygen, and the resulting enolic radical, **H1**˙, is more difficult to reduce than the starting compound. Consequently, fast dimerization of the enol radicals may compete with further reduction. For other substrate types, especially in aprotic solvents containing added acids, proton transfer is to carbon

(Scheme 1), and the resulting radical, $\mathbf{1H}^{\cdot}$, is more easily reduced than the substrate, which leads to the dihydro product, $\mathbf{1H_2}$.



Scheme 3

The competing reactions in Scheme 1 are influenced by the nature of the substrate and the reaction conditions. In dry aprotic solvents, polymerization is common on a preparative scale, whereas on voltammetric time scales reversible dimerization or enhanced chemical stability of the radical anion may be observed. Addition of proton donors may prevent polymerization. However, hydrogenation of the double bond competes with dimerization if the proton donor is sufficiently acidic. The common hydrodimerization pathway (Scheme 1), leading to the linear hydrodimer (LHD), is not always followed. When the activating group is a carboxylic acid derivative, including cyano, or a carbonyl group, intramolecular addition leading to a cyclic hydrodimer (CHD) is often favored over the final protonation step.

The hydrodimers may be formed by more than one pathway (Schemes 1–3). The main distinctions, much discussed in the literature, are between: (1) coupling of two species in the same redox state (often referred) to as an RR or RRC mechanism), i.e., coupling between two species at the one-electron reduction level as in Schemes 1 and 3; (2) coupling between two species in different redox states, i.e., coupling between a substrate molecule and its counterpart reduced to the one-electron level (Scheme 2, referred to as an RS or RSC mechanism); and (3) between a substrate molecule and its counterpart reduced to the two-electron level (referred to as an ISC mechanism).

The ISC mechanism is not normally considered to be plausible. Both the RR and the RS mechanism may be further classified according to the sequence of microscopic steps (electron transfer, coupling, protonation and/or cyclization) and with reference to which of the steps is rate determining. For the RS mechanism, the second electron transfer may take place by a reaction in solution (as indicated in Scheme 2) or at the electrode if the coupling step is very fast.

2. Common Methods for Mechanistic Analysis

Distinction between different mechanistic pathways is not always straightforward (see Chapter 2). Even minor changes in the experimental conditions may lead to changes in the sequence of reaction steps and/or in the rate-determining step, and several examples can be found in the literature where different mechanistic conclusions have been drawn for the EHD reaction of a single substrate. Most electroanalytical methods have been applied to the study of EHD reactions. It is beyond the scope of this chapter to detail how different techniques are used and how the mechanistic and kinetic information is extracted from the experimental data. In general, however, techniques that operate on a time scale comparable to the half-life time of the electrogenerated intermediate can detect the intermediate and are well suited for determination of rate constants. These methods include cyclic voltammetry (CV), derivative cyclic voltammetry (DCV), double-potential-step chronoamperometry (DPSC), double-potential-step chronocoulometry (DPSCC), rotating ring-disk electrodes (RRDE), scanning electrochemical microscopy (SECM) and current-reversal chronopotentiometry. The same is possible for spectroelectrochemical methods

where the electrochemically formed intermediate is detected by a spectroscopic method (ESR, UV, IR, etc.). The theoretical data necessary for determination of rate constants, and to some extent to distinguish between different EHD mechanisms, have been published for RRDE [5], current-reversal chronopotentiometry [6], DPSC [7–9], DPSCC [10,11], and DCV [9]. Steady-state techniques where the time scale of the measurement is long compared to the half-life of the intermediate generated at the electrode (polarography, RDE and LSV) are primarily used to obtain mechanistic rather than kinetic information. Diagnostic criteria for different EHD mechanisms under steady-state conditions were established in the 1970s [12]. More detailed description of the application of the different methods can be found in Chapter 2.

3. Relationship Between Experiments on an Analytical and on a Preparative Scale

Commonly, EHD reactions have been studied in polar aprotic solvents such as DMF, NMP, DMSO or MeCN with controlled addition of water or other weak proton donors and in the presence of different types of cations. Experiments can be carried out in scrupulously dried solvents on an electroanalytical scale, but the stoichiometry of the overall reaction [Eq. (1)] shows that formation of stable products requires the presence of a proton source. Several preparative studies confirm that in the absence of water or metal cations the reduction process consumes less than 1 F, and unidentified polymeric products are formed instead of dimers (cf. Scheme 1). In contrast, use of protic solvents usually leads to large amounts of the hydrogenation product in a 2-F process and/or different product distributions.

The effect on the reaction mechanism of added proton donors, particularly water, has been much debated. The dimerization mechanism for a series of radical anions of α,β-unsaturated nitriles, esters, and ketones under weakly acidic conditions (DMF or MeCN containing varying amounts of water) was examined in an early study [13], leading to the conclusion that when the water content was small, the mechanism could in all cases be described by rate determining coupling of two radical anions. On an analytical scale it is a common observation that the dimerization process is accelerated upon addition of water, an effect that cannot be ascribed to initial protonation of the radical anion or to protonation of the dimer dianion. The effect has been variously described as solvation [14] or complexation [15] or hydrogen-bonding [16], in each case between the radical anion and one or more water molecules. The ensuing stabilization of the negative charge facilitates the dimerization step. Where dimerization is relatively slow, an effect of added water on the formal reduction potential, $E^{0'}$, has been observed [14] that is consistent with solvation/hydrogen-bonding interaction between water and the radical anion.

4. Stereochemistry

When $R^1 \neq R^2$ in **1**, two new stereocenters are formed in the dimerization process [Eq. (1)]. Recent studies have focused on the stereoselectivity in the coupling step, that is, the possibility of selective formation of the (±) or the *meso* form of the dimer and, more lately, on the enantioselectivity of the coupling step when chiral substrates are used. Stereoselectivity of the coupling step seems to be much higher, and in favor of the (±) isomer, when the reduction is carried out in aprotic solvents (containing residual or added water) as opposed to protic solvents. Templating of two radical anions by one or more water molecules has been suggested as an explanation of the high stereoselectivity in favor of the (±) isomer in the dimerization in DMF of alkyl cinnamate radical anions [16] (see Sec. II.A.7). Similar preference for the (±) isomer has been observed for other EHD

reactions in aprotic solvents [17–20], and an analogous templating effect can be invoked as explanation of the enhanced stereoselectivity in the presence of metal cations [21,22]. Similar selectivity is observed when SmI_2 in HMPA/THF [23,24] or alkali amalgams [25] are used as chemical reductants.

The stereochemistry of the coupling of π-radical anions (radical behavior) and of addition to alkenes or carbonyl functions (generally nucleophilic behavior) is often conveniently viewed as being under stereoelectronic control. In practice this means that coupling of delocalized radical anions is favored when orthogonal approach is unhindered. Thus, for dimerization of the alkyl cinnamate radical anions the templating involving hydrogen-bonding to the two ester groups favors (±) β,β'-coupling over the *meso* coupling, which would involve eclipsing of the two phenyl groups.

Stereoelectronic effects are also important for intramolecular cyclizations, which are discussed in Secs. II.B, III.B, and IV.B. In these cases, Baldwin's rules usually apply [26,27].

5. Slightly Activated Double Bonds

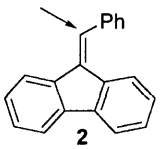
Hydrodimerization of slightly activated double bonds is exemplified by reduction of stilbene in DMF (Bu_4NI) [28], which gives a modest yield ($\leq 30\%$) of the hydrodimer, 1,2,3,4-tetraphenylbutane, together with the 2-F product, bibenzyl. Similarly, 9-benzylidene fluorene (**2**) and 2-phenylbutadiene give hydrodimers upon reduction in DMF/water ($Me_3BuNOTs$) [29], **2** giving 66% of the dimer, whereas the major product formed from 2-phenylbutadiene was the 2-F hydrogenation product.

The competition between hydrogenation and dimerization has been examined for α-arylstyrenes (**3**) [30]. Higher substrate concentrations gave smaller coulometric n-values and higher yields of the dimer (Table 1). Addition of an excess (30–100 times with respect to substrate) of D_2O gave rise to increasing values of n and enhanced yields of the hydrogenation product as a result of an enhancement of the rate of protonation of the radical anions [30]. From the data in Table 1 there appears to be a correlation between the value of E_p^{red} and the competition between dimerization and protonation; the more easily the substrate is reduced, the more favored is dimerization.

Table 1 Effect of Substrate Concentration on the Competition Between Dimerization and Hydrogenation in the Reduction of α-Arylstyrene (**3**)[a]

Ar	E_p^{red} (V)	n[b]	Yield of dimer[b]	n[c]	Yield of dimer[c]
2-Naphthyl	−2.30	1.37	66%	1.32	79%
2-Pyridinyl	−2.27	0.93	100%	1.01	100%
Phenyl	−2.52	1.97	0%	1.66	43%
2-Thiophenyl	−2.33	1.63	39%	1.51	48%
2-Furanyl	−2.48	1.77	29%	1.60	39%

[a] DMF, Et_4NBF_4, div. cell, Hg-cath., CPE: $E_w = E_p^{red} + 0.1$. Overall yield >95%. From Ref. 30.
[b] $C^* = 8$ mM.
[c] $C^* = 40$ mM.



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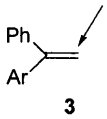

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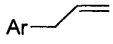

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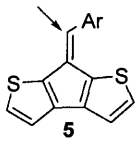

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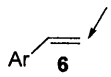


6

a: Ar = 2-pyridinyl
b: Ar = 4-pyridinyl
c: Ar = 3-pyridinyl

Allylbenzene and ring substituted derivatives (**4**) show no reduction waves before the background in DMF [31]. However, reduction at constant current gives an electrogenerated base (EGB), probably OH^-, which catalyzes isomerization to the conjugated alkenes, β-methylstyrenes, which are reducible at accessible potentials. Isomerization was complete after the passage of 0.5 F, and further reduction resulted in mixtures of the hydrodimer of the β-methylstyrene and the corresponding hydrogenation product (Table 2). The dimerization reaction showed a high degree of stereoselectivity, with the (±) isomer being the major isomer [31].

Compounds of the type **5** (4-ylidene-substituted cyclopentadithiophenes) form radical anions that in the presence of water dimerize following the RR mechanism (as determined by LSV) with $k_{dim} \approx 10^5\ M^{-1}s^{-1}$, yielding a stereoisomeric mixture of hydrodimers. In the absence of water the dimer dianions are relatively stable and may on a voltammetric time scale be reoxidized at a potential 0.7–0.8 V anodic relative to the reduction potential of **5** [32]. Interestingly, the polymers (linked through the thiophen rings) formed by oxidation of **5** may also undergo reductive coupling, thereby forming cross-linked polymer chains. Oxidative polymerization of the hydrodimers, formed by the reduction of **5** in the presence of water, results in a polymer with the same properties as the one obtained by reduction of a preformed polymer in the presence of water [32].

Reduction of 2-vinylpyridine (**6a**) in H_2O (Et_4NOTs) and of 4-vinylpyridine (**6b**) in DMF/H_2O ($MeEt_3NOTs$) gives good yields (69% and 82%, respectively) of the LHDs [33]. Later experiments in DMF have shown that electrolysis of **6** at a potential corresponding to the foot of the reduction wave gives good yields of the 0-F product *trans*-1,2-dipyridinylcyclobutane. This results from a radical anion-catalyzed cycloaddition reaction

Table 2 Effect of Substrate Structure on the Competition Between Dimerization and Hydrogenation in the Reduction of Ring-Substituted Allylbenzenes (**4**)[a]

Ar	Yield of dimer	(±) Isomer	Yield of hydrogenation product
Phenyl[b]	64%	84%	14%
2-Tolyl[b]	61%	87%	13%
3-Tolyl[c]	65%	88%	6%
4-Tolyl[b]	6%	86%	55%
4-*t*-Butylphenyl[b]	9%	90%	57%
2-Anisyl[d]	41%	87%	22%
4-Anisyl[e]	3%	[f]	57%
4-Cyanophenyl[b]	54%	[f]	[f]

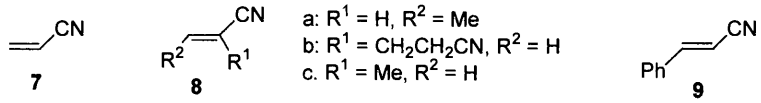
[a] DMF, Bu_4NClO_4, div. cell, Pt-cath., CCE. From Ref. 31.
[b] 2 F passed.
[c] 2.5 F.
[d] 4 F.
[e] 3 F.
[f] Not determined.

[34] (cf. Scheme 2), under conditions where a high ratio of substrate to radical anion is maintained. The change in product with the change in working potential indicates that the rate constant for reaction between radical anion and substrate is smaller but comparable to the rate constant for reaction between two radical anions. The mechanistic details of the catalyzed cycloaddition reaction are not known. The 0-F reaction of **6** is similar to the 0-F reaction of aryl vinyl sulfones (see Sec. II.A.10).

6. Nitriles

The industrially important hydrodimerization of acrylonitrile (**7**) to the LHD, adiponitrile, is carried out in water with high chemical yields despite the fact that aqueous conditions normally favor hydrogenation of the double bond. The process was developed on the basis of the finding [1] that when high concentrations of **7** (> 10%) was electrolyzed in aqueous solution containing large amounts of Et_4NOTs as supporting electrolyte, dimerization was favored over hydrogenation. Since then much effort has gone into the investigation of the effect of surfactants on the product distribution and the reaction mechanism for simple EHDs, especially that of acrylonitrile (**7**) [35–50]. Surfactants are molecules or ions containing a polar "head" and a nonpolar "tail" and that form organized structures at the interface of the electrode surface and the aqueous solution. This phenomenon is often described as (specific) adsorption of the surfactant at the electrode. The main effect of the surfactants seems to be the displacement of water molecules from the electrode surface. The adsorption of such organic additives to electrode surfaces is dependent on the electrode material, the potential, and the nature of other ions in the solution [38,43] and can be probed by differential capacity measurements. Simple monoactivated alkenes such as **7** are so difficult to reduce (< −1.8 V) that anionic, neutral, and some cationic surfactants are desorbed at the required working potential. However, cationic surfactants such as dodecyltrimethylammonium and methyltrioctylammonium ions are, like Et_4N^+, adsorbed at mercury, cadmium, and glassy carbon electrodes in the potential range where simple activated alkenes are reduced. With **7** present in solution the effect of surfactants has been observed as a splitting of the two-electron polarographic reduction wave into two one-electron waves when the concentration of **7** was higher than 0.1 *M* [38]. Electrolysis at the potential of the first wave (−1.78 V) was reported to give more than 98% yield of the LHD [38]. (The yield has been questioned [43] since it may have included hydrotrimers; nevertheless, there was little hydrogenation.) In addition to the displacement of water from the electrode surface, some surfactants have been suggested to promote the coadsorption of **7** [38,43,44].

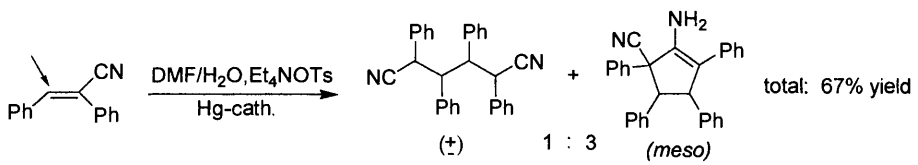
Preparative-scale reduction of **7** in aprotic solvents mainly gives oligomers/polymers. The radical anion reacts rapidly, and only few mechanistic studies have been reported. In DMF solution the mechanism was suggested to be RS on the basis of LSV measurements at low scan rates [43]. Scanning electrochemical microscopy (SECM) has also been used to study the EHD of **7** in DMF [51]. Low concentration (1–2 m*M*) of **7** in dry solvent was used in order to minimize polymerization and hydrogenation, respectively. The results obtained were in accord with an RR mechanism (although the RS mechanism was not ruled out). Assuming that the dimerization proceeds by rate determining coupling of two radical anions, a value of $k_{dim} = (6 \pm 3) \times 10^7\ M^{-1}\ s^{-1}$ was calculated. In liquid NH_3 ($T = -43°C$) reduction of **7** also leads to polymerization ($n = 0.05$) unless a proton donor such as *i*-PrOH is added ($n = 0.96$). Stronger proton donors such as AcOH give $n = 2$, corresponding to hydrogenation [52].



Electrolysis of other simple α,β-unsaturated nitriles (**8**) in water–DMF mixtures containing large amounts of Et_4NOTs give LHDs in varying yields [2,53,54]. Electrolysis of crotonitrile (**8a**) under these conditions was reported to give the LHD (55%) in a 1:1 ratio of (±) and *meso* forms [54].

Cinnamonitrile (**9**) and substituted analogues are easier to reduce than the simple nitriles and form less reactive radical anions. The mechanism and kinetics of the EHD of **9** has therefore been much studied. In DMF $n \approx 1$, and RRDE measurements were in agreement with the RR mechanism at substrate concentrations <8 mM [55]. The rate constant for the rate-determining dimerization step (RR mechanism) has been determined by several methods in DMF (Table 3). In liquid ammonia ($T = -43°C$), dimerization is considerably slower (Table 3), and, significantly, even in the presence of *i*-PrOH the coulometric *n*-value was small (0.05–0.27), indicating considerable polymerization [52].

The nature and stereochemistry of the products obtained from electrolysis of **9** and derivatives in DMF depend on the amount of water present. Reduction of α-phenylcinnamonitrile results in two forms of the hydrodimer [Eq. (2)], the LHD and a CHD [56]. By NMR the LHD was assigned to result from (±) coupling, and the CHD from *meso* coupling (although later findings would suggest the opposite assignments, cf. Sec. II.A.7). In DMF (Et_4NBF_4) containing no added water only the CHD (55%) is formed by reduction of β-methylcinnamonitrile (together with 15% of the hydrogenated monomer) [57]. The CHD was a mixture (13:1) of two stereoisomers resulting from (±) and *meso* coupling, respectively.



(2)

The choice of aprotic solvent is important. The acidity of MeCN is much higher than that of DMF or DMSO, and MeCN may be deprotonated by anionic intermediates. The conjugate base of MeCN, $^-CH_2CN$, can initiate a chain reaction by Michael addition to unreacted substrate leading to oligomers, and the reactions proceed with coulometric *n*-values less than one. If the oligomerization is terminated after the first Michael addition (by proton transfer from another solvent molecule), the substrate is cyanomethylated. With the proper choice of conditions (low substrate concentration, high temperature, and low current density) the reduction of **9** in MeCN may lead mainly (80%) to the glutaronitrile derivative, $PhCH(CH_2CN)_2$ via cyanomethylation [57].

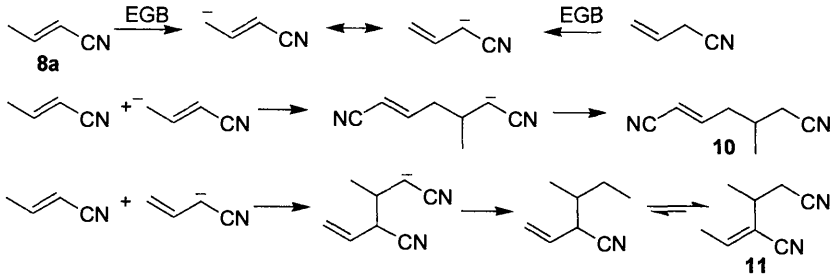
The γ-protons in α,β-unsaturated nitriles and the α-protons in β,γ-unsaturated nitriles are also acidic, and anionic intermediates may deprotonate such substrate molecules. Thermodynamically these nitriles are more acidic than water (when compared in DMSO) and more acidic than MeCN. This may lead to double-bond isomerizations or oligomerization/polymerization reactions. An example of a base-induced isomerization is the electrolysis of 3-butennitrile in $MeCN/H_2O$ (Et_4NOTs). The 3-butennitrile is converted into **8a** and the LHD of **8a** found as the main product [58]. Oligomers formed via substrate deprotonation contain a double bond, since oligomerization is initiated by

Table 3 Selected Rate Constants for Dimerization of Monoactivated Alkenes

Substrate	Conditions	Method	k_{dim}(RR) ($M^{-1}s^{-1}$)	Ref.
trans-Ph–CH=CH–CN (**9**)	DMF, Bu_4NI, room temp.[a]	RRDE	$(8.8 \pm 0.4) \times 10^2$	[55]
9	DMF, Bu_4NI, 23°C	ESR	$(2.1 \pm 0.5) \times 10^3$	[70]
9	DMF, Bu_4NI, room temp.	DPSC/DPSCC	$(8.77 \pm 0.21) \times 10^2$	[71]
9	DMF, Bu_4NI, room temp.	CV	7.9×10^2	[55]
9	NH_3, $MeBu_3NI$, 2 eq. *i*-PrOH, −43°C[b]	CV	5.7	[52]
trans-PH–CH=CH–COOR (**12**)				
R = *t*-Bu, $E^{0\prime} = -1.833$ V	DMF, 0.28 *M* H_2O,Et_4NBr, 22°C	DCV	$(4.1 \pm 0.1) \times 10^2$	[16]
R = menthyl, $E^{0\prime} = -1.794$ V	DMF, 0.28 *M* H_2O,Et_4NBr, 22°C	DCV	$(5.4 \pm 0.1) \times 10^2$	[16]
R = bornyl, $E^{0\prime} = -1.794$ V	DMF, 0.28 *M* H_2O,Et_4NBr, 22°C	DCV	$(5.6 \pm 0.2) \times 10^2$	[16]
R = Et (**12a**) $E^{0\prime} = -1.789$ V	DMF, 0.28 *M* H_2O,Et_4NBr, 22°C	DCV	$(5.4 \pm 0.7) \times 10^2$	[16]
R = Me (**12b**), $E^{0\prime} = -1.778$ V	DMF, 0.28 *M* H_2O,Et_4NBr, 22°C	DCV	$(7.8 \pm 0.7) \times 10^2$	[16]
R = *N*-butylephedrine, $E^{0\prime} = -1.767$ V	DMF, 0.28 *M* H_2O,Et_4NBr, 22°C	DCV	$(5.8 \pm 0.8) \times 10^2$	[16]
R = *N*-tosylephedrine, $E^{0\prime} = -1.708$ V	DMF, 0.28 *M* H_2O,Et_4NBr, 22°C	DCV	$(1.6 \pm 0.2) \times 10^3$	[16]
R = 4-methoxyphenyl, $E^{0\prime} = -1.654$ V	DMF, 0.28 *M* H_2O,Et_4NBr, 22°C	DCV	$(6.1 \pm 0.6) \times 10^3$	[16]
R = 4-methoxyphenyl, $E^{0\prime} = -1.547$ V	MeOH, Et_4NBr, 22°C	LSV	3.9×10^5	[67]
R = Ph, $E^{0\prime} = -1.631$ V	DMF, 0.28 *M* H_2O,Et_4NBr, 22°C	DCV	$(8.1 \pm 0.4) \times 10^3$	[16]
R = Ph, $E^{0\prime} = -1.524$ V	MeOH, Et_4NBr, 22°C	LSV	7.3×10^5	[67]
R = 4-cyanophenyl, $E^{0\prime} = -1.521$ V	DMF, 0.28 *M* H_2O,Et_4NBr, 22°C	DCV	$(5.7 \pm 0.4) \times 10^3$	[16]
R = 4-cyanophenyl, $E^{0\prime} = -1.438$ V	MeOH, Et_4NBr, 22°C	LSV	2.0×10^6	[67]
R = Et (**12a**)	DMSO, Bu_4NI	RRDE	2.4×10^2 [d]	[63]
12a	DMSO, Et_4NI	RRDE	4.2×10^2 [d]	[63]
12a	DMSO, Me_4NBF_4	RRDE	5.6×10^2 [d]	[63]
12a	DMSO, KNO_3	RRDE	4.7×10^3 [d]	[63]
12a	DMF, Bu_4NI, room temp.	DPSC/DPSCC	1.4×10^2	[71]
(*E*)–Ph–CH=(Me)NO_2(**19b**)	DMF, Bu_4NI, room temp.[c]	RRDE	1.7×10^4	[72]
4-methylcoumarine (**14b**), $E^{0\prime} = -1.813$ V	DMF, Et_4NBr, room temp.	DCV	1.5×10^5	[73]
14b, $E^{0\prime} = -1.625$ V	MeOH, Et_4NBr, room temp.	LSV	1.7×10^7	[73]
Methyl 4-*t*-butylchyclohex-1-enecarboxylate (**15**)	DMF, Et_4NBr, 27°C	DCV	$(9.7 \pm 0.4) \times 10^3$	[74]

[a] $n = 0.96$; [b] $n = 0.27$; [c] $n = 0.98$; [d] The observed rate constant may be interpreted as arising from three parallel reactions, according to which species are coupling: $2\,A^{\cdot}$, $A^{\cdot} + A^{-}/M^{+}$ or $2\,A^{-}/M^{+}$.

Michael addition of the deprotonated substrate to unreacted substrate. The oligomerization reactions proceed with coulometric n values less than one, smaller for the longer chain. This type of reaction takes place when **8a** is reduced in dry MeCN. The oligomerization chain is short, and a double-bond-containing dimer isolated as the major product (>35%) [59]. The structures **10** and **11** have been suggested for the dimer [59,60], corresponding, respectively, to attack of the conjugate base of **8a** by C-2 or C-4 (Scheme 4).



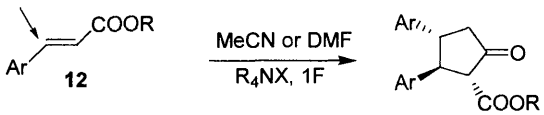
Scheme 4

The similarities in product distributions found for reduction of 2-pentennitrile and 3-pentennitrile in MeCN [59] most likely arise by base-catalyzed isomerization of the two double-bond isomers.

7. Esters

Esters of cinnamic acid and ring-substituted derivatives (**12**) have received considerable attention for decades from a preparative point of view [2,61], as model compounds for early kinetic studies [10,11,62] and for examination of effects of medium [63], cations [63], proton donors [64], and complexing agents [65] on products, mechanisms, or kinetics. Series of cinnamates have more recently been the subject of systematic stereochemical, kinetic and mechanistic studies [16,66,67].

Electrolyses of substrates of the cinnamic acid ester family (Table 4) in anhydrous MeCN were shown to result in formation of 7–60% of the CHD [Eq. (3)], corresponding exclusively to the (±) coupling as determined from the stereochemistry of the cyclopentanone formed by hydrolytic decarboxylation [61]. The stereochemistry was later verified by x-ray crystallography [65]. The stereoselectivity in the coupling step was originally rationalized in terms of orientation of the substrate molecules at the electrode surface [61]. However, later kinetic studies have shown that dimerization of the radical anions is fairly slow (Table 3), and takes place in the diffusion layer at a distance from the electrode.



a. Ar = Ph, R = Et
b. Ar = Ph, R = Me (3)

Higher yields of the CHD were obtained in another series of the cinnamic acid esters (Table 4) upon reduction in DMF [68,69], and similar yields were obtained from substances with a Me, Et or Ph substituent at the β-carbon in **12** [68].

For a series of cinnamic acid esters formed from chiral alcohols, reduction in DMF gave the CHD with from 0% de for the (−)-menthyl ester up to >95% de for the (−)-*endo*-bornyl ester [66] (Table 4). The menthyl and the bornyl cinnamates have virtually

Table 4 Effect of Substituents and Experimental Conditions on the Yields of LHD and CHD From Cinnamates (**12**)

Ar	R	Conditions[a]	CHD	LHD	Ref.
Ph	Et	A	52%(±)	—	[61]
Ph	$CH_2C{\equiv}CPh$	A	8%(±)	—	[61]
Ph	$CH_2CH{=}CHPh$	A	13%(±)	—	[61]
3,4-Dimethoxyphenyl	Et	A	52% (±)	—	[61]
3,4-Dimethoxyphenyl	*t*-Bu	A	7%(±)	—	[61]
3,4-(OCH_2O)-Phenyl	Me	A	60% (±)	—	[61]
3,5-Dimethoxyphenyl	Et	A	28% (±)	—	[61]
Ph	Me	B	76%[b]	Trace	[68,69]
2-Pyridinyl	Me	B	62%[b]	—	[68,69]
4-Anisyl	Me	B	52%[b]	—	[68,69]
4-Tolyl	Me	B	64%[b]	—	[68,69]
4-Chlorophenyl	Me	B	75%[b]	—	[68,69]
Ph	Me	C	74%[b]	Trace	[69]
Ph	Me	D	23%[b]	30%[b]	[69]
Ph	Me	E	9%[b]	45%[b]	[69]
Ph	Me	F	Trace	75%[b]	[69]
Ph	(−)-Menthyl	G	92%(±)(de 0%)	—	[66]
Ph	(+)-$CH(CH_3)COOEt$	H	86% (±) (de 33%)	—	[66]
Ph	(−)-CH(Ph)COOMe	H	99% (±) (de 45%)	—	[66]
Ph	(−)-CH(Ph)COO*i*Pr	H	85% (±) (de 40%)	—	[66]
Ph	(+)-*N*-methylephedrinyl	H	69% (±) (de 36%)	—	[66]
Ph	(+)-*N*-propionylephedrinyl	H	95% (±)[c]	—	[66]
Ph	(+)-*N*-tosylephedrinyl	G	94% (±) (de 35%)	—	[66]
Ph	(−)-*endo*-Bornyl	H	98% (±) (de >95%)	—	[66]
Ph	Ph	H	85%[d] (±):*meso*=5		[16]

[a] A: MeCN, Et_4NBr, div. cell, CPE, Hg-cath. B: DMF, Et_4NOTs, div. cell, CCE (4 F), Cu-cath., 10–15°C. C: MeCN, Et_4NOTs, div. cell, CCE (4\ F), Cu-cath., 10–15°C. D: DMSO, Et_4NOTs, div. cell, CCE (4 F), Cu-cath., 10–15°C. E: *i*-PrOH, Et_4NOTs, div. cell, CCE (4 F), Cu-cath., 10–15°C. F: MeOH, Et_4NOTs, div. cell, CCE (4 F), Cu-cath., 10–15°C. G: DMF, $LiClO_4$, div. cell, CPE, Hg-cath. H: DMF, Et_4NBr, div. cell, CPE, Hg-cath.

[b] Stereochemistry not reported.

[c] The de could not be determined.

[d] Yield of the decarboxylated product, 3,4-cyclopentanone.

identical values of $E^{0'}$ and of the second order rate constant for dimerization [16] (Table 3), and the large difference in the ability of the two chiral groups to induce diastereoselectivity is therefore most likely caused by their difference in bulkiness.

Basic hydrolysis under the conditions of electrolysis in DMF has been observed for aryl cinnamates [16], which in general give lower yields of the CHD (and mainly as 3,4-diphenylcyclopentanone) than the alkyl cinnamates and not exclusively the (±)-isomer (Table 4).

Examination of the reduction of **12b** in a range of solvents [69] showed a significant change in distribution of the dimer on the CHD and the LHD as the proton donor ability of the solvent was changed (Table 4). The more protic the solvent, the higher is the yield of the LHD. The effect of even more protic conditions on the product distribution was examined for **12b** in MeOH/DMF (1:9) containing different amounts of AcOH. Electrolysis at constant current gave mixtures of the hydrogenation product, the LHD [(±) and *meso*], and the CHD (±). The yields of hydrogenation product increased (from 20% to 60%), while the total yield of dimers decreased with increasing amounts of AcOH. Particularly the yield of the CHD decreased, from 55% to < 1%. However, the relative amounts of dimers arising from (±)-coupling and from *meso*-coupling (ratio 5:1) were fairly independent of C^*_{AcOH}, current density, and mass transport efficiency (rotating cathode) [75].

In DMF, β-cyclodextrin and **12a** form a 1:1 complex with the aromatic ring of **12a** included in the hydrophobic cavity of the β-cyclodextrin. Electrolysis under these conditions results in a product distribution close to that obtained in DMF/MeOH mixtures: 71% 2 F product, 19% LHD, and only 1% CHD [65]; i.e., the hydroxy groups at the rim of the cyclodextrin function as proton donors.

Reduction of **12a** in aqueous H_2SO_4 gave the LHD with (±):*meso* ≈ 1 accompanied by formation of only traces of the hydrogenation product [54].

Most—if not all—of the preparative results just presented for reduction of **12** can be rationalized within the RR mechanism when effects of hydrogen-bonding and proton transfer are taken into account. Under conditions with very low proton donor concentrations DPSCC measurements on **12a–b** in DMF indicate that the initial dimerization step is reversible with a large equilibrium constant, and the rate-determining step is protonation (or cyclization) of the dimer dianion [10,11]. Assuming this mechanism, the equilibrium constants for the dimerization were determined: $K_{dim} = 109\ M^{-1}$ for **12a** and $K_{dim} = 53.1\ M^{-1}$ for **12b** at 25°C, while the pseudo-first-order rate constants for the rate-determining protonation of the dimer dianion at 25°C was 3.7 s^{-1} for **12a** and 9.2 s^{-1} for **12b** [11]. The overall energy of activation was also determined for the reaction: 5.9 kcal/mol for **12a** and 5.8 kcal/mol for **12b**. Other measurements by DCV under strictly anhydrous conditions for **12b** in MeCN gave results which were interpreted as a change to an RS mechanism with rate-determining electron transfer to the dimer radical anion from $\mathbf{12b}^{-\cdot}$ [62]. However, another possible interpretation of the data is that the RR dimerization reaction is reversible as already described, due to the absence of proton donors necessary to drive the dimerization toward product, and/or that the dimer dianion initiates a polymerization reaction (as observed on a preparative scale) by a partially rate-determining addition to a molecule of substrate.

The overall rate of reaction for $\mathbf{12}^{-\cdot}$ increases with increasing water content in DMF [16] and in MeCN [62]. Above a certain (low) level, the accelerating effect of increasing amounts of water cannot be ascribed to a shift in the rate-determining step but rather to stabilization of the radical anions by hydrogen-bonding to the carbonyl oxygen, thereby facilitating the coupling of two negatively charged species.

A similar accelerating effect of small cations has been observed. In DMSO a clear correlation between the radius of the supporting electrolyte cation and the magnitude of the observed second-order rate constant was found for dimerization of **12a**$^{-\cdot}$; the smaller the cation, the higher is the rate (Table 3) [63]. The data were interpreted as a result of three parallel dimerization reactions: dimerization of two "free" radical anions, with a second-order rate constant k_i, coupling of a free radical anion with an ion-paired radical anion, k_{ii}, and dimerization of two ion-paired radical anions, k_{iii}, the rate constants increasing in the order $k_i < k_{ii} < k_{iii}$. Using Bu_4N^+ as supporting electrolyte cation, a linear correlation between $\log(k_{obs}\ M^{-1}s^{-1})$ and the Gutmann DN was observed for a range of solvents; the smaller the DN, the faster the reaction, indicating that the less efficient the cation (even Bu_4N^+) is solvated, the larger is the equilibrium constant for ion-pair formation with **12a**$^{-\cdot}$ and, consequently, the larger the observed rate constant for dimerization [63].

Under identical experimental conditions (DMF, 0.28 *M* H_2O, 0.1 *M* Et_4NBr), a thorough study of a large series of cinnamic acid esters led to the conclusion that the EHD reaction followed the RR mechanism with rate-determining dimerization [16]. The rate constants for dimerization were shown to correlate closely with the $E^{0'}$ values for the reduction process; the more easily the substrate is reduced, the faster is the dimerization (Table 3) [16]. The phenomenon can for this closely related series of compounds be rationalized in terms of a systemic change of the unpaired electron density at the position of dimerization [76].

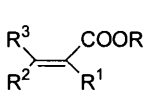
It is obvious from the data in Table 4 that the major product obtained by reduction of **12** in aprotic solvents containing residual water or (small) amounts of added water is the CHD resulting from initial (±)-coupling. This stereoselectivity has been rationalized as arising by a templating of two radical anions by one or more water molecules via hydrogen bonding to the carbonyl oxygens [16] (Sec. II.A.4). The smaller (±):*meso* ratio observed for reduction of **12b** in DMF/MeOH (9:1) [75] compared to that in DMF/0.28 *M* H_2O is likely to be caused by less efficient templating under the former conditions.

Within a series of cinnamates the strength of the water templating is expected to depend on the basicity of the radical anions. One way to characterize the basicity of the radical anions is to measure the rates of protonation by a common proton donor. For the series of cinnamates, the rate of protonation by phenol in DMF has been measured [76] and was found to change systematically. The more easily the substrate is reduced the lower is the basicity of the radical anion [76], which is the opposite of the trend found for the dimerization rate constants [16]. The change in basicity may then explain the reduced stereoselectivity of the CHD coupling product from the aryl esters (which are more easily reduced than alkyl esters). All the aryl esters form mixtures of the (±) and the *meso* form of the CHD, and the (±):*meso* ratio decreases from 5 to 2 going from the phenyl ester to the most easily reduced 4-cyanophenyl ester [16].

The change in product distribution upon addition of increasing amounts of AcOH to DMF/MeOH during the reduction of **12b** can be understood as a competition between initial dimerization of two hydrogen-bonded (by MeOH) radical anions and initial protonation of the radical anion. Like PhOH in DMF [76], AcOH in DMF/MeOH seems to protonate at carbon, which leads to further reduction and formation of the hydrogenation product. Because the (±):*meso* ratio of the dimers was constant independently of the amount of acid present, the conclusion was [75] that the dimerization followed the RR mechanism at all acid concentrations. A shift from coupling of two radical anions at low acid concentrations to coupling of two neutral radicals formed by protonation at high acid concentrations would be expected to show up as a change in the ratio [75].

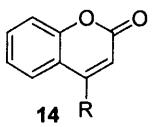
In pure MeOH *trans*-esterification of the cinnamates takes place under preparative conditions except for **12b**. However, electroanalytical experiments and coulometric experiments taken only to partial conversion could be carried out for a series of cinnamates [67]. The change from an aprotic to a hydroxylic solvent reveals distinct differences, which may all be explained by the hydrogen-bond donor and proton donor ability of the solvent: (1) The esters are more easily reduced due to specific solvation by hydrogen bonding; (2) the rate of reaction of the radical anions is 2–3 orders of magnitude higher than in DMF; and (3) the most basic radical anions (alkyl cinnamates) undergo protonation at the carbonyl oxygen in the rate-determining step, whereas the least basic (aryl cinnamates) dimerize on a voltammetric timescale [67]. The neutral radicals formed by protonation at oxygen either dimerize non-stereo-selectively or tautomerize to the radical with the proton at carbon, which, in contrast to the radical formed by protonation at oxygen, is reduced more easily than the substrate. For **12b** this results in a mixture of the hydrogenation product and the (±) and *meso* LHD in a 1:1 ratio on a preparative scale [67].

The stereochemically unselective formation of the LHD formed upon reduction of **12a** in aqueous H_2SO_4 [54] can similarly be explained by dimerization of two neutral radicals, in this case formed directly in the reduction step since preprotonation (at oxygen) is expected.



13

a: R = Me, R^1=R^2=R^3 = H
b: R = Et, R^1 = H, R^2=R^3 = Me
c: R = Et, R^1=R^3 = H, R^2 = Me
d: R = Et, R^1=R^2=R^3 = H
e: R = Et, R^1= Me, R^2=R^3 = H



14

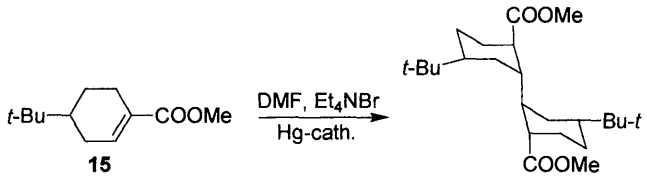
a: R = H
b: R = Me

Ester-activated alkenes that contain no aromatic groups are more difficult to reduce and the radical anions more reactive. Methyl acrylate, **13a**, undergoes hydrodimerization in buffered aqueous solutions containing tetramethylammonium phosphate. The optimum conditions were found to be a tin cathode, pH 8.5–12 and high concentrations of **13a**, resulting in a yield around 50% using constant current [77]. Side products were the hydrogenation product and a high-boiling, probably oligomeric material. The cinnamates are only very slightly soluble in water but, for example, **12a** may be solubilized either by the use of large amounts of Et_4NOTs (> 2 *M*) or by the use of micelle-forming surfactants such as Triton X-100 (< 0.1 *M* is sufficient). Under these conditions, polarographic analysis indicates that **12a** undergoes hydrodimerization and not hydrogenation [48]. As in MeOH, the dimerization reaction is much faster ($k_{dim} > 10^8\ M^{-1}\ s^{-1}$) than in aprotic solvents.

Ethyl 3,3-dimethylacrylate, **13b**, gives the LHD upon reduction in DMF/H_2O (Et_4NOTs) [54]. Under similar conditions ethyl crotonate, **13c**, and the corresponding ethyl 3-butenoate give the same LHD in near-identical yields, and the only unconverted monomer is **13c** [58]. During the electrolysis the basicity of the medium is sufficiently high for base-catalyzed isomerization of the two species to take place in a manner analogous to the nitriles (Scheme 4). The side products found correspond to Michael addition of the conjugated base of the substrate (C-2 or C-4) to starting material [58].

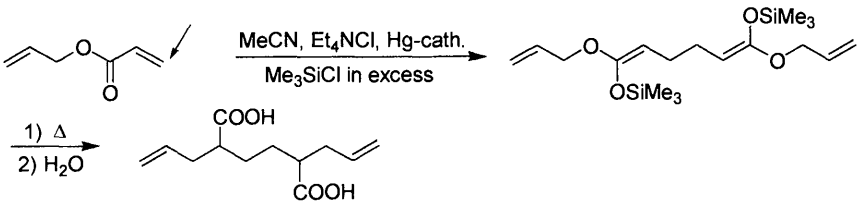
An exception to the high reactivity of radical anions derived from ester-activated alkenes lacking aryl substituents is the radical anion derived from methyl 4-*t*-butylcyclohex-1-enecarboxylate, **17**, which undergoes coupling following the RR mechanism with a second-order rate constant comparable to those found for aryl cinnamates [74] (Table 3). The product isolated after reduction was the LHD formed by diaxial coupling of the cyclohexyl rings [Eq. (4)]. This demonstrates the effect of stereoelectronic control, which

requires the orthogonal approach, leading to the diaxial coupling despite a considerable steric hindrance [74] (Sec. II.A.4).



(4)

An interesting reductive dimerization of allyl acrylates (and alkyl substituted analogues) has been reported. Reduction in the presence of an excess of chlorotrimethylsilane leads to the corresponding bis-keteneacetal, which upon heating undergoes Claisen rearrangement to the trimethylsilyl 2,5-diallyladipates. These can be hydrolyzed to the 2,5-diallyladipic acids in up to 68% yield [78] (Scheme 5). The point on the reaction pathway at which oxygen is silylated is not known.



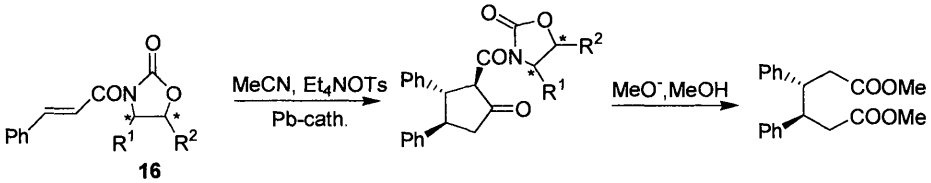
Scheme 5

Lactones such as coumarin and its derivatives (**14**) undergo hydrodimerization even in acidic hydroxylic media. When the supporting electrolyte contains Li^+, coumarin (**14a**) gives the 4,4′-hydrodimer in ~ 90% yield in a methanol/acetate buffer (pH 5) [79]. The mechanism of the reduction of 4-methylcoumarin (**14b**) in DMF, MeOH, and MeOH/H_2O has been examined [73]. In all cases the mechanism of dimerization was found to be of the RR type, again with a considerable increase in the observed second-order rate constant in going from aprotic to protic solvents (Table 3), [73].

8. Amides and Oxazolidinones

Activation of alkenes by amides and *N*-alkylamides has not been used as much as activation by ester groups. The amides are more difficult to reduce than the corresponding esters but have been reported to give the LHDs in 40–80% yields [2,4].

Chiral *N-trans*-cinnamoyl-2-oxazolidinones (**16**) give upon reduction in dry MeCN the all-*trans* CHD in high yields with a diastereomeric excess up to 66% [80] (Table 5). The products are hydrolyzed and esterified to give the dimethyl 3,4-diphenyladipate with up to 70% ee (Scheme 6). The chiral 2-oxazolidinones could be recovered in > 90% yield.



Scheme 6

Table 5 Effect of the Chiral Oxazolidinone on the Yield and Diastereoselectivity of the Dimerization of **16**[a]

R^1	R^2	Yield of (±) CHD[b]	Ratio of diastereomers
i-Pr (*S*)	H	88%	81:19
i-Bu (*S*)	H	95%	83:17
Bu (*S*)	H	83%	70:30
Ph (*R*)	H	81%	68:32
Me (*S*)	Ph (*R*)	92%	76:24
H	H	86%	—

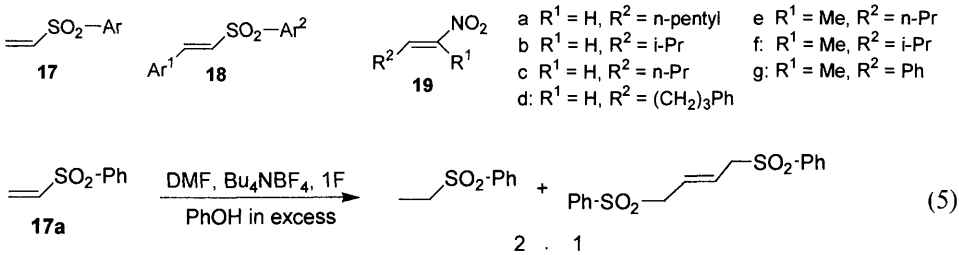
[a] MeCN, Et_4NOTs, undiv. cell, Pb-cath., CPE, $E_w = -1.8$ V. From Ref. 80.
[b] In all cases the amount of the 2-F product was < 10%.

9. Carboxylic Acids

Few hydrodimerizations of alkenes activated by carboxylic acid groups have been reported [56,81–84]. In all cases the reductions were carried out in acidic media at Hg cathodes using constant current. Reduction in 28% H_2SO_4 mixed with an organic cosolvent (DMF or EtOH) gave the LHD of cinnamic acid (42–55%) with a (±) : *meso* ratio close to 1, together with 5–10% of the 2-F hydrogenation product and polymeric side products [82,84]. Ring-substituted derivatives of cinnamic acid (Cl, MeO, OH) gave similar yields of the LHD, whereas substitution with NO_2, CN, or NH_2 mainly led to monomeric reduction products [82,83]. Also α-phenylcinnamic acid gave low yields of the LHD when reduced under similar conditions [56]. In 50% ethanolic acetate buffers, cinnamic acid undergoes two-electron reduction [81], giving 3-phenylpropionic acid as the major product [84].

10. Miscellaneous Activating Groups

Aryl vinyl sulfones (**17**) undergo electrocatalytic cycloaddition to *trans*-1,2-diarylsulfonylcyclobutane (20–75%) in dry DMF (Et_4NClO_4) (Scheme 2), when electrolysis (0.1–0.2 F) is carried out at a potential corresponding to the foot of the reduction peak or by application of an electron transfer mediator [85]. In DMSO ($LiClO_4$), up to 95% of the cyclobutane could be obtained after passage of 0.1 F [86]. No cyclobutane was formed in MeCN [86]. When reduction of **17a** was carried out at the reduction peak potential in the presence of a small excess of PhOH or AcOH, a 2:1 mixture of the hydrogenation product and an unsaturated dimer was obtained [Eq. (5)] in an overall 1-F process [87]. The reaction pathway is not known.



When the double bond in **17** is substituted with alkyl groups in the β-position and electrolysis is carried out in dry solvents, a mixture of products is obtained [18]. Initial

conversion of the vinylic substrate into the thermodynamically more stable allylic isomer by an EGB has been proposed as an explanation [18].

In contrast to β-alkyl substitution, β-aryl substitution of **17** gives substrates (**18**), which upon reduction in DMF or DMSO give fairly stable radical anions [86]. Electrolysis of **18** in dry DMSO ($LiClO_4$) leads to formation of the corresponding LHDs in good yields (50–75%) with a (±):*meso* ratio within the range 10–15. Addition of phenol changes the reduction process to a chemically irreversible 2-F process associated with protonation of the radical anion, further reduction (hydrogenation) and/or cleavage of the C–S bond [18,86,88]. An RS dimerization mechanism was suggested by the authors on the basis of LSV measurements [88]. This seems somewhat speculative, since the CV data [86,88] indicate that the reaction is too slow for application of LSV. The strong preference for formation of the (±) isomer may be explained by a templating effect of Li^+ (or hydrated Li^+) in the dimerization of two radical anions, similar to that observed for other dimerizations which follow the RR coupling pathway.

Alkenes activated by nitro groups show little tendency to undergo EHD compared to other activated alkenes due to lower spin density on the β-carbon [89]. Due to the acidity of the γ-hydrogens, reduction in aprotic solvents gives mostly base-induced reactions of the type described for the corresponding nitriles (Scheme 4), which are catalytic with respect to current. In the presence of proton donors, either reduction of the nitro group or cleavage takes place. However, by proper choice of reaction conditions, it has been demonstrated [89,90] that the LHD (β,β'-coupling) may be obtained at 40–95% for a series of nitro-activated alkenes, **19a–19f**, in MeCN (Bu_4NBF_4) [89]. The dimerization reaction is favored over the base-induced reaction (most likely induced by proton transfer from a substrate molecule to a radical anion or a dimer dianion) by high concentrations of the radical anion (RR mechanism), that is, by high current densities obtained by the use of an undivided cell and closely positioned electrodes [89].

Although no product was isolated, the results obtained by polarography, CV, RRDE, and coulometry for the reduction of 1-phenyl-2-nitropropene (**19g**) in DMF were consistent with fast dimerization according to the RR mechanism [72] (Table 3).

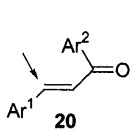
11. Ketones

Enones may react either as ketones (cf. Chapter 10) or as activated alkenes thus giving pinacols, β,β'-coupling, or mixed coupling products. Another feature of enone reduction is that the radical anions, $A^{-\cdot}$, in the presence of proton donors are protonated at oxygen in a fast process, and the resulting enol radical, $B^{\cdot}$, is more difficult to reduce than the neutral substrate (Sec. II.A.1). Radical anions derived from other activated double bonds tend to protonate at carbon in the presence of proton donors, and the resulting radical is more easily reduced than the neutral substrate (Schemes 1 and 3).

As a consequence, hydrogenation competes to a much smaller extent with coupling in the reduction of enones than in the reduction of other activated double bonds, since the enol radical also participates in coupling reactions. Overall 1-F reduction is therefore observed in most experimental conditions. Whether the coupling takes place at the radical anion stage, $A^{-\cdot}$, or at the radical stage, $B^{\cdot}$, depends on the acidity of the medium.

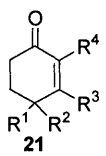
A number of studies have been made of the reduction of model enones in buffered aqueous or buffered ethanolic solutions in order to elucidate the sequence of electron transfer, proton transfer, and coupling steps as a function of pH [39–42,91–95]. The experimental methods applied include polarography, CV, LSV, and chronocoulometry.

The general conclusions are that under acidic conditions (pH < 5–6) the electroactive species is the enone preprotonated at oxygen, which by a one-electron reduction gives directly the enol radical B˙, which undergoes dimerization in the rate-determining step. For the less soluble substrates, such as **20a** [40] and **21a** (in aqueous buffers [41]), the coupling seems to take place in the adsorbed state. At pH > 7–8 the neutral substrate is the species undergoing reduction, but only at high pH values (pH > 11) does a rate-determining dimerization of $A^{-\cdot}$ take place. The simple vinyl methyl ketone, **22a**, is electroinactive at these pH values since the β-hydroxyketone anion is formed [91]. For **20a** dimerization of $A^{-\cdot}$ only takes place in the presence of a surfactant, Triton X-100 [39]. In the intermediate pH range, initially formed $A^{-\cdot}$ is protonated to B˙ either in a fast preequilibrium or in a rate-determining step followed by coupling between two B˙ or between $A^{-\cdot}$ and B˙. The rate constant for dimerization of two neutral radicals is high—for **20a** (in the presence of a surfactant) the value of k_{dim} was estimated to be $> 10^8\ M^{-1}s^{-1}$ [39]. Also for **20a**, a value of $k_{dim} = 4 \times 10^5\ M^{-1}\ s^{-1}$ was determined at pH 11 (in the presence of surfactant) where the dimerization is between two $A^{-\cdot}$ [39].

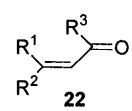


20

a $Ar^1 = Ar^2 = Ph$
b. $Ar^1 = Ph$, Ar^2 = 9-anthryl

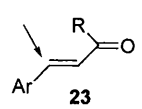


21



22

a: $R^1 = R^2 = H$, $R^3 = Me$
b: $R^1 = R^2 = R^3 = Me$
c: $R^1 = H$, $R^2 = R^3 = t\text{-}Bu$

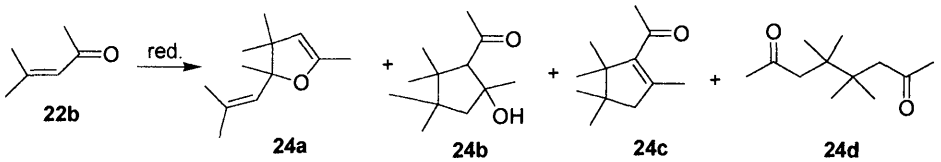


23

a: Ar = Ph, R = Me
b: Ar = Ph, R = t-Bu

Structural and steric factors are important in determining the coupling position (β-carbon or carbonyl carbon). Vinyl alkyl ketones (**22**), and simple alkyl-substituted cycloalkenones such as **21** in general give mixtures of dimeric products arising from β,β′-coupling, carbonyl–carbonyl coupling or mixed carbonyl-β-coupling. In contrast, styryl alkyl ketones (**23**) and styryl aryl ketones (**20**) almost exclusively give "normal" LHDs or CHDs arising from initial β,β′-coupling.

The CHDs formed by intramolecular addition often eliminate water to give another α,β-unsaturated ketone. For mesityl oxide (4-methyl-3-pentene-2-one), **22b**, the influence of the reaction conditions on the product distribution was examined in detail [96]. Mixtures of four dimeric species were observed, resulting from initial 4,4′-coupling (**24b–d**), or from mixed 2,4′-coupling, **24a**. Pinacol formation (2,2′-coupling) was not observed [Eq. (6)].



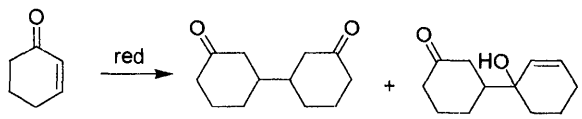
(6)

Optimization of the experimental conditions for selective formation of **24a–d** in an undivided cell was examined [96]. The product of mixed coupling, **24a**, was favored (88%) by reduction in $AcOH/Ac_2O$ (1:1). Most other conditions (strongly acidic, aprotic, or basic) favored 4,4′-coupling. The dehydrated cyclic compound **24c** (62%) and the hydrated form **24b** (20%) were formed in strongly acidic conditions (pH 1.1). Product **24b** (*cis*/*trans* = 1:1) was favored by reduction in aprotic solvents (DMF, Et_4NOTs) or by basic conditions. Cyclization was best avoided by reduction at elevated temperature

(65°C), in a 1:1:1 (v:v:v) mixture of H_2O, MeCN, and THF (HOAc/KOAc); this gave **24d** (56%) [96].

Hindrance at the carbonyl group (e.g. **22c**) favors β,β'-coupling. The radical anion derived from **22c** is stable on a voltammetric time scale in DMF (n-Pr_4NClO_4) and reacts slowly under preparative conditions giving 30% of the LHD, exclusively as the (±) isomer [20]. When water or Li^+ is added, the rate of reaction is increased. Electrolysis in a mixture of DMF and aqueous buffer (pH 9 or pH 13) gave an increased yield of the LHD (55–60%) predominantly as the (±) isomer (< 5% *meso*). The (±) isomer was also the product obtained by chemical reduction using Na in HMPA [20].

For reduction of **21a** in aqueous buffers [41], the 3,3′-coupling product, **25a**, and the product of mixed coupling, **25b** [Eq. (7)], were formed in the ratio 2:3, both at pH 5, where the coupling is expected to take place in the adsorbed state, and at pH 9, where coupling takes place in solution [41]. In most other conditions, reduction of **21a** gives **25a** as the major product (Table 6).

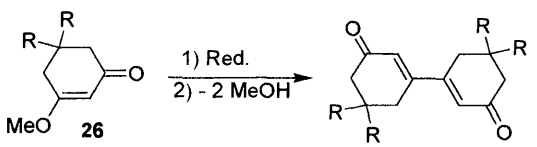


(7)

In MeCN both the water content and the substitution pattern influence the preferred coupling of 2-cyclohexen-1-ones (**21**) [97,98]. More 3,3′-dimer was formed in the absence of water and in the absence of substituents, whereas pinacol formation was favored by the presence of water (Table 6). The 4,4-dimethyl-2-cyclohexen-1-one only gave pinacol (35%) together with unidentified polymeric material when reduced in DMF, where the dimerization according to LSV measurements follows the RR mechanism [99].

Reduction of 2-cyclopenten-1-one in aqueous buffers gave in the pH range 8–13.5 only the LHD (3,3′-coupling) (45–50%) as a mixture of *meso* and (±) together with unidentified polymers [94]. These conditions correspond to exclusive reduction of the unprotonated substrate [94]. Under acidic conditions, the same LHD was obtained in lower yields (25–30%) [95].

Mono-enol ethers of β-diketones (**26**) are formally alkoxy substituted enones, and by reductive coupling followed by hydrolysis they yield conjugated bis-enones [Eq. (8)]. This is the more stable product, independent of whether the initial coupling product is a pinacol, a bis-ketone, or mixed coupling product. Reduction of the substrates (**26a–b**) in ethanol/water (1:1) (Me_4NCl) gave the corresponding bis-enones in 20–40% yield [101].



a. R = H
b R = Me

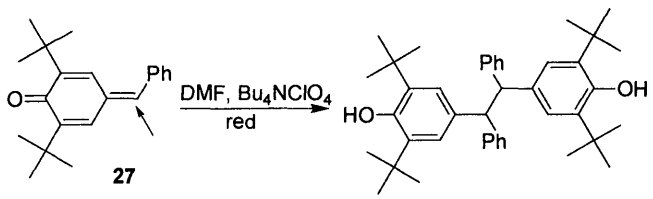
(8)

Formation of an LHD by exclusive coupling in the 5-position in a conjugated dienone is observed for the quinonemethide **27** and is favored by the formation of an aromatic ring [102] [Eq. (9)]. The yield was improved to 80% when the product was methylated prior to workup. Additional substituents in the 5-position prevented dimerization [102].

Table 6 Influence of Structure and Experimental Conditions on Product Structure and Yields Obtained by Reduction of 2-Cyclohexenones (**21**)

Substrate	Conditions	Products and Yields	Ref.
$R^1 = R^2 = R^3 = R^4 = H$ (**21a**)	MeCN, KCl, 1 *M* HCl	LHD 50%[a], mix coupl. 21%	[100]
21a	MeCN, AcONa, 2 *M* AcOH	LHD 64%[a], mix coupl. 18%	[100]
21a	MeCN, KCl, 1 *M* NaOH	LHD 72%[a], mix coupl. 8%	[100]
21a	MeCN, Bu_4NBF_4, Hg-cath., CPE	LHD 97%	[98]
21a	MeCN, 5% H_2O, Bu_4NBF_4, Hg-cath., CPE	LHD 95%	[98]
$R^1 = R^2 = Me, R^3 = R^4 = H$	MeCN, Bu_4NBF_4, Hg-cath., CPE	LHD 52%, mix coupl. 31%, pinacol 16%	[98]
$R^1 = R^2 = Me, R^3 = R^4 = H$	MeCN, 5% H_2O, Bu_4NBF_4, Hg-cath., CPE	LHD 28%, mix coupl. 4%, pinacol 67%	[98]
$R^1 = R^2 = R^4 = Me, R^3 = H$	MeCN, Bu_4NBF_4, Hg-cath., CPE	LHD 10%, mix coupl. 40%, pinacol 50%	[98]
$R^1 = R^2 = R^4 = Me, R^3 = H$	MeCN, 5% H_2O, Bu_4NBF_4, Hg-cath., CPE	Mix coupl. 10%, pinacol 90%	[98]
$R^1 = R^2 = R^3 = Me, R^4 = H$	MeCN, Bu_4NBF_4, Hg-cath., CPE	LHD 10%, mix coupl. 60%, pinacol 30%	[98]
$R^1 = R^2 = R^3 = Me, R^4 = H$	MeCN, 5% H_2O, Bu_4NBF_4, Hg-cath., CPE	Mix coupl. 45%, pinacol 50%	[98]

[a] (±) : *meso* < 1.



(9)

As mentioned, styryl alkyl ketones, **23**, form only β,β'-coupled LHDs upon reduction. In DMF the yield of the LHD increased with increasing size of the alkyl group [103] (Table 7). Polarography of **23a** in dry DMSO shows two one-electron reductions. The height of the first wave is unperturbed by addition of water, but a new wave, between the original two, increases at the expense of the second [17]. The new wave may be ascribed to the reduction of the oxygen-protonated radical anion, which is more difficult to reduce than the substrate. In DMSO containing small amounts of water (< 0.05 M) the dimerization of **23b**$^{-\cdot}$ takes place by the RR mechanism, $k_{dim} = 1.4 \times 10^3$ M^{-1} s^{-1}, according to current reversal chronopotentiometry [6]. The value of k_{dim} is enhanced remarkably upon addition of Na^+ or Li^+. Using $LiClO_4$ as supporting electrolyte gave a rate enhancement of approximately three orders of magnitude [17] for **23b**, and on a preparative scale 75% of the (±) LHD was formed (Table 7) [17].

In dry DMF, polymers were formed in addition to the (±) LHD (Table 7). However, in the presence of a stoichiometric concentration of metal cations (Li^+, Cr^{2+}, Mn^{2+}, Fe^{2+}, Co^{2+}, or Zn^{2+}), polymerization was avoided and a yield of >90% of dimers obtained [21]. With Li^+ the (±) LHD was obtained exclusively, whereas with Fe^{2+} or Co^{2+} the CHD was the sole product. The stereochemistry of the CHD was assigned by NMR to arise from *meso* coupling [21], but later studies have shown the stereochemistry to correspond to (±) coupling by application of ^1H NOESY NMR and x-ray crystallography [105]. The metal cations are expected to form ion-pairs with the radical anions (an anodic shift of the reduction peak was observed). Thus a templating effect is a likely explanation of the stereoselectivity, and stabilization of the dimer dianion by ion-pairing may prevent polymerization.

The influence of the same metal cations on the yields and products of reduction of ring-substituted chalcones, **20**, in DMF (Bu_4NBr) is similar to the effect already described for styryl alkyl ketones. In all cases, polymerization was prevented and mixtures of the LHD and the CHD in an overall yield of 70–90% were obtained. Except for Mn^{2+}, the presence of the metal ions favored the CHD [22].

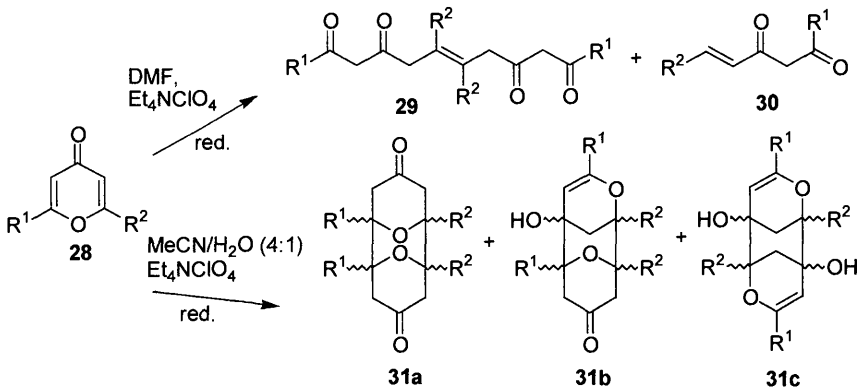
In EtOH/aqueous buffer at pH 5, polarography of **23a–b** shows two one-electron waves [17], and the potential of the second wave corresponds to the "new" wave formed when water is added to DMSO as described earlier. Electrolysis at the potential of the first wave gives the LHD, but in this case the *meso* isomer predominates [17]. For **23b** in acidic aqueous buffer (20% EtOH), the first wave corresponds to dimerization of the enol radical [50], in agreement with the change in stereoselectivity in the products [17] as compared with those for reaction in DMSO.

Reduction of substituted pyranones (**28**) leads to several products, with the distribution depending on the choice of solvent (Scheme 7). In DMF the major isolated product (40% or less) is the linear, ring-opened dimer, **29**, and in a single case the ring-opened monomer, **30**, which may be an intermediate in the formation of **29** [106]. Upon reduction in $MeCN/H_2O$, the product mixture contains only the tricyclic compounds, **31a–c**, resulting from "double coupling" in an overall 2-F process [106,107]. The distribution of the

Table 7 Influence of Structure and Experimental Conditions on Product Structure and Yields Obtained by Reduction of Alkyl Styryl Ketones (**23**)

Substrate	Conditions	Products and yields	Ref.
Ph–CH=CH–COMe (**23a**)	H_2O, Et_4NOTs, Hg-cath., div. cell	LHD 74%	[104]
23a	EtOH/H_2O (1:1), acetate buff., pH 5, Hg-cath., CPE (−1.1 V)	LHD (*meso*), $n = 0.99$	[17]
23a	DMF, Et_4NBr, Hg-cath., CPE	0% LHD, polymer	[103]
Ph–CH=CH–COPr	DMF, Et_4NBr, Hg-cath., CPE	25% LHD (±) and *meso*, polymer	[103]
Ph–CH=CH–CO(*i*)Pr	DMF, Et_4NBr, Hg-cath., CPE	65% LHD (±) and *meso*, polymer	[103]
Ph–CH=CH–CO(*t*)Bu (**23b**)	DMF, Et_4NBr, Hg-cath., CPE	95% LHD (±) and *meso*	[103]
23b	EtOH/H_2O (1:1), acetate buff., pH 5, Hg-cath., CPE (−1.15 V)	40% LHD (*meso*), smaller amounts of LHD (±), $n = 0.96$	[17]
23b	DMSO/H_2O (93:7), $LiClO_4$, Hg-cath., CPE (−1.7 V)	75% LHD (±), $n = 0.96$	[17]
23b	DMF, Bu_4NBr, Hg-cath., CPE	50% LHD (±), 50% polymer	[21]
23b	DMF, $LiClO_4$, Hg-cath., CPE	98% LHD (±)	[21]
23b	DMF, Bu_4NBr, 1 eq. Fe^{2+}, Hg-cath., CPE	>95% CHD (±) (see text)	[21]

three cyclic products depends on the substituents (Table 8). The sequence of reaction steps leading to **31a–c** is not easily envisaged.



Scheme 7

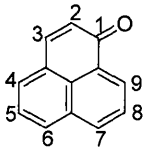
In MeCN the radical anion derived from 9-anthryl styryl ketone, **20b**, dimerizes ($k_{dim} = 10^5\ M^{-1}\ s^{-1}$), forming a stable dimeric dianion, most likely via coupling in the β-position [108]. On a coulometric scale the stable dimeric dianion can be reoxidized to the starting material at a potential ~ 1 V anodic relative to the reduction of **20b**. In contrast, the related 9,10-anthryl bis(styryl ketone) undergoes two consecutive one-electron reductions ($\Delta E^0 = 36$ mV corresponding to the statistical factor for reduction of two identical, noninteracting electroactive groups) with formation of a monomeric dianion, which is completely stable on a coulometric time scale. The lack of electronic interaction between the two styryl-keto groups in the monomeric dianion, as well as the rapid dimerization of $\mathbf{20b}^{-\cdot}$ is probably caused by the styryl groups being rotated almost completely out of plane of the anthracene ring.

In a few examples, radical anions derived from enones have been trapped by electrophiles other than a proton, and the coupling reaction proceeds through neutral radicals. For instance, **32** is reduced in DMF (Bu_4NClO_4) to give a stable solution of the radical anion. Subsequent addition of Ac_2O gives *O*-acylation in a fast process. The resulting neutral radicals dimerize slowly enough for examination by ESR [109]. Since the unpaired electron density in the neutral radical as determined by ESR is similar in positions 3, 4, 6, 7, and 9, the radicals may couple in several ways. The initially formed, singly linked dimer undergoes ring closure accompanied by loss of AcOH or hydrogen, depending on the initial coupling position, resulting in mixtures of the general structure **33** with 0 (10%), 1 (15%), or 2 (15%) AcO substituents [109].

Table 8 Influence of Structure on Product Structure and Yields Obtained by Reduction of 4-Pyrones (**28**)[a]

Substrate	Products and yields
$R^1 = R^2 = Me$	**31a** 45%, **31b** < 5%, **31c** trace
$R^1 = R^2 = Ph$	**31b** 25%, **31c** 60%
$R^1 = Me, R^2 = Ph$	**31a** 6%, **31b** 14%, **31c** 40%

[a]$MeCN/H_2O$ (4:1), Et_4NClO_4, Hg-cath., CPE. From Refs 106 and 107.



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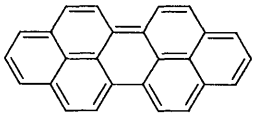

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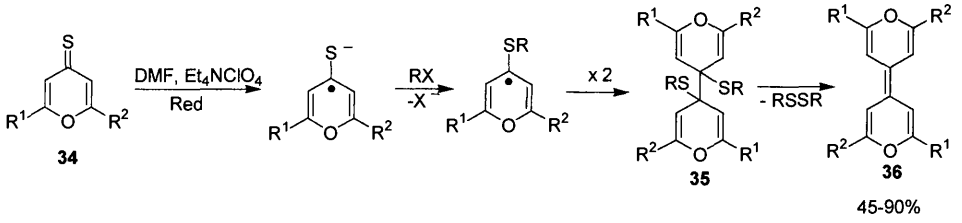
Another example of a coupling reaction initiated by reaction of the radical anion with an electrophile is the reductive coupling of substituted 4*H*-pyran-4-thiones (**34**) in the presence of alkyl halides (Scheme 8) [110,111]. The neutral radical formed by alkylation at sulfur is apparently not reduced at the potential of the electrolysis but undergoes dimerization. If the substrate is methylated prior to reduction, the sulfonium cation is reduced more easily than the neutral substrate to give the same dimeric product. The initially formed dimer (**35**) eliminates disulfide in an oxidatively induced process during the electrolysis, yielding the final bipyranilidene (**36**) [110].

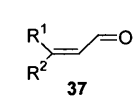


34 **35** **36**

Scheme 8

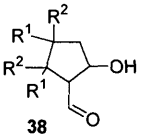
12. Aldehydes

In general, reduction of alkenes activated by CHO, such as **37**, gives preferentially products of mixed coupling (1,3′-coupling). The 3,3′-coupling only takes place when $R^1 = H$ or $R^2 = H$. Both 3,3′- and 1,3-coupling products undergo cyclization to the cyclopentane (**38**) or the tetrahydrofuran (**39**) derivatives. Often these eliminate water to give cyclopentene (**40** or dihydrofuran (**41** derivatives. The pinacol formed by 1,1′-coupling is the only linear dimer formed.



37

a $R^1 = R^2 = Me$
b $R^1 = H$, $R^2 = Me$



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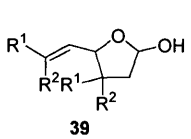

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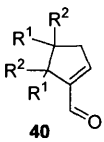

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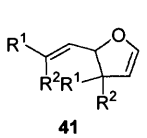


41

A mixture of pinacol and cyclized mixed coupling products, **39a** and **41a** were formed upon reduction of 3-methylcrotonaldehyde (**37a**) at pH 5 (Table 9) [112]. Under these conditions, the intermediates undergoing coupling are expected to be the neutral radicals obtained by protonation at oxygen. The effect of increasing size of R^2 in **37** on the dimeric products [113] is shown in Table 9. In all cases, **39** resulting from the mixed 1,3′-coupling was the major isomer [113].

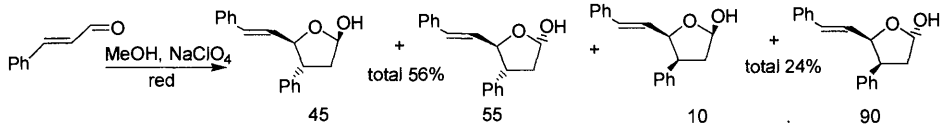
Unsymmetrical coupling is even more prominent in the reduction of cinnamaldehyde in MeOH. Only four stereoisomeric cyclic products were observed (total 80% yield), all derived from mixed coupling [Eq. (10)] [114]. Semi-empirical calculations of the stabilities

Table 9 Influence of Structure on Product Structure and Yields Obtained by Reduction of α,β-Unsaturated Aldehydes (**37**)

Substrate	Conditions[a]	Products and yields	Ref.
$R^1 = R^2 = Me$ (**37a**)	A	**39** 46%, pinacol 8%	[113]
37a	B	**39** 28%, **41** 10%, pinacol 4%	[112]
$R^1 = H, R^2 = Me$ (**37b**)	C	**38** 26%, **39** 53%, pinacol 15%	[113]
$R^1 = H, R^2 = Ph$	D	**39** 80% (see text)	[114]
$R^1 = Me, R^2 = Me_2C{=}CHCH_2CH_2$	A	**39** 36%, pinacol 18%	[113]
(*E*, *E*) ($R^1 = Me, R^2 =$ $Me_2C{=}CHCH_2CH_2C(Me){=}CHCH_2CH_2$)	A	**39** 33%, pinacol 18%	[113]

[a] A: EtOH/acetate buffer (1:1), pH 5, div. cell, Hg-cath., CPE. B: Acetate buffer, pH 5, div. cell, Hg-cath., CPE. C: Acetate buffer, pH 4.7, div. cell, Hg-cath., CPE. D: MeOH, $NaClO_4$, div. cell, Hg-cath., CPE.

of the two sets of stereoisomers indicate that the product distribution is thermodynamically controlled [114].



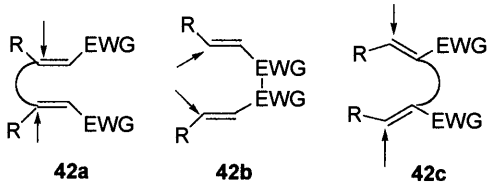
(10)

B. Intramolecular Hydrodimerizations (Hydrocyclizations)

When two identical activated alkene functions are included in the same molecule, intermolecular coupling has to compete with intramolecular hydrocyclization. In most cases the intramolecular reaction, which corresponds to an overall two-electron process, takes precedence. Few mechanistic studies of intramolecular couplings have been reported. The main question is whether the coupling takes place at the mono-radical anion stage in an RS-type reaction (one unit reduced, the other not reduced), or at the bis(radical anion) stage in an RR-type reaction (both units reduced). The last case implies weak electronic interaction between the electrophores.

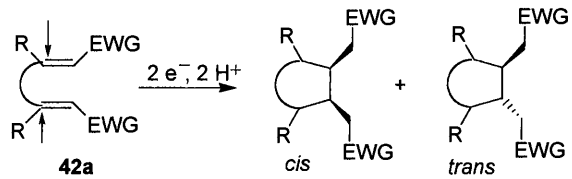
The formal kinetics and diagnostic criteria for the different mechanistic pathways for intramolecular hydrodimerizations under steady-state conditions (LSV, RDE and polarography) have been established [115–117]. For the RS-type mechanisms it is normally assumed that the cyclized radical anion (or the neutral, cyclic radical formed by subsequent protonation) is more easily reduced than the starting material. For the RR-type mechanisms $\Delta E^{0'}$ (the difference in reduction potential of the two electroactive groups) is normally assumed to equal the statistical difference expected for two electronically isolated groups in the same molecule.

The two activated alkene functions may be linked via the β-carbons, **42a**, via the activating group, **42b**, or, less commonly, via the α-carbons, **42c**. Where the two alkene units are linked by direct bonding between the α- or the β-carbons, the two alkenes form a single, conjugated π-system.



1. Intramolecular Coupling of Electrophores Linked Through the β-Carbons

The efficiency of reductive coupling of **42a** depends on the size of the resulting ring, with three- to six-membered rings in general being favored (Table 10) [118]. In the medium of choice, MeCN/water mixtures, the hydrocyclization (HC) products formed from the general structure **42a** by coupling in the β-position were mixtures of the *cis* and *trans* isomers [Eq. (11)], analogous, respectively, to the bimolecular *meso* and (±) couplings in the formation of LHDs. In most of the cases [118], hydrogenated products (2 F and 4 F) and oligomers were formed as well.



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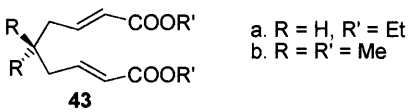


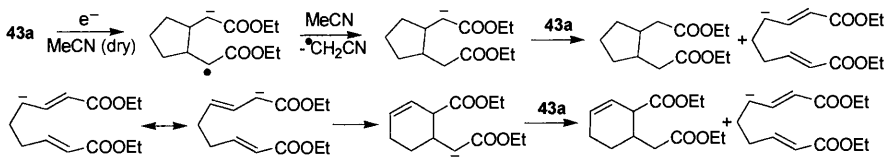
A systematic study of the influence of added water on the reduction of **43a** in MeCN revealed that in the presence of 20% water the HC product (~90%) was obtained as a mixture of *cis* and *trans* isomers in a ratio of ~1:3, but with a charge consumption slightly lower (1.8 F) than the expected 2 F. Decreasing the water content gradually led, with concomitant reduction in charge, to decreasing amounts of HC product and increasing amounts of cyclic (0 F) products arising from base-induced intramolecular Michael addition [119]. With no added water, the HC product (27%) and the Michael addition product (57%) were formed with consumption of 0.4 F. The suggested mechanistic interpretation of these results was that at low water concentrations the intramolecular coupling involves

Table 10 Influence of Structure on Hydrocyclizations of **42a**[a]

EWG	Link	Products and yields
COOEt	$-C(Me)_2-$	HC 57%, *cis*/*trans* ≈ 1:1
COOEt	$-(CH_2)_2-$	HC 34%, *cis* and *trans*, 4-F prod. 20%, LHD 18%
COOEt	$-(CH_2)_3-$	HC 52%, *cis*/*trans* ≈ 1:4, LHD 8%
COOEt	$-O-(CH_2)_2-O-$	HC 42%
COOEt		HC 48% only *trans*, 4-F prod. 19%
CN	$-(CH_2)_2-$	HC 16%, *cis*– and *trans*, oligomers 54%

[a]MeCN/H_2O, Et_4NOTs, Hg-cath., div. cell, CPE. Yields based on current. From Ref. 118.

radical addition to the unreduced function (i.e., an RS-type coupling) followed by hydrogen atom abstraction from the solvent, MeCN (the radical, $^{\cdot}CH_2CN$, being consumed in an unidentified, nonreductive chemical reaction). The resulting anion of the HC product abstracts a proton from unreacted substrate that initiates intramolecular Michael addition (Scheme 9). At higher water concentrations the radical anion is stabilized. This allows formation of the bis(radical anion) and subsequent RR type coupling. At the same time, the water serves as proton donor, thereby inhibiting the Michael addition [119].

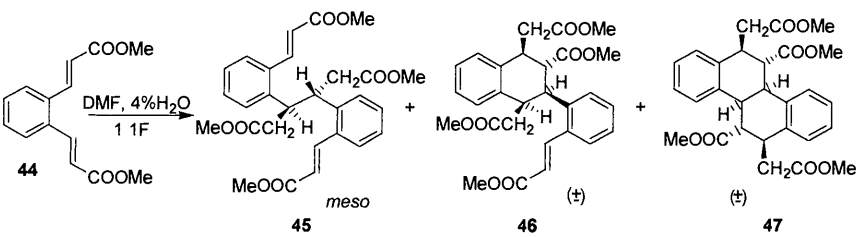


Scheme 9

A similar relationship between product distribution and water content was observed for the analogous substrate containing an extra methylene unit in the link [119]. The Michael addition products were slightly more difficult to reduce than the parent compounds [119].

Formation of the *trans* isomer of the HC product is enhanced in the presence of metal cations and by using a carbon rather than an oxygen acid. For reduction of **43b** in MeCN, the *trans*:*cis* isomer ratio changed from 2.6:1 in MeCN/H_2O (9:1) using AcOH as proton source, to 7.5:1 in MeCN using diethyl malonate as proton source. The selectivity was further enhanced to 14.8:1 when 1.3 equivalents of $CeCl_3$ was added with a total 73% yield of the HC product [19]. As for the bimolecular EHD reactions, the (±) coupling is preferred in the presence of templating cations.

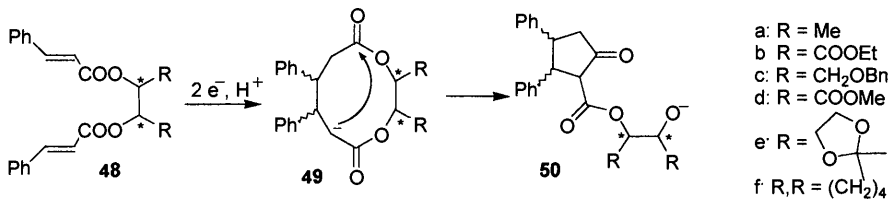
Intramolecular coupling by the RS mechanism would be expected for reduction of **44**. Since the two halves of the molecule interact electronically through the aromatic ring, the first and the second electron transfers are separated by ~ 300 mV [120]. Consequently, only the mono-reduced substrate can participate in coupling following the first electron transfer. However, only intermolecular coupling products (59%) were found upon reduction [Eq. (12)] [121]. The fully hydrogenated monomer (28%) and the half-hydrogenated monomer (7%) were also formed with an overall consumption of 1.1 F. In light of the mechanism for alkyl cinnamate reductions, the intermolecular coupling will be of the RR type, and the initial dimer, **45**, can then under the conditions of the electrolysis undergo one or two Michael additions to yield **46** and **47** (62%). The products **46** and **47** were shown by x-ray crystallography to result from initial (±) coupling, whereas **45** resulted from *meso* coupling [121].



(12)

2. Intramolecular Coupling of Electrophores Linked Through the EWG Groups

Intramolecular reductive coupling of the substrates **48a–c**, where (chiral) diols have been used to link two cinnamoyl units through the activating group, has been tried [80]. The yields of HC products, **50**, are normally low (< 50%) and the enantiomeric excess modest (36–50%, as determined for the 3,4-diphenyladipates obtained after hydrolysis and esterification) [80]. The low yields are most likely due to the necessary formation of a 10-membered cyclic intermediate such as **49**, which subsequently may undergo Dieckmann condensation in aprotic solvents (Scheme 10). Hydrolysis and polymerization have been found as the main reactions in similar systems (**48d–e**) [66]. Voltammetric studies of **48f** (which yields 33% of the HC product) showed that $\Delta E^{0'}$ for reduction of the two electrophores was larger (80 mV) than the statistical value of $\Delta E^{0'}$, and that the intramolecular coupling of the two units in this case takes place at the bis(radical anion) stage [16]. The conclusion is that linking through the EWG via a diol is an approach that is unlikely to be successful due to the necessary formation of large rings in the course of reaction.

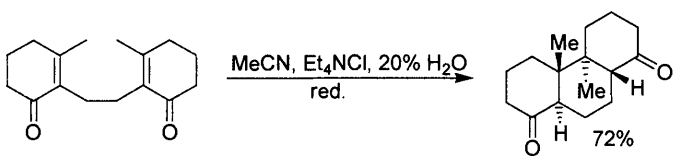


Scheme 10

3. Intramolecular Coupling of Electrophores Linked Through the α-Carbons

Dibenzylidene succinic acid derivatives are examples of substrates with a direct link between the α-carbons. Voltammetry of dimethyl dibenzylidenesuccinate shows two reduction peaks separated by 200 mV, and preparative-scale reduction under a variety of conditions gave none of the cyclobutane derivatives expected from intramolecular cyclization. Monomeric products (2 F or 4 F depending on the working potential) were found together with varying amounts of oligomers [122].

Intramolecular coupling of two α-linked cyclohexenone units can in principle give products corresponding to intramolecular β,β′-coupling, carbonyl–carbonyl-coupling, and mixed β–carbonyl-coupling. However, only the β,β′-coupling HC product corresponding to formation of the most stable *trans–anti–trans* perhydrophenanthrene ring system [Eq. (13)] was formed upon reduction [123].

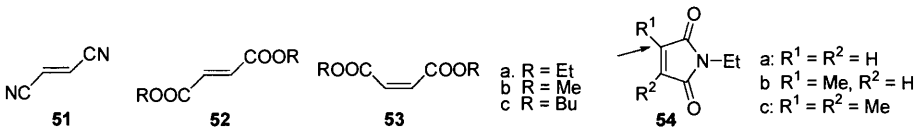


(13)

C. Multiply Activated Alkenes

1. α,β-Diactivated Alkenes

Alkenes activated by electron-withdrawing groups at both ends of the double bond are more easily reduced than the analogous singly substituted alkenes, and the radical anions formed are less reactive. Examples include fumarodinitrile compared to acrylonitrile and dialkyl fumarates compared to alkyl acrylates. Fumarodinitrile (**51**) [2,35,36,48,55,70,71, 124] and simple alkyl fumarates (**52**) [7,10,15,55,70,125,126] have therefore been the subjects of a number of mechanistic studies as models for acrylonitrile and alkyl acrylates. Examples of the formation of LHDs on a preparative scale are given later, in Table 12.



On electroanalytical scales the reductions of **51** and **52** in DMF are 1-F processes, and the data obtained are consistent with dimerization of two radical anions, that is, an RR mechanism. The rate constants for dimerization have been determined by several methods (Table 11), and show a very large difference between **51** and **52**, with the rate constant for dimerization of $\mathbf{51}^{-\cdot}$ being 3–4 orders of magnitude higher than that for dimerization of $\mathbf{52}^{-\cdot}$.

On a coulometric scale, however, the n values for reduction of **51** and **52** were found to be less than one in DMF (see Table 11), probably due to polymerization under the dry conditions [7,55], a behavior similar to but less pronounced than that found for reduction of monoactivated alkenes. Addition of alkali metal cations did not change the n value significantly for **51** [71] but led to an increase in n for **52** [7,71]. At the same time, the overall rate of reaction of $\mathbf{52}^{-\cdot}$ increased considerably [71], an effect interpreted similarly to that observed for monoactivated alkenes (Sec. II.A.7).

In dry MeCN, $n = 0.6$ was found for **51**, but the value increased to 0.94 on addition of water up to 10% [13]. For **52a** in very dry MeCN, the mechanism of the reductive dimerization was examined and the experimental results were interpreted as an RS mechanism under these conditions [125]. However, addition of water increased the rate of reaction considerably, and in the presence of water the kinetic measurements were in accord with the RR mechanism [126]. In DMF, addition of water also accelerates the dimerization process for **52** [7,10], similar to what is observed for many monoactivated alkenes (Sec. II.A.7). The accelerating effect of water in DMF on the dimerization of $\mathbf{52a}^{-\cdot}$ has been studied in greater detail [15]. On the basis of a reaction order in water close to 1, it was suggested that the dimerization reaction takes place between a "free" radical anion and a hydrogen-bonded radical anion [15]. The involvement of hydrogen bonding between radical anions and water may also account for the low activation energies found for the reductive dimerization of **52a** in MeCN [126] and in DMF [10] (see Table 11).

In aqueous solution (0.5 M NaBr), the reduction of **51** is a 2-F process, but addition of small amounts of Bu_4NBr (1 mM) has a pronounced influence on the reduction, which changes into a 1-F process [35]. Addition of Et_4NOTs has the same effect but has to be used in higher concentrations (50 mM) [36]. Similar effects have been observed for other organic additives [35]. The presence of small amounts (10^{-4}–10^{-3} M) of strong surfactants has been shown—regardless of the charge of the surfactant—to cause EHD to take place with high current yields in aqueous solution [36]. The effect of the additives is proposed to

Table 11 Selected Rate Constants for Dimerization of Diactivated Alkenes

Substrate	Conditions	Method	$k_{dim}(RR)$ (M^{-1} s^{-1})	Ref.
trans-NC–CH=CH–CN (**51**)	DMF, Bu_4NI, room temp.[a]	RRDE	7×10^5	[55]
51	DMF, Bu_4NI, 23°C	ESR	$> 10^5$	[70]
51	DMF, Bu_4NBF_4	SECM	2.0×10^5	[124]
trans-EtOOC–CH=CH–COOEt (**52a**)	DMF, Bu_4NI, 25°C[b]	DPSC	37	[7]
52a	DMF, 50 m*M* H_2O, Bu_4NI, 25°C	DPSC	46[h]	[7,10]
52a	DMF, Bu_4NI, 23°C	ESR	30 ± 5	[70]
52a	DMF, Bu_4NI, room temp.	DPSC/DPSCC	44	[71]
52a	MeCN, 35 m*M* H_2O, Bu_4NBF_4, 0°C	DPSC	5.5×10^3 [i]	[126]
52a	MeCN, 555 m*M* H_2O, Bu_4NBF_4, 0°C	DPSC	2.22×10^5 [i]	[126]
52a	NH_3, $MeBu_3NI$, −43°C[c]	CV	0.1	[52]
trans-MeOOC–CH=CH–COOMe (**52b**)	DMF, Bu_4NI, room temp.[d]	RRDE	1.1×10^2	[55]
52b	DMF, Bu_4NI, room temp.[d]	CV	1.6×10^2	[55]
52b	DMF, Bu_4NI, 23°C	ESR	$(1.60 \pm 0.26) \times 10^2$	[70]
52b	DMF, Bu_4NBF_4	SECM	1.7×10^2	[124]
52b	DMF, Bu_4NI, room temp.	DPSC/DPSCC	1.2×10^2	[71]
trans-BuOOC–CH=CH–COOBu (**52c**)	DMF, Bu_4NI, room temp.	DPSC/DPSCC	25	[71]
cis-EtOOC–CH=CH–COOEt (**53a**)	DMF, Bu_4NI, room temp.[e]	RRDE	9.1×10^4	[127]
cis-MeOOC–CH=CH–COOMe (**53b**)	DMF, Bu_4NI, room temp.[f]	RRDE	1.9×10^5	[127]
cis-BuOOC–CH=CH–COOBu (**53c**)	DMF, Bu_4NI, room temp.[g]	RRDE	6.9×10^4	[127]
57a	DMF, 0.05–0.4 *M* H_2O, Bu_4NBF_4, 21.7°C	DCV	7.3×10^5	[128]
57b	DMF, 0.05–0.4 *M* H_2O, Bu_4NBF_4, 5.6°C	DCV	5.6×10^5	[128]
57b	MeCN, 0.3–10% H_2O, Et_4NClO_4	CPSV	1.3×10^7	[129]
57c	DMF, 0.05–0.4 *M* H_2O, Bu_4NBF_4, 6.5°C	DCV	6.6×10^5	[128]
57d	DMF, 0.05–0.4 *M* H_2O, Bu_4NBF_4, 17.5°C	DCV	2.2×10^6	[128]
57e	DMF, 0.05–0.4 *M* H_2O, Bu_4NBF_4	DCV	$> 10^7$	[128]

[a] $n = 0.44$.
[b] $n = 0.6$, increases to 1 when Li^+ is added.
[c] $n = 0.5$, even when *i*-PrOH or AcOH are added as proton donors.
[d] $n = 0.62$.
[e] Rate constant for isomerization of $\mathbf{53a}^{\cdot-}$ to $\mathbf{52a}^{\cdot-}$ equal to 6.0 s^{-1}.
[f] Rate constant for isomerization of $\mathbf{53b}^{\cdot-}$ to $\mathbf{52b}^{\cdot-}$ equal to 2.2 s^{-1}.
[g] Rate constant for isomerization of $\mathbf{53c}^{\cdot-}$ to $\mathbf{52c}^{\cdot-}$ equal to 6.7 s^{-1}.
[h] $E_a = 4.6$ kcal/mol.
[i] $\Delta H^{\neq} = -3.5$ kcal/mol, $\Delta S^{\neq} = -50$ cal/K/mol when C_{H_2O} in the range 70–278 m*M*.

be attenuation of the rate of protonation when water is excluded from the electrode surface by adsorption of organic species. Similarly for **52a**, small amounts of strong surfactants prevent protonation in aqueous solution and favor the (fast) dimerization of the radical anions [48]. In these conditions the rate-determining step is suggested to be dimerization of two ion-paired radical anions (ion pairing with the supporting electrolyte cations) [36]. The rate constant for the dimerization step was estimated to be in the range 10^8–10^{10} M^{-1} s^{-1} on the basis of DPSCC measurements [36], that is, 2–4 orders of magnitude higher than the value determined for dimerization in DMF (Table 11).

Dialkyl maleates (**53**) are more difficult to reduce (by ~ 0.3 V) than the corresponding dialkyl fumarates (**52**), but at the radical anion stage the maleates isomerize to the fumarates. The rate constant for the isomerization increases with increasing size of the alkyl group (Table 11) [127]. Interestingly, the rate constant for dimerization of $\mathbf{53}^{\cdot-}$ is more than three orders of magnitude higher than that for the corresponding $\mathbf{52}^{\cdot-}$ (Table 11), and the cross-coupling of $\mathbf{53}^{\cdot-}$ and $\mathbf{52}^{\cdot-}$ was found to be negligible [127].

Large-scale EHD of alkyl fumarates and maleates has been studied, since the tetracarboxylate product has industrial interest [130]. In MeOH the undesired hydrolysis of **53b** is prevented during electrolysis. The use of sodium or lithium acetate as supporting electrolyte, rather than R_4N^+ salts, enhances the formation of dimer compared to hydrogenation product [130]. The best preparative results (> 80% LHD, ~ 10% hydrogenation product and ~ 5% resulting from addition of MeOH to the double bond) were obtained using a graphite felt cathode in an undivided flow cell [130]. There are significant differences in the solubility of **53b** and of **52b** in MeOH: **53b** is miscible with MeOH up to 50% w:v, but **52b** is only soluble in 3% w:v. The rate constant for dimerization was found by application of a RRDE to be 10^7 M^{-1} s^{-1} for both radical anions under these conditions [131]. At the same time isomerization of **53b** to **52b** took place at the radical anion stage. From FT-IR measurements in MeOH (NaOAc) it was found that the amount of **52b** present in the solution increased during the electrolysis, and it was estimated that 30% of the **53b** initially reduced was converted to **52b** [131].

When substituted *N*-ethyl maleimides (**54**) were reduced in aqueous buffers at neutral pH, two of the substrates, **54a** and **54b**, gave predominantly the LHDs whereas the third substrate, **54c**, only gave the hydrogenation product (Table 12). Under acidic conditions, all three substrates were reduced to the hydrogenated monomer [133].

Hydrodimerization of unsymmetrically α,β-diactivated alkenes may in principle give rise to three types of coupling products: the α,α'-LHD formed by coupling between the two α-carbons, the β,β'-LHD formed by coupling between the two β-carbons, and the α,β'-LHD formed by coupling between the α-carbon in one molecule and the β-carbon in the other. Examples are given in Table 12.

2. α,α,-Diactivated Alkenes

A significant difference is expected between α,β- and α,α-diactivated alkenes since α,α-diactivation will tend to localize the unpaired spin density at the β-carbon, thereby facilitating dimerization. Reduction of 3-carbethoxy- and 4-carbethoxy-coumarin, **55** (α,α-diactivated) and **56** (α,β-diactivated), in DMF and in aqueous/ethanolic buffers [134] shows distinct differences in the competition between dimerization and hydrogenation. In hydroxylic media, **56** leads to the hydrogenation product under acidic conditions and to product mixtures (1–2 F) under basic conditions. In DMF, $\mathbf{56}^{\cdot-}$ is stable on a voltammetric time scale. In contrast, reduction of **55** is a 1-F process both in hydroxylic media

Table 12 Hydrodimerization of α,β-Diactivated Alkenes

Substrate	Conditions[a]	Products and yields	Ref.
trans-NC–CH=CH–CN (**51**)	A	LHD[b]	[2]
trans-EtOOC–CH=CH–COOEt (**52a**)	B	LHD 83%[c]	[4]
cis-EtOOC–CH=CH–COOEt (**53a**)	B	LHD 94%, 2-F prod. 5%[d]	[132]
cis-BuOOC–CH=CH–COOBu (**53c**)	C	LHD 70%[c]	[2]
trans-$[Me(CH_2)_3CH(Et)CH_2OOCCH=]_2$	D	LHD 80%[c]	[2]
cis-$[Me(CH_2)_3CH(Et)CH_2OOCCH=]_2$	D	LHD 66%	[2]
trans-Ph(O)C–CH=CH–C(O)Ph	B	LHD 44%[b,c]	[4]
54a ($R^1 = R^2 = H$), $E_{1/2} = -0.77$ V	E	LHD 99%, 2-F prod 1%, $n = 1.12$	[133]
54b ($R^1 = Me$, $R^2 = H$), $E_{1/2} = -0.90$ V	E	LHD 79%, 2-F prod. 21%, $n = 1.31$	[133]
54c ($R^1 = R^2 = Me$), $E_{1/2} = -1.02$ V	E	LHD 0%, 2-F 100%, $n = 1.73$	[133]
NC–C_βH=C_αH–C(O)Ph	F[e]	β,β'-LHD 55%[b,c]	[4]
NC–C_βH=C_αH–COOEt	B	β,β'-LHD 80%, α,β'-LHD 4%[c]	[4]
EtOOC–C_βH=C_αH–C(O)Ph	F	β,β'-LHD 69%[a] α,β'-LHD 21%[c]	[4]
Me_2NOC–C_βH=C_αH–COOEt	B	β,β'-LHD 63%, α,β'-LHD 30%[c]	[4]

[a] A: MeCN/H_2O, Et_4NOTs. B: DMF/H_2O, Et_4NOTs, Hg-cath., div. cell, CCE. C: H_2O, $MeBu_3NOTs$, Hg-cath., div. cell, CCE. D: EtOH/H_2O, $MeBu_3NOTs$, Hg-cath., div. cell, CCE. E: EtOH/buffer (1:3), KNO_3, pH 6, Hg-cath., div. cell, CPE. F: acrylonitrile/H_2O, Et_4NOTs, Hg-cath., div. cell, CCE.

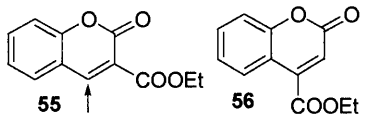
[b] Mixture of *meso* and (±).

[c] Based on current passed.

[d] Based on substrate consumed. Two stereoisomers of the LHD were formed in the ratio 93:7 but not assigned.

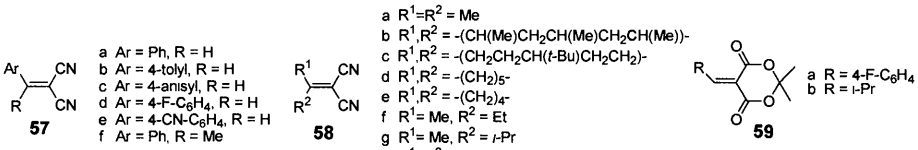
[e] Acid added during electrolysis to keep solution neutral.

(independent of pH) and in DMF, with the product being a diastereomeric mixture of LHDs [134].



55 56

The presence of two electron-withdrawing groups at the α-carbon reduces the basicity of the radical anions considerably, and, for example, the radical anions derived from **57a** [135,136] and **59a** [137] are not protonated by AcOH in DMF and MeCN, respectively. Also alkylidenemalonitriles (**58**) dimerize in competition with hydrogenation in the presence of AcOH (Table 13).



Kinetic data for the dimerization of the radical anions of substituted benzylidene malonitriles (**57**) were in agreement with the simple RR mechanism, and the rate of reaction was not influenced by the concentration of water (Table 11) [128]. Compound **57b** was studied over a very broad concentration range (2–100 m*M*) by chronopotentiometry [138], in order to investigate possible mechanistic changes in going from the low concentrations normally applied for analytical work to the high concentrations suited for preparative work. When the water content in the DMF solution was high relative to the substrate concentration (10% water), the dimerization followed the RR mechanism independently of substrate concentration. In dry DMF the data indicated that although the mechanism was unchanged, changes in the (specific) solvation of the radical anions with increasing substrate concentration affected the rate of the dimerization step [138]. The same mechanistic conclusion was drawn in a study of **57b** in MeCN with various amounts of water by CPSV, where the rate constant for dimerization was considerably higher than the one measured in DMF [129] (Table 11).

On a preparative scale, different ratios of *cis* and *trans* isomers of the CHD, 2-amino-4,5-diaryl-2-cyclopentene-1,1,3-tricarbonitrile, formed upon reduction of benzylidenemalonitrile (**57a** under apparently identical conditions (DMF, 1 *M* AcOH) have been reported: *cis*:*trans* = 1:1 [139] and exclusively *trans* [140]. In a later systematic study of the reduction of **57a** in DMF (1 *M* AcOH), the *cis*:*trans* ratio was shown to change within the range 1:1 to 0:1 as a function of substrate concentration, nature of supporting electrolyte, and the degree of conversion. Only the *trans* isomer was formed when an electron transfer catalyst was used [135]. Small cations and low substrate concentrations favored formation of the *cis* isomer, and progressively more *cis* was formed as the electrolysis progressed. The authors invoke a competition between the RR and the RS mechanism as a possible explanation, although not all the experimental data are in accord with the suggestion [135].

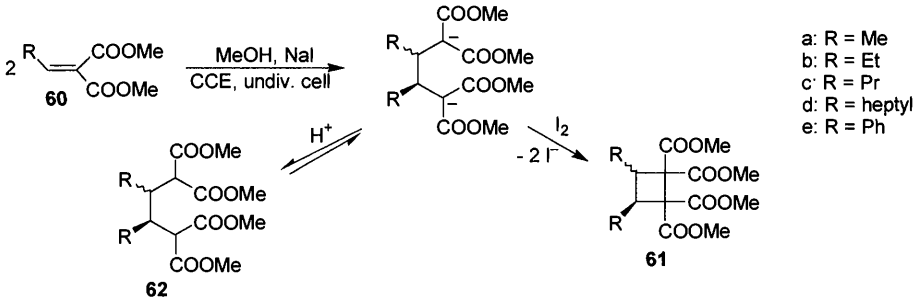
Reduction of alkylidene malonates (**60**) in MeOH in an undivided cell using alkali metal halides as supporting electrolytes results in the unusual formation of 3,4-disubstituted 1,1,2,2–cyclobutanetetracarboxylates, **61** [141]. Cyclobutane formation requires 4–7 F and is not a radical anion-catalyzed cycloaddition. The process was explained by the mechanism in Scheme 11, where the cyclization takes place by chemical oxidation of the

Table 13 Hydrodimerization of α,α-Diactivated Alkenes

Substrate	Conditions	Products and yields	Ref.
57a	DMF, Bu_4NI, 1 *M* AcOH, C-cath., div. cell, CPE	CHD 95% (±) : *meso* = 1:1[a]	[139]
57a	MeCN, $LiClO_4$, 1 *M* AcOH, Hg-cath., div. cell, CPE	CHD 85%[b]	[142]
57f	DMF, Bu_4NI, 1 *M* AcOH, C-cath., div. cell, CPE	CHD 90% (±) : *meso* = 3:2[a]	[139]
57f	MeCN, $LiClO_4$, 1 *M* AcOH, Hg-cath., div. cell, CPE	CHD 93%[b]	[142]
58a	MeCN, $LiClO_4$, 1 *M* AcOH, Hg-cath., div. cell, CPE	LHD 87%[b]	[142]
58b	DMF, $LiClO_4$, 1 *M* AcOH, Hg-cath., div. cell, CPE	CHD 60%[b]	[142]
58b	MeCN, $LiClO_4$, 1 *M* AcOH, Hg-cath., div. cell, CPE	CHD 75%[b]	[142]
58c	DMF, Bu_4NI, 1 *M* AcOH, Hg-cath., div. cell, CPE	CHD 70%[b] 2-F prod. 15%	[142]
58d	DMF, Bu_4NI, 1 *M* AcOH, Hg-cath., div. cell, CPE	CHD 70%[b] 2-F prod. 20%	[142]
58e	DMF, Bu_4NI, 1 *M* AcOH, Hg-cath., div. cell, CPE	CHD 64%[b] 2-F prod. 15%	[142]
60a	DMF/H_2O, Et_4NOTs, Hg-cath., div. cell, CCE	LHD 90%[a]	[2]
60e	DMF/H_2O, Et_4NOTs, Hg-cath., div. cell, CCE	LHD 45%[a]	[2]
60a	MeOH, NaI, GC-cath., undiv. cell, CCE, 60°C	**61a** 73% *trans*/*cis* = 1.35	[141]
60b	MeOH, NaI, GC-cath., undiv. cell, CCE, 60°C	**61b** 69% *trans*/*cis* = 1.30	[141]
60c	MeOH, NaI, GC-cath., undiv. cell, CCE, 60°C	**61c** 58% *trans*/*cis* = 1.23	[141]
60d	MeOH, NaI, GC-cath., undiv. cell, CCE, 60°C	**61d** 52% *trans*/*cis* = 1.17	[141]
60e	MeOH, NaI, GC-cath., undiv. cell, CCE, 60°C	**61e** 56% *trans*/*cis* = 3.00	[141]

[a] Based on current passed.
[b] Stereochemistry not reported.

dianion of the LHD by anodically formed halogen. The LHD, **62** was formed initially as determined by interruption of the electrolysis after the passage of 2 F. The yield of **61** decreased when the size of R increased (Table 13), and the *trans* isomer was formed in slight excess. Electrolysis using $NaClO_4$ as supporting electrolyte gave only the LHD, **62**, with a (±):*meso* ratio close to 1. Hydrogenation, addition of MeOH to the double bond, and oxidative rearrangement of the substrate were found to be side reactions [141].



Scheme 11

The derivatives of Meldrum's acid, **59a–b**, undergo reductive dimerization in MeCN, and the mechanism has been studied [137,143]. An RS mechanism with rate-determining electron transfer has been invoked either as the only mechanism (for **59b**) or as one of two parallel reaction pathways (for **59a**) in order to explain the apparent reaction orders found by DCV or LSV in the presence of AcOH [137]. However, AcOH (pK(AcOH) = 12.3 in DMSO [144]) is not likely to be strong enough to protonate the dimer dianion, since the basicity of the dimer dianion is expected to be close to that of the conjugate base of Meldrum's acid (pK(Meldrum's acid) = 7.3 in DMSO [145]). Consequently, the dimerization may be reversible, and this, in turn, may lead to anomalous apparent reaction orders, although the coupling is of the RR type [76].

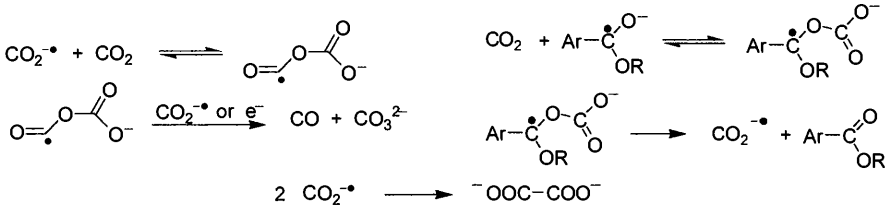
D. Hydrodimerization of CO_2

Compounds containing carbon–oxygen or carbon–nitrogen multiple bonds may undergo reductive carbon–carbon bond-forming reactions. Reductive dimerizations of aldehydes and ketones are covered in Chapter 10, reductive couplings of esters and other carboxylic acid derivatives are covered in Chapter 12, and reductive couplings involving carbon–nitrogen double bonds are covered in Chapter 11. Here only reductive couplings involving reductive dimerization of CO_2 will be mentioned.

The abundance of CO_2 makes it attractive as a carbon source (Cl chemistry), and consequently the utilization of CO_2 as substrate in C–C bond-forming electrochemical reactions is of considerable interest. Direct reduction of CO_2 takes place at rather low potentials (< -2.2 V in aprotic medium) and normally leads to mixtures of the C–C coupling product, oxalate, and CO + CO_3^{2-} when carried out in aprotic solvents at inert electrodes such as Hg or Pb (Scheme 12). Monomeric products dominate when the reduction is carried out at electrodes at which either CO_2 or the reduction products are chemisorbed. Numerous attempts have therefore been made to catalyze the reduction and optimize the yield of oxalate.

For direct reduction at constant current in DMF (Bu_4NClO_4) at an Hg cathode, it was found that low CO_2 concentrations and high temperatures favored formation of

oxalate compared to CO + CO_3^{2-} [146]. Indirect reduction of CO_2 using radical anions derived from aromatic esters and nitriles [147] in anhydrous DMF leads exclusively to formation of oxalate (Scheme 13). Based on these two sets of experiments, it is proposed that oxalate formation takes place via the coupling of two radical anions in solution (with a second-order rate constant around $5 \times 10^8\ M^{-1}\ s^{-1}$, whereas the formation of CO + CO_3^{2-} takes place via the two first reactions in Scheme 12. These reactions are restricted to the electrode surface where nonspecific electrostatic interactions make the formation of the CO_2–$CO_2^{-\cdot}$ adduct exothermic [146]. Analysis of kinetic data for the indirect reduction of CO_2 within the framework of Marcus theory indicates that the catalyst radical anions (derived from aromatic esters or nitriles) do not react with CO_2 via outer-sphere electron transfer. More likely, the catalysts react via bond formation followed by homolytic bond cleavage leading to the $CO_2^{-\cdot}$ and the neutral catalyst precursor [147] (Scheme 13). For other types of organic radical anions the reaction with CO_2 may lead to carboxylation rather than to electron transfer (see Sec. IV.A.1).



Scheme 12

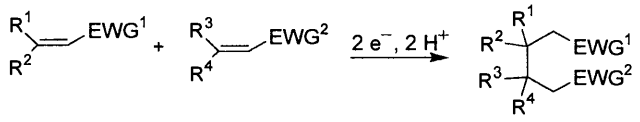
Scheme 13

Metal complexes have also been used as catalysts for CO_2 reduction, but only few examples are known where the major product is oxalate [148 and refs. therein]. The reductions are inner-sphere processes, and oxalate formation takes place at significantly higher potentials than by direct reduction or reduction via organic catalysts (which typically have values of $E^{0'}$ in the range −1.95 V to −2.25 V). Catalytic dimerization of CO_2 in MeCN has been reported to take place at −1.5 V using the complex $[(RhCp^*)_3(\mu_3\text{-}S)_2]^{2+}$, at −0.7 V using the complex $[(CoCp^*)_3(\mu_3\text{-}S)_2]^{2+}$, and at −1.6 V using $[(IrCp^*)_3(\mu_3 - S)_2]^{2+}$ [148].

III. MIXED HYDROCOUPLING OF ACTIVATED ALKENES

A. Intermolecular Mixed Hydrocouplings

Coelectrolysis of different activated alkenes may lead to cross-coupling and formation of the mixed hydrocoupling product (MHC) [Eq. (14)]. Only cross-couplings where a simple activated alkene (acrylonitrile, **7**, or, e.g., **13a**) is one of the substrates have been studied systematically [4,29,104,149,150].



(14)

The MHCs are normally additional to the two LHDs formed by homocoupling. Mechanistic studies on cross-couplings are scant and inconclusive. The two main mechanistic proposals are (1) Michael addition of the radical anion (or dianion) of the more easily

reduced substrate to the other, neutral substrate, and (2) coupling between the two types of radical anions. In preparative work it has been found that (a) the relative yield of the MHC increases at potentials where both substrates are reduced [149,150]; (b) in controlled-potential electrolysis at a mercury pool cathode the potential distribution is significantly nonuniform [150]; and (c) for reduction at the potential of the most easily reduced alkene, the yield of the MHC depends on the difference in reduction potentials and on the relative concentrations, being favored by small differences and an excess of the more difficultly reduced substrate. Under the latter conditions, formation of the LHD of the less activated alkene is suppressed.

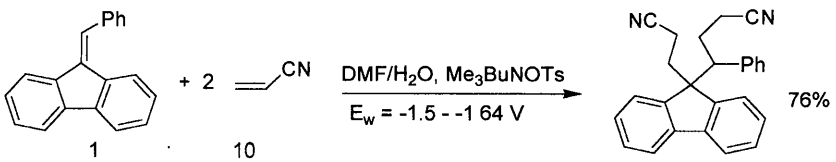
These findings, together with those of more general mechanistic work on homocoupling of acativated alkenes, indicate that the most likely pathway for MHC formation is coupling between the two different radical anions. The beneficial effect of a small difference in reduction potentials is consistent with electron transfer to the less activated alkene either directly at the cathode or by electron transfer in solution from the other radical anion. Similarly, formation of an adequate concentration of the radical anion of the less activated alkene is favored by the use of this alkene in excess.

Obviously, the relative magnitudes of the rate constants for the two LHD reactions and of that for the cross-coupling of the two different radical anions will affect the efficiency of MHC production. Even for equal concentrations of the two radical anions, the three individual rate constants must be similar to result in the statistical distribution of MHC and LHD products.

1. Couplings With Acrylonitrile

Reduction of **7** takes place at approximately −1.9 V. Thus, **7** is normally the component that is most difficult to reduce and used in excess or even as solvent (Table 14). In a few cases, mixed coupling of **7** with less-activated alkenes (hydrocarbons) has been attempted (Table 14). In most cases, hydrogenation (2 F) of one or both of the alkenes takes place in addition to coupling, analogous to results from attempted homocoupling of poorly activated alkenes.

For some substrates the product of mixed coupling with **7** contains two or more acrylonitrile units, as in Eq. (15) [29], probably formed by Michael addition of relatively stable anionic intermediates to acrylonitrile.



(15)

One of the few mechanistic studies of mixed coupling reactions involves the reduction of dimethyl fumarate, or diethyl maleate, in the presence of the less easily reduced compounds **7** or cinnamonitrile, [151]. In anhydrous DMF (Bu_4NI), the individual rate constants for dimerization of **52b**$^{-\cdot}$ and of **9**$^{-\cdot}$ are known (110 and 880 M^{-1} s^{-1}, respectively, (Tables 11 and 3); that is, **9**$^{-\cdot}$ dimerizes faster than **52b**$^{-\cdot}$ by a factor of 8, and $\Delta E_{1/2} = 0.41$ V. With a twofold excess of **9** RRDE experiments at potentials where only **52b** is reduced indicated that the normal RR homocoupling of **52b**$^{-\cdot}$ took place with a second-order rate constant identical to that measured in the absence of **9**. RRDE experiments at a potential where both substrates are reduced revealed that electron transfer from **9**$^{-\cdot}$ to unreduced **52b** was the major reaction of $^{-\cdot}$ [151]. No product studies were reported for

Table 14 Mixed Hydrocouplings With Acrylonitrile (7) and Ethyl Acrylate (**13d**)

Substrate	$C_{substrate}/C_X$	Conditions	Products and yields	Ref
X = 7				
Hydrocarbons:				
Ph–CH=CH_2(≈ −2.4 V)	3:1[a]	DMF, 2.5% H_2O, Et_4NOTs, div cell, E_w = −2.45 V	MHC 48%,[b] LHD-**7**, 2F of Ph–CH=CH_2 (major)	[149]
Ph_2C=CH_2(≈ −2.2 V)	3:1[a]	DMF/H_2O, Et_4NOTs, div. cell, E_w = −2.30 V	MHC (major), LHD-**7**, LHD of Ph_2C=CH_2, 2 F of **7**	[149]
Nitriles:				
CH_2=C(CN)CH_2CH_2CN (**8b**)	1:1	DMF/H_2O, $MeEt_3NOTs$	MHC, LHD-**7**, LHD-**11b** (statistical distribution)	[53]
NCCH=$CHCH_2CH_2CN$ (≈ −1.9 V)	1:1	H_2O, K_2HPO_4, div. cell, CCE	MHC 54%[c]	[153]
CH_2=CHCH=CHCN (−1.5 V)	1.6	H_2O, Et_4NOTs, E_w = −1.71 V	MHC 57%[d,e]	[154]
58a,e-i (≈ −1.7 V)	1·2	H_2O, K_2HPO_4, pH 5–6, div. cell, Pb cath.	MHC: **58a** 24%, **58f** 19%, **58g** 13%, **58h** 14%, **58i** 6%, **58e** 21%[c]	[155]
Esters.				
CH_2=CHCOOMe (**13a**)	1.8·1	H_2O, K_2HPO_4, pH 6–8, undiv. cell, graphite cath., CCE	MHC 50%, LHD-**13a** 2.5%, LHD-**7** 15.5%[c]	[156]
CH_2=CHCOOEt (**13d**) (≈ −1.8 V)	1:5	H_2O, Et_4NOTs, E_w = −1.8 V	MHC 60%[d], LHD-**7**	[157]
13d (≈ −1.8 V)	1:1	DMF/H_2O, $MeEt_3NOTs$, E_w = −1.83 to −1.85 V	MHC, LHD-**7** major, LHD of CH_2=CHCOOEt minor	[154]
CH_2=(COOEt)(NHCOMe)	1:10	H_2O, Et_4NOTs, E_w = −1.75 V	MHC 30%, [d] LHD-**7**	[154]
trans-EtOOCCH=CHCOOEt (**52a**) (−1.54 V)	[f]	**7**, H_2O, Et_4NOTs[g]	MHC	[4]
cis-EtOOCCH=CHCOOEt (**53a**)	1: > 10[h]	DMF/H_2O, Et_4NOTs, E_w = −1.5 V[g]	MHC, LHD-**53a** minor, LHD-**7**, 2 F of **53a** major	[150]
53a(≈ −1.4 V)	1:2	DMF/H_2O, Et_4NOSO_2Ph, E_w = −1.3 to 1.4 V[g]	MHC 11%, LHD-**53a** 80%[d]	[154]
Ketones:				
CH_2=CHCOMe (**22a**)	[f]	**7**, H_2O, Et_4NOTs	MHC minor, CHD-**22a**, LHD-**7**	[54]
Me_2C=CHCOMe (**22b**)	1:10	Et_4NOTs, H_2O, E_w = −1.65 to 1.7 V	MHC major	[104]
PhCH=CHCOMe (**23a**)	1:8	Et_4NOTs, E_w = −1.43 to −1.5 V[g]	MHC small amount, LHD-**23a** major	[104]
Difunctional.				
trans-NCCH=CHCOOEt	1: > 20	DMF/H_2O, Et_4NOTs, E_w = −1.5 V[g]	MHC, LHD of NCCH=CHCOOEt major, 2 F of NCCH=CHCOOEt	[150]
trans-NCCH=CHCOOEt (−1 45 V)	[f]	**7**, H_2O, Et_4NOTs[g]	MHC trace	[4]
trans-Me_2NCOCH=CHCOOEt (−1.76 V)	[f]	**7**, H_2O, Et_4NOTs[g]	MHC 50%[d,i] LHD of Me_2NCOCH=CHCOOEt, 2 F of Me_2NCOCH=CHCOOEt	[4]
X = 13d				
9-Benzylidenfluorene (**2**)	1:10	DMF, H_2O, $Me_3BuNOTs$, E_w = −1.5 V[j]	MHC <20%[k], 2 F of **2**	[29]
NCCH=$CHCH_2CH_2CN$ (≈ −1.9 V)	1:2[l]	H_2O, K_2HPO_4, div. cell, CCE	MHC	[153]
CH_2=CHCH=CHCN (−1.5 V)	1:8	MeCN, H_2O, Et_4NOTs, E_w = −1.67 to −1.70 V	MHC[m]	[154]
58a,e–i (≈ −1.7 V)	1:2[n]	H_2O, K_2HPO_4, pH 5–6, div. cell, Pb cath.	MHC: **58a** 19%, **58f** 15%, **58g** 8%, **58h** 8%, **58i** 2%, **58e** 13%[k]	[155]
cis-EtOOCCH=CHCOOEt (**53a**)	1: > 10[n]	DMF, H_2O, Et_4NOTs, E_w = −1.5 V[j]	MHC, LHD-**53a** minor, 2 F of **53a** major, 2 F of **13d**	[150]

[a] **7** added gradually; [b] 5-Phenylpentannitrile and 4-phenylpentannitrile (15·1), yield based on **7**; [c] Yield based on current; [d] Based on substrate.; [e] 1,6-Dicyanohexane isolated after catalytic hydrogenation, i e., product derived from coupling in δ-position; [f] **7** as solvent, substrate added slowly during electrolysis; [g] AcOH added during electrolysis to keep medium acidity constant.; [h] Substrate added slowly during electrolysis.. [i] Coupling α to COOEt/coupling α to $CONMe_2$ (1:2).: [j] AcOH added during electrolysis to keep medium acidity constant; [k] Based on substrate; [l] Methyl acrylate was used in stead of ethyl acrylate; [m] The product derived from coupling in δ-position was isolated after catalytic hydrogenation (in small amounts); [n] Substrate added slowly during electrolysis.

mixed coupling of **52b** with **9**. For **7** and **52b** $\Delta E_{1/2} > 0.4$ V, and direct formation of the dianion of **52b** takes place before the reduction of **7**. Even in the presence of ~50-fold excess of **7** the perturbation of the RRDE and CV response of **52b** is modest at the potential where $\mathbf{52b}^{-\cdot}$ is formed, giving rise only to a slight increase in the rate of disappearance of $\mathbf{52b}^{-\cdot}$ [151].

The voltammogram of diethyl maleate, **53a**, is, unlike that of **52b**, significantly altered in the presence of a 50-fold excess of **7**. The reduction potentials of the maleates are shifted approximately 0.3 V cathodic relative to the reduction potentials of the fumarates (see Sec. II.C.1) [151], and electron transfer from $\mathbf{53a}^{-\cdot}$ to **7** is therefore expected to be faster than from $\mathbf{52b}^{-\cdot}$. However, dimerization of $\mathbf{53a}^{-\cdot}$ is much faster than of $\mathbf{52b}^{-\cdot}$ (see Sec. II.C.1), and since the presence of **7** affects the voltammogram of **53a**, reaction between $\mathbf{53a}^{-\cdot}$ and **7** must also be fast.

Coelectrolysis of equal amounts of **7** and α-methyleneglutaronitrile (**8b**) (**7** and **8b** are reduced at about the same potential) gives a mixture of the three expected products (the two LHDs and the MHC) in relative amounts corresponding to random coupling of the radical anions [53]. In this case the two components are structurally similar, suggesting that the individual dimerization rate constants may also be similar. The alkylidenemalonitriles, **58**, which are all reduced around −1.7 V, gave modest amounts of the MHC when coelectrolyzed with a twofold excess of **7** (Table 14), with the yield decreasing with increasing size of R^2.

2. Couplings With Alkyl Acrylate and Crotonate

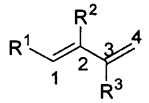
Simple alkyl acrylates have been used as partner in mixed hydrocoupling reactions in a number of cases (Table 14). Like mixed couplings with **7**, LHD formation and hydrogenation compete with formation of the MHC of alkyl acrylates. Coelectrolysis of ethyl 3,4-dimethoxycinnamate ($E_{1/2} = -1.94$ V) with ethyl crotonate ($E_{1/2} = -2.37$ V) in a molar ratio of 1:7.2 in MeCN at $E_w = -2.03$ V gave none of the MHC but only the CHD of the cinnamate. The only product derived from the crotonate was diethyl 2-ethylidene-3-methylglutarate (49%) formed by action of an EGB, most likely the dimer dianion of the cinnamate [61].

3. Other Intermolecular Mixed Hydrocouplings

Reduction of diethyl fumarate, **52a**, and the simple enone **22a** (1:10) in MeCN/water (Et_4NOTs) at a potential between the two reduction potentials ($\Delta E \approx 0.2$ V) gave the MHC as the major product [104]. Reduction of dibutyl maleate, **53c**, and 2-vinylpyridine, **6a** (1:5), in DMF/water (Et_4NOTs) at a potential where only the maleate is reduced ($\Delta E \approx 0.15$ V), leads to a mixture of the two LHDs and the MHC. Analogous results were found for coelectrolysis of 4-vinylpyridine, **6b**, with an excess of the simple enone, **22a** ($\Delta E \approx 0.1 V$) [33]. The distribution between the different hydrodimers was reported.

Mixed hydrocoupling, in DMF, between simple 1,3-dienes, **63** (R^1, R^2, R^3 = H, Me), and alkenes activated by ester or keto groups has been attempted [152]. Yields of the MHC are usually poor (0–58%), the LHD of the activated alkene predominating. Again, yields of the MHC increase as the difference between the reduction potentials of the two components decreases; for example, no MHC was formed when ethyl 3,3-diphenylacrylate (−1.70 V) or **22b** (−1.89 V) was coelectrolyzed with butadiene (**63a** (−2.66 V), or if cyclopentadiene (< −2.8 V) was coelectrolyzed with ethyl 3-methylcrotonate, **13b** (−2.46 V). The only combination giving reasonable yield (58%) of the MHC was coelec-

trolysis of **63a** with **13b** (−2.46 V) [152]. This indicates that electron transfer in solution is required for mixed coupling.

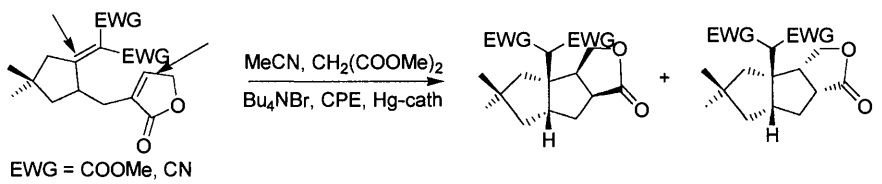


63

a: $R^1 = R^2 = R^3 = H$

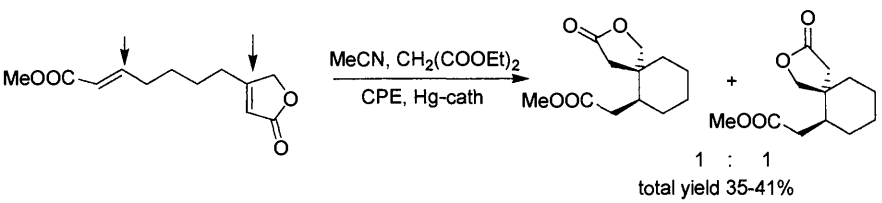
B. Intramolecular Mixed Hydrocouplings

Intramolecular mixed hydrocoupling was achieved for the system displayed in Eq. (16) (dimethyl malonate added as a proton donor). Two stereoisomeric tricyclic products (1:1) were obtained (90% with EWG = COOMe and 23% with EWG = CN). For EWG = CN, higher yields and higher stereoselectivity were obtained using as supporting electrolyte $LiClO_4$ (77% yield with 3:1 ratio of isomers) or $Mg(ClO_4)_2$ (62%, 11.4:1). The stereoselectivity is probably due to chelation of the metal cation with the carbonyl oxygen of the lactone and one of the cyano nitrogens, which favors the two functions being on the same face of the new ring [158]. Reduction of the monoester and of the mononitrile under identical conditions gives hydrogenation of the double bond of the lactone unit and no cyclization. This indicates that the α,β-unsaturated lactone is more easily reduced than the α,β-unsaturated monoester/mononitrile. The α,β-unsaturated dinitrile and diester are the electrophores in the cases where cyclization was achieved.



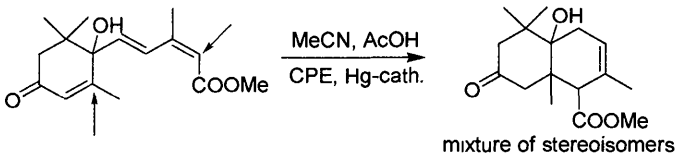
(16)

Under similar conditions, reduction of an α,β-unsaturated lactone linked to a linear α,β-unsaturated ester gave modest yields of two isomeric spirolactones, [Eq. (17)]. CV of simple monofunctional compounds indicates that in this case the α,β-unsaturated ester function is the electrophore [159]. The regioselective coupling (β to the ester group) and the presence of a proton donor (diethyl malonate) indicate that the probable reaction pathway is α-protonation of the radical anion, further reduction, and Michael addition of the resulting β-anion to the lactone.



(17)

The analogous α,β–γ,δ-unsaturated ester on the other hand, did not undergo cyclization under these conditions [159], whereas the methyl ester of abscisic acid [Eq. (18)], which also contains an α,β–γ,δ-unsaturated ester function, undergoes cyclization upon reduction in MeCN (containing AcOH) [160].



(18)

Cyclic voltammetry of monofunctional model compounds indicated that the unsaturated ester functionality is the one most easily reduced in the case of Eq. (18). In the absence of the OH group coupling was not observed [160], since enolization of the enone to the enol with conjugation of the four double bonds with the ester group takes place.

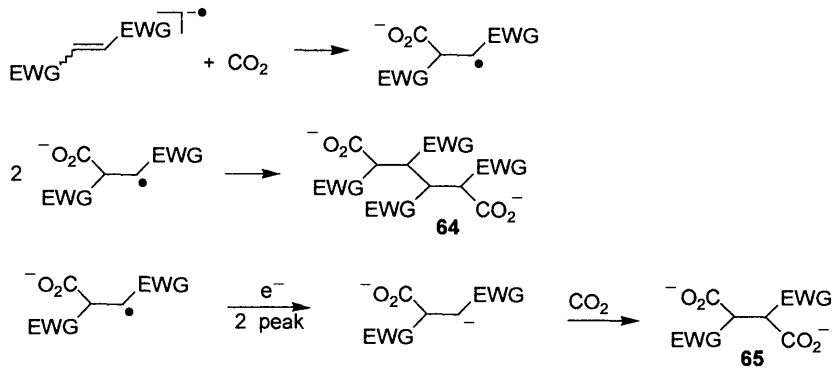
IV. REDUCTIVE COUPLING OF ALKENES WITH OTHER TYPES OF SUBSTRATES

A. Intermolecular Reductive Coupling of Alkenes with Other Types of Substrates

1. Coupling with CO_2

Radical anions derived from α,β-diactivated alkenes such as dialkyl maleates, react with CO_2, and at high CO_2 concentrations this process effectively competes with LHD formation [161,162]. Experimentally, CV of **53b** still shows a one-electron reduction peak in the presence of CO_2, but higher scan rates are required to detect the radical anion on the reverse scan than in the absence of CO_2. At the same time, a new reduction peak appears approximately 200 mV cathodic of the original reduction peak [163]. Preparative-scale coelectrolysis of **53b** and CO_2 at the potential of the first reduction peak gave the dicarboxylated dimer, **64**, whereas electrolysis at the potential of the "new" peak gave the dicarboxylated monomer, **65**, in a 2-F process [163–165]. This can be interpreted according to the mechanism in Scheme 14, i.e., the initially generated **53b**$^{-\cdot}$ adds rapidly to CO_2, forming a distonic radical anion that is *not* reduced at the potential of the initial reduction. The distonic radical anion then dimerizes, leading to the dianionic dicarboxylated dimer (which can be isolated after alkylation).

Electron transfer between **53b**$^{-\cdot}$ and CO_2 is too slow to be important because of the large difference (> 0.4 V) between the reductions potentials of **53b** and CO_2. The mechanism in Scheme 14 seems to be general for α,β-diactivated alkenes in their reaction with CO_2 [161]. The kinetics of the reaction between the radical anions of fumarates, **52a–c**, and maleates, **53a–c**, with CO_2 in DMF (Bu_4NI) has been studied by RRDE [162]. Reaction between the radical anion and CO_2 prior to dimerization was confirmed for **53a** by preparative and electroanalytical experiments at different substrate concentrations [165]. The radical anions **53**$^{-\cdot}$ reacted with CO_2 20–50 times faster than did the analogous species **52**$^{-\cdot}$, for which the pseudo-first-order rate constants were determined to be in the range 0.35–1.5 s^{-1} [162].



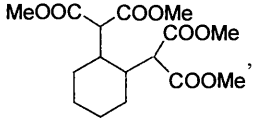
Scheme 14

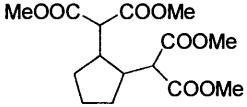
Alkyl cinnamates, **12**, are more easily reduced than CO_2 by ~0.4 V. Reduction of **12** in DMF (containing water) changes from a 1-F to a 2-F process in the presence of CO_2. The radical anions react much faster than in the absence of CO_2, and much faster than can be accounted for by electron transfer to CO_2 [161]. On a preparative scale the isolated products are mainly β-carboxylated monomer, **66**, together with the hydrogenation product. From methyl cinnamate, **12b**, at low water concentrations, small amounts of the dicarboxylated monomer, **67**, are also formed (Table 15), whereas with increasing water concentration the amount of hydrogenation product increases at the expense of the β-carboxylated monomer [161]. This indicates that the H_2O + CO_2 equilibrium increases the acidity of the medium sufficiently for protonation of the radical anion to compete with both dimerization and nucleophilic addition to CO_2. β-Carboxylation (rather than expected α-) can be rationalized by assuming that the neutral radical arising from α-protonation of the radical anion is more easily reduced than the substrate [76], and the resulting β-carbanion adds to CO_2 in competition with further protonation (Scheme 15, R = Ar).

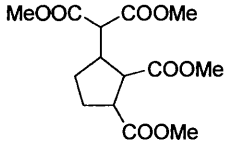
Much smaller potential differences (< 0.2 V) between alkene and CO_2 reduction are found for monoactivated alkenes such as acrylonitrile, **7**, or methyl acrylate, **13a**, and the electron-transfer pathway is expected to be significant. For ethyl acrylate, **13d**, reduction in DMF under very dry conditions is a catalytic process in the presence of CO_2, with the height of the reduction peak increasing approximately threefold [161,166]. In DMF or MeCN containing residual water, the height of the peak corresponding to reduction of the acrylate only doubles when a relatively high concentration of CO_2 is introduced, corresponding to a transition from a 1 F to a 2 F process [161]. Preparative scale reduction gives predominantly the α,β-dicarboxylated monomer, **67**, when carried out with a large excess of CO_2 (Table 15). The most plausible mechanism is outlined in Scheme 15, R = H or R = alkyl, that is, initial electron transfer from the acrylate radical anion to CO_2, coupling of $CO_2^{-\cdot}$ with an acrylate radical anion in the normal β-position, with formation of a distonic dianion, which from the α-position adds to CO_2. Further evidence for $CO_2^{-\cdot}$ formation is that oxalic acid derivatives are side products [163] (Sec. II.D). At high acrylate concentrations, homocoupling is favored over coupling with $CO_2^{-\cdot}$, and the major product is the dicarboxylated dimer, **68**, probably formed as outlined in Scheme 15. In the presence of water (2.8 *M*) **7** behaves similarly to **12** when reduced in the presence of CO_2 and gives the β-carboxylated monomer [163].

Table 15 Reductive Coupling of Alkenes and Alkynes with CO_2[a]

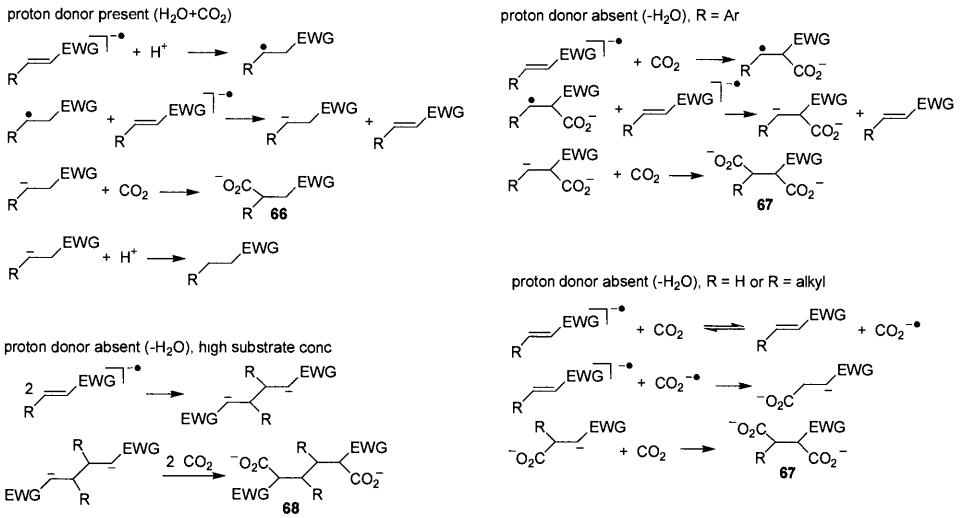
Substrate[b]	Conditions	Products and yields	Ref.
PhCH=CHPh	DMF, Bu_4NI, CCE	**68** (*meso*) 92%	[28]
CH_2=CHCN (**7**) (−2.14 V)	MeCN, Et_4NOTs, CPE[c]	**67** 41%[d]	[163]
7	CH_3CH_2CN, Bu_4NBF_4, 2.8 *M* H_2O, CCE	**66** 50%[d]	[163]
7	MeCN, Et_4NOTs, CCE[c]	**67** 41%[d]	[164]
PhCH=CHCN (**9**) (−1.78 V)[e]	DMF, Et_4NClO_4, H_2O	**66**, 2 F of **9**, **67**; no yields given	[161]
CH_2=C(Me)CN (**8c**) (−2.31 V)	MeCN, Et_4NOTs, CCE[c]	**67** 28%[d]	[163]
PhCH=CHCOOMe (**12b**) (−1.78 V)[e]	DMF, Et_4NClO_4, H_2O (0.056 *M*–2.78 *M*)	**66** 25–70%, 2 F of **12b** 20–65%, **67** < 10%[f,g]	[161]
PhCH=CHCOOEt (**12a**) (−1.80)[e]	DMF, Et_4NClO_4, H_2O (0.056 *M*–2.78 *M*)	**66** 30–40%, 2 F of **12b** 5–50% (see text)[f]	[161]
CH_2=CHCOOMe (**13a**) (−2.10 V)	MeCN, Et_4NOTs, CPE[c]	**67** 61%[d]	[163]
13a	MeCN, Et_4NOTs, CCE[c]	**67** 52%[d]	[164]
13a	MeCN, Et_4NOTs, CCE[h]	**68** 47%, **67** 8%[d]	[165]
CH_2=C(Me)COOMe (−2.27 V)	MeCN, Et_4NOTs, CCE[c]	**67** 42%[d]	[163]
MeCH=CHCOOMe (−2.48 V)	MeCN, Et_4NOTs, CCE[c]	**67** 38%[d]	[163]
MeOCH=CHCOOMe (−2.67 V)	MeCN, Et_4NOTs, CCE[c]	**67** 10%[d]	[163]
cis-MeOOCCH=CHCOOMe (**53b**) (−1.53 V)	MeCN, Et_4NOTs, CPE (new peak)[c]	**65** 31%[d]	[163,164]
53b	MeCN, Et_4NOTs, CPE (first peak)[c]	**64** 46%[d]	[164,165]
CH_2=CHCOMe (**22a**) (−1.91 V)	MeCN, Et_4NOTs, CPE[c]	**66** 22%, **67** 16%[d]	[163]
22a (−1.91 V)	MeCN, Et_4NOTs, CPE[c]	**66** 22%[d]	[164]
$[MeOOCCH{=}CH]_2(CH_2)_2$	MeCN, Et_4NOTs, CPE	72%[i]	[165]
$[MeOOCCH{=}CH]_2(CH_2)_3$	MeCN/H_2O, Et_4NOTs, CPE	100%[j]	[165]
$[MeOOCCH{=}CH]_2(CH_2)_4$	MeCN/H_2O, Et_4NOTs, CPE	80%[k]	[165]
H–C_α≡C_β–Pr	DMF, Bu_4NBF_4, 0.1 eq. $Ni(bpy)_2(BF_4)_2$[l]	C_α:7%, C_β: 59%[m]	[169]
Pr–C≡C–Pr	DMF, Bu_4NBF_4, 0.1 eq. $Ni(bpy)_3(BF_4)_2$[l]	93%[m]	[169]
H–C_α≡C_β–Ph	DMF, Bu_4NBF_4, 0.1 eq. $Ni(bpy)_3(BF_4)_2$[l]	C_α: 16%, C_β: 39%[m]	[169]
Me–C_α≡C_β–Ph	DMF, Bu_4NBF_4, 0.1 eq. $Ni(bpy)_3(BF_4)_2$[l]	C_α: 45%, C_β: 27%[m]	[169]
Ph–C≡C–Ph	DMF, Bu_4NBF_4, 0.1 eq. $Ni(bpy)_3(BF_4)_2$[l]	70%[m]	[169]

[a] Solvent saturated with CO_2.
[b] $E_{1/2}$ vs. SCE.
[c] Alkene added dropwise.
[d] Current yield.
[e] E^0 vs. SCE.
[f] Chemical yield.
[g] More **67** formed at low water conc., see text.
[h] High alkene concentration (1.32 *M*), low current, electrolysis run to 20% conversion, i.e., alkene concentration >0 at electrode surface.
[i] Product: 

, lower yield when MeCN/H_2O used as solvent.
[j] Product 

, lower yield in MeCN.
[k] Product: 

only 7% yield in MeCN.
[l] Undiv. cell, Mg-anode, $E_w = -1.2$ V.
[m] Carboxylation at α- or β-carbon as indicated, cf. Eqs. (19) and (20).



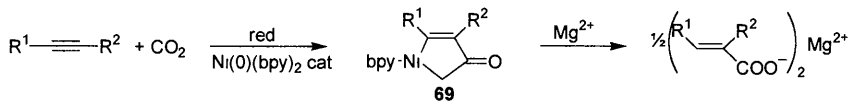
Scheme 15

Bis(activated alkenes) such as **42a** have been reduced in the presence of CO_2, and the extend to which intramolecular coupling takes place was shown to depend on the length of the link and on the medium [165] (Table 15). In this case, electron transfer from the radical anion of the substrate to CO_2 is also possible.

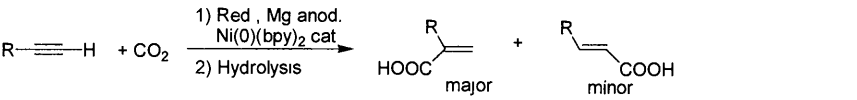
For alkenes more difficult to reduce than CO_2, such as butadiene (**63a**), electron transfer from $CO_2^{-\cdot}$ to the alkene may be involved. Cross-coupling of CO_2 and **63a** in MeCN has been carried out in an undivided flow cell at constant current. Using Et_4N^+ salts of formate or oxalate as supporting electrolyte, the anode process is formation of CO_2 and H^+, which are both consumed in the cathode process [167]. The outcome (up to 63% total yield) was a mixture of isomers of C_5, C_6, and C_{10} unsaturated carboxylic acids and diacids. The detailed mechanism is not known, but the products may arise from initial addition of $CO_2^{-\cdot}$ to the unreduced butadiene [167], although electron transfer from $CO_2^{-\cdot}$ to **63a** or direct reduction of **63a** (present in large excess) cannot be ruled out. Based on the observed influence of experimental parameters on the distribution of the C_5, C_6, and C_{10} acid products, the authors suggest that the reactions take place between adsorbed intermediates [167].

Reduction of ethene is so difficult that electron transfer from $CO_2^{-\cdot}$ is prohibited. Reduction of mixtures of CO_2 and ethene in DMF using sacrificial Al anodes gives mixtures of aluminum salts of mono- and diarboxylates containing 1–4 ethylene units [168]. Alkynes and allenes undergo carboxylation to a mixture of products in modest yields upon direct reduction in a divided cell. In these cases CO_2 is the more easily reduced partner, and for unactivated alkynes ($E^{red} < -2.8$ V) electron transfer is unlikely to take place. Product selectivity and yields (up to 80%) are enhanced using Ni complexes with nitrogen-containing polydentate ligands as catalysts in an undivided cell with sacrificial Mg anodes [168] and refs. therein]. For unactivated alkynes in DMF, the coupling reaction takes place at -1.2 V in the presence of $Ni(II)(bpy)_3^{2+}$, that is, at the potential of $Ni(0)(bpy)_2$ formation [169], but stoichiometric amounts of the Ni complex are necessary, when the reaction is carried out in a divided cell. The metallacycle, **69**, has been identified after electrolysis, and the monocarboxylated alkene can be isolated after hydrolysis.

Catalytic amounts of the Ni complex are, however, sufficient for reaction in an undivided cell using a sacrificial Mg anode. Here the intermediate, **69**, can be cleaved by Mg^{2+} to give the magnesium carboxylate, which is not reducible under the reaction conditions. Subsequent hydrolysis yields the product of monocarboxylation (60–80% based on the alkyne) [Eq. (19)]. *Cis* addition of H and CO_2 is preferred, but Ni(0) catalyzes the *cis–trans* isomerization, and under the catalytic conditions 15% of the *trans* product was formed (Table 15). For terminal alkynes the ratio of the two possible carboxylation products was always in favor of the 2-carboxylated product [Eq. (20)], with ratios up to (10:1) [169].



(19)

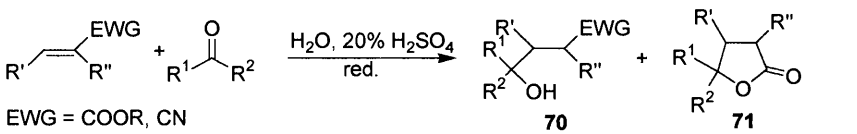


(20)

2. Coupling With Aldehydes and Ketones

Reduction potentials of simple ketones depend strongly on pH in aqueous media (cf. Chapter 10) due to preprotonation or preassociation of the ketone carbonyl group. In acidic conditions often used for coupling with simple ketones (H_2O, 20% H_2SO_4), reduction of the ketone is easier than reduction of most monoactivated alkenes, and leads directly to the neutral radical. Cross-coupling of alkenes activated by carboxylic acid derivatives with ketones is often followed by lactone formation at low pH [Eq. (21)]. The yield of cross-coupling products, **70** and **71**, decreases upon substitution at the β-position of the alkene (Table 16), and the current yield decreases at working potentials where proton reduction becomes more important [170]. Alkenes without electron-withdrawing groups, such as butadiene and styrene, generally give poor yields of the coupling products (Table 16).

When the reduction potential of the alkene is close to that of the (protonated) ketone, as is the case for α,β-diactivated alkenes, hydrogenation of the alkene takes precedence (2 F) due to rapid protonation of the alkene radical anion in the highly acidic medium [171] (Table 16). In neutral aqueous solution even monoactivated alkenes are more easily reduced than acetone, and LHD formation and hydrogenation compete with cross-coupling [172] (Table 16).



(21)

The mechanistic discussion has focussed on whether the radical formed by reduction of the preprotonated ketone is the reactive species attacking the alkene or whether it is the anion formed by further reduction, and data supporting both views have been presented [172–175].

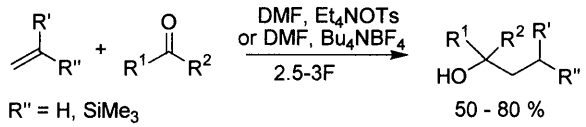
In aprotic media, only unactivated alkenes are more difficult to reduce than dialkyl ketones. Reduction of dialkyl ketones in DMF in the presence of unactivated terminal

Table 16 Examples of Reductive Coupling of Alkenes With Aldehydes and Ketones in (Acidic) Aqueous Medium

Alkene	Aldehyde/ketone R^1–CO–R^2		Conditions	Products and yields	Ref.
	R^1	R^2			
CH_2=CHCN (**7**)	Me	H	H_2SO_4, H_2O, div. cell, CCE, Hg cath.	**71** 12%, **70** 6%, polymer of **7**[a]	[177]
7	Me	Me[b]	H_2SO_4, H_2O, div. cell, $E_w = -1.2$ V, Hg cath.	**71** 8%, **70** 67%[a]	[172,177]
7	Me	Me[b]	H_2O, Et_4NOTs, div. cell, $E_w = -1.9$ V, Hg cath.	**71** 12%, LHD of **7** 39%, 2 F of **7** 34%[a]	[172]
7	Me	Me[b]	H_2O, K_2HPO_4, pH 7–8, div. cell, graphite cath., CCE	**71** 48%, **70** 4%, 2 F of **7**	[178]
7	Me	Et[c]	H_2O, K_2HPO_4, pH 7–8, div. cell, graphite cath., CCE	**70** 35%, LHD of **7**[a]	[177,179]
7	Me	Hexyl[d]	H_2SO_4, H_2O, MeOH, div. cell, $E_w = -1.20$ V, Hg cath.	**71** 48%, **70** 24%[a]	[170]
7	$-(CH_2)_4-$		H_2O, K_2HPO_4, pH 7–8, div. cell, graphite cath., CCE	**70** 13%[a]	[179]
CH_2=C(Me)CN (**8c**)	Me	Me[b]	H_2O, K_2HPO_4, pH 7–8, div. cell, graphite cath., CCE	**70** 20%[a]	[179]
NCCH=CHCH$_2$CH$_2$CN	Me	Me[e]	20% H_2SO_4, H_2O, div. cell, CCE, Hg cath.	**70** 30%[a]	[179]
CH_2=CHCOOMe (**13a**)	Me	Me[b]	H_2O, K_2HPO_4, pH 7–8, div. cell, graphite cath., CCE	**71** 70%, LHD of **13a**[a]	[179]
13a	Me	Me[b]	H_2SO_4, H_2O, div. cell, $E_w = -1.2$ V, Hg cath.	**71** 40%, **70** 28%[a]	[177]
CH_2=CHCOOEt (**13d**)	Me	Me[b]	20% H_2SO_4, H_2O, undiv. cell, CCE, Hg cath.	**71** 95%[f]	[171]
13d	Me	Et[d]	H_2SO_4, H_2O, MeOH, div. cell, $E_w = -1.26$ V, Hg cath.	**71** 80%[a]	[170]
13d	Me	Pr[d]	H_2SO_4, H_2O, MeOH, div. cell, $E_w = -1.26$ V, Hg cath.	**71** 70%[a]	[170]
13d	Me	Pentyl[d]	H_2SO_4, H_2O, MeOH, div. cell, $E_w = -1.26$ V, Hg cath.	**71** 74%, 51%[a,g]	[170]
13d	Me	Hexyl[d]	H_2SO_4, H_2O, MeOH, div. cell, $E_w = -1.26$ V, Hg cath.	**71** 47%, 42%[a,g]	[170]
CH_2=C(Me)COOMe	Me	Me[b]	H_2O, K_2HPO_4, pH 7–8, div. cell, graphite cath., CCE	**71** **19%**[a]	[179]
MeCH=CHCOOMe	Me	Me[b]	H_2O, 20% H_2SO_4, div. cell, CCE, Hg cath.	**71** 38%[f]	[174]
MeCH=CHCOOEt (**13c**)	Me	Me[b]	20% H_2SO_4, H_2O, undiv. cell, CCE, Hg cath.	**71** 30%[f]	[171]
Me$_2$C=CHCOOEt (**13b**)	Me	Me[b]	20% H_2SO_4, H_2O, undiv. cell, CCE, Hg cath.	**71** trace	[171]
PhCH=CHCOOEt (**12a**)	Me	Me[b]	20% H_2SO_4, H_2O, undiv. cell, CCE, Hg cath.	No coupling	[171]
trans-EtOOCCH=CHCOOEt (**52a**)	Me	Me[b]	20% H_2SO_4, H_2O, undiv. cell, CCE, Hg cath.	**71** 21%[f,h] 2 F of **52a**	[171]
cis-EtOOCCH=CHCOOEt (**53a**)	Me	Me[b]	20% H_2SO_4, H_2O, undiv. cell, CCE, Hg cath.	**71** 59%[f,h] 2 F of **53a**	[171]
MeCH=CHCOOH	Me	Me[b]	20% H_2SO_4, H_2O, undiv. cell, CCE, Hg cath.	**71** 26%[f]	[171]
CH_2=CHCOOH	Me	Me[b]	H_2SO_4, H_2O, div. cell, $E_w = -1.2$ V, Hg cath.	**71** 51%[a]	[177]
cis-HOOCCH=CHCOOH	Me	Me[b]	20% H_2SO_4, H_2O, div. cell, $E_w = -0.85$ V, Hg cath.	**71** 2%, succinic acid 94%[a]	[172]
CH_2=CHPh	Me	Me[b]	H_2O, K_2HPO_4, pH 7–8, div. cell, graphite cath., CCE	**70** 8%[a]	[179]
Butadiene (**63a**)	Me	Me[b]	H_2O, K_2HPO_4, pH 7–8, div. cell, graphite cath., CCE	2,7-Dimethyl-2,7-octanediol 6%[a,i]	[179]

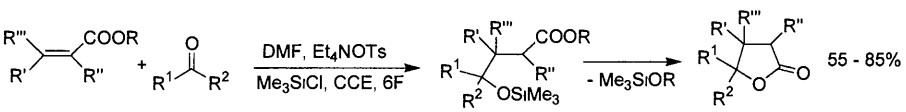
[a] Yields based on current; [b] In excess; [c] Equal amounts of alkene and ketone; [d] Ketone in 25 times excess; [e] In 2 times excess; [f] Chemical yield based on alkene; [g] Yields depending on amount of material and working potential, lower yields obtained on larger scale; [h] Distribution on products depend on water content and acidity: less water and more H_2SO_4 favors coupling; optimum yields given; [i] Coupling of acetone to both terminal carbons.

alkenes gives coupling at the terminal carbon atom [Eq. (22)] [176]. In similar conditions, conjugated dienes also undergo regioselective reductive coupling with dialkyl ketones at the least substituted carbon [176]. However, terminal disubstituted alkenes give much lower yields of the coupling product unless one of the substituents is a trimethylsilyl group. In this case, the trimethylsilyl-substituted tertiary alcohol is obtained (~ 70%) [180]. Unsaturated silanes are not reducible in DMF, so the mechanism is assumed to be attack of the radical anion of the ketone on the terminal carbon of the alkene. The silyl group may then stabilize the anion formed by further reduction of the distonic radical anion [180].



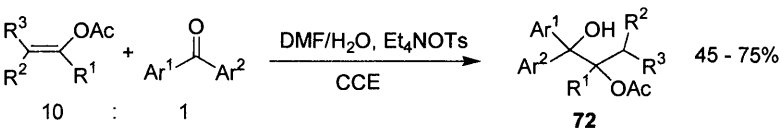
(22)

When the alkene is activated and undergoes reduction more easily than the ketone, cross-coupling generally fails in DMF. However, addition of trimethylchlorosilane, Me_3SiCl, to DMF facilitates reductive coupling of monoactivated alkenes with aliphatic aldehydes or dialkyl ketones. The lactones, **71**, are obtained in good chemical yields when the alkene is activated by an ester group [181] [Eq. (23)], but it is necessary to use a considerable excess of charge. For cyanoactivated alkenes, the coupling product is the hydroxynitrile, **70**. The role of Me_3SiCl is not known, but an intermediate of the type shown in Eq. (23) has been suggested [181]. Addition of Me_3SiCl does not lead to cross-coupling if the reduction potentials are reversed, as is the case when aromatic aldehydes or aryl ketones are coelectrolyzed with monactivated alkenes.



(23)

Reduction of diaryl ketones in DMF in the presence of an excess of the less easily reduced enol acetates gives cross-coupling products of the type **72**. This involves coupling at the α-position of the enol acetate [Eq. (24)]. For $R^1 \neq H$, the cross-coupling product is only obtained if $R^2 = H$ [182].



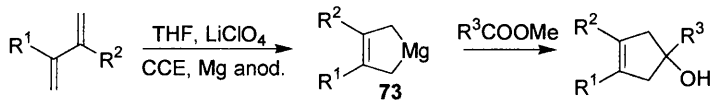
(24)

Reductive coupling of alkenes with ketones can also be carried out chemically using SmI_2 in THF/HMPA (10:1) with added *i*-PrOH or *t*-BuOH [183]. For reduction of unactivated terminal alkenes, the yields are generally high, 70–100% [183].

For terminal alkynes it has been demonstrated [184] that direct proton reduction in DMSO (Pt cathode) leading to the anion is possible. When carried out in the presence of dialkyl ketones, nucleophilic attack leads to alkynylation of the ketone in high current yields (up to 1000%), since the alcoholate is able to deprotonate another alkyne molecule [184].

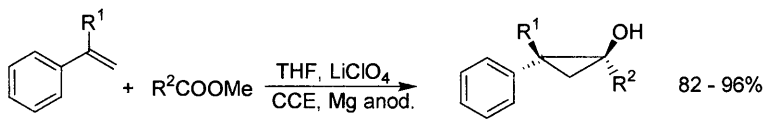
3. Coupling With Esters and Anhydrides

Anodically generated Mg^{2+}, in undivided cells, acts as an ion-pairing/bonding template for reactions of cathodically generated radical anions or dianions. In several cases such conditions have led to highly efficient coupling, especially when very reactive anionic intermediates are involved. An example is the reduction of 2,3-disubstituted butadienes in THF in the presence of esters of aliphatic carboxylic acids [185], which leads to the substituted 3-cyclopentenols of Eq. (25).



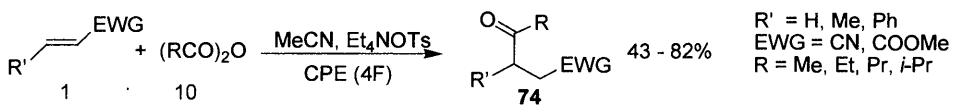
(25)

The authors suggest that the key intermediate is **73**, formed by two-electron reduction of the butadiene. This is supported by the fact that the same product is obtained if the butadiene is completely reduced prior to addition of the ester [185]. The reaction also proceeds if one of the double bonds is part of a ring (endocyclic). For styrene the reaction is stereospecific, giving one diastereoisomer of the phenyl substituted cyclopropane [Eq. (26)]. The presence of Mg^{2+} is essential but its role is unclear [185].



(26)

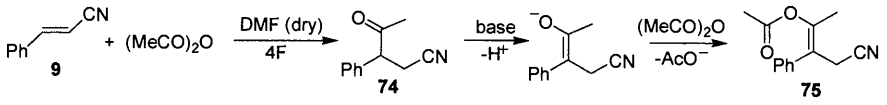
Reduction of activated alkenes in dry DMF or MeCN in the presence of an excess of acetic anhydride or other simple anhydrides gives the corresponding β-acylated compound, **74** [Eq. (27)], in moderate to good yields.



(27)

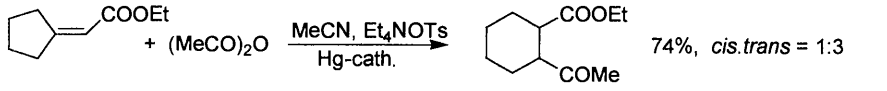
The mechanism is not clear. The alkene is the more easily reduced reactant, since in MeCN (at a carbon electrode) acetic anhydride is reduced at approximately −2.8 V [186]. Thus, electron transfer from the radical anion of the activated alkene to acetic anhydride seems unlikely, although the acylation at the β-position is the expected product of coupling between the radical anions. An alternative mechanism involves nucleophilic attack of the radical anion on the anhydride, giving rise to carboxylate and a neutral radical, which is further reduced and protonated. Initial α-acylation would be expected here because the charge density in α-position is assumed to be higher than in β-position. Also, significant amounts of α,β-diacylated product would be expected, formed by nucleophilic attack on acetic anhydride from the anion formed in the second electron transfer (Scheme 15). Less than 3% α,β-diacylated product was formed except when the alkene was α-Me substituted. For ethyl cinnamate, **12a**, an additional side reaction is hydrogenation (14%) [186]. Thus, conditions were sufficiently acidic for protonation of the radical anion to compete with dimerization and reaction with acetic anhydride. A mechanism for β-acylation analogous to that for carboxylation in Scheme 15 (proton donor present) can then be envisaged. In dry DMF (Al_2O_3 present in the cell) 2% α-acylation together with the LHD of $12a_{10}$ were reported as side products [187]; that is, the composition of the electrolyte plays a significant role. For cinnamonitrile, **9**, the major product in dry DMF is **75**, presumably

formed by nucleophilic attack of the enolate ion of **74** on the anhydride [Eq. (28)] [187]. In MeCN only **74** was isolated [186].



(28)

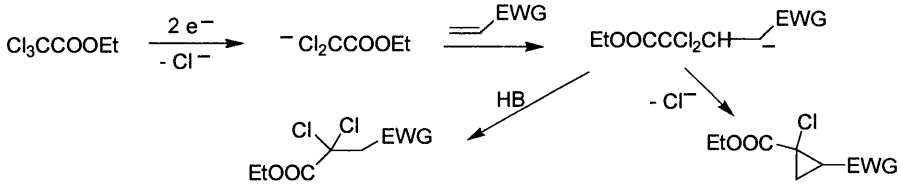
In a single case, shown in Eq. (29), the coupling reaction was accompanied by ring enlargement [186].



(29)

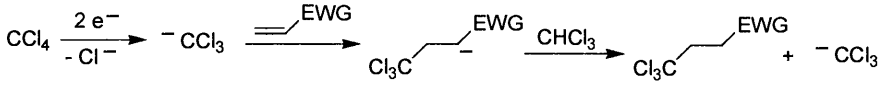
4. Coupling With Organic Halides

Easily reduced polyhalides such as CCl_4 (−0.75 V) and $Cl_3CCOOEt$ (−0.65 V) form anions upon two-electron reduction and cleavage of a halide ion. The anion may add to activated, but less easily reduced, alkenes such as acrylonitrile or alkyl acrylates. With excess alkene and no added proton donor, cyclopropanes are formed via Michael addition followed by intramolecular S_N2 reaction [188] (Scheme 16).



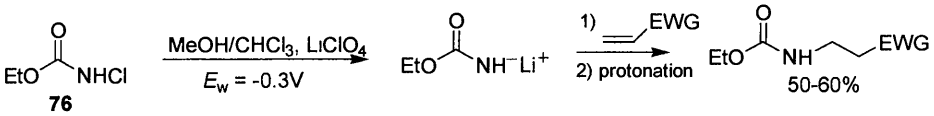
Scheme 16

Catalytic reaction, with respect to current, is found for reduction of CCl_4 in the presence of $CHCl_3$, which acts as a proton donor. The reaction becomes catalytic, since the anion, $^-CCl_3$, is regenerated upon proton transfer to the anion of the coupling product [Eq. (30)]. Current yields up to 350% have been reported for the reaction between acrylonitrile (**7**) and CCl_4 in DMF containing $CHCl_3$ [188] (Table 17).



(30)

N-Haloamides such as **76** are reductively cleaved (2 F) to give an anion by loss of a halide ion; coupling takes place when an excess of an activated alkene is added, as in Eq. (31) [189].



(31)

Allyl chloride is more difficult to reduce than diethyl fumarate, **52a**, by ~0.5 V, but allyl bromide and iodide are only slightly more difficult to reduce than **52a**. Coelectrolysis

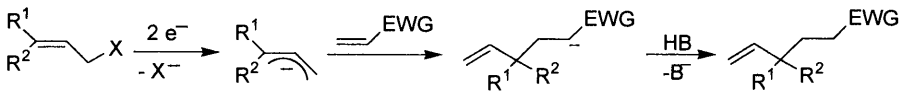
Table 17 Reductive Coupling of Alkenes With Very Easily Reduced Alkyl Halides in Aprotic Medium[a] [188]

Alkene	Alkyl halide	Conditions	Products and yields
CH_2=CHCN (**7**)[b]	CCl_4(−0.75 V)	$CHCl_3$, Et_4NOTs, E_w = −0.98 V	$Cl_3CH_2CH_2CN$ 347%
7[c]	$Cl_3CCOOEt$ (−0.65 V)	DMF, LiCl, E_w = −0.84 V	*c*-Propane 80%[d], $EtOOCCCl_2CH_2CHClCN$ 20%
7[e]	$BrCH_2COOEt$ (−0.88 V)	Et_4NOTs (H_2O), E_w = −1.83 V	Ethyl 2-cyanocyclopropylcarboxylate < 34%,[f] CH_3COOH, polymer
CH_2=CHCOOEt (**13d**)[g]	CCl_4 (−0.75 V)	$CHCl_3$, CH_2Cl_2, Et_4NCl, E_w = −1.30 V	$Cl_3CH_2CH_2COOEt$ 114%
13d[b]	$Cl_3CCOOEt$ (−0.65 V)	DMF, Et_4NCl, E_w = −0.85 V	*c*-Propane 100%[d]
13d[b]	$BrCH_2COOEt$ (−0.88 V)	DMF, Et_4NOTs (H_2O), E_w = −1.50 V	Diethyl *c*-propanedicarboxylate 76%[f], CH_3COOH 15%
trans-EtOOCCH=CHCOOEt (**52a**)[h]	CCl_4 (−0.75 V)	DMF, $CHCl_3$, Et_4NCl, E_w = −1.20 V	Linear 38%, cycl. 28%[d] EtOOC-C(CCl_3)=CCOOEt 50%
cis-EtOOCCH=CHCOOet (**53a**)[i]	$Cl_3CCOOEt$ (−0.65 V)	DMF, LiCl, E_w = −0.75 V	*c*-Propane 55%[d]

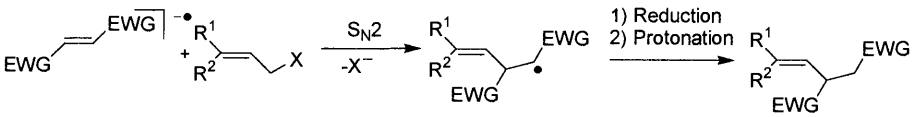
[a] General conditions: div. cell, CPE, Hg cath. Yields based on current passed.
[b] 10 × excess.
[c] 2 × excess, $Cl_3CCOOEt$ added slowly.
[d] See Scheme 16.
[e] **7** used as solvent.
[f] Probably formed via initial deprotonation of $BrCH_2COOEt$.
[g] 5 × excess.
[h] Equimolar amount, $Cl_3CCOOEt$ added slowly.
[i] Equimolar amount.

of allyl halides and **52a** (in excess) results in cross-coupling [190], with the bromide giving the highest yield (Table 18).

Based on these results and results for reduction of other combinations of allyl halides and activated alkenes, it has been suggested that when the allyl halide is more easily reduced than the alkene, the allylic anion (2-F reduction) adds to the activated double bond of the alkene, giving predominantly the terminal alkene [Eq. (32)]. In contrast, initial formation of the radical anion of the (di)activated alkene may lead to an S_N2 reaction between the radical anion and the allyl halide followed by further reduction of the intermediate radical and final protonation [Eq. (33)] [190,191]. However, electron transfer between the alkene radical anion and especially allyl iodide followed by coupling of the allyl radical and a radical anion cannot be ruled out.



(32)



(33)

The S_N2 mechanism is ruled out for reaction between the tertiary halide, *t*-BuBr, and radical anions derived from the more easialy reduced compounds cinnamonitrile (**9**) ethyl cinnamate (**12a**), methyl styryl ketone (**23a**), and phenyl styryl ketone (**20a**). Reduction of the activated alkenes in the presence of an excess of *t*-BuBr leads to mixtures of products where a *t*-Bu group has been introduced in α- or β-position or in the phenyl ring. For **9** and **12a** small amounts of butylated hydrodimers were obtained in addition, and for the enone **23a** formation of the unsaturated alcohol with introduction of the *t*-Bu group at C-1 was a major product [192]. In this case the mechanism is unambiguously reduction of the activated alkene followed by electron transfer to *t*-BuBr concerted with halide cleavage, in

Table 18 Reductive Coupling of Alkenes With Allyl Halides in Aprotic Medium[a] [190]

Alkene	Allyl halide	Products and yields
$MeC_\beta H{=}C_\beta HCOOMe$	$Me_2C{=}CHCH_2Cl$	β-Coupl. 22%[b]
trans-EtOOCCH=CHCOOEt (**52a**)[c]	$CH_2{=}CHCH_2Cl$	15%[d]
52a[c]	$CH_2{=}CHCH_2Br$	70%[d]
52a[c]	$CH_2{=}CHCH_2I$	39%[d]
52a[e]	$Me_2CCH{=}CHCH_2Cl$	15%[d]
52a[c]	$MeOOCC_\alpha H{=}CHCH_2Br$	α-Coupl. 39%
52a[c]	$MeOOCC_\alpha H{=}CHCH_2I$	α-Coupl. 11%

[a] General conditions: DMF, Et_4NOTs, undiv. cell, CCE, Pt cath., chemical yield, based on halide after passage of 2 F.
[b] See Eq. (32).
[c] 10 × excess.
[d] See Eq. (33).
[e] 2 × excess.

competition with dimerization of the alkene radical anions. The *t*-butylated products arise from coupling between *t*-Bu$^{\cdot}$ and the radical anion of the activated alkene, or from attack of *t*-Bu$^{\cdot}$ on the alkene or the hydrodimer [192]. Consistent with this is the fact that if a very easily reduced activated alkene such as **20a** ($E_{1/2} = -1.34$ V) is used, no mixed coupling product is found since electron transfer from radical anion to halide is very slow owing to the large difference in reduction potentials. The general problem of electron transfer from (more stable) organic radical anions to alkyl halides and the competition between coupling and further reduction of the alkyl radical has been investigated in great detail [193 and refs. therein] (see also Sec. V.C and Chapter 29). Sacrificial anodes (typically Mg, Fe, Zn, or Al), in undivided cells, offer advantages also in the reductive couplings between alkenes and halides. One example is the reductive coupling of dihalides with activated alkenes leading to formation of three-, five-, or six-membered rings in NMP using a sacrificial Al anode [194], whereas mainly a linear coupling product was obtained in a divided cell [194]. Generally, yields are higher when the alkene is more easily reduced than the dihalide, but only by a few hundred millivolts (Table 19). For instance, reduction of dimethyl fumarate, **52b** (−1.45 V), dimethyl maleate, **53b** (−1.6 V), and methyl cinnamate, **12b** (−1.85 V), in the presence of a 2-fold excess of 1,3-dibromopropane (−2.1 V), gives the corresponding *trans*-substituted cyclopentanes (respective yields 18%, 50%, and 66%). Reduction of an excess of methyl acrylate, **13a** (ca. −2.1 V), gives only 10% of the cyclopentane. Whether the radical anion of the alkene reacts by electron transfer to the dihalide, by S_N2 reaction with the dihalide, or undergoes further reduction to an ion-paired dianion could not be distinguished.

Further studies of the formation of substituted cyclopropanes from reduction of different combinations of diactivated alkenes (**52b**, **53b**) and *gem*-polyhalo compounds in DMF using an undivided cell with an Al anode [195] showed that (a) increased temperature (70°C) in general led to improved yields of the cyclopropanes (up to 60%); (b) **52b** in all cases gave better yields (of the same product) than **53b**; (c) the LHDs of the alkenes and hydrogenation products of the halo compounds (occasionally also dimers of the halo compounds) were found as side products, and (d) no mixed coupling products were obtained if very easily reduced halides [CBr_4, $BrCCl_3$, $Br_2C(COOMe)_2$, and Cl_3CCN] were used in combination with any of the alkenes (all more difficult to reduce than the halides) [195]. Michael addition therefore seems *not* to be operating when a sacrificial Al anode is used. The main mechanism appears to be electron transfer from the radical anion of the alkene to the *gem*-dihalo compound, leading to an α-halo radical, which can couple with an alkene radical anion, followed by an intramolecular S_N2 reaction to give the cyclopropane. The products yields are, however, low to moderate.

Later, two different mechanisms for the coupling between activated alkenes and less easily reduced alkyl halides were suggested, depending on whether the reduction takes place in a divided cell or in an undivided cell equipped with a sacrificial A1 anode [196] (Scheme 17). For bromomethylcyclopropane (−2.3 V) the product distribution was shown to depend on the experimental conditions (Table 20). The cyclopropylmethyl radical formed by electron transfer from the alkene radical anion is known to ring-open to the linear radical with a first-order rate constant close to 10^8 s^{-1}, and coupling of the cyclopropylmethyl radical with the alkene radical anion can therefore not compete. Consequently, only linear coupling products are found when the reaction is carried out in a divided cell. The amount of cross-coupling product increases at the expense of the LHD of the activated alkene, when the reduction potential of the alkene approaches that of the bromomethylcyclopropane. This observation is consistent with an increase in the

Table 19 Reductive Coupling of Alkenes With Polyhalides in Aprotic Medium[a]

Alkene	Polyhalide	Products and yields	Ref.
CH_2=CHPh (−2.2 V)[b]	$BrCH_2CH_2CH_2Br$ (−2.0 V)	*c*-Pentane 10%[c,d]	[194]
CH_2=CHCOOMe (**13a** (−2.1 V)[b]	$BrCH_2CH_2CH_2Br$ (−2.0 V)	*c*-Pentane 10%, CH_2=$CH(CH_2)_3COOEt$ 9%[c]	[194]
13a (−2.1 V)[b]	$PhCHCl_2$	*trans c*-Propane 30%[c,d]	[194]
PhCH=CHCOOMe (**12b**) (−1.85 V)	$BrCH_2CH_2CH_2Br$ (−2.0 V)[e]	*trans c*-Pentane 66%, lin. 5%[f]	[194]
12b (−1.85 V)	CH_2Cl_2[b]	*trans c*-Propane 40%[f]	[194]
trans-MeOOCCH=CHCOOMe (**52b**) (−1.45 V)[g]	$CH_3CBr_2CH_3$(−2.1 V)[e]	*trans c*-Propane 60%[f]	[195]
52b (−1.45 V)[g]	CH_3CHBr_2 (−2.3 V)[e]	*trans c*-Propane 35%[f]	[195]
52b (−1.45 V)[g]	$Cl_3CCOOMe$ (−1.6 V)[e]	*trans c*-Propane 40%[f]	[195]
52b (−1.45 V)	$BrCH_2CH_2CH_2Br$(−2.0 V)[e]	*trans c*-Hexane 18%[f]	[194]
cis-MeOOCCH=CHCOOMe (**53b**) (−1.6 V)	CH_2Br_2 (−2.1 V)[b]	*trans c*-Propane 41%[f]	[194]
53b (−1.6 V)	$ClCH_2CH_2Cl$[b]	*trans c*-Butane 5%[f]	[194]
53b (−1.6 V)	$BrCH_2CH_2CH_2Br$ (−2.0 V)[e]	*trans c*-Pentane 50%, lin. 10%[f]	[194]
53b (−1.6 V)	CH_2=$C(CH_2Cl)_2$[e]	*trans* c-Pentane 16%, lin. 10%[f]	[194]
53b (−1.6 V)	$BrCH_2(CH_2)_2CH_2Br$[e]	*trans c*-Hexane 40%[f]	[194]
53b (−1.6 V)	*cis*-$ClCH_2CH$=$CHCH_2Cl$[e]	*trans c*-Hexene 15%[f]	[194]
PhCH=CHCOMe (**23b**) (−1.7 V)	$BrCH_2CH_2CH_2Br$ (−2.0 V)[e]	*trans c*-Pentane 35%[f]	[194]

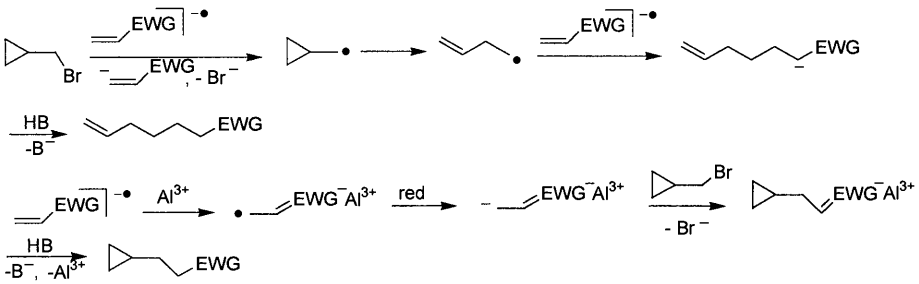
[a] General conditions: NMP, Bu_4NBF_4 + Bu_4NI, undiv. cell, CCE, stainless steel cath., Al anode.
[b] 4 × excess.
[c] Chemical yield, based on halide.
[d] See Scheme 16.
[e] 2 × excess.
[f] Chemical yield, based on activated alkene.
[g] As in (a) but DMF, 70°C.

Table 20 Reductive Coupling of Alkenes with *c*-Pr-CH_2Br (−2.3 V) in Aprotic Medium[a] (see Scheme 17) [196]

Alkene	Conditions	Products and yields
CH_2=CHPh (−2.2 V)	Div. cell.	Open chain 60%
CH_2=CHPh (−2.2 V)	Undiv. cell, Al anode	Open chain 70%
PhCH=CHCOOMe (**12b** (−1.7 V)	Div. cell	Open chain 35%, LHD of **12b**
12b (−1.7 V)	Undiv. cell, Al anode	Open chain 20%, cycl. 30%
cis-MeOOCCH=CHCOOMe (**53b**) (−1.5 V)	Div. cell	Open chain 28%, LHD of **53b**
53b (−1.5 V)	Undiv. cell, Al anode	Open chain 16%, cycl. 24%

[a] General conditions: NMP, $Bu_4NBF_4 + Bu_4NI$, CCE, stainless steel cath. Alkene used in 2 × excess.

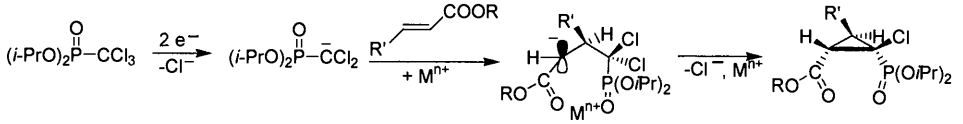
rate of electron transfer and thereby in the concentration of the ring-opened radical, when the difference in reduction potentials is diminished.



Scheme 17

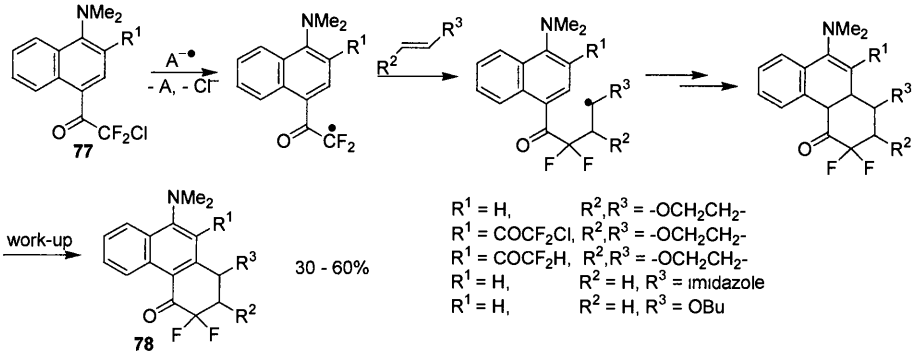
In the undivided cell, on the other hand, a significant amount of cross-coupling products containing the cyclopropyl group is found (for **12b** and **53b**), indicating an S_N2 pathway rather than an electron-transfer pathway. According to the authors, formation of the dianion of the activated alkene is now competing with the electron transfer to the bromide due to strong interaction between the Al^{3+} (generated at the anode) and the radical anions of **12b** and **53b**. The resulting dianion (strongly ion-paired) may then react with the bromide in an S_N2 reaction leading to the cyclopropyl containing cross-coupling product (Scheme 17). The radical anion derived from the nonpolar styrene interacts more weakly with Al^{3+}, and the electron-transfer pathway is the only one operating [196].

The electrosynthesis of cyclopropylphosphonates by reductive coupling of trichloromethylphosphonates with activated alkenes in DMF also benefits from the use of a Mg anode [197]. First, the amount of charged passed (based on the trichloromethylphosphonate) for full conversion decreases from the required 2 F to 0.8 F, which has been explained as a chemical reduction of the trichloromethylphophonate initiated by the Mg *anode*. Similar observations have been made in other cases and are discussed in Chapter 5. Second, the diastereoselectivity of the reaction is greatly enhanced (to 80–100%) when the activating group of the alkene is an ester, **12a**, **13c**, **13e**, or PhCH=$C(COOEt)_2$, which is attributed to the templating effect of Mg^{2+} as outlined in Scheme 18, keeping the phosphonate and the ester group at the same side of the cyclopropane ring in the product t.



Scheme 18

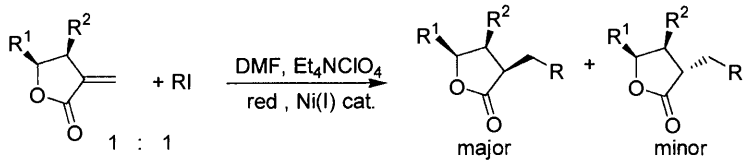
The low yields generally obtained from cross-coupling of simple monohalides with alkenes via direct reduction of the halides are due to the fact that the radicals formed by loss of halide often are reduced at the potential where they are formed in competition with radical addition to the alkene. The resulting anions are highly basic and are normally protonated by the medium. As an example, direct reduction of **77** ($E_p = -1.45$ V) in MeCN (Et_4NBF_4) in a divided cell in the presence of an excess of electron rich alkenes only leads to the 2 F product of **77** where Cl has been replaced by H. However, if the reaction is carried out using nitrobenzene ($E^0 = -1.10$ V) or 4-nitropyridine *N*-oxide ($E^0 = -0.70$ V) as a redox catalyst, the initial cleavage of Cl^- from $\mathbf{77}^{-\cdot}$ is not followed by further reduction and protonation. The radical adds to the alkene followed by cyclization, finally leading to the tricyclic ring system in an overall 2-F process. Upon worp the product is rearomatized to *78* (Scheme 19) [198].



Scheme 19

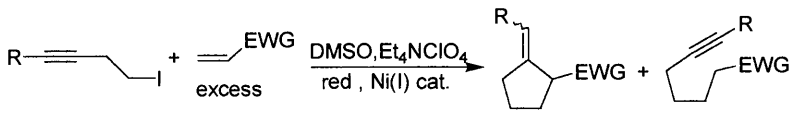
Transition-metal catalysts have been successfully used in a number of coupling reactions involving organic halides during the last decade [199], and also in the mixed coupling of alkenes with halides. One example is the coupling between simple butyl iodides and α-methylenebutyrolactones [200,201] catalyzed by $Ni(II)(tmc)^{2+}$ (tmc = a cyclic tetradentate nitrogen ligand; see Sec. IV.B.5), which is reduced at −0.95 V. This Ni(II) complex and other similar Ni(II) complexes with macrocyclic tetradentate nitrogen ligands are reduced to the corresponding Ni(I) complexes, which are the active species. The catalytic effect appears to be an inner-sphere reduction of alkyl halides to alkyl radicals and halide ions. Since the reduction of the Ni(II) species takes place at a potential that is anodic with respect to the reduction of simple alkyl radicals [193], the follow-up reaction is of the radical type. In the case of α-methylenebutyrolactones the double bond is attacked by the alkyl radical, leading to a new radical, which is more easily reduced (due to the α-carbonyl group). The protonation of the resulting anion by residual water from the less hindered side of the ring determines the stereochemistry of the product [Eq. (34)] [201]. That the major reaction pathway of the product radical is further reduction rather than hydrogen abstraction from the solvent (DMF) is supported by the fact that addition of D_2O to the

reaction mixture led to 80% D at the α-carbon, whereas the use of DMF-d_7 gave no deuteration. Except for *t*-BuI, the yields are generally in the range 50–70% with a high *cis*/*trans* ratio when both R^1 and R^2 are different from H [201].



(34)

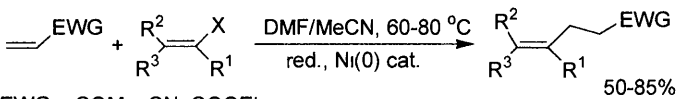
The yield of cyclized product for coupling between simple activated alkenes and butynyl iodides depends on the reduction potential of the Ni catalyst [200], since the radical resulting from the initial attack of the butynyl radical may either be reduced or cyclize (5–*exo*) on to the triple bond [Eq. (35)]. The lower the reduction potential of the catalyst, the more noncyclized product is formed. The yield of the cyclized product was in the range 30–60% [200].



(35)

Coupling between cyclohexenone and alkyliodides can be catalyzed by Co(I) species formed in situ from vitamin B_{12} or similar Co(III) complexes at ~ -0.85 V [202]. The alkyl halide reacts with the Co(I) complex by oxidative addition, and the alkyl radical can be obtained photochemically (visible light), with subsequent addition to the double bond in the β-position (in competition with hydrogen abstraction). Alternatively, the Co-alkyl species can be further reduced at -1.45 V, giving the alkyl anion. The yields of coupling products were significantly higher (40-80%) using the photochemical method than using the reductive method. Only when the reaction was carried out in a microemulsion CTAB/1-pentanol/tetradecane/water (17.5/35/12.5/35, w/w%) did the coupling reaction compete to some extent with protonation of the alkyl anion formed by the reductive method, giving 10–40% coupling [202].

The mechanism of Ni(0) catalysis of cross-couplings between vinyl or aryl halides and alkenes is believed to be quite different from the Ni(I)- or Co(I)-catalyzed reactions discussed earlier, since both reaction partners are bonded to the metal and the coupling takes place within the ligand sphere. The reductive coupling between simple activated alkenes and alkenyl halides can be carried out in good yields in an undivided cell using 0.2 eq. $NiBr_2$ as Ni(0) catalyst precursor and a sacrificial Fe anode [Eq. (36)] [203]. Alkenyl bromides and iodides give similar or higher yields than the chlorides, with the *E*, *Z*-isomeric purity of the products > 93%.

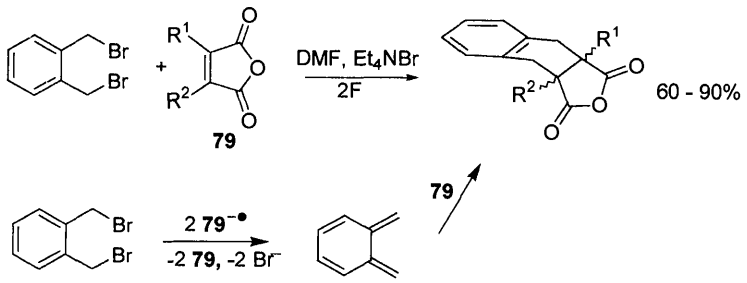


(36)

EWG = COMe, CN, COOEt
X = Cl, Br, I

Reduction (2 F) of 1,2-bis(bromomethyl)benzene leads to a highly reactive *o*-quinodimethane, which in the presence of a dienophile may serve as the diene in a Diels–Alder reaction. The dienophiles are typically analogues of maleic anhydride (**79**), *N*-phenylmaleimide, and benzoquinone, which are all more easily reduced than the 1,2-bis(bromomethyl)benzene. The radical anion of the dienophile mediates the reductive cleavage of the

1,2-bis(bromomethyl)benzene to give the *o*-quinodimethane. This then undergoes Diels–Alder reaction with the dienophile as shown in Scheme 20 [204,205].



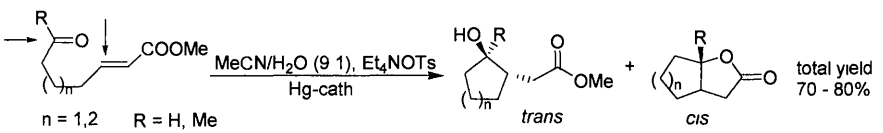
Scheme 20

B. Intramolecular Coupling of Alkenes or Alkynes With Other Types of Substrates

Reductive cyclizations have recently been reviewed [206], and applications to natural product synthesis can be found in Chapter 19. In this section only intramolecular reactions involving carbon–carbon multiple bonds (i.e., similar to the intermolecular reactions discussed earlier) will be treated.

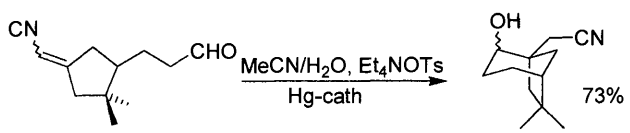
1. Coupling of Activated Alkenes With Aldehydes and Ketones

In aprotic solvents the activated alkene rather than the aldehyde or keto group is the moiety undergoing electrochemical reduction. Electrochemical reduction of α,β-unsaturated esters linked to aldehydes or ketones leads to five- or six-membered cyclization products in which the new bond is formed between the β-carbon of the unsaturated ester and the carbonyl carbon of the aldehyde or keto group [Eq. (37)]. The *trans* isomer was formed in excess, with the *trans*/*cis* ratio in the range 1.4:1 to 11.4:1 [207,208]. The *trans*/*cis* ratio increased with decreasing temperature [208], and the *cis* isomer was detected as the lactone. Hydrogenation of the alkene was found to be a side product, but the importance of this side reaction was minimized in dry MeCN using 2 eq. diethyl malonate as proton source instead of AcOH [207]. Reductive coupling also worked well for cyclopentanone or cyclohexanone functionalized at the 2-positions by a chain containing an α,β-unsaturated ester.



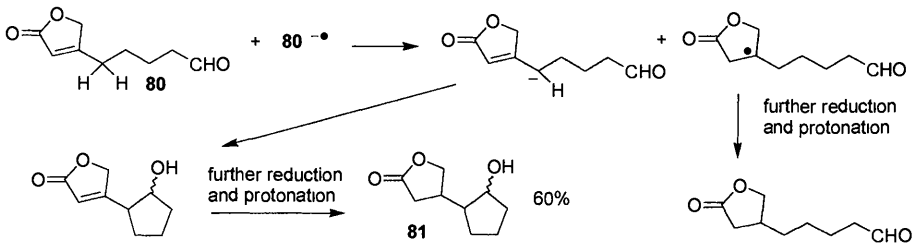
(37)

Using a cyano group for activation of the alkene may also lead to the cyclized product [208] as illustrated in Eq. (38).



(38)

Attempted formation of a spiro compound, through reductive cyclization in MeCN of compound **80**, was unsuccessful. This is in contrast to the intramolecular coupling product obtained when the α,β-unsaturated lactone was linked to an unsaturated ester [Eq. (17) in Sec. III.B], rather than to the aldehyde. Reduction of **80** gave mainly the bicyclic compound **81** arising by self-protonation of the radical anion by the acidic hydrogen at C-1 of the side chain. The conjugate base of the starting material then cyclizes onto the aldehyde group, leading eventually to **81**, after hydrogenation of the C–C double bond in the lactone ring (Scheme 21) [159]. The self-protonation reaction took place even if the reduction was carried out in the presence of 4 eq. diethyl malonate as an external proton donor [159].

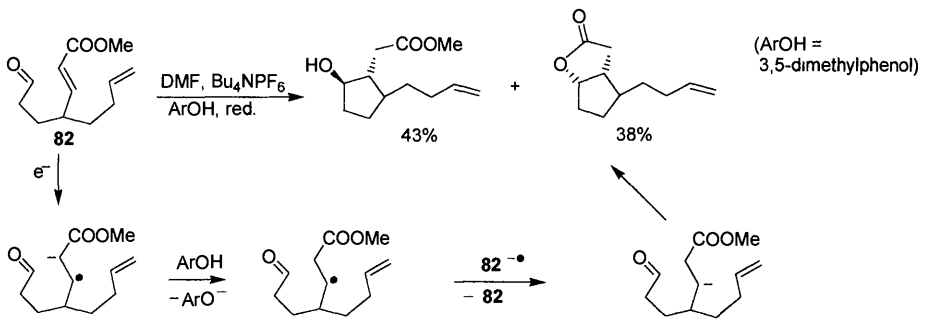


Scheme 21

The intramolecular coupling between activated alkenes and carbon–oxygen double bonds has been investigated in detail only for the reaction in Eq. (39) [117].

(39)

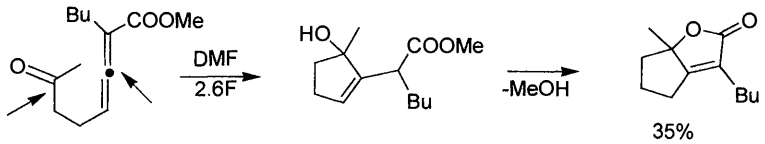
Based on the results of LSV at low scan rates, it was concluded that the mechanistic pathway consists of initial, rate-determining protonation of the radical anion at the α-carbon of the activated double bond followed by further reduction in solution of the resulting radical. The localized anion adds to the carbonyl group, and the alcoholate is finally protonated [117]. Cyclization at the anion stage was supported by the fact that the substrate **82** exclusively gave products derived from cyclization onto the carbonyl group and not onto the alkene double bond (Scheme 22). In both cases a five-membered ring would be obtained, but it is known that anions react much faster with carbon–oxygen than with carbon–carbon double bonds, whereas radicals react with comparable rates with the two types of double bonds upon formation of five-membered rings, but the reaction with the carbon–oxygen double bond is reversible and thermodynamically unfavored [117,209].



Scheme 22

A similar mechanism has been suggested for the reductive cyclization of ketones linked to α,β-unsaturated esters by Mg in MeOH at −23°C, which gives high chemical yields (80–100%) of the cyclic alcohols [210].

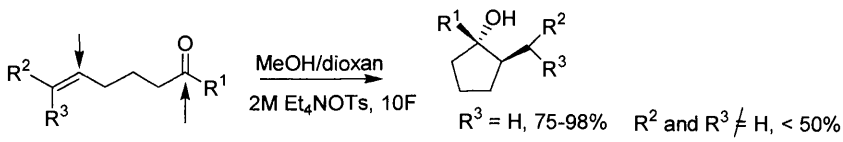
Reductive cyclization of a keto group linked to an ester-activated allene affords cyclization to the cyclopentenol, which is isolated as the lactone [Eq. (40)] [211]. Higher yields (64–96% as a mixture of diastereomers) are obtained when the keto group is replaced with an α,β-unsaturated ester group. That cyclization, however, only takes place in an undivided cell (and with a consumption of 4.5–11.3 F) [211].



(40)

2. Coupling of Unactivated Alkenes with Aldehydes and Ketones

For intramolecular reductive coupling between aldehyde or ketone functions and less easily reduced alkenes, the carbonyl radical anion (or radical resulting from *O*-protonation) is the species attacking the alkene, to give in almost all cases exclusively 5-*exo*- or 6-*exo*-cyclization. Cyclobutanes and rings containing more than six atoms are normally not formed [212]. The chemical yields are reported to be high when the reduction is carried out at constant current in an undivided cell (carbon cathode) [Eq. (41)]. Substituents on the alkene carbon to which the bond is formed normally inhibit the cyclization while bulky R^2 and R^3 substituents lower the yield to somewhat below 50%, with concomitantly higher amounts of the linear, unsaturated alcohol [212,213]. The reaction is highly stereoselective (OH and CHR^2R^3 *trans*). Formation of bicyclic tertiary alcohols from cyclic ketones linked to terminal alkenes also proceeds smoothly (37–87%) [213].

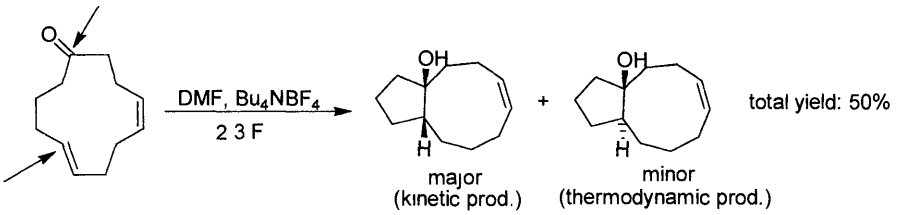


(41)

Reduction of 7-octen-2-one mediated by $(DMP)Hg_5$ (DMP^+ = dimethylpyrrolidinium) formed in situ gave the cyclized product with higher current yields (72%) than by direct reduction (35%). Similar results were obtained for 6-hepten-2-one [214].

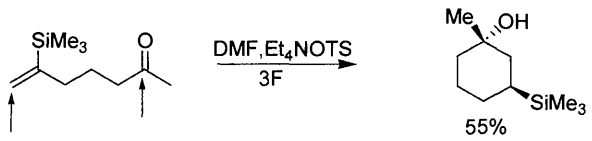
Outer-sphere electron transfer by organic catalysts also promotes the reductive cyclization of 6-hepten-2-one in DMF [215]. From a study of the effect of variation of the amount of the catalyst and its reduction potential, and from reaction in DMF-d_7, it was concluded that the ketyl radical anion cyclizes onto the carbon–carbon double bond, giving preferentially the product where the two methyl groups are *cis*. The distonic radical anion thus produced does not abstract hydrogen but is further reduced. When the further reduction or the protonation at oxygen is a fast follow-up reaction (high concentration of the mediator or high concentrations of water), equilibration to the more stable product (methyl groups *trans*) is prevented [215].

Cyclization also takes place when the alkene and the keto group are included in a macrocyclic system such as 4-cycloocten-1-one (64%) [212]. When the dienone (*Z*,*E*)-4,8-cyclododecadien-1-one is reduced, 5-*exo*-cyclization gives a mixture of the two diastereomers [Eq. (42)] [216]. The major product isomer has a higher calculated strain energy, but the ratio between the two isomers decreases with time, from 2:1 in the beginning to 1.5:1 at the end of the electrolysis. This suggests that the ring formation is reversible, probably due to proton deficiency at later stages of the electrolysis. The relative yield of the thermodynamically favored product therefore increases with time [216].



(42)

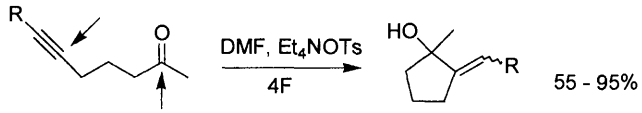
In the case of 6-trimethylsilyl-6-hepten-2-one, the 6-*endo*-cyclization product was obtained exclusively, probably due to steric inhibition of 5-*exo*-cyclization and electronic effects favoring radical formation in the 6-*endo*-cyclization [Eq. (43)] [180].



(43)

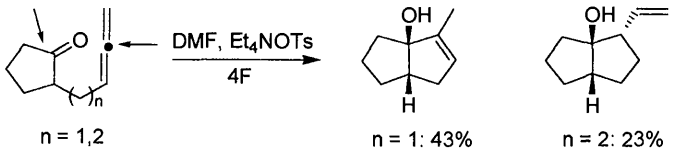
3. Coupling of Alkynes or Allenes With Aldehydes and Ketones

Reduction of non-conjugated acetylenic ketones at constant current gives methylidenecyclopentanols [Eq. (44)] [217]. The highest yields were obtained from terminal alkynes, and bicyclic systems could be formed from alkyne-functionalized cyclopentanones and cyclohexanones [217].



(44)

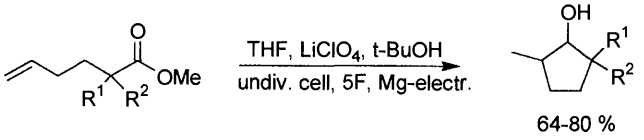
Unactivated allenes linked to ketones undergo reduction to give exclusively five-membered rings [218], affording either *trans* methyl cyclopentenols or ethenyl cyclopentanols depending on the length of the link:



(45)

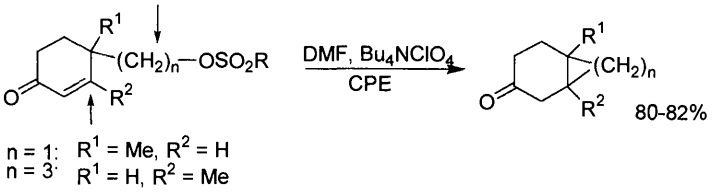
4. Coupling of Alkenes With Esters

Intramolecular coupling between unactivated terminal alkenes and ester groups has been reported [219], and the reaction is very similar to the intramolecular coupling between alkenes and keto groups (Sec. IV.B.2). Good yields of the alcohols are obtained [Eq. (46)], with the isomer having the hydroxy and the methyl groups *trans* in excess, but only five-membered rings can be formed. The reduction is carried out in an undivided cell, and the use of Mg electrodes (the polarization alternated every 15 s) is crucial [219].



(46)

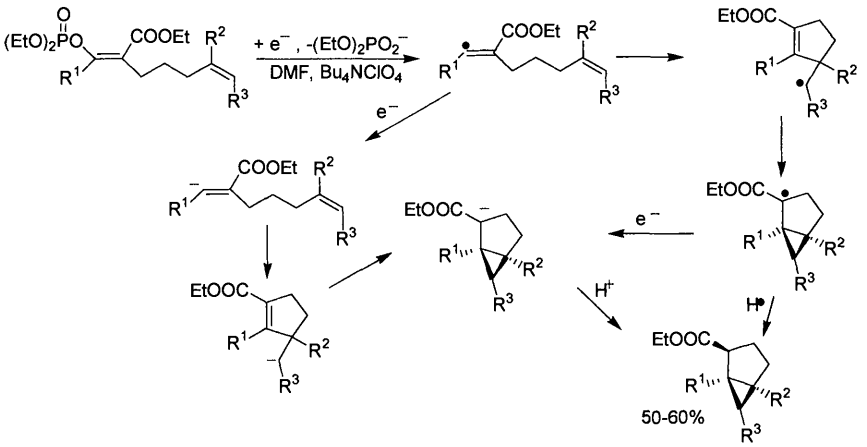
A completely different type of intramolecular reductive coupling involving ester groups are reactions in which sulfonates or phosphates function as anionic leaving groups. Reduction of α,β-unsaturated ketones linked through the β-position to an alkyl group with a terminal sulfonate group gives, in dry DMF, ring closure to the β-position in good yields [220,221] [Eq. (47)]. Direct reduction of sulfonates is known to cleave the S–O bond to give the alcohol, and reduction of the activated alkene is therefore the initial step. Protonation and further reduction (overall 2 F) leading to the β-anion and cyclization by an intramolecular S_N2 reaction is a possible pathway.



(47)

The yields depend on the size of the ring formed, decreasing in the order $3 > 5 > 6 \gg 4 \approx 7$. Formation of five-membered rings is inhibited in the presence of a proton donor (dimethyl malonate) and cyclization to four-, six- and seven-membered rings is completely prevented. However, these conditions have little effect on the formation of the three-membered rings [221]. The authors interpret the results of their preparative studies as a competition between protonation and intramolecular S_N2 reaction on the radical anion stage. However, it seems more likely that the competition is between protonation and cyclization of the β-carbanion formed en route to hydrogenation.

Initial, electrochemical reduction of β-dicarbonyl enol phosphates linked to an olefinic chain gives cleavage of the phosphate with formation of a vinylic radical [222–224]. Reduction in DMF takes place in the potential range −2.0 to −2.3 V and may lead to bicyclic products as illustrated in Scheme 23.

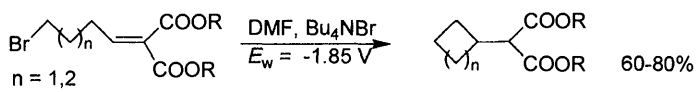


Scheme 23

The vinylic radical participates in a tandem cyclization either through a radical mechanism or through an anion mechanism (Scheme 23). The radical pathway seems the more likely, with reduction of the final bicyclic radical being facilitated by the electron-withdrawing group. The stereochemistry at this center is determined by preferred protonation from the least hindered side. Ketones and esters can both function as the activating group. Generally, formation of six-membered rings is less favored than that of five-membered rings, and if $R^3 \neq H$ the yields are also lowered [222]. More examples are given in Refs. 223 and 224.

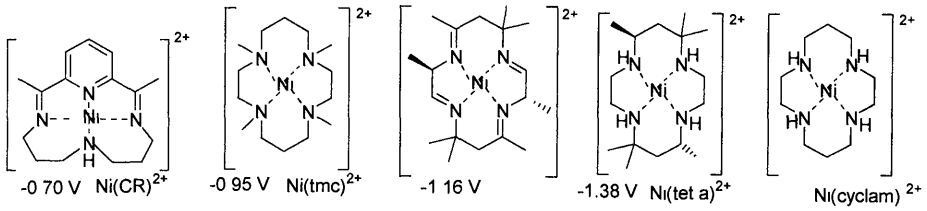
5. Coupling of Activated Alkenes With Organic Halides

Formation of 4- or 5-membered rings follows reduction of dialkyl bromoalkylidenemalonates by cyclization onto the β-carbon of the diactivated double bond [Eq. (48)] [225]. A plausible mechanism may involve C–Br cleavage through inter- or intramolecular electron transfer from the initially formed radical anion to the σ^* orbital. The radical so formed may add intramolecularly to the activated alkene function. An alternative, S_N2 reaction between the alkene radical anion and the bromide would be expected to occur from the α-carbon of the activated alkene, which bears the higher charge density.

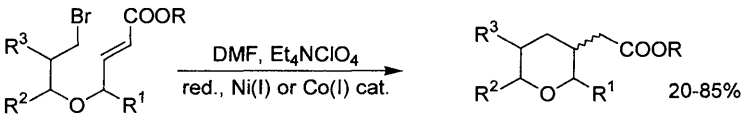


(48)

Similarly to the intermolecular couplings between alkenes and halides (Sec. IV.A.4), yields of intramolecular couplings may be improved by using the same type of transition-metal catalysts. Examples of some commonly used Ni(II) catalyst precursers are shown next. Here and in Sec. IV.B.6 only a few examples of their application are given; more can be found in Chapters 8 and 29.



Six-membered rings are formed in reductions, catalyzed by electrogenerated Co(I) or Ni(I) complexes, of α,β-unsaturated esters linked through the β-position to a chain bearing a bromo atom. The complexes include vitamin B_{12a} (Co) and Ni(II)(tmc)$^{2+}$ [226], which, as mentioned in Sec. IV.A.4, are both known to cleave organic halides to alkyl radicals rather than carbanions. Coupling therefore involves radical attack on the activated carbon–carbon double bond, in this case with 6-*exo*-cyclization [Eq. (49)]. The yields are in the range 40–85%, being higher for monoactivated alkenes than for diactivated ones. For diactivated alkenes (R^1 being a carbonyl oxygen) the yields are lower (~20%), which may be accounted for by competing, direct reduction of the alkene. The products were mixtures of stereoisomers except in a single case where the configuration at the double bond was *cis*. Here the *trans* product was formed exclusively (85%) [226].

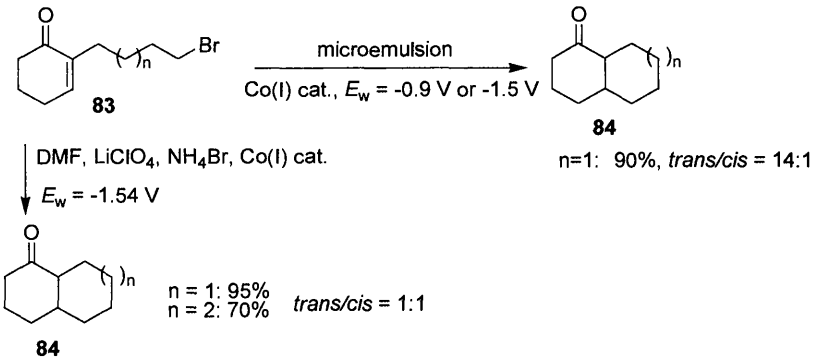


(49)

Vitamin B_{12a} has been used as catalyst precursor for the reductive coupling of **83** to **84** [202,227–229]. The electrochemical reduction at −1.5 V of the Co(III)–alkyl complex formed by oxidative addition of the bromide to the Co(I) species (formed at ~−0.9 V) probably leads to the anion, which may add to the double bond in competition with protonation. In DMF, reduction at −1.54 V gave the cyclized product **84** but with no *trans*/*cis* selectivity (Scheme 24) [227].

In a microemulsion of CTAB/1-pentanol/tetradecane/water (17.5/35/12.5/35, w/w%) with the same Co(I) catalyst, the same reaction led to **84** with a *trans*/*cis* ratio of 14:1, independently of whether the reduction was carried out at −0.9 V or at −1.5 V [202] (Scheme 24). The stereoselective formation of the *trans*-1-decalone in the microemulsion was ascribed to equilibration of the two isomers via OH^- catalyzed keto–enol tautomerization [230].

For **83** with n = 3, reduction at −0.9 V gave little cyclization (20%) neither in DMF nor in microemulsions, indicating that the radical is not significantly undergoing 5-*endo*-cyclization [228]. At −1.5 V, where the anion is formed, the competition between Michael addition and protonation was different for reaction in DMF and in microemulsions, giving 19% cyclization in DMF and 62–70% in microemulsions, indicating that the anion is formed in a water-free part of the microemulsion.

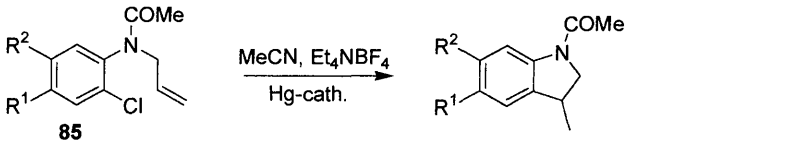


Scheme 24

6. Coupling of Unactivated Alkenes With Organic Halides

Unactivated alkenes give intramolecular coupling with halide functions only in catalyzed reactions, since the low potentials required for direct reduction result in formation of highly reactive carbanionic intermediates. Even the direct reduction of aryl halides, linked to an *ortho*-alkene side chain, normally gives the aryl anion rather than the radical since the potential of the initial reduction is lower than that required for further reduction of the phenyl radical. Cyclized products may be obtained but normally in low yields, due to competing protonation of the phenyl anion, as demonstrated by addition of D_2O to the solvent [231]. Outer-sphere electron transfer reagents may afford reduction at potentials where either the phenyl radical is stable toward further reduction or the rate of reduction by bimolecular reaction with the catalyst is so slow that intramolecular coupling or hydrogen abstraction competes. This has been tested for *o*-(3-butenyl)bromobenzene; where the results of direct reduction ($E_w = -2.65$ V) were compared with reductions using *m*-tolunitrile as an electron-transfer mediator ($E_w = -2.25$ V) [231]. The mediated reduction afforded a higher ratio of cyclized to uncyclized product (8:1 vs. 1:1) and, in contrast to direct reduction, the mediated reduction was little affected by added proton donor. Radical cyclization to the five-membered ring was estimated to have a rate constant of $\geq 10^7\ s^{-1}$ [231]. The carbon–fluorine bond of an aryl radical anion cleaves more slowly than does the carbon–bromine bond, and consequently aryl radical formation takes place in solution following direct reduction. In this case a ratio of cyclized to uncyclized product of 2.5:1 was found for direct reduction [232] even in the presence of 0.5 *M* H_2O.

Another example is the direct reduction of **85a–b**, where the presence of the cyano group facilitates reduction, and which gave hydroindole coupling products (30–35%) [Eq. (50)]. The major side products were the dehalogenated starting materials. Intramolecular coupling of the analogues **85c** containing no cyano group was only obtained by indirect electrolysis using either anthracene or stilbene as mediator [233].



85

a: R^1 = CN, R^2 = H
b: R^1 = H, R^2 = CN
c. R^1 = R^2 = H

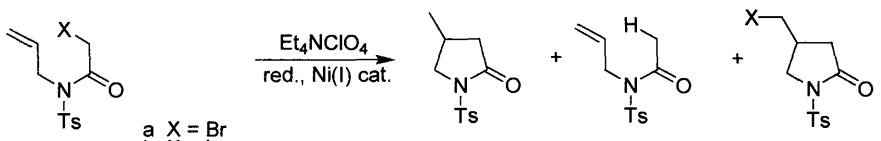
85a-b: 30%
85c: 80%, stilbene as catalyst

(50)

Particularly the variety of Ni(II) complexes with macrocyclic tetradentate nitrogen ligands (cf. the examples in Sect. IV.B.5) have been applied as catalyst precursors for coupling of unactivated alkene functions with halides, since the reactivity of the active, reduced Ni(I) form varies with the reduction potential. Selected Ni complexes can therefore be used to catalyze intramolecular reductive couplings for different types of halogen compounds with varying carbon–halogen bond strengths.

The Ni complexes have been used to perform intramolecular cyclizations to five-membered rings with a variety of substrate types containing unactivated double bonds linked to various halides, such as alkyl [234–236], vinyl [237,238], and aryl halides [236,239]. Standard conditions are reduction at the potential of the Ni(II) complex (0.1–0.2 eq.), in DMF with tetraalkylammonium salts as supporting electrolyte. The appropriate Ni(II) complex can be chosen as the one most easily reduced for which catalysis takes place on a voltammetric time scales [235].

Since the Ni(I) catalysis gives radicals, the initial products of the 5-*exo*-cyclizations are also radicals, which (in contrast to those obtained by addition to *activated* alkenes) are normally not reduced under the conditions of the electrolysis. The follow-up processes are therefore radical reactions, normally assumed to be H-atom abstraction from the solvent. This has been demonstrated for **86a** [Eq. (51)], where the yield of cyclized product was shown to be higher in DMF than in MeCN, DMF being a better H-atom donor than MeCN [235]. Cyclization from **86a** in MeCN could be improved by addition of Ph_2PH as an external H-atom donor, otherwise, the main product was the halogenated cyclized compound formed by halogen atom abstraction from another molecule of starting material. However, addition of Ph_2PH also increased formation of acyclic products due to competing H-atom abstraction of the initially formed radical [235] [Eq. (51)]. Using **86b** rather than **86a** and carrying out the electrolysis in MeCN without Ph_2PH, it was possible to obtain the iodo compound as the only cyclic product due to the lower activation energy for iodine radical abstraction than for bromine radical abstraction [236].



86

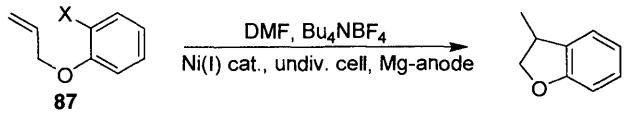
a X = Br
b X = I

(51)

86a, DMF.	41%	5%	14%
86a, DMF, 2 eq. Ph_2PH	59%	8%	-
86a, MeCN	8%	-	33%
86a, MeCN, 2 eq. Ph_2PH	58%	15%	-
86b, MeCN	-	14%	61%

Under conditions similar to those in Eq. (51) (DMF as solvent, divided cell), reduction of **87** (X = I) gives 75% of the cyclized product [234]. The yield was improved (90%)

using an undivided cell and a sacrificial Mg anode [Eq. (52)] [239]. The yields increased in the order Cl < Br < I.

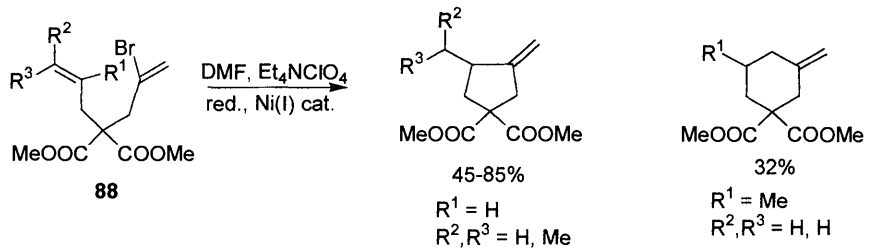


87

X = Cl, Br, I

(52)

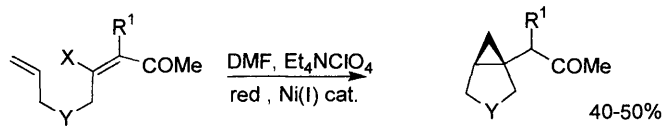
The carbon–halogen bond is stronger in vinyl halides than in alkyl halides, and Ni complexes with slightly lower reduction potentials have to be used to catalyze the reductive cyclization of vinyl halides on to alkene functions. Using conditions similar to those for the alkyl and aryl halides, 5-*exo*-cyclized products were obtained from **88** [237]. In a single case (methyl substitution at the position of 5-*exo*-attack), only the 6-*endo*-product was obtained [Eq. (53)] [237].



88

(53)

Tandem cyclization was not obtained for **88**. However, this could be achieved for **89** in which the vinyl halide was further activated with an acetyl group [Eq. (54)] and the catalyst was used in a larger amount (0.3–0.5 eq.) [238]. In explanation of the difference, it was proposed that the subsequent formation of the cyclopropyl ring by 3-*exo*-cyclization is reversible. The electron withdrawing group at the final radical center promotes its rapid reduction [by the "excess" Ni(I) complex] to a carbanion that is quickly protonated [238].



89

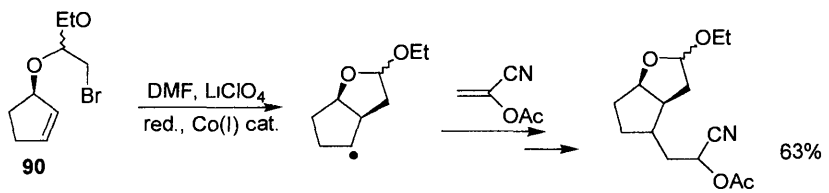
R^1 = H, Me, Ph

X = Br, I

Y = $C(COOEt)_2$,N-Ts, N-allyl

(54)

The substrate **90** has been cyclized using reduced vitamin B_{12a} as a catalyst (0.01 eq.). The radical formed by cyclization can be trapped with an activated alkene (added in excess) to form a new radical, which probably undergoes reduction and protonation to give a mixture of diastereomeric products [240]:



90

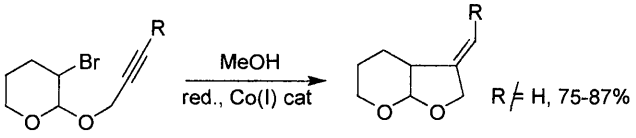
(55)

7. Coupling of Alkynes With Organic Halides

Cyclization by direct reduction of alkynes linked to halides is usually ineffective. Phenyl-substituted alkynes are more easily reduced than alkyl chlorides but more difficult to reduce than alkyl bromides and iodides. Simple alkynes are more difficult to reduce than any of the halides. Consequently, direct reduction of 6-bromo-1-phenyl-1-hexyne at a potential of cleavage of the C–Br bond only affords 12% yield of benzylidenecyclopentane, whereas the corresponding chloride gives the saturated benzylcyclopentene in 45% yield [241], or at low substrate concentrations (< 2 mM) the benzylidene cyclopentane (80%) [242].

Not surprisingly, Ni(I)-catalyzed reductive cyclization of halides onto alkynes requires conditions similar to the Ni(I)-catalyzed reductive cyclization of halides onto alkenes. The alkynes are converted into alkylidene- or benzylidene-substituted five-membered rings [234–236,243].

Cobaloxime(I) has been shown to catalyze intramolecular reductive coupling of cyclic bromo acetals with double and triple bonds, although fairly large amounts of the catalyst (0.5 eq.) had to be used [244]. Significantly better yields (75–87%) were obtained when MeOH was used as solvent instead of MeCN or DMF [Eq. (56)]. Formation of six-membered rings could not be achieved [244].



(56)

In contrast to the allyl ethers (**87**) the analogous propargyl ethers were cyclized in poor yield (~30%) to the corresponding benzofuran using the same conditions as in Eq. (52) [245].

V. REDUCTIVE COUPLINGS INVOLVING ATOMS IN AN AROMATIC RING

Intramolecular reductive couplings between alkenes and aromatic halides have been mentioned in sec. IV.B.5 and IV.B.6. Here, discussion centers on reductive coupling either between two aromatic rings or between an aromatic ring and another, nonolefinic molecule.

A. Intermolecular Couplings

Intermolecular reductive couplings between aromatic rings mostly involve either reactive aryl σ-radicals, for example, derived from aromatic halides by cleavage of the radical anions, or relatively stable π-radical anions derived from aromatic compounds activated by electron-withdrawing substituents.

1. Coupling Between Aromatic Halides

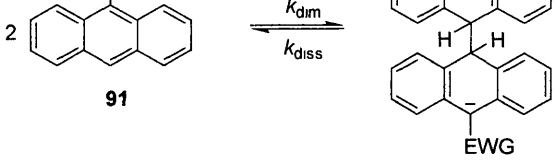
Homo- and heterocouplings of aromatic halides are almost always carried out using transition-metal catalysts, commonly Ni(0) or Pd(0) species. The practicability of these inner-sphere reactions has been developed in the last two decades and mechanistic details have been elucidated in a number of cases. Preparative aspects of transition-metal-cata-

lyzed couplings of aryl halides have recently been reviewed [199] (see also Chapter 8). The subject is therefore not treated here.

2. Dimerization of Aromatic Compounds Activated with Electron-Withdrawing Substituents

Reductive dimerization of unactivated aromatic hydrocarbons is rare, although, for example, formation of 9,9′,10,10′-tetrahydro-9,9′-biphenanthrene (~ 40%) upon reduction of phenanthrene in DMF has been reported [246].

Reduction of 9-substituted anthracenes, (**91**), leads to radical anions, which, because of the electron-withdrawing substituents, are quite stable with respect to protonation and cleavage in aprotic solvents. In polar aprotic solvents the radical anions exclusively dimerize, and the reaction has been the subject of a number of studies [247–258]. The products are the "tail-to-tail" dimeric dianions as in Eq. (57), which are fairly stable. In CV the dimer dianions can be detected as a new oxidation peak on the reverse scan at a potential several hundred millivolts anodic relative to the potential of radical anion formation. On preparative or semipreparative scales the dimer dianion has in a single case been detected by ^{1}H-NMR [249], and oxidative electrolysis of the dimer dianions in most cases restores the starting material.



a: EWG = NO_2
b: EWG = COMe
c: EWG = COOMe
d: EWG = CHO
e: EWG = CN

(57)

The tetrahydrobianthryl products formed by protonation of the dimeric dianions have been isolated (up to 90% yield) in some cases after addition of acids [253,255,256]. Unless the dimer dianion is trapped by acid (or in a single case by methyl iodide [259]), air oxidation of the dimer dianion to starting material takes place during work-up [249–254].

Reversibility of the dimerization step on a voltammetric time scale has been verified for several of the 9-substituted anthracenes in the absence of added acids [259]. For **91a** and **91e** the reversibility of the dimerization step was shown to be prevented by addition of AcOH, which protonates the dimer dianion in a fast follow-up reaction (the radical anions are not protonated by AcOH) [251]. Since the rate and equilibrium constants for dimerization, k_{dim} and K_{dim}, for **91e** are of magnitudes that conveniently can be measured using CV and DPSC [247,248,250–253,257,259,260], **91e** has been used as a model compound for mechanistic studies of systems undergoing reversible dimerization, and values of k_{dim} and K_{dim} have been determined under a number of different conditions (Table 21).

The addition of AcOH simplifies the kinetics by making the dimerization irreversible but had little influence on the measured values of k_{dim} [251]. Addition of a metal cation or water to the aprotic solvents accelerates the dimerization reaction of **91e**$^{\cdot-}$, i.e., effects similar to those observed for EHD of some activated alkenes (Sec. II), and the interpretation is similar. Acceleration of the dimerization reaction with increasing water concentration was demonstrated for **91e** in DMF and DMSO [251,261] and is entirely related to solvation of the anionic intermediates, since water is too weak an acid to protonate neither the radical anion nor the dimer dianion.

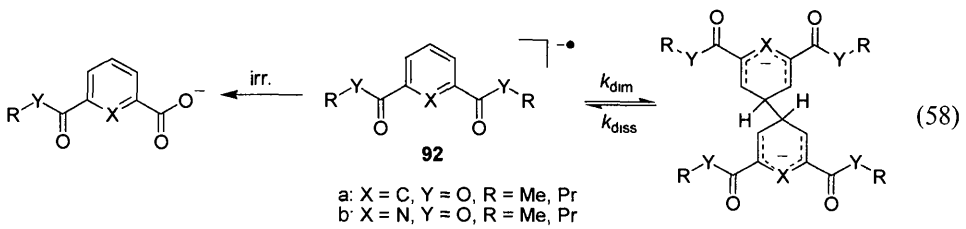
Table 21 Selected Rate and Equilibrium Constants for Dimerization of Radical Anions Derived From Substituted Aromatics

Substrate	Conditions	k_{dim} ($M^{-1}s^{-1}$)	K_{dim} (M^{-1})	Comments	Ref.
9-Cyanoanthracene (**91e**)	DMSO, $LiClO_4$, 20°C, DPSC, LSV	2.8×10^5	5.7×10^4	$\alpha = 0.4, k_s = 0.8$ cm s^{-1}	[253]
91e	DMSO, Bu_4NBF_4, 20.5°C, DPSC	1.9×10^4	4.5×10^4	E_a(dim) = 10.2 kJ/mol, $A = 7.9 \times 10^8$ M^{-1} s^{-1}, E_a(diss) = 72.8 kJ/mol	[248]
91e	DMF, Bu_4NBF_4, AcOH, 20.6°C, DPSC	1.9×10^5	[b]	$\Delta H^{\neq}_{dim} = 1.2$ kcal/mol, $\Delta S^{\neq}_{dim} = -30$ cal/K/mol	[251]
91e	DMF, Bu_4NBF_4, 25°C, DPSC	1.6×10^5	2.2×10^4	$\Delta H^{\neq}_{dim} = 1.7$ kcal/mol, $\Delta S^{\neq}_{dim} = -29$ cal/K/mol	[260]
91e	MeCN, Bu_4NBF_4, 25°C, DPSC	5.3×10^5	8.2×10^4	$\Delta H^{\neq}_{dim} = 2.2$ kcal/mol, $\Delta S^{\neq}_{dim} = -25$ cal/K/mol	[260]
91e	PC, Bu_4NBF_4, 25°C, DPSC	1.5×10^5	2.9×10^4	$\Delta H^{\neq}_{dim} = -0.5$ kcal/mol, $\Delta S^{\neq}_{dim} = -37$ cal/K/mol	[260]
91e	HMPA, Bu_4NBF_4, 25°C, DPSC	4.1×10^4	2.2×10^3	$\Delta H^{\neq}_{dim} = 4.5$ kcal/mol, $\Delta S^{\neq}_{dim} = -23$ cal/K/mol	[260]
91e	Pyridine, Bu_4NBF_4, 25°C, DPSC	2.2×10^5	2.3×10^4	$\Delta H^{\neq}_{dim} = 0.7$ kcal/mol, $\Delta S^{\neq}_{dim} = -32$ cal/K/mol	[260]
91e	CH_2Cl_2, Bu_4NBF_4, 25°C, DPSC	1.5×10^5		$\Delta H^{\neq}_{dim} = 2.7$ kcal/mol, $\Delta S^{\neq}_{dim} = -25$ cal/K/mol	[260]
9-Formylanthracene (**91d**)	DMF, Bu_4NBF_4, 22°C, DCV	3.1×10^5[a]		$\Delta H^{\neq}_{dim} = 2.6$ kcal/mol, $\Delta S^{\neq}_{dim} = -25$ cal/K/mol	[251, 259]
91d	DMF, Et_4NClO_4, CV	10^5	[c]		[268]
91d	MeCN, Et_4NClO_4, CV	$> 4 \times 10^5$	[c]		[268]
91d	HMPA, $LiClO_4$, CV	2×10^4	[c]		[254]
9-Formyl-10-methylanthracene	DMF, Et_4NClO_4, CV	[e]			[254]
9-Nitroanthracene (**91a**)	DMF, Bu_4NBF_4, 22°C, DCV	1.6×10^6[a]		$\Delta H^{\neq}_{dim} < 1.2$ kcal/mol, $\Delta S^{\neq}_{dim} < -26$ cal/K/mol	[259]
91a	DMF, Bu_4NBF_4, AcOH, 22°C, DCV	2.3×10^6	[b]	$\Delta H^{\neq}_{dim} = -0.2$ kcal/mol, $\Delta S^{\neq}_{dim} = -30$ cal/K/mol	[251]
91a	DMF, Bu_4NClO_4, DCV	10^6	[d]		[269]
1,3-Benzenedicarbonitrile	DMF, Bu_4NClO_4, 25°C, CV, LSV	1.1×10^5	10^6		[262]
Acridine (**95**)	DMF, Bu_4NClO_4, DCV	2×10^3	[c]		[270]
95	NH_3, CF_3SO_3K, 22°C, 8.1 bar	2.8×10^5	1.6×10^4	E_a(dim) = 17 kJ/mol, $A = 3 \times 10^8$ M^{-1} s^{-1}, E_a(diss) = 65 kJ/mol	[271]
Quinoline (**96**)	NH_3, CF_3SO_3K, 21°C, 8.1 bar	4.8×10^3	8.4×10^2	E_a(dim) = 12 kJ/mol, $A = 7 \times 10^5$ M^{-1} s^{-1}, E_a(diss) = 55 kJ/mol	[271]

[a] Dissociation reaction not taken into account.
[b] Irreversible due to protonation.
[c] Not reversible on CV time scale.
[d] Reversibility not considered.
[e] Radical anion stable on CV time scale but dimer dianion formed on preparative time scale.

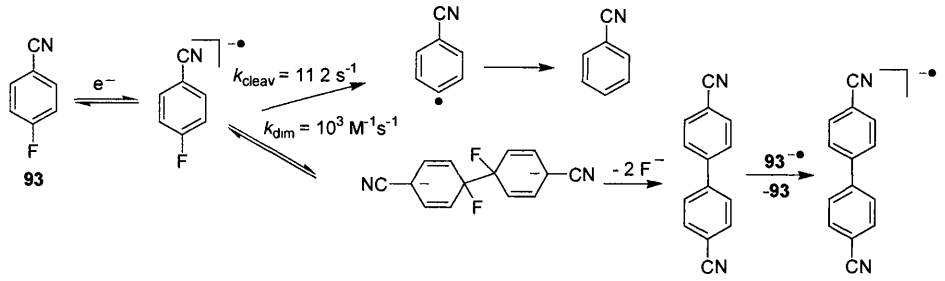
For **91e** the effect on k_{dim} and on K_{dim} induced by change of the solvent (Table 21) is modest and not easily interpreted [260]. The activation enthalpies for the dimerization step, $\Delta H^{\neq}_{dim}$, are small (< 5 kcal/mol, and even negative for **91a**) compared to the values of k_{dim} [248,251,259,260]. Two mechanisms have been suggested to account for the experimental data: (a) preassociation of two radical anions in a fast preequilibrium followed by reversible bond formation [251,259,260], and (b) simple, reversible dimerization of two radical anions [257]. Since the rate laws are identical for the two mechanisms as long as the equilibrium constant for formation of the intermediate precomplex is small, kinetic measurements can not be used to distinguish between them. Within the first mechanistic interpretation the low $\Delta H^{\neq}_{dim}$ values are explained by a negative enthalpy of formation of the precomplex. The nature of such a precomplex, however, is not easily envisaged. Within the second mechanistic interpretation the low values of $\Delta H^{\neq}_{dim}$ are explained by opposing effects of coulombic repulsion and increased solvation when the two negatively charged radical anions become located within the same solvent cage.

Like the other aromatic substrates with electron-withdrawing groups, the radical anions derived from 1,3-benzenedicarbonitrile dimerize reversibly as indicated by the persistence of a—low-intensity—ESR spectrum of the radical anion [262 and refs. therein]. Results obtained by CV put a value of $10^6\ M^{-1}$ on K_{dim}, and also in this case k_{dim} increases upon addition of water [262]. The reversible dimerization of the radical anions of dialkyl benzene-1,3-dicarboxylate (**92a**), dialkyl pyridine-1,3- dicarboxylate (**92b**), and their sulfur analogues (Y = S) [Eq. (58)] has been characterized by CV and ESR spectroscopy [263], and values of $k_{dim} \approx 10^3$–$10^4\ M^{-1}\ s^{-1}$ and of $k_{diss} \approx 0.1 - 1\ s^{-1}$ were found for all substrates in MeCN (Bu_4NBF_4). On a preparative scale, a competing slow, but irreversible, first-order reaction gave the monocarboxylate anions as the sole product [263].



(58)

For aromatic compounds substituted with both an electron-withdrawing group and a potential leaving group, dimerization of the radical anions competes with cleavage. In cases where dimerization is the favored pathway, the initially formed dimer dianion may subsequently lose two anions in a fast reaction leading to stable biaryl products rather than to the dihydro products discussed above. This is the case for 4-fluorobenzonitrile (**93**) [264], polyhalonitrobenzenes [265], 9-cyano-10-chloroanthracene [266], and cyanodiphenyl ether (**94**) [267]. Reduction of **93** in DMF leads at high substrate concentrations to formation of 4,4′-dicyanobiphenyl (in the reduced form, since the product is more easily reduced than the substrate) (Scheme 25). In contrast, reduction of 2-fluorobenzonitrile leads only to formation of benzonitrile, although the primary reaction also in this case is dimerization of two radical anions. The values of k_{dim} are comparable for 2- and 4-fluorobenzonitrile radical anions, but since both radical anions are assumed to undergo coupling in the 4-position (largest unpaired spin density), only the dimer dianion of **93** can reestablish the aromatic structure by loss of two F^- [264].



Scheme 25

Slightly different behavior was found for reduction of 2- and 4-cyanodiphenyl ether (**94b** and **94a**) in DMF [267]. On CV and DPSC time scales, the radical anions of **94a** dimerize irreversibly to the 4,4′- and 2,4′- (with respect to the CN group) dimer dianions in the ratio 1:3.

Aromaticity is restored in the 4,4′-dimer dianion by loss of two PhO^-, giving the product 4,4′-dicyanobiphenyl, which is reduced to the dianion at the potential where it is formed. The 2,4′-dimer dianion quickly loses one PhO^-, and the resulting anion can be observed either as a new one-electron reduction peak at a potential slightly cathodic of the substrate reduction peak or as a two-electron oxidation peak [267]. On CV and DPSC time scales the radical anion of **94b** undergoes reversible dimerization to a mixture of 2,4′-, 4,4′-, and 4,6′-dimer dianions. Only the 2,4′-dimer dianion reacts further by loss of one PhO^-, and the resulting anion can undergo oxidation followed by proton loss to afford the neutral 2′,4-dicyano-3-phenoxybiphenyl [267].

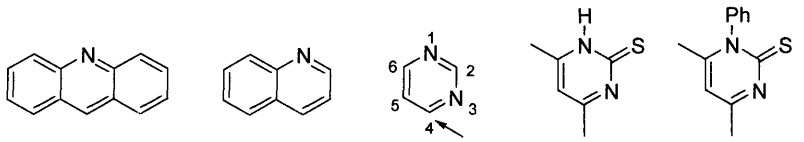
Reduction of pentafluoronitrobenzene in DMF or MeCN also leads to a radical anion that undergoes dimerization, $k_{dim} = 3.8 \times 10^5\ M^{-1}\ s^{-1}$, followed by rapid loss of two F^- to give 4,4′-dinitrooctafluorobiphenyl. However, this compound is more easily reduced than the starting material and is further reduced to either the mixed amino–nitro or the diamino derivative [265]. Significantly, the radical anion of pentafluoronitrobenzene is stable on a voltammetric time scale when MeOH/water mixtures are used as solvent, indicating important differences in the solvation of the radical anion in protic and aprotic solvents [265]. The higher rate of cleavage of the carbon–chlorine bond than of the carbon–fluorine bond favors first-order cleavage of the pentachloronitrobenzene radical anion over dimerization, and a mixture of dimeric and monomeric products is formed [265]. A similar change from second-order to first-order reaction was observed for radical anions of 9-cyano-10-haloanthracenes, with the chloro compound undergoing a second-order reaction to give the dimer, 9,9′-bianthryl-10,10′-dicarbonitrile (65%), in MeCN, whereas the bromo compound underwent cleavage [266].

3. Coupling of *N*-Heteroaromatic Compounds

Radical anions derived from *N*-heteroaromatic compounds are more distonic than their hydrocarbon analogues because of the electronegative nitrogen atom. As a consequence, these radical anions are generally more reactive.

Radical anions of acridine (**95**) dimerize in DMF to give the corresponding dimer dianion [270] (Table 21). The reduction remained a 1-F process upon addition of 10% (v:v) water but led to a fivefold increase in the value of k_{dim}. On a voltammetric time scale, the dimerization appeared irreversible in the absence as well as in the presence of water. On a preparative scale, the dimer 9,9′,10,10′-tetrahydro9,9′-biacridyl could be isolated

(60–70%) only when the reduction was carried out in DMF containing 7–10% water [270]. The dimerization in ammonia (CF_3SO_3K) of the radical anions of **95** and of quinoline, **96**, has been studied over a 200° temperature range (−70°C to 150°C) utilizing a special cell constructed for working in ammonia at high pressures and high temperatures [271]. Several electroanalytical techniques (CV, LSV, and DPSC) were applied in order to characterize the kinetics and thermodynamics of the dimerization reactions. In both cases the dimer dianions were stable with respect to further irreversible reactions, and by varying the temperature and the scan rate the dimerization processes could be shifted through several kinetic zones in which the dimerization either did not take place at all, appeared reversible, or appeared irreversible. The choice of supporting electrolyte cation was important; when K^+ was changed to Bu_4N^+, k_{dim} decreased by about two orders of magnitude for $\mathbf{96}^{-\cdot}$ [271]. Kinetic and thermodynamic data for the two dimerization processes are found in Table 21. Low activation energies are also found for these dimerizations (Table 21).



95 **96** **97a** **97b** **97c**

Pyrimidine, **97a**, undergoes one-electron reduction in MeCN to a radical anion, which undergoes a second-order reaction, and on a coulometric time scale $n = 1.05$ was found. The product was not isolated, but dimerization at the 4-position was assumed to take place [272]. A new anodic peak corresponding to oxidation of the dimer dianion (or its monoprotonated form) was observed. The value of k_{dim} was estimated by CV to $\sim 8 \pm 5 \times 10^5\ M^{-1}\ s^{-1}$ [272]. In acidic aqueous solution (pH < 5), reduction of **97a** is also a one-electron process, since the preprotonated (at nitrogen) species is more easily reduced than the resulting neutral radical [272]. Because the initial reduction is pH dependent whereas the reduction of the radical is not, the two reduction steps merge into a two-electron process at pH > 5. The dimerization in acidic aqueous solution has recently been studied by a variety of electroanalytical methods [273]. Preparative-scale reduction of **97a** in aqueous solution at pH 0.6 gave the hydrodimer, 4,4′-tetrahydrobipyrimidine, in a clean 1 F process [274]. The product could subsequently be oxidized by $KMnO_4$ to bipyrimidine.

In DMF the two substituted thio derivatives of pyrmidine, **97b** and **97c**, were found to dimerize upon reduction in the absence as well as in the presence of acid [275]. For **97b**, however, the coulometric *n*-value was close to 0.5 in the absence of proton donors, indicating that the *N*-proton in **97b** is sufficiently acidic to protonate either the radical anion or the dimer dianion, thereby leaving half of the substrate on the unreducible anionic form. In the presence of stoichiometric amounts of $HClO_4$, the reduction takes place via the preprotonated substrate as for **97a** [275]. The rate constant for dimerization of $\mathbf{97c}^{-\cdot}$ (in the absence of acid) was found to be close to that for $\mathbf{97a}^{-\cdot}$ [275].

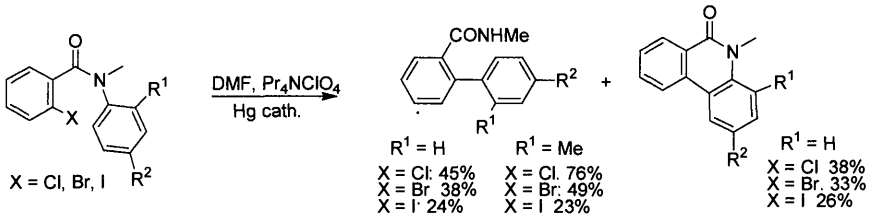
B. Intramolecular Couplings

The major reason for using transition-metal catalysts in the intermolecular coupling of aryl halides is to minimize the competition from further reduction of the radical formed by carbon–halogen bond cleavage of the radical anion. The competition from further reduction is less severe when a suitably proximate second aryl group is present, which may react

intramolecularly with the σ-aryl radical. The slower the cleavage reaction, the further away from the electrode is the radical formed, which favors coupling in competition with further reduction. However, since coupling between phenyl radicals and aryl groups normally is slower than between phenyl radicals and alkenes, the same drawbacks as discussed in Sec. IV.B.6 pertain to these reactions.

The scope of the reaction type has been explored in particular by Grimshaw and coworkers [276–286]. Since the rate constant for cleavage of the carbon–halogen bond decreases in the order I > Br > Cl > F, yields of coupling products are usually higher using chloro rather than bromo compounds. Most of the studies have been carried out by controlled potential electrolysis ($E_w \approx -2.1$ V for the chloro compounds) in DMF using divided cells and Hg cathodes [276–285].

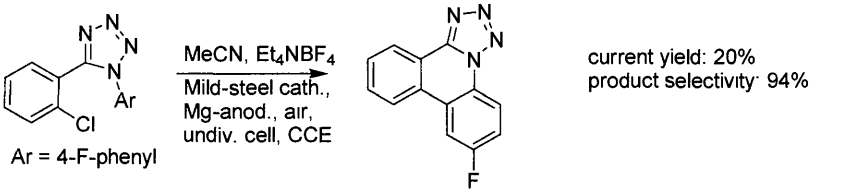
Where an aryl halide is connected to the "receiving" aryl function by an amide linkage, as in Eq. (59), two different types of cyclization occur, depending on where the initial radical attack takes place [276,278–280]. The relative yields of the two cyclization products depend on the substitution pattern in the aryl group being attacked [278]. Only the *syn* conformation of the radical anion can give rise to coupling, and rotation about the amide bond is particularly slow when *o*-substituents are present. Where the aryl group under attack is *o*-disubstituted, <40% cyclization is obtained, and only if both *o*-positions are unsubstituted is the tricyclic product formed [278].



(59)

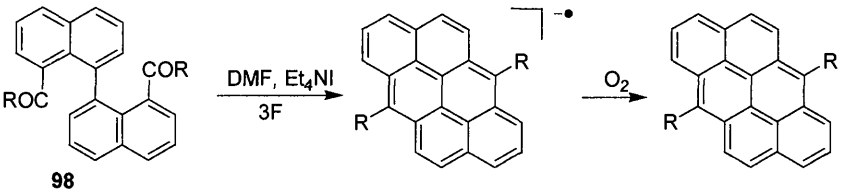
The process that leads to the final, formal, loss of a hydrogen atom to the 0 F tricyclic products is not clear. In contrast, the formation of the 2 F biaryl products can be explained by further reduction of the cyclized radical followed by cleavage of the carbon–nitrogen bond and protonation. Unless the two aryl groups in the substrate are linked through an electron-withdrawing function with respect to the aryl halide ring, the reduction potential is shifted cathodic and the current yields drop significantly due to hydrogen formation [281]. A series of *N*-phenyl nitrogen heterocyclic systems such as pyrroles [283], imidazoles [281,283], oxazolinones [277], triazoles [282], and tetrazoles, [283,284,286] have also been used as "linkers" to the aryl halide. The *N*-heterocycles give exclusively coupling of the chloro substrates to tetracyclic products (formally 0-F products) in yields up to 90% when reduced under conditions similar to those in Eq. (59).

The reduction of the tetrazoles [Eq. (60)] has been used as a model for optimization of the chemical yield using an undivided cell and constant current rather than constant potential electrolysis [285,286]. Electrolysis under air rather than under nitrogen lowered the current yield from 43% to 20% (assuming a 1-F process) but increased the product selectivity (from 50% to 94%), since the intermediate, partly hydrogenated fluorophenyl ring was dehydrogenated, probably by electrogenerated superoxide ion [286].



(60)

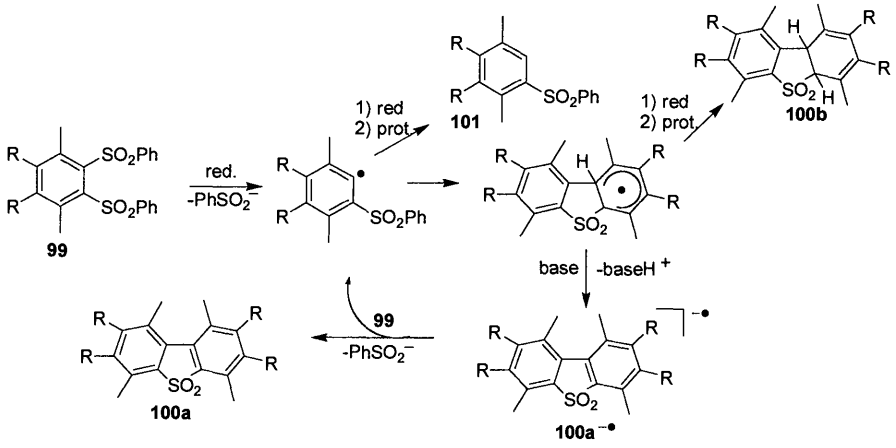
Reduction, in dry DMF, of 1,1′-binaphthyl systems of the type **98** has been shown to result in "double" intramolecular couplings, giving the enlarged aromatic anthanthrene system [Eq. (61)] in almost quantitative yields [287].



(61)

The reaction is most probably initiated by radical attack of a reduced carbonyl function on the aromatic ring in the adjacent system. The product is formed as the radical anion but reoxidized by air during work-up. In the presence of proton donors, or in alcoholic solvents, reduction of **98** gives a mixture of acyclic and partly hydrogenated cyclic products [288]. Substituted **98**, such as the 4,4′,5,5′-tetracarboxylic acid, gives coupling in basic alcoholic medium but not in DMF [289].

When the methyl substituted derivatives of *o*-bis(phenylsulfonyl)benzene (**99**) are reduced in DMSO, good yields of the intramolecularly coupled products are obtained. These are methyl-substituted dibenzothiophene dioxides (**100a**), formed after initial cleavage of $PhSO_2^-$ from the radical anion followed by intramolecular attack of the aryl radical on the phenyl group [290] (Scheme 26).

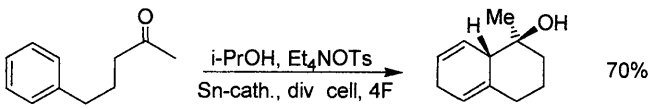


Scheme 26

The reaction was shown to be catalytic with respect to current in the presence of an external base, which indicates the reaction pathway in Scheme 26, that is, formation of the radical anion of the product by deprotonation of the intermediate radical. In the presence

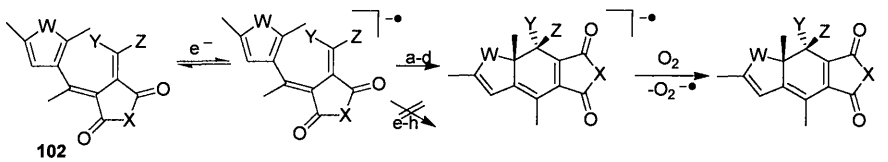
of 2 eq. AcO^- as base, the reaction became a 0.14-F process, and the yield of cyclized product increased to >95%. In the absence of added base, $PhSO_2^-$ is probably the active but less efficient base, leading only to 68% of **100a** along with the hydrogenated derivative, **100b**, and the noncyclized 2-F product, **101** [290] (Scheme 26). Although the electron transfer from $\mathbf{100}^{-\cdot}$ to **99** is endothermic, the overall reaction is driven by the fast cleavage of $\mathbf{99a}^{-\cdot}$.

Intramolecular reductive couplings between aromatic rings (phenyl, naphthyl, anthryl) and nonconjugated keto groups have been achieved in 25–70% yield [291] [Eq. (62)]. Lower yields were obtained with other combinations of solvents and electrolytes and by application of other cathode materials. However, only six-membered rings were formed successfully, and only nonaromatic ketones could be used [291]. The reaction is initiated by reduction of the keto group, and the reaction is highly stereospecific with the hydroxy group and the hydrogen at the coupling site *cis*. The neutral medium and observed effects of substituents in the aromatic ring indicate that the coupling involves an ion-paired radical anion, and that the diastereoselectivity is controlled by coulombic interactions [291].



(62)

Compounds **102** are nonplanar and undergo 1-F reduction in MeCN around −2 V [292]. The radical anions derived from **102a–d** undergo stereoselective cyclization according to Eq. (63), whereas **102e–h** give stable radical anions. The initial product, the cyclized radical anion, is air-oxidized upon work-up, giving the 0-F cyclized product, which is identical to the product obtained by photoexcitation [292]. The radical anions that fail to cyclize are those in which extended delocalization is not achieved by flattening of the ring systems or in which steric hindrance prevents coplanarity of the ring systems [292].



102

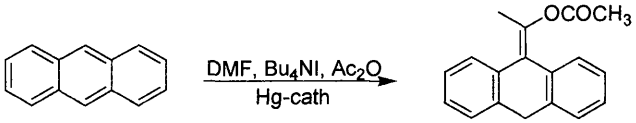
(63)

a W = X = O, Y = Z = Me
b W = X = O, Y = H, Z = Me
c W = S, X = O, Y = Z = Me
d W = S, X = NBz, Y = Z = Me
e W = X = O, Y, Z = adamantylidene
f W = S, X = NPh, Y = Z = Me
g W = S, X = $NC_6H_4NO_2$, Y = Z = Me
h W = S, X = NCH_2COH, Y = Z = Me

C. Coupling Between Aromatic Rings and Other Reagents

Reductive coupling, in aprotic solvents, of aromatic hydrocarbons with CO_2 has long been known. Reduction of naphthalene in DMF in the presence of CO_2 leads to 1,4-dicarboxy-1,4-dihydronaphthalene (~ 50%) [246]. Under similar conditions, phenanthrene gives *trans*-9,10-dicarboxy-9,10-dihydrophenanthrene (~ 30%) [246]. Carboxylation of aromatic halides can be achieved in aprotic solvents either by using transition metal catalysts or by direct reduction using sacrificial anodes in undivided cells (cf. Chapter 8).

Reduction of anthracene in the presence of an excess of acetic anhydride led to formation of the enol acetate of 9-acetyl-9,10-dihydroanthracene [293]:



(64)

In each case the hydrocarbon is the species reduced, but whether or not the ensuing radical anion is involved in electron transfer to CO_2 or Ac_2O prior to coupling was not investigated.

Intermolecular coupling between aromatic rings and nonaromatic organic halides has been observed in a number of cases [294 and refs. therein]. The mechanism of these reactions is well understood. The aromatic compound is reduced and electron transfer to the halide takes place in solution; the radical resulting from cleavage of the halide may either be reduced or undergo coupling with the aromatic radical anion, depending on the relative reduction potentials of the radical and the aromatic system. In cases where coupling takes place, the anion formed in the coupling process may either be protonated by the medium or undergo S_N2 reaction with another molecule of halide. An example of the first type of coupling reaction is the *t*-butylation of pyrene [295]. Upon reduction of pyrene in DMF in the presence of *t*-BuCl, 1-*t*-butylpyrene is formed as the major product (52%) after coupling, protonation, and autooxidation of the dihydro compound [295]. An example of the second type of coupling is the formation of 9,10-ethano-9,10-dihydroanthracene (57%) by reduction of anthracene in DMF in the presence of a moderate excess of 1,2-dichloroethane [296]. The reaction type is further discussed in Chapters 8 and 29.

Intermolecular coupling of pyridines with ketones under acidic conditions has received attention but like the intramolecular reductive coupling of aromatic rings linked to aliphatic ketones [Eq. (62)], the reaction is essentially a ketone reduction, and the reader is referred to Chapter 10.

D. Reductive Dimerization of Positively Charged Aromatic Systems

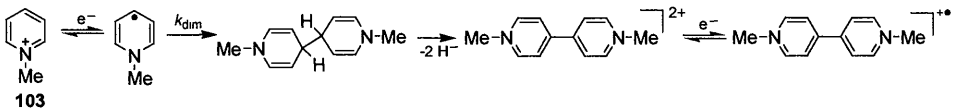
One-electron reduction of positively charged systems leads to neutral radicals, and independently of the structure the most common follow-up reaction is fast dimerization of two neutral radicals. In contrast to neutral radicals formed by cleavage, those formed by reduction of positively charged aromatic systems are not reduced at the potential where they are formed, and formation of 2-F products therefore only competes via H-atom abstraction. For *N*-heterocyclic systems in aqueous acidic media, protonation of the radical and further reduction leading to the dihydro-monomeric system may compete with dimerization.

1. *N*-Alkylpyridinium and Related Systems

The electrochemical reduction of pyridinium cations and other positively charged *N*-heteroaromatic systems has received considerable attention as models for nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate ($NADP^+$).

The major reaction pathway in all cases consists of reduction to the neutral radical followed by coupling, primarily or exclusively in the 4-position with respect to the ring nitrogen. Like the dimeric dianions formed by dimerization of, for example **91**$^{-\cdot}$, the neutral dimeric products obtained from positively charged *N*-heteroaromatic systems are in many cases difficult to isolate since they are easily reoxidized back to the substrate cations.

Reduction of the simple *N*-methylpyridinium ion, **103**, is believed initially to give the expected *N*,*N*′-dimethyltetrahydro-4,4′-bipyridine, but the end product (in the absence of oxygen) is the *N*,*N*′-dimethylbipyridine radical cation formed by a formal loss of two hydride ions and one-electron reduction of *N*,*N*′-dimethylbipyridinium [297,298]. The isolated product, *N*,*N*′-dimethylbipyridinium dication, results from air-oxidation of the radical cation [298]:



(65)

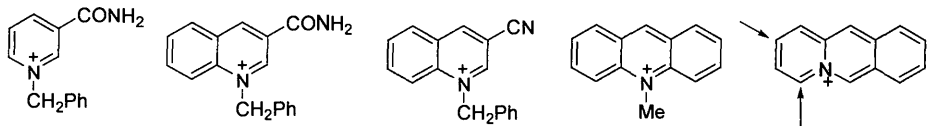
The reaction pathway in Eq. (65) dominates for pyridinum ions unsubstituted in the 4-position, whereas 4-alkylpyridinium ions undergo reductive coupling to the 4,4′-tetrahydrobipyridine derivatives [299]. Values of k_{dim} have been determined for several pyridinyl radicals in MeCN [299] (Table 22). Despite the complication of air oxidation, the dimers have been isolated in 40–70% yield.

Reductive dimerization of the NAD^+ analogues **104a–c**, in MeCN, and the reoxidation of the dimers have been studied in detail by CV and LSV [300]. This allowed the estimation of the $E^{0\prime}$ values and the dimerization rate constants (Table 22). Also in aqueous medium, **104a** undergoes fast reductive dimerization, and the 4,4′-tetrahydrodimer was isolated as a mixture of two diastereomers [301].

Table 22 Rate Constants for Reductive Coupling of *N*-Substituted Pyridinium, Quinolinium, and Acridinium Compounds

Substrate	Conditions	k_{dim} (M^{-1} s^{-1})	E^0/V	Ref.
N-Methylpyridinium (**103**)	H_2O, KCl, pH 5–11, 25°C, polarogr.	$> 10^7$	−1.372[a]	[305]
1,2,4,6-Tetramethylpyridinium	MeCN, Et_4NClO_4, CV	2.5×10^6		[299]
2-Ethyl-1,4,6-trimethylpyridinium	MeCN, Et_4NClO_4, CV	2.5×10^6		[299]
4-Ethyl-1,2,6-trimethylpyridinium	MeCN, Et_4NClO_4, CV	1.8×10^6		[299]
2,6-Diethyl-1,4-dimethylpyridinium	MeCN, Et_4NClO_4, CV	2.6×10^6		[299]
2,4,6-Triethyl-1-methylpyridinium	MeCN, Et_4NClO_4, CV	1.5×10^6		[299]
1-Ethyl-2,4,6-trimethylpyridinium	MeCN, Et_4NClO_4, CV	2.0×10^6		[299]
1,4-Diethyl-2,6-dimethylpyridinium	MeCN, Et_4NClO_4, CV	8.0×10^5		[299]
NAD^+	H_2O, Et_4NCl, pH 9.1, 25°C, CV, LSV, DPSC	3×10^7	−1.155	[302]
104a	MeCN, Et_4NBF_4, 20°C, CV, LSV	7.9×10^8	−1.105	[300]
104b	MeCN, Et_4NBF_4, 20°C, CV, LSV	2.0×10^8	−0.720	[300]
104c	MeCN, Et_4NBF_4, 20°C, CV, LSV	5.0×10^8	−0.520	[300]
105	MeCN, Et_4NBF_4, 20°C, CV, LSV	2.5×10^7	−0.465	[300]
105	MeCN, Et_4NBF_4, 20°C, DPSC	$(3 \pm 1) \times 10^7$	−0.460	[304]

[a] V vs. NHE. Strong adsorption of the dimer was found for $C^\circ > 2 \times 10^{-4}$ *M*.

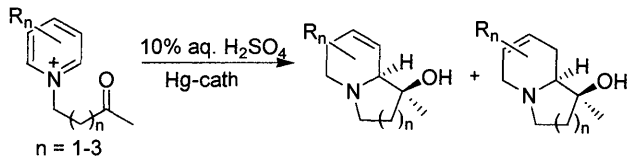


104a **104b** **104c** **105** **106**

The kinetics of the reductive dimerization of NAD^+ in aqueous buffer (pH 9.1) have been studied by DPSC, CV, and LSV (Table 22) [302]. Reduction of $NADP^+$ on a preparative scale in 0.1 *M* NH_4Cl/NH_3 buffer (pH 9.3) leads to a mixture of dimers formed by coupling of the pyridine ring systems. The three diasteromeric 4,4′-dimers were the major products (~ 70%) formed along with minor amounts of the 4,6′-dimers [303]. Reduction of *N*-methylacridinium ion (**105**) in MeCN gives the expected dimer, 10,10′-dimethyl-9,9′-biacridine [300]. The value of k_{dim} for **105** was found [300,304] to be about an order of magnitude smaller than that for the radical derived from **104** (Table 22), probably due to the greater delocalization in the radical derived from **105**.

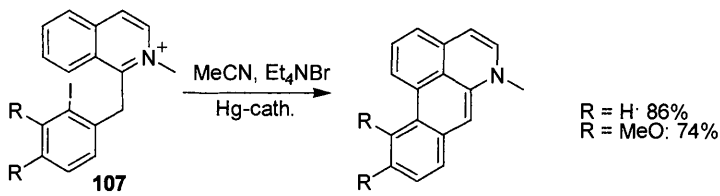
Reduction of acridizinium ion (**106**) and substituted acridizinium ions in MeCN or DMF gives a dimer (~ 80%) [306]. Although not confirmed experimentally, the most likely positions for coupling are indicated. The results of LSV measurements were in agreement with rate-determining dimerization of neutral radicals, and for **106** a lower limit for the rate constant of $10^7\ M^{-1}\ s^{-1}$ was obtained by CV measurements [306]. The dimer could be quantitatively reoxidized to the substrate cations either electrochemically (at a potential ~ 0.5 V anodic relative to the initial reduction peak) or by action of oxygen [306].

Inter- and intramolecular cross-couplings involving pyridinium rings are known. The cross-coupling of pyridine with acetone in acidic medium mentioned earlier is analogous to the intramolecular reductive cross-coupling of 1-(oxoalkyl)pyridinium ions [Eq. (66)]. In contrast to the intramolecular coupling between phenyl groups and keto groups, [Eq. (62)], which only gives rise to six-membered rings, good chemical yields are obtained of both five- and six-membered rings in the case of pyridinium ions (whereas formation of seven-membered rings is inefficient) [307]. The reaction is 4 F overall, since the pyridine ring also undergoes partial hydrogenation to form almost equal amounts of two tetrahydro isomers [Eq. (66)]. The current efficiency is low due to competing proton reduction. The diastereoselectivity of the reaction is high and opposite to that found in Eq. (62) in which coupling was expected to involve the radical anion. The acidic medium used in Eq. (66) ensures that the coupling involves the neutral radical formed by ketone reduction. The diastereoselectivity in this case has been explained by hydrogen-bond interaction between the OH group and the ring nitrogen in the TS leading to the preferred diastereomer, and an unfavorable steric interaction between the ring and the alkyl group in ths TS leading to the other diastereomer [307].



(66)

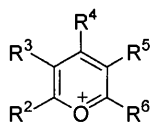
Intramolecular reductive coupling between the isoquinolinium systems (**107**) and an attached aromatic halide [Eq. (67)] [308], gives products similar to those obtained by the intramolecular coupling of aromatic halides with other aryl groups (Sec. V.B).



107 (67)

2. Other Positively Charged Systems

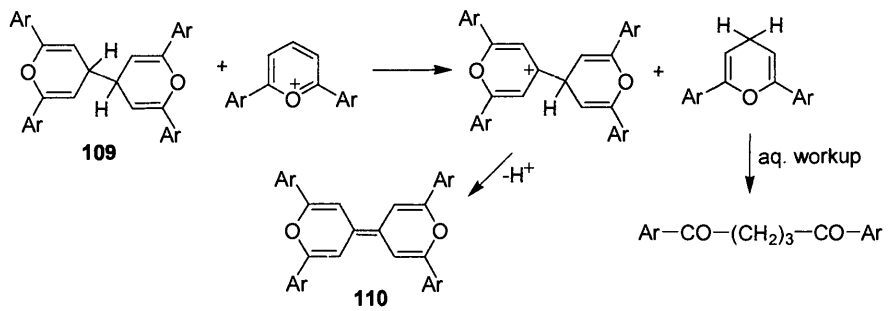
The pyranyl radicals formed by reduction of pyrylium cations (**108**) dimerize at the 4-position, and anodic oxidation of the dimers leads to regeneration of the pyrylium cations [309 and refs. therein]. Where the 4-position is unsubstituted, the dimerization process is very fast and irreversible, and a rate constant of $2.5 \times 10^9\ M^{-1}\ s^{-1}$ has been measured for the dimerization step in the reduction of 2,6-diphenylpyrylium cation (**108a**) in MeCN by combination of LSV and fast CV using microelectrodes [310]. If a substituent other than H or Me is present in the 4-position, the dimerization process becomes reversible and in favor of the free radicals [309].



108

a: $R^2 = R^6$ = Ph, $R^3 = R^4 = R^5$ = H
b: $R^2 = R^6$ = *p*-tolyl, $R^3 = R^4 = R^5$ = H
c. $R^2 = R^6$ = *p*-anisyl, $R^3 = R^4 = R^5$ = H

In preparative-scale reduction of **108a** in MeCN, bipyrilene (**110**) has been observed as a side product in addition to the bi-4*H*-furan, **109** [311]. Clean 1-F reduction was found ($n = 0.8$–1.0) in all cases, and at low substrate concentrations (5 m*M*) **109** was the only product. However, at substrate concentrations in the range 30–100 m*M* up to 48% of the product was **110** together with ~ 15% 1,3-dibenzoylpropane.

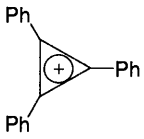


109 **110**

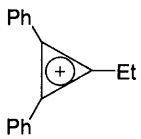
Scheme 27

The conversion was not initiated by base or by the presence of oxygen, and the mechanistic explanation includes (Scheme 27) slow hydride transfer from the initially formed **109** to the substrate cation, followed by elimination of a proton and formation of **110**. The 4*H*-pyran formed by hydride transfer reacts with water during workup to give the dibenzoylpropane, and the apparent 1-F coulometry may be due to reduction of the liberated proton, since the reduction was carried out using a Pt cathode [311]. Similar results were obtained in the reduction of **108b** and **108c**.

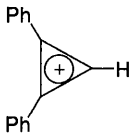
The 1,2,3-triphenylcyclopropenyl cation (**11a**) and cycloheptatrienyl cation (**112**) give, like the heteroaromatic cations, free radicals by one-electron reduction, and these undergo almost quantitative dimerization in aprotic solvents [312,313]. Also **111b** undergoes reductive dimerization, with the coupling position being exclusively a phenyl-substituted carbon atom [314]. After reduction of **11c** in MeCN only the rearranged dimer, 1,2,4,5-tetraphenylbenzene, was isolated (39%), together with *N*-acetyldiphenylcyclopropenylamine (24%) formed in a reaction with the solvent [312].



111a



111b



111c

112

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22
Electrolytic Oxidative Coupling

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References

I. INTRODUCTION

For the construction of organic molecules, for example natural products, compounds for commercial use or molecules of theoretical interest, two types of reactions are used: carbon–carbon bond-forming reactions, and functional-group interconversions. The first ones assemble a large target molecule from small units; the latter ones introduce the functionality into the target molecule and activate the building units for the carbon–carbon bond formation.

The large number of carbon–carbon bond-forming reactions can be summarized in four groups:

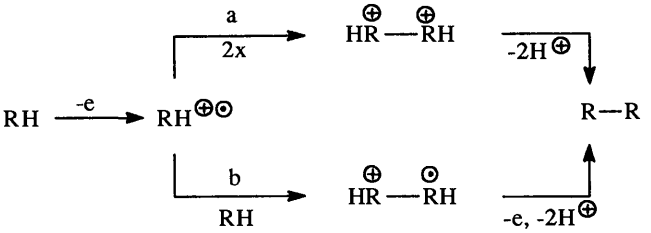
1. Polar reactions between an activated acceptor and a donor or vice versa.
2. Radical coupling and addition reactions.
3. Pericyclic reactions, especially cycloadditions.
4. Transition metal-catalyzed reactions.

Electrochemistry can contribute to those transformations, especially to polar [1] and radical reactions [2]. The reactive intermediates involved, namely, radical ions, cations,

anions, and radicals, can be generated by electron transfer at the electrode more simply, in larger variety, and more cheaply than with chemical reagents. This chapter deals with carbon–carbon bond-forming reactions at the anode.

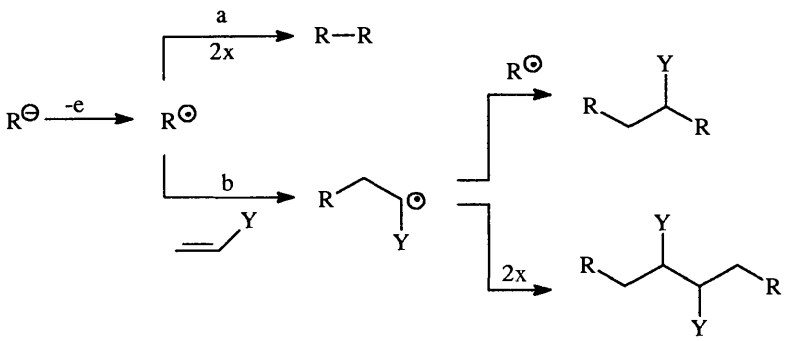
II. GENERAL SURVEY

Anodic coupling reactions may be arranged according to the reactive intermediates involved. These are radical cations that couple either by radical dimerization [Eq. (1), path a] or by electrophilic addition to the nucleophilic starting compound [Eq. (1), path b]:



(1)

Radicals generated by oxidation of anions can either dimerize [Eq. (2), path a] or add to double bonds to yield additive monomers or dimers [Eq. (2), path b]:



(2)

These reactions can lead to carbon–carbon or carbon–heteroatom bonds, and their course can be intermolecular or intramolecular. Furthermore, cycloadditions can be initiated by anodic generation of the dienophile or by inducing a chain reaction with a radical cation as dienophile.

The arrangement of the conversions according to reactive intermediates makes the broad scope of these reactions more obvious and comprehensible than an arrangement according to educt and product. However, one must keep in mind that this organization is not free from arbitrary action, since the mechanisms of many anodic couplings are not accurately known.

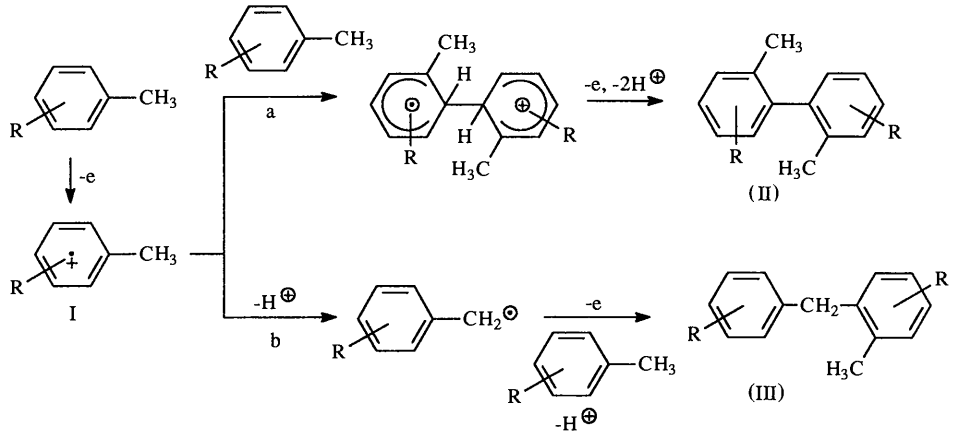
Reviews on oxidative coupling at the anode are summarized in Ref. 1.

III. COUPLING VIA RADICAL CATIONS

A. Aromatic Compounds

1. Hydrocarbons

Representative couplings of aromatic hydrocarbons are summarized in Table 1. Alkyl-substituted aromatic hydrocarbons can be coupled to diphenyls and/or diphenylmethanes depending on their substitution pattern (Table 1, numbers 1–6). The initially formed radical cation **I** [Eq. (3)] reacts with the starting compound to the diphenyl (**II**) (Eq. (3), path a] or loses a proton to form a benzyl radical [Eq. (3), path b], which after oxidation to the cation undergoes an electrophilic aromatic substitution at the starting compound to form the diphenylmethane (**III**). A low charge density on an unsubstituted carbon atom of **I** favors path a, whereas a low charge density on a substituted carbon atom favors path b [4].

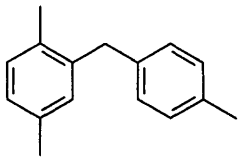
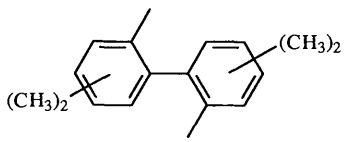
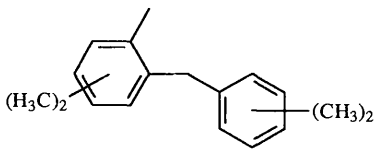
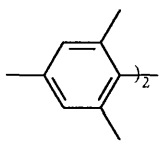
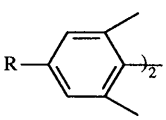
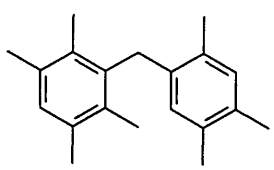
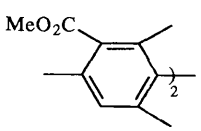


(3)

For mesitylene and durene, the kinetics have been followed by specular reflectance spectroscopy [17]. The results indicated that mesitylene produces a fairly stable radical cation that dimerizes. That of durene, however, is less stable and loses a proton to form a benzyl radical, which subsequently leads to a diphenylmethane. The stability of the radical cation increases with increasing charge delocalization, blocking of reactive sites, and stabilization by specific functional groups (phenyl, alkoxy, and amino) [18]. The complex reaction mechanisms of radical cations and methods of their investigation have been reviewed in detail [19a]. Fast-scan cyclovoltammetry gave kinetic evidence for the reversible dimerization of the radical cations of thianthrene and the tetramethoxy derivative of it. Rate constants and enthalpy values are reported for this dimerization [19b].

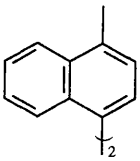
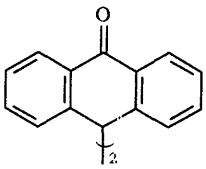
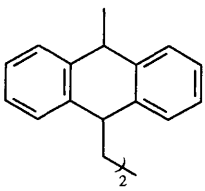
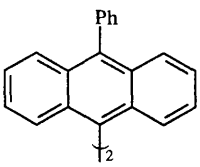
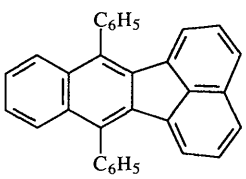
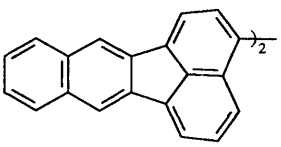
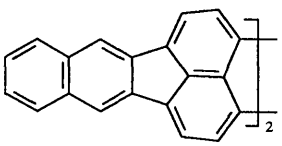
To favor the coupling reaction, the competing side reaction of the radical cation with nucleophiles must be suppressed by the use of a medium of low nucleophilicity. The solvent of choice is dichloromethane. Especially in electroanalytic studies, neutral alumina is frequently added to suppress hydroxylation of the radical cation [20]. The reversible cyclic voltammetric behavior of radical cations is also enhanced in mixtures of methylene dichloride, trifluoroacetic acid, and trifluoroacetic anhydride (TFAn) with $TBABF_4$ as supporting electrolyte. With acetonitrile as solvent, acetamides, formed in a Ritter reaction, are often the major products. The selective dimerization of mesitylene in acetonitrile is exceptional (Table 1, number 3). Dichloromethane, however, is reducible at the cathode.

Table 1. Anodic Coupling of Aromatic Hydrocarbons

Number	Substrate	Conditions	Products	Yield (%)	Reference
1	*p*-Xylene	C, CH_2Cl_2 TFA, $TBABF_4$		22	2
2	1,2,4-Trimethyl-benzene	C, CH_3NO_2, Bu_4NBF_4		17	3
				21	
3	1,3,5-Trimethyl-benzene	Pt, Bu_4NBF_4, CH_3CN		71	4
4	5-Alkyl-substituted *m*-xylenes		 R = Me, Et, i-Pr, t-Bu	4-82	5
5	1,2,4,5-Tetramethyl-benzene	C, CH_2Cl_2 $TBABF_4$		85	2
6	2-Carbomethoxy-1,3,5-trimethylbenzene	Conditions not given		50	6

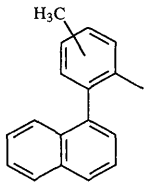
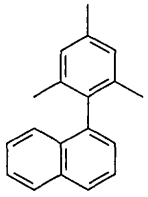
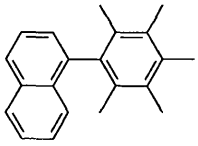
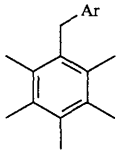
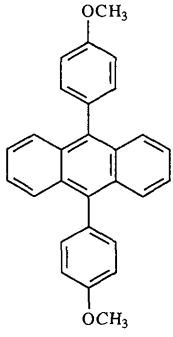
(Continued)

Table 1. (Continued)

Number	Substrate	Conditions	Products	Yield (%)	Reference
7	1-Methylnaphthalene	PbO_2 anode, acetone, H_2SO_4, water		10	7
8	Anthracene	MeCN, EtOH, $LiClO_4$		91	8
9	9,10-Dimethyl-anthracene	$LiClO_4$, MeCN 2,6-dimethylpyridine		Yield not given [a]	9
10a	9-Phenyl-anthracene	$TEAClO_4$, MeCN		37	10a
10b		benzene/ acetonitrile, $TBAPF_6$		24	10b
				no yield given	
11	1,5-Dichloro-anthracene	MeCN, EtOH	1,1',5,5'-Tetrachlorobianthrone	75 [b]	12

(Continued)

Table 1. (Continued)

Number	Substrate	Conditions	Products	Yield (%)	Reference
	Mixed coupling				
12	Naphthalene, *m*-Xylene	Pt, Bu_4NBF_4, MeCN, AcOH	1,1'-Binaphthyl 	28 0.4	13
13	Naphthalene, mesitylene	Pt, Bu_4NBF_4, MeCN, AcOH	1,1'-Binaphthyl 	22 19	14
14	Naphthalene, pentamethyl-benzene	Pt, Bu_4NBF_4, MeCN, AcOH	1,1'-Binaphthyl 	1.6 64	13
15	Hexamethylbenzene and aromatic hydro-carbons (benzene, toluene, *p*-xylene, mesitylene)	Pt, CH_2Cl_2· TFA (9.1), $TBABF_4$		8-66	15
16	Anthracene, anisole	Pt, Bu_4NBF_4, CH_2Cl_2-TFA-TFAn (47 2.1)		70	16

[a] In the presence of acetate ion a diarylmethane type of dimer is formed [11].
[b] The presence of EtOH is essential for the selectivity.

The chloride formed thereby may react as nucleophile or may be oxidized at the anode to chlorine, which leads to unwanted chlorinated side products. This reductive cleavage can be avoided by addition of strong acids, such as trifluoroacetic acid, methanesulfonic acid, or trifluoromethanesulfonic acid [2]. These acids effectively suppress the chlorination, because H^+ is reduced at the cathode rather than dichloromethane. However, they also decrease the yield of biaryl products and increase the yield of diphenylmethanes.

The anodic oxidation of benzene produces a mixture of polyphenylene compounds. This oligomerization can be performed in acetonitrile [21] or in liquid sulfur dioxide [22]. Mixed coupling between naphthalene and alkyl benzenes has also been demonstrated (Table 1, numbers 12–16). The relative yield of mixed coupling products increases with the basicity of the alkyl benzene; with mesitylene 19%, with tetramethylbenzene 42%, and with pentamethylbenzene 64% of mixed coupling products are obtained. This suggests an electrophilic reaction between naphthalene cation radicals and alkylbenzenes. The mixed coupling reaction of phenanthrene with anisole has been studied kinetically. The results indicate that initially a complex $PA^{+\cdot}$ is formed between the phenanthrene radical cation and anisole, followed by an electron transfer from the complex. The resulting PA^{2+}–anisole complex then decomposes to the product [23].

Bibenzyls can be obtained in a remarkable reaction from toluene, *p*-xylene, or ethylbenzene in 60–100% yield [24]. For this reaction, catalytic amounts of quinones are irradiated in the presence of the alkylbenzenes and the anode potential is held at that of the quinone–hydroquinone couple. The photo excited quinone abstracts a benzyl hydrogen to form a radical, which dimerizes. The resulting hydroquinone is reoxidized to the quinone.

Cyanation of aromatic hydrocarbons, also a carbon–carbon coupling reaction, is achieved in the case of anthracene in MeCN–Et_4NCN to yield 54% 9,10-dicyanoanthracene [25]. The cyanation is simplified when it is carried out in an emulsion system (aqueous sodium cyanide, dichloromethane, and $TBAHSO_4$). Its synthetic utility in this mode has been demonstrated for the preparation of 4-alkoxy-4-cyanobiphenyls, a class of liquid crystals [26].

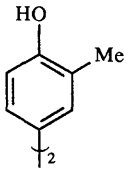
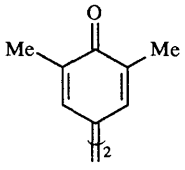
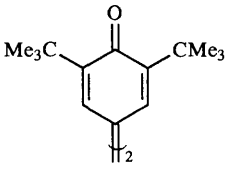
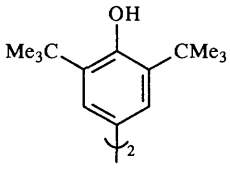
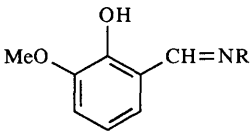
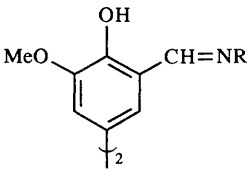
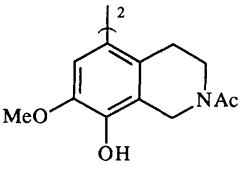
Anions of CH-acidic compounds (dimethyl malonate and nitromethane) can be coupled to aromatics (benzene, toluene, naphthalene, and 1,4-dimethoxybenzene) when they are coelectrolyzed in methanol-sodium methoxide [27].

2. Phenols

The earlier literature on oxidative coupling of phenols is reviewed in Ref. 28 and that on anodic coupling in Ref. 29; representative examples of the coupling reactions are summarized in Table 2.

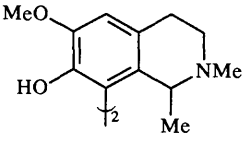
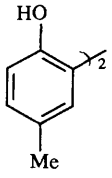
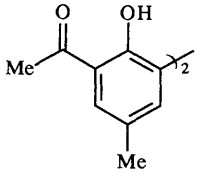
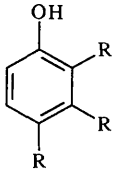
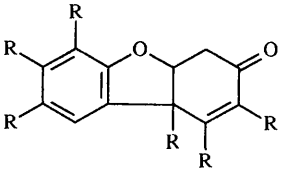
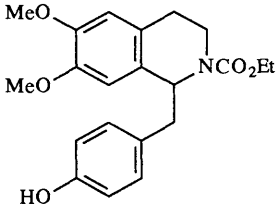
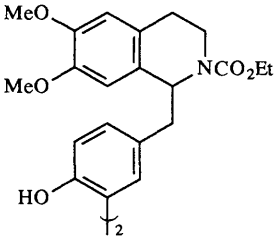
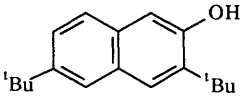
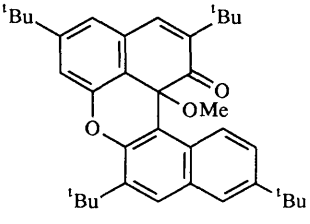
Phenols are coupled mostly in alkaline media by oxidation of the phenolates to phenoxy radicals. However, coupling in neutral or acidic medium by way of phenoxy radical cations and phenoxonium cations as intermediates is also known. To generate the phenolate ion, bases as alkali hydroxides, Et_4NOH, or 2,6-lutidine are used. The anodically generated phenoxy radicals react by carbon–carbon and carbon–oxygen coupling to dimers, which additionally can be further oxidized. This frequently leads to product mixtures that are synthetically not very useful. Blocking of the 2-, 4-, or 6-position makes the coupling reaction more selective. Phenols with unsubstituted *para*-position usually form *para,para*-coupling products as the major dimer (Table 2, numbers 1–5). If the 4-position is blocked, *ortho,ortho*-coupling is the main reaction (Table 2, numbers 6–13).

Table 2. Anodic coupling of Phenols

Number	Phenol	Conditions	Products	Yield (%)	Reference
1	*o*-Cresol	PbO_2, H_2SO_4		5	30
2	2,6-Dimethyl-phenol	Pt, MeCN, $NaClO_4$, 2,6-lutidine		90	31
3a	2,6-Di-t-butyl-phenol	Nickelhydroxide electrode, 70°C		92	32a
3b	2,6-Di-t-butyl-phenol	$MeOH/CH_2Cl_2$, $LiClO_4$, Pt, periodic current reversal in divided cell		93	32b
4	 R = i-Pr, t-But, $CH_2CH(CH_3)CO_2H$, Me, Et, Benzyl	Glassy carbon, MeCN, $NaClO_4$		41-100	33
5	2-Acetyl-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline	Graphite, MeCN		31	34

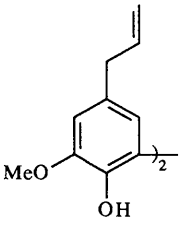
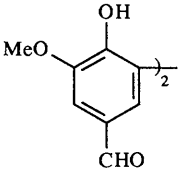
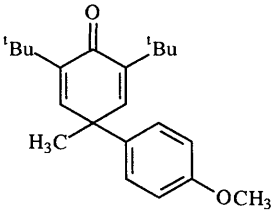
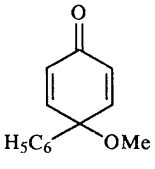
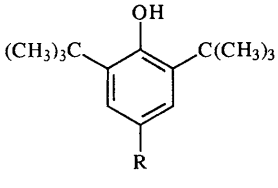
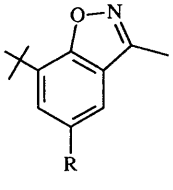
(Continued)

Table 2. (Continued)

Number	Phenol	Conditions	Products	Yield (%)	Reference
6	1,2-Dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydro-isoquinoline	Graphite felt, MeONa, MeCN, $TEAClO_4$		69[a]	35
7	*p*- Cresol	PbO_2, H_2SO_4		11	30
8	2-Acetyl-4-methyl-phenol	0.1 M NaOH, H_2O, MeOH, Pt		26	36
9	 R = H, CH_3, C_2H_5	CH_3CN, H_2O, $TEABF_4$		20-37	37
10		Graphite felt, MeCN, $TEAClO_4$		45[b]	38
11		CH_3OH-ether, 1% KOH		65	39

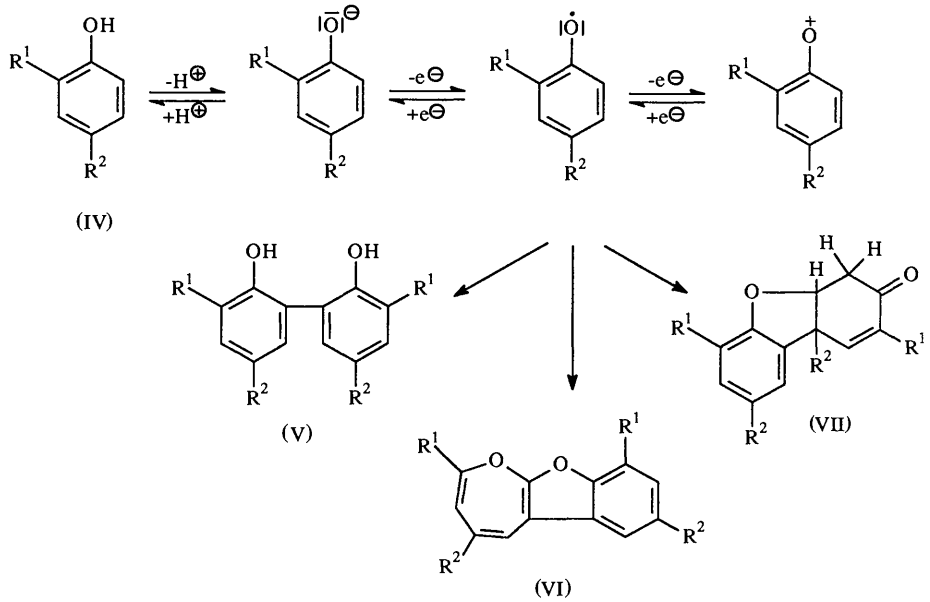
(Continued)

Table 2. (Continued)

Number	Phenol	Conditions	Products	Yield (%)	Reference
12	2-Methoxy-4-allyl-phenol	Pt, MeOH-$LiClO_4$, NaOH		100	40
13	Vanillin	Pt, MeCN, $NaClO_4$, Et_4NOH, 0.25V (SCE)		65	41
14	2,6-Di-t-butyl-cresol, anisole	Pt, MeCN, Bu_4NBF_4		81	42
15	Phenol	Graphite, CH_3OH, benzene, $LiClO_4$		23	43
16	 R = t-Bu, Ph, Ac CN, CHO, CO_2H	Pt, MeCN, $NaClO_4$		7-70	48

[a] Only one of three possible diastereomers is obtained; additionally, 7%, O-C coupling product is found.
[b] Additional O–C coupling product is found.

A series of 1,2,3,4-tetrahydroisoquinolines with phenolic OH groups has been oxidized to carbon–carbon and carbon–oxygen dimers. Optimum conditions for the coupling are the oxidation of the sodium salts in MeCN using $TEAClO_4$ as supporting electrolyte and a graphite felt anode. The products depend strongly upon the location of the phenolic OH group in the aromatic ring (Table 2, number 5) [34]. The ratio of C,C to C,O coupling depends also on the size of the 1-substituent in the tetrahydroisoquinoline; with the 1-H derivative predominantly C,C, and with the 1-CH_3 and 1-C_2H_5 compound only C,O coupling is found [44]. The dimerization of the tetrahydroisoquinoline, shown in Table 2, number 6, yields only one of three possible diastereomers. This outcome is best explained as a result of a surface reaction on the graphite electrode, at which only molecules of identical configuration couple. The anodic oxidation of phenols **IV** [Eq. (4)] at −300 to 250 mV (CH_3OH, 1% KOH) leads, depending on the substituents (Table 3), to bisphenol **V**, to oxepinobenzofuran **VI**, or to the Pummerer ketone **VII** [39].



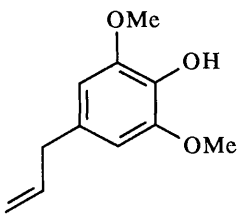
(4)

Ortho,ortho'-coupling of the phenoxy radical produces **V**, its further oxidation forms via an arene oxide the benzofuran **VI**, and the *ortho, para'*-coupling leads after a subsequent Michael addition to the Pummerer ketone **VII**.

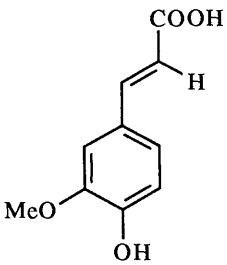
Table 3. Yields of the Oxidation of **IV**

IV		Yield (%)		
R^1	R^2	V	VI	VII
^{t}Bu	OEt	81	-	-
^{t}Bu	^{t}Bu	-	85	-
^{t}Bu	Me	-	-	41

In the electrolysis of **VIII** and **IX** a mixture of C,O and C,C coupling products (symmetrical, unsymmetrical, aryl–olefin, aryl–aryl, and olefin–olefin coupling) is obtained; the products are related to lignans and neolignans [45]. 2,4,6-Tri-*t*-butylphenolate is reversibly oxidized at −0.2 V (vs. SCE) to the phenoxy radical; at a higher potential (+1.0 V) the phenoxonium ion is formed irreversibly. Kinetics of the follow-up reactions are evaluated by CV [46].

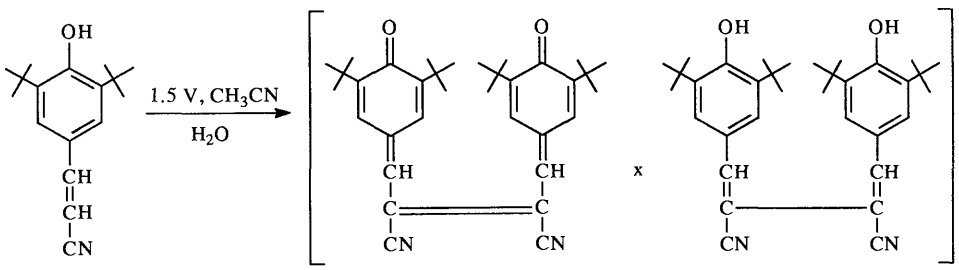


(VIII)



(IX)

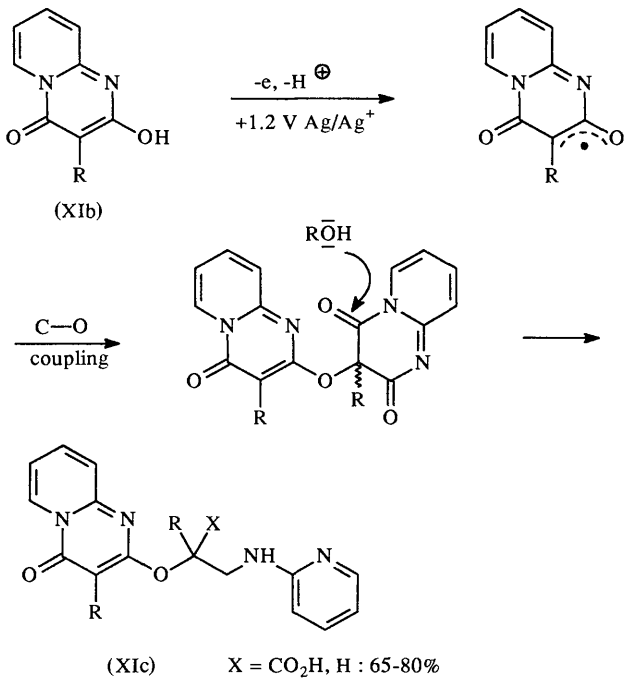
In neutral or acidic medium, phenols are oxidized to phenoxonium ions, which can undergo an electrophilic aromatic substitution, for example with anisole to *para*-methoxyphenylcyclohexadienones (Table 2, number 14). In the oxidation of **X** [Eq. (5a)], the intermediate phenoxonium ion disproportionates to phenoxy radicals, which couple in 95% yield to the quinhydrone **XIa** [47a]:



(X) (XIa)

(5a)

Oxidation of phenol in methanol-benzene (1:1) leads to a phenylcyclohexadienone in addition to the quinone monoacetal. The phenylation is thought to occur through electrophilic attack of the phenoxonium ion on benzene, followed by anodic methoxylation (Table 2, number 15). Anodic oxidation of 15 differently substituted 2,6-di-*t*-butyl-4-alkylphenols in MeCN leads to the corresponding 7-*t*-butyl-2-methylbenzoxazoles in 7–70% yield. The reaction is suggested to involve the oxidation to the phenoxonium ion and its electrophilic attack on MeCN. The resulting nitrilium ion undergoes an electrophilic aromatic substitution with elimination of one *t*-butyl group (Table 2, number 16). The hydroxy-substituted pyridopyrimidine **XIb**, which is obtained by condensation of 2-aminopyridine with substituted dialkylmalonates, undergoes a smooth C–O coupling in dichloromethane/trifluoroacetic acid, followed by a ring cleavage to yield **XIc** (Eq.5b) [47b].



(5b)

Examples of inter- and intramolecular cycloadditions of phenols to double bonds are given in Chapter 5.

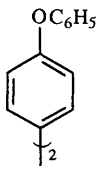
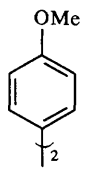
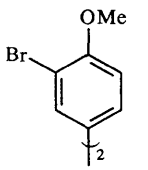
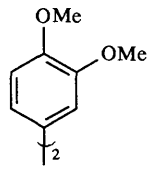
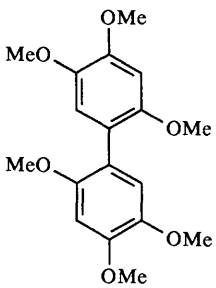
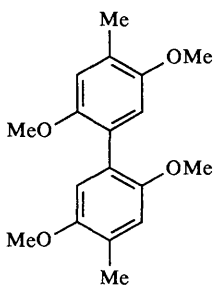
3. Aryl Ethers

The anodic coupling of aryl ethers is reviewed in Ref. 49, Aryl ethers are more selectively coupled than phenols, for the following reasons: The carbon–oxygen coupling is made impossible, and the *ortho*-coupling and the oxidation to quinones become more difficult. A mixture of trifluoroacetic acid (TFA) and dichloromethane proved to be the most suitable electrolyte [50]. TFA enhances the radical cation stability and suppresses the nucleophilicity of water. Of further advantage is the addition of alumina or trifluoroacetic anhydride [51]. Table 4 summarizes representative examples of the aryl ether coupling.

The coelectrolysis of veratrole with anisole derivatives afforded in TFA–CH_2Cl_2 good yields of aryl-substituted triphenylene derivatives (Table 4, number 9). Product formation probably occurs by initial coupling of the veratrole cation radical with anisole to an unsymmetrical dimer. This is followed by coupling of the dimer and intramolecular cyclization to the product.

The trimethylsilyloxy (TMSO) group is stable under the coupling conditions in acetonitrile (Table 4, number 11). After oxidative dimerization the TMS ether can be mildly hydrolyzed (H^+ and H_2O) to the phenol or converted to a dibenzofuran. 1,2-Dialkoxybenzenes have been trimerized to triphenylenes (Table 4, numbers 9, 12, and 13). The reaction product is the triphenylene radical cation, which is reduced to the final product either by zinc powder or in a flow cell consisting of a porous anode and cathode [60]. Dibenzo-crown ethers are converted by anodic oxidation to electroactive polymers. Films of these polytriphenylenes exhibit unusual doping properties 62–64].

Table 4. Anodic coupling of Arylethers

Number	Aryl ethers	Conditions	Products	Yield (%)	Reference
1	Diphenyl ether	Pt, CF_3CO_2H-CH_2Cl_2 (1:2), Bu_4NBF_4		56	50
2	Anisole	Pt, CF_3CO_2H-CH_2Cl_2 (1:2), Bu_4NBF_4		63	50
3	2-Bromo-anisole	Pt, CF_3CO_2H-CH_2Cl_2 (1:2), Bu_4NBF_4		43	50
4	1,2-Dimethoxy-benzene	CF_3CO_2H-CH_2Cl_2 (1:2), Bu_4NBF_4		86	50
5	1,2,4-Trimethoxy-benzene			85	52
6	2,5-Dimethoxy-toluene	MeCN, water, $TEAClO_4$		No yield given	53

(Continued)

Table 4. (Continued)

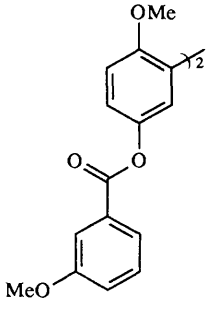
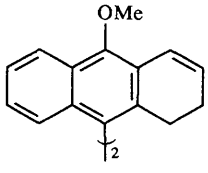
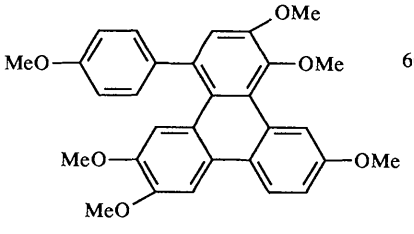
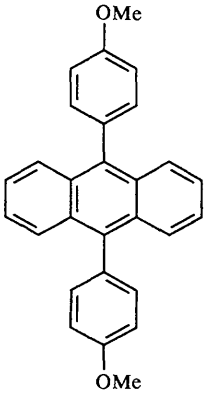
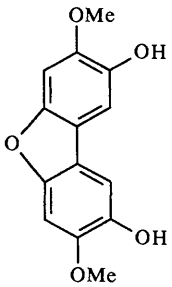
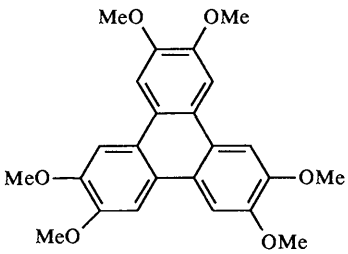
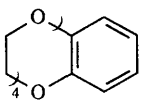
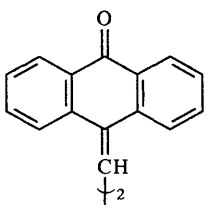
Number	Aryl ethers	Conditions	Products	Yield (%)	Reference
7	4-Methoxyphenyl-3-methoxybenzoate	MeCN, $NaClO_4$		65	54
8	9-Methoxy-anthracene	MeCN, TFA, Bu_4NBF_4		95	55
9	Anisole, 1,2-dimethoxy-benzene	MeCN, TFA, Bu_4NBF_4		60	56
10	4-Anisyl-anthracene, anisole	CH_2Cl_2, MeCN, TFA, Bu_4NBF_4		90	57

Table 4. (Continued)

Number	Aryl ethers	Conditions	Products	Yield (%)	Reference
11	2-Methoxy-1,4-bis(trimethylsiloxy)benzene	CH_3CN, $LiClO_4$		65	58
12	1,2-Dimethoxybenzene	CH_2Cl_2, TFA, Bu_4NBF_4		50	59
13		MeCN or CH_2Cl_2, TFA	Cyclotrimer	30	60
14	9-Methoxy-10-methyl-anthracene	MeCN, $LiClO_4$		50	61

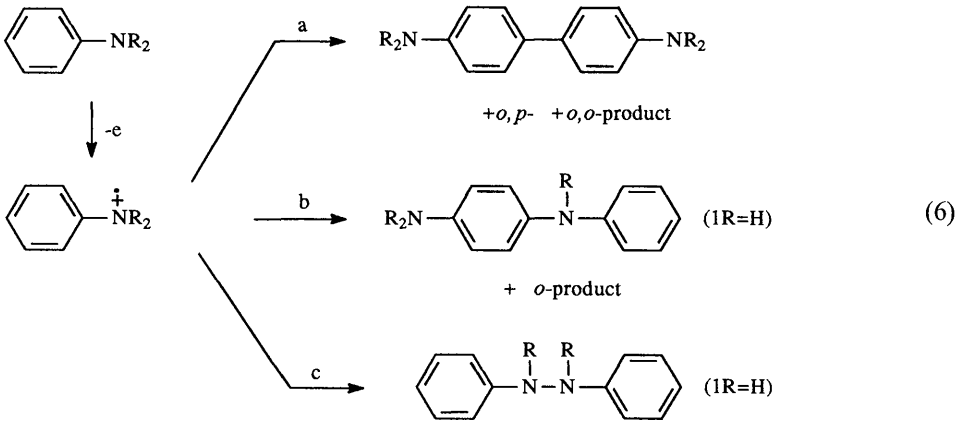
A variety of dimethoxybiphenyls has been investigated by voltammetry. The biphenyl linkage was shown to have a remarkable stabilizing effect on both cation radicals and dications. In the series of *para*-substituted compounds [$MeO(C_6H_4)_nOMe$], maximum stability of ions was observed with $n = 2$ and 3 [65]. The pathways for the coupling of 1,4-dimethoxybenzene and 2,5-dimethoxytoluene to biphenyls and a dimethoxyphenyl-*p*-benzoquinone have been elucidated by controlled-potential electrolysis (CPE) and cyclic voltammetry (CV) [66].

Coupling at the benzylic position occurs with 9-methoxy-10-methylanthracene. The dimer of a quinone-methide is obtained in about 50% yield. The product is thought to be formed by deprotonation of the initially formed cation radical, dimerization of the benzyl radicals, and subsequent oxidative demethylation at the methoxy group (Table 4, number 14).

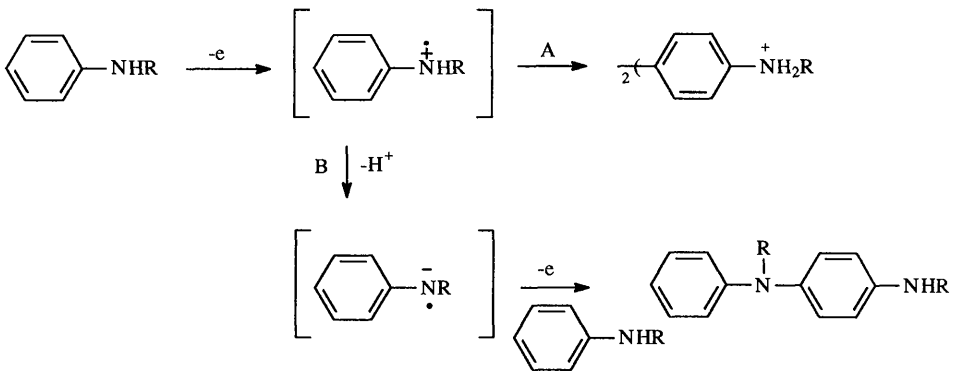
Cyanation of aryl ethers, also a carbon–carbon coupling reaction, proceeds in MeCN–Et_4NCN with fair to excellent yields to methoxybenzonitriles. Here a methoxy group is replaced by cyanide [67].

4. Arylamines

The oxidation of arylamines leads to three principal products: benzidines, aminodiphenylamines, and azo compounds. In these oxidations the first intermediate is in general the radical cation of the amine. This can lose a proton, react with a nucleophile, or couple in three different ways [Eq. (6)]: (a) in a carbon–carbon coupling reaction leading to benzidines, (b) in a carbon–nitrogen coupling reaction with aminodiphenyl amines as products, and (c) in a nitrogen–nitrogen coupling reaction forming hydrazobenzenes. These products are often easily further oxidized. The earlier work is covered by a review [18], and representative examples are summarized in Table 5.



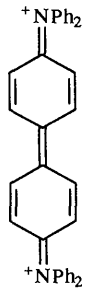
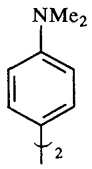
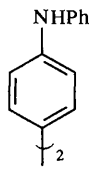
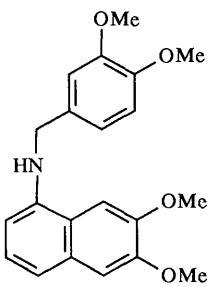
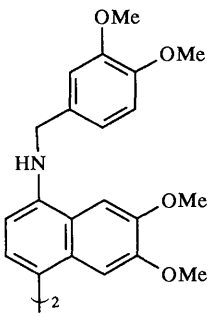
(6)



R	%A	%B
Me	50	50
Et	60	40
i-Prop	65	35
t-Bu	100	0

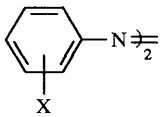
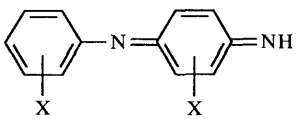
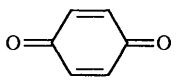
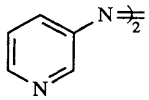
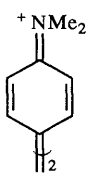
(7)

Table 5. Anodic coupling of Arylamines

Number	Arylamine	Conditions	Products	Yield (%)	Reference
1	Triphenylamine	MeCN, Et_4NClO_4, Pt			68
2	Dimethylaniline	MeCN, Et_4NClO_4		40-50	72
3a	Diphenylamine	MeCN, Et_4NClO_4		80	73
3b		MeCN, Et_4NClO_4, Pt		42	92
4a	*p*-Substituted anilines	MeCN, Pyr, $NaClO_4$, Pt		X % NO_2 39 Cl 24 2,4-Cl 30 OMe 5	75

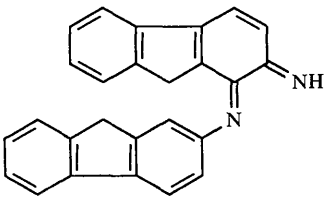
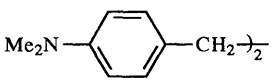
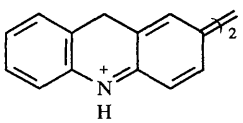
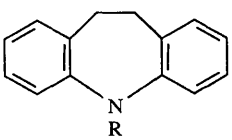
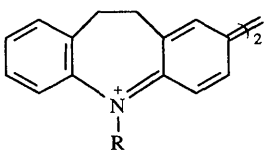
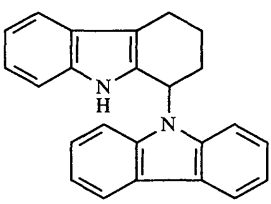
(Continued)

Table 5. (Continued)

Number	Aryl ethers	Conditions	Products	Yield (%)	Reference
4b	Substituted anilines	H_2O-KOH or H_2O, MeCN, NaOAc		X: % H: 30; 2,4-NO_2: 38; 2,4-Cl: 48; 4-CH_3: 37; 2-SO_3H: 3; 4-SO_3H: 33; 3-Me: 3	75, 77
				X: % 2-SO_3H: 70; 4-SO_3H: 40; 3-Me: 37	
4c	Aniline	6 M H_2SO_4	 Benzidine	80-90; 10-20	75
4d	3-Aminopyridine	Buffer at pH 9-10 in Water, Pt		28	78
5a	*N*-Ethylaniline	MeCN, Et_4NClO_4	*N,N'*-Diethylbenzidine	70-80	75
5b	*N*-t-Butylaniline	MeCN, Et_4NClO_4	*N,N'*-Di-t-butylbenzidine	100	75
6	4-Chloro-dimethyl-aniline	MeCN, Bu_4NBF_4, Pt		-	76

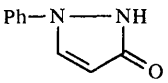
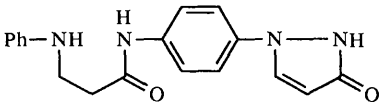
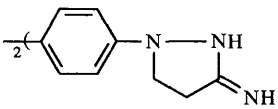
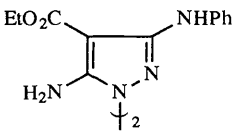
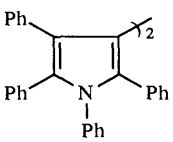
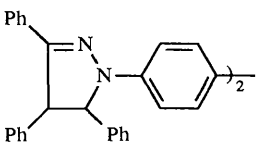
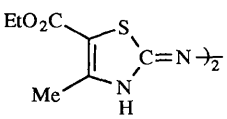
(Continued)

Table 5. (Continued)

Number	Aryl ethers	Conditions	Products	Yield (%)	Reference
7	2-Aminofluorene	Pt, MeCN, $NaClO_4$, pyridine		70	79
8	N,N-dimethyl-P-toluidine			-	80
9	Carbazole	MeCN, Et_4NClO_4, Pt		-	87
10	 R = H, CH_3	MeCN, Bu_4NClO_4, Pt		-	90
11	1,2,3,4-Tetrahydrocarbazole	MeCN, H_2O, $LiClO_4$, C		nearly quantitative	91

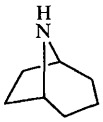
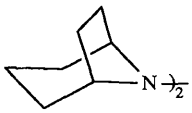
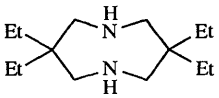
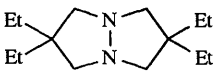
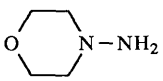
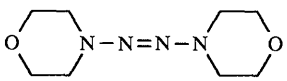
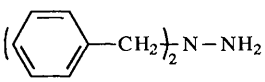
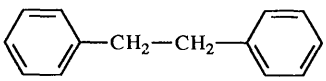
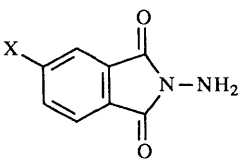
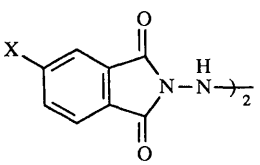
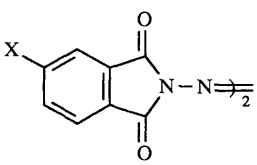
(Continued)

Table 5. (Continued)

Number	Aryl ethers	Conditions	Products	Yield (%)	Reference
12	1-Phenyl-pyrazolidin-3-one	Pt, MeCN, $TEAClO_4$	 	75	93
13	3-Amino-4,5-dihydro-1-phenyl pyrazole	Pt, MeCN, $TEABF_4$		90	94a
14a	Ethyl 5-amino-3-anilino-pyrazolo-4-carboxylate	MeCN, $TEAClO_4$, pyridine		42	95
14b	1,2,3,5-Tetraphenyl-pyrrole	MeCN, $LiClO_4$		-	98
15	1,3,4,5-Tetraphenyl-Δ^2-pyrazoline	MeCN, $LiClO_4$, pyridine		70	94b
16	2-Amino-5-ethoxycarbonyl-4-methyl-thiazole	MeCN, $NaClO_4$		50	97
17	t-Butylamine	Li-cyclohexyl-amide, THF, $LiClO_4$	$^tBu-N=N-^tBu$	25	101

(Continued)

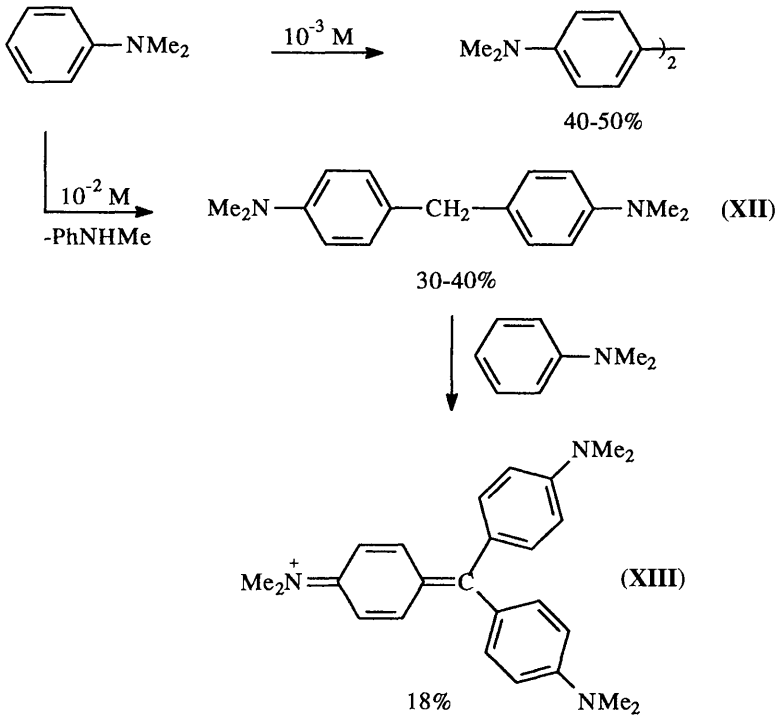
Table 5. (Continued)

Number	Aryl ethers	Conditions	Products	Yield (%)	Reference
18		PhCN, $LiClO_4$ NaOH		58	102
19		MeCN, $LiClO_4$ Et_4NOTos		10	103
20	1,1-Dimethyl-hydrazine	MeCN, TEAP, Na_2CO_3	$Me_2N-N\rightarrow_2$	85	104
21	1,1-Dimethyl-hydrazine	MeCN, $LiClO_4$, pyridine	$Ph_2N-N\rightarrow_2$	100	105
22		NiOOH, H_2O, K_2CO_3		80	106
23		NiOOH, H_2O, K_2CO_3		91	106
24	 X = H, NO_2	Pt, MeCN, Bu_4NBF_4	 	0-80 51-86	107

Triphenylamines are coupled to the tetraphenylbenzidines, which may be reversibly further oxidized to their dications (Table 5, number 1). The rates of the coupling reaction have been measured, and a fairly complete picture of the oxidation pathways has emerged [68]. *para*-Substituted triphenylamines cyclize to some extent to carbazoles [69].

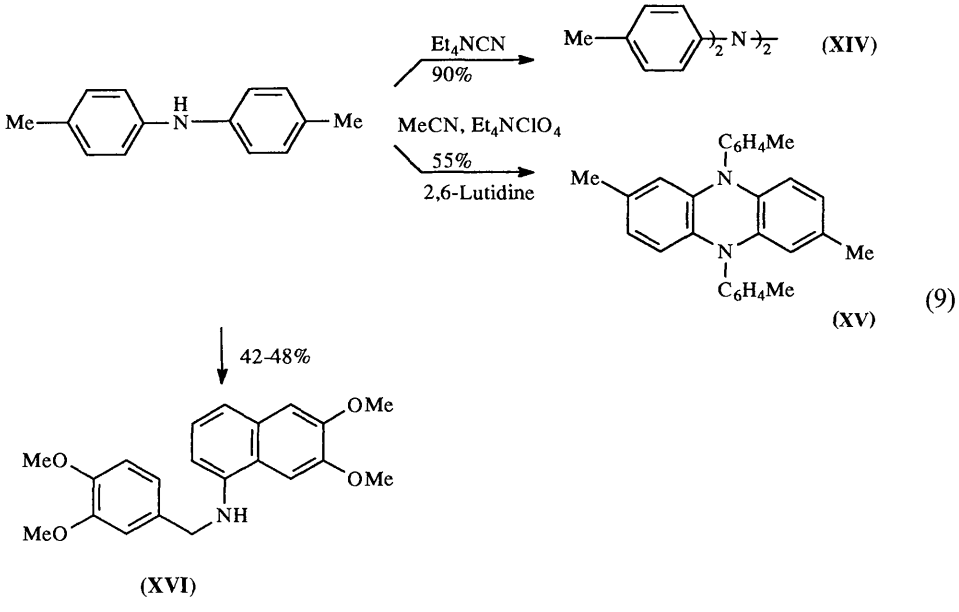
With anilines and *N*-alkylanilines the way of dimerization is influenced by the reaction conditions and the substitution of the aryl ring [70]. The benzidines predominate in strongly acidic aqueous media. The formation of benzidine is further favored by a low substrate concentration and a high current density. The benzidine derivatives may be reversibly oxidized to their dications. Diphenylamines are the major products under neutral conditions and higher pH values, a low current density, a high substrate concentration, a small alkyl group in monoalkylanilines, and a nonaqueous solvent [Eq. (7)]. Under weakly acidic conditions in aqueous medium, an additional electron discharge followed by hydrolysis produces benzoquinones in almost quantitative yield.

The electrooxidation of *N*,*N*-dimethylaniline (DMA, Table 5, number 2) has been studied by cyclovoltammetry and rotating ring-disk voltammetry in strongly acidic aqueous media [71]. The results are qualitatively consistent with a mechanism involving deprotonation of the DMA cation radical and subsequent coupling between neutral radicals. *N*,*N*-Dimethylaniline forms different products [Eq. (8)] in MeCN–TEAP, depending on the substrate concentration and the electrolysis period. At low concentrations (about 10^{-3} *M*) benzidine is the major product, at intermediate concentrations (10^{-2} *M*) coupling at the *N*-methyl group to **XII** occurs, and at a still higher concentration and a longer electrolysis time crystal violet (**VIII**) is being formed [72].



8,8′-Dianilino-5,5′-binaphthalene-1,1-disulfonates can be efficiently synthesized (25–50% yield) from the corresponding naphthylamines [74], analogously to the coupling of diphenylamines (Table 5, number 3a).

Para-Substituted anilines are oxidized in low to moderate yields to azobenzenes in basic solution (Table 5, number 4a). By elimination of one *para*-substituent (Cl or OMe) during the reaction, they can also couple to 4-substituted 4-aminodiphenylamines [76]. Carbon–carbon coupling can occur with 4-substituted arylamines as substrates. The *para*-substituent is eliminated and a *para*-benzidine is obtained (Table 5, number 6), *ortho* carbon–carbon coupling occurs (number 7), or a benzyl radical is formed, which subsequently couples (number 8). The *ortho*- and *meta*-substituted anilines yield at graphite cloth electrodes in 6*N* H_2SO_4 substituted benzidines and 4-aminodiphenylamines. The latter products are converted by further oxidation and hydrolysis to 2-substituted *para*-benzoquinones, sometimes in substantial yields (e.g., 35%) [81].

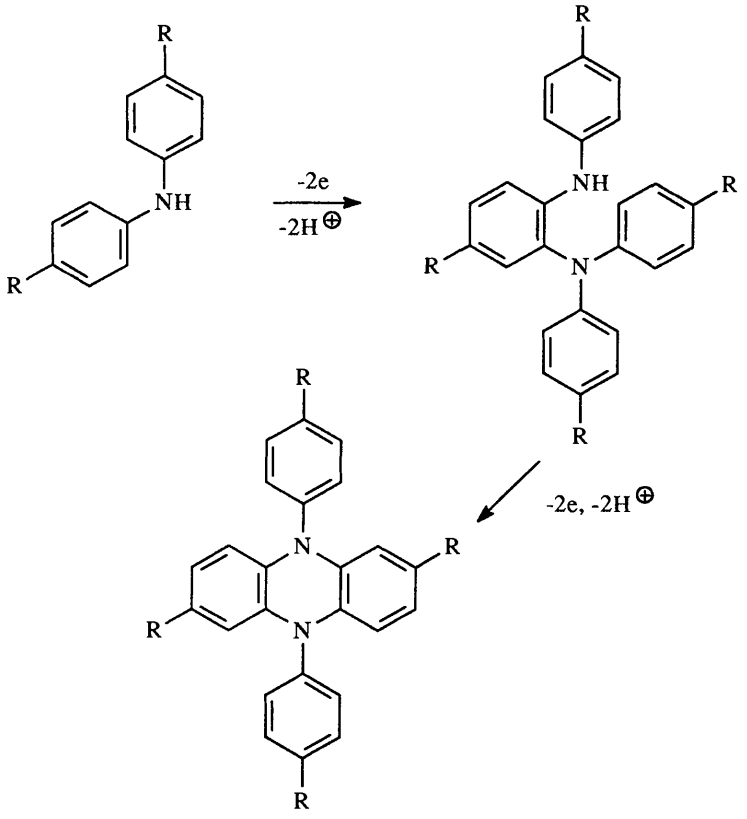


(9)

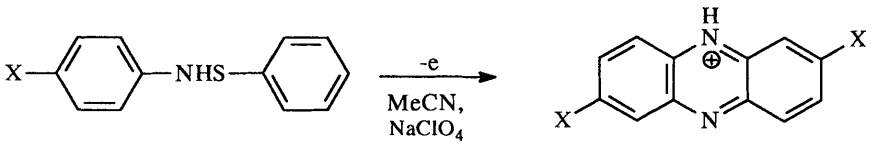
Electrolysis of di-*para*-tolylamine in MeCN-Et_4NCN affords 90% of the hydrazine **XIV** [Eq. (9)]; with lutidine as base, however, the dihydrophenazine **XV** is formed as major product [82]. Electrolysis of *N*-phenyl-*p*-bromoaniline in basic medium (MeCN, TEAP, and Et_4NCN) produces the *N*,*N* coupling product in 70% yield, whereas in acidic medium (H_2O and $HClO_4$) the benzidine type of product is formed in 87% yield [83].

The attempted intramolecular cyclization of the substituted naphthylamines **XVI** failed and led only to an intermolecular coupling [92]. 4-Substituted diphenylamines form in a remarkable cyclodimerization 5,10-dihydro-5,10-diphenylphenazines [Eq. (10)] [84]. One requirement is that all *para* positions must be substituted by groups that are not eliminated and not strongly electron withdrawing. Yields are increased by electrolyzing at low current densities. Di-(2-naphthyl)amine undergoes the same reaction anodically, but

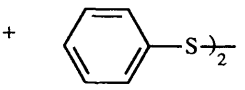
the analogous oxidation with permanganate fails [85]. Benzenesulfene anilides can be coupled to 2,7-disubstituted phenazines [Eq. (11)] [86].



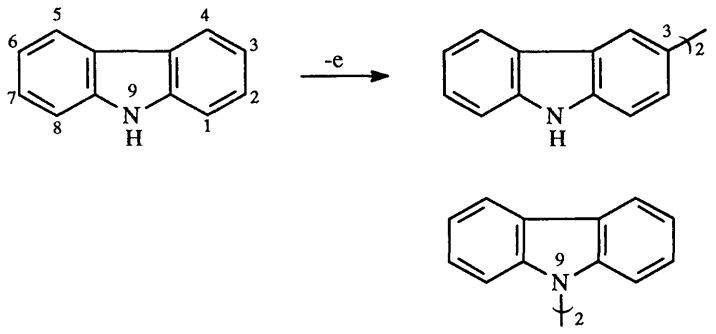
(10)



X	Yield (%)
OMe	39
Me	42



(11)



(12)

Anodic oxidation of electron-rich *N*-heterocyclic compounds follows a pattern of predominant *para,para'* and *N,N'* coupling. Carbazole leads preponderantly to the oxidized form of the 3,3'- and 6,6'-dimer, together with some 9,9'-dimerization [Eq. (12) and Table 5, number 9] [87,88]. These observations are confirmed by results from the investigation of 76 ring-substituted carbazoles [89]. In basic solutions (2,4,6-collidine as base) the *N,N'* coupling is often the exclusive reaction. 1-Phenylpyrazolidin-3-one forms besides the pyrazolinone as major product a *para* carbon–nitrogen coupling product (Table 5, number 12); the corresponding imine leads to the expected *para,para'* dimer (Table 5, number 13). Other couplings of nitrogen heterocyclic compounds can be found in Table 5, numbers 14–16, and in a review [96a]. 1-Methylindole is oxidized to a stable tetrameric radical cation with 2,3- and 3,3-coupling of the monomer. 2-Methylindole undergoes 2,3- and 3,3-coupling to dimers and 3-methylindole forms 3,3- and 1,2-2,3-coupled trimers [96b].

Aliphatic amines are mainly converted to α-substituted products [99,100], whereby especially the α-methoxylation leads to valuable reagents for synthesis. The intermediate iminium salts can be directly trapped by silyl enol ethers to form Mannich bases [108]. If the α-position is blocked or steric conditions favor it, *N,N* coupling to hydrazo or azo compounds occurs (Table 5, numbers 17–19). 1,1-Disubstituted hydrazines are dimerized to tetrazenes in fair to excellent yields (Table 5, numbers 20–24). The intermediate diazenium ions can attack enolizable carbonyl compounds to form aza-Mannich bases [109]. Arylazonaphthols undergo anodic oxidation, producing radical cations. These couple to biphenylbisazo compounds (up to 34%) or can be trapped by anisidine to form azodiphenylamines (up to 74%) [110a].

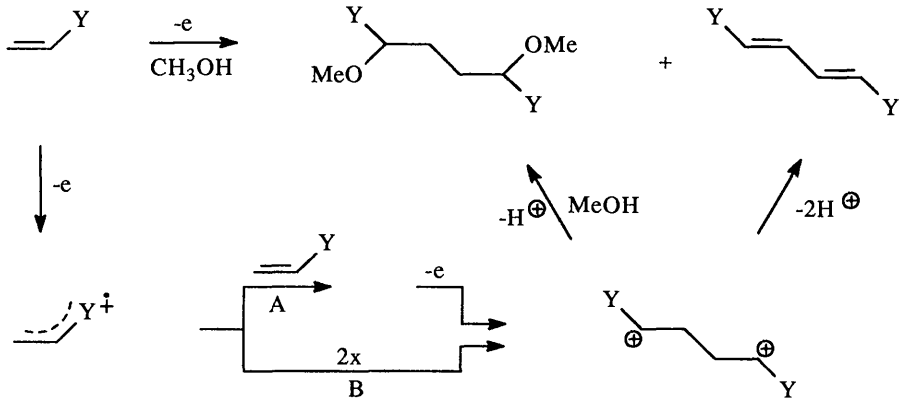
The alkaloid anhydrovinblastine has been prepared in an elegant way by anodic fragmentation of the radical cation of catharanthine to a distonic radical cation, which after oxidation to the dication undergoes an electrophilic aromatic substitution at vindoline to afford the complex target alkaloid [110b].

The C,C coupling reactions of sulfur compounds are less numerous. One example is mentioned here. When 1,3-dithioles are oxidized in MeCN containing pyridine, tetrathiofulvalenes are obtained in moderate to fair yields (13–40%) [111].

B. Olefins

Olefins with electron-donating substituents as the alkoxy, acylamino, phenyl, or vinyl groups can be coupled in methanol to give 1,4-dimethoxy dimers and/or dienes [Eq. (13)]. The first intermediate in this coupling reaction is a radical cation, which either by electrophilic addition to the olefin and subsequent $1e^-$-oxidation (path A) or by radical dimerization (path B) leads to a dimer dication that undergoes methanolysis or

deprotonation. Representative examples of this coupling reaction are summarized in Table 6.



Y = Ph, OR, $OSiMe_3$, NHCOR

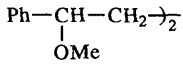
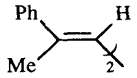
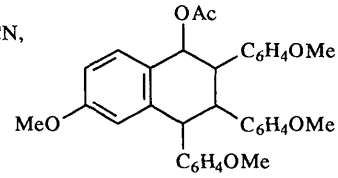
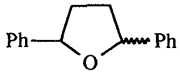
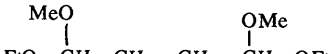
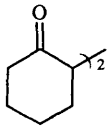
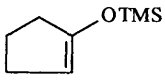
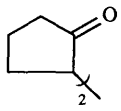
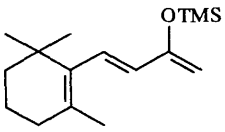
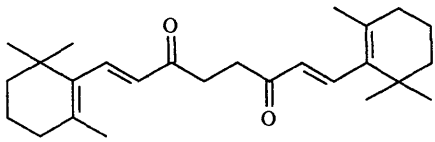
(13)

Styrene and indene derivatives [Eq. (13), Y = Ph] are dimerized to 1,4-dimethoxy-1,4-diphenylbutanes or 1,4-diphenylbutadienes (Table 6, numbers 1 and 2) [112,113]. The product distribution is in some cases strongly dependent on the anode potential and the supporting electrolyte. By substitution of sodium perchlorate for sodium camphorsulfonate or by increasing the anode potential, olefins are formed at the expense of methyl ethers. This may be explained by an increased displacement of methanol from the electrode surface through the stronger adsorbed camphorsulfonate or at higher potentials through the increased adsorption of anions compared to the adsorption of the polar solvent [99]. The surface concentrations of the reactants (solvent and styrene) govern the relative rates of solvolysis to the monomer and the addition reaction to the dimer and determine the product distribution. The styrene surface concentration is effectively influenced by the adsorption equilibria on different anode materials (C, Fe_3O_4, PbO_2, and Pt) [114]. β-Alkyl substituents drastically decrease the yield of dimers and favor the formation of dimethoxylated monomers.

For the dimerization of 4,4′-dimethoxystilbene, it has been possible to demonstrate spectroelectrochemically [115] and at the rotating ring-disk electrode [116] that the product is formed mainly by radical dimerization of the intermediate radical cations [path B, Eq. (13)]. Fast derivative CV, however, supports for the same olefin a complex ECE pathway [path A, Eq. (13) [117]. Depending on the oxidation potential and the kind of the nucleophiles (acetate, water, or methanol), a tetrahydronaphthalene derivative (Table 6, number 3) [118], a monomer diacetate [118], a tetrahydrofuran [115], or a dimer dimethoxy compound is found. When methanol is replaced by aqueous dichloromethane or by aqueous acetonitrile emulsions as solvent, styrene (Table 6, number 4) [119a] and α-methylstyrene [119b] yield 2,5-diphenyltetrahydrofurans. In some cases cyclization occurs by electrophilic aromatic substitution (analogous to Table 6, number 3).

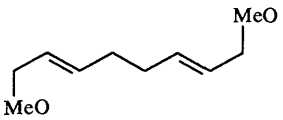
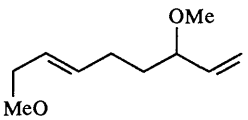
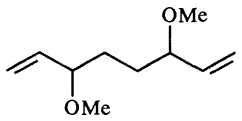
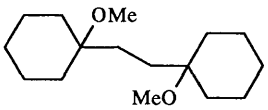
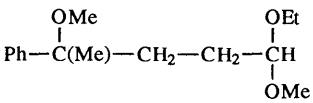
Enol ethers (Eq. (13), Y = OR] with half-wave potentials between $E_{1/2} = +1.2$ and +1.8 V (Ag/AgCl) couple in methanol with 2,6-lutidine as base at a graphite anode to give the acetals of 1,4-dicarbonyl compounds in 30–60% yield (Table 6, numbers 5, 6) [120,122]. The tail-to-tail coupling of the monomers and the electrochemical reaction

Table 6. Anodic Oxidation of Ethylenic Compounds

Number	Substrate	Conditions	Products	Yield (%)	Reference
1	Styrene	MeOH, NaOAc, $NaClO_4$, C		64	112
2	α-Methylstyrene	MeOH, NaOAc, $NaClO_4$, C		64	112
3	4,4'-Dimethoxystilbene	+0.9 V, MeCN, HOAc		-	118
4	Styrene	CH_2Cl_2-H_2O, $TBAHSO_4$		52	119
5	Vinyl ethyl ether	MeOH, NaI, C		51	121
6	1-Ethoxycyclohexene	MeOH, $NaClO_4$, 2,6-lutidine, C		48	121
7		CH_2Cl_2, MeOH, Bu_4NBF_4		50	123
8		MeCN, MeOH, $LiClO_4$		78	123

(Continued)

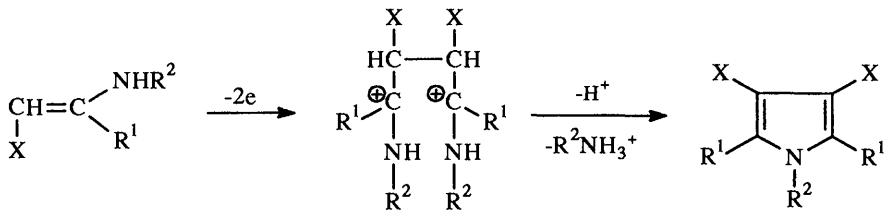
Table 6. (Continued)

Number	Substrate	Conditions	Products	Yield (%)	Reference
9	1,1-Bis(dimethylamino)-ethylene	DMF, Et_4NClO_4	$((Me_2N)_2CH{=}CH)_2$	-	125
10	Butadiene	C, MeOH, $NaClO_4$		17	129a
				16	
				16	
11	Methylenecyclohexane	C, MeOH, $NaClO_4$		38	133
12	α-Methylstyrene, vinyl ethyl ether	C, MeOH, $NaClO_4$		32	134

order ($\nu_{enolether} = 1.0$, $\nu_{methanol} = 0$) support the radical cation as intermediate in the dimerization.

Silyl enol ethers [Eq. (13), $Y = OSi(CH_3)_3$] can be dimerized to 1,4-dicarbonyl compounds in good yields. To suppress the methanolysis of the silyl enol ethers, MeCN–5% MeOH is used as solvent and the electrolysis is conducted within 1 h by the use of a capillary gap cell, which allows high currents (Table 6, numbers 7 and 8) [123]. In this way, unsymmetrical ketones can be coupled selectively in the α- or α′-position, since the corresponding silyl enol ethers can be prepared regioselectively [124].

Examples for the coupling of enamines are rare (Table 6, number 9). In most cases the enamines undergo methanolysis to electroinactive aminoacetals prior to the coupling reaction. Enamino ketones or enamino esters, however, yield via dimerization of the radical cations and subsequent ring closure pyrrole derivatives [Eq. (14a)] [126]:



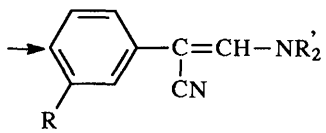
(14a)

X= CO_2Me, COMe, CN

R^1= CH_3, H, 4-MeO-C_6H_4

R^2= H, Me, $CH_2C_6H_5$, Ph

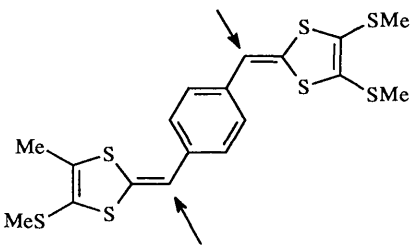
9 - 54%



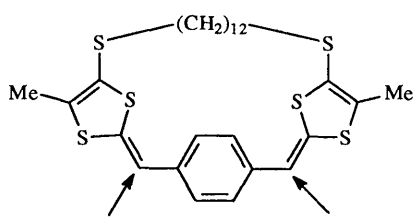
(XVIIa)

In the case of the enaminonitrile **XVIIa**, coupling through the phenyl ring is observed [127a]. Enamines related to the key intermediate in thiamine diphosphate-dependent enzymatic pathways lead to dimers in a one-electron oxidation via a thiazolium cation radical as intermediate [127b]. Anodic oxidation of enaminones, prepared from *p*-substituted acetophenones and *N*,*N*-dimethylformamide dimethylacetal, afford dimers and substituted furans in fair yield [127c].

1,4-Dithiafulvenes are dimerized to the dimer dication, which can be reduced to the dimer [128a]. Trisubstituted ketenedithioacetals afford dimers upon oxidation in aqueous acetonitrile/$NaClO_4$ [128b]. Controlled-potential electrolysis of ketenedithioacetals in aqueous acetonitrile/0.2 *M* $NaClO_4$ affords dimers as main products [128c]. The 1,4-bis(1,4-dithiafulven-6-yl)benzenes **XVIIb** and **c** have been cyclooligomerized at the indicated carbon atoms to afford new kind of cyclophanes [128d].



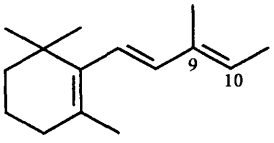
(XVIIb)



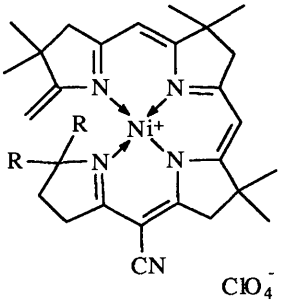
(XVIIc)

Dienes [Eq. 13), Y = vinyl] are dimerized to dimethoxyoctadienes or are dimethoxylated to dimethoxybutanes at graphite, platinum, or glassy carbon anodes in an electrolyte consisting of methanol-sodium perchlorate (Table 6, number 10) [120,129]. Dimerization

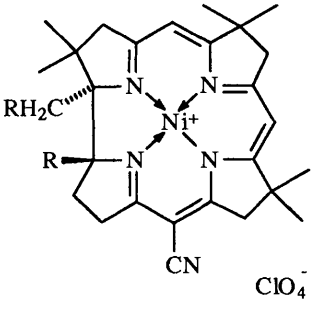
is favored by graphite or carbon cloth anodes, by high olefin concentrations, and by terminally unsubstituted dienes [129,130]. The ratio of monomer to dimer is determined mainly by the anode material. Anodes with a smooth surface, such as platinum, gold, and glassy carbon, promote the formation of monomers; porous materials, such as soft graphite or carbon cloth, favor the dimers. Qualitatively this can be explained by lower real current densities at the porous surfaces. This leads to a less depleted diene concentration at the electrode surface, which favors the electrophilic addition of the radical cation [Eq. (13), path A] to the dimer, compared to the methanolysis yielding the dimethoxylated monomer. Butadienyl acetate and the β-ionone derivative **XVIII** could not be dimerized but yielded dimethoxylated monomers, whereby **XVIII** regioselectively forms 73% of the 9,10-dimethoxy product [129].



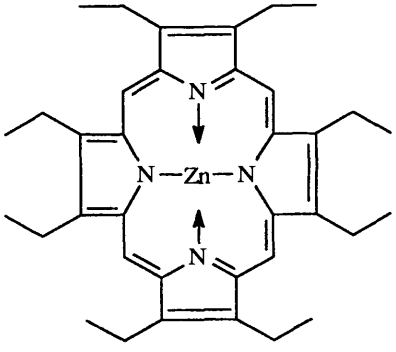
(XVIII)



(XIX)



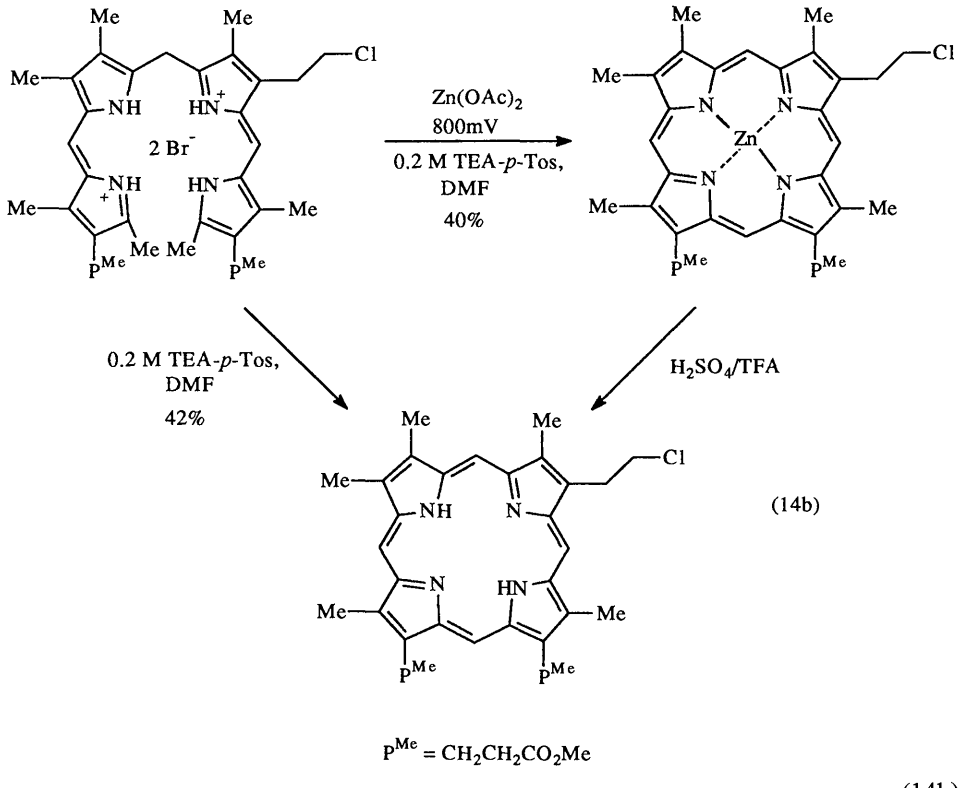
(XX)



(XXI)

The polyene derivative **XIX** can be cyclized to form 18% of the nickel corrin complex **XX** (R = H), if it is first oxidized at +1.22 V to the radical cation, which undergoes a 1,16-hydrogen shift and then is coupled intramolecularly through cathodic reduction (−0.3 V) [131a].

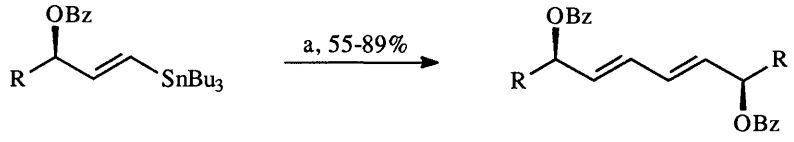
Porphyrines are obtained by anodic cylization of 1′,8′-disubstituted a,c-biladiene salts. The reaction involves formation of an *exo*-methylene group via a radical cation, electrocyclization of the 18π-system and nucleophilic displacement of a CH_3 group (Eq. 14b) [131b].



(14b)

Zinc octaethylporphin (**XXI**) may be cyanated anodically at the *meso* positions via the cation radical; by variation of the oxidation potential and the extent of electrolysis, it is possible to obtain optimum yields of mono-, di-, tri-, and tetracyanooctaethylporphyrins [132a].

Alkenylstannanes can be subjected to a homocoupling reaction by a copper(II)-mediated anodic oxidation [Eq.(14c)] [132b].



(14c)

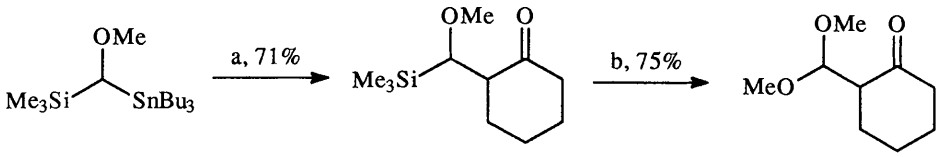
a: Pt-anode, divided cell, $CuCl_2$, Bu_4NClO_4, DMF,
R= C_5H_{11}, $PhCH_2CH_2$, C_8H_{17}, i-Pr

Alkenes without +M substituents can be coupled if they are dialkylated at one carbon atom of the double bond and are unsubstituted at the other (Table 6, number 11). This is a further indication that the dimerization of radical cations responds sensitively to steric hindrance.

Unsymmetrical dimers are accessible through the coelectrolysis of different olefins (Table 6, number 12).

Carbocations can be generated from precursors that have appropriate leaving groups, such as the stannyl or silyl group. These facilitate anodic oxidation and are termed

electroauxiliaries. The electrogenerated carbocations react with silylenolethers or allylsilanes as carbon nucleophiles [Eq. (14d)] [132c].



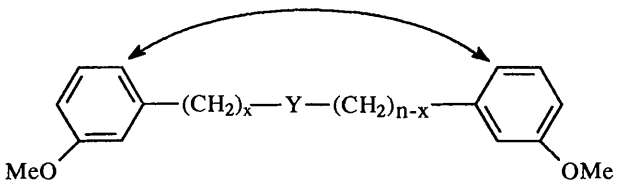
a: C-anode, 0.2 M Bu_4NBF_4, CH_2Cl_2, 5 eq. 1-trimethylsilyloxycyclohexene. -
b: C-anode 0.2 M Et_4NOTos, MeOH.

(14d)

Activated alkynes, like diarylacetylene, can be anodically coupled, too. In acetonitrile/$LiClO_4$ they afford dimers: tetraaryl-1,4-enediones (14–47%) and monomers: 1,2-diketones (20%) [132d].

C. Intramolecular Coupling

A large number of 1,4-bis(methoxyphenyl)alkenes (**XXII**) have been coupled intramolecularly to afford biphenyls with connected rings of different size. The reaction is a method to prepare in few steps *meta*-cyclophanes, polycyclic hydroaromatics, and intermediates for the synthesis of steroids, heterocyclic compounds, and alkaloids. The section is organized according to an increasing number n of methylene groups in **XXII**, with Y being carbon or a heteroatom, mainly nitrogen.



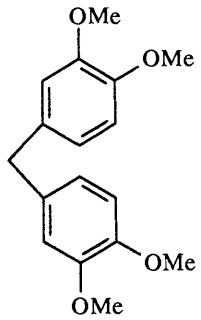
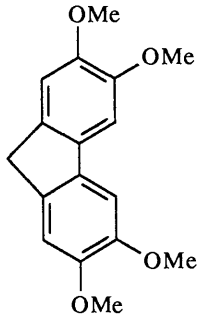
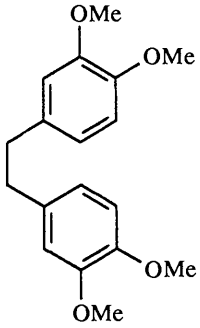
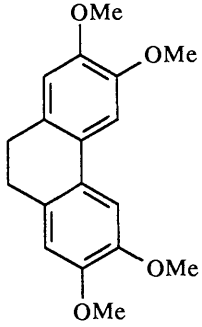
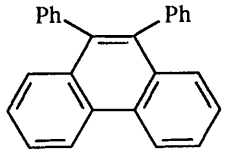
(XXII)

The coupling sites and yields in the anodic coupling of the diarylalkanes (**XXII**) are strongly dependent on the value of n, the position of substituents in the aryl ring, the choice of the electrolyte–electrode system, the pH of the medium, the current density, and the oxidation potential.

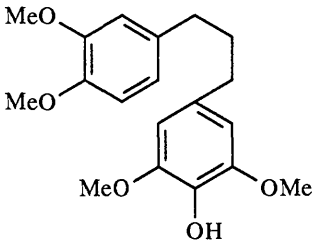
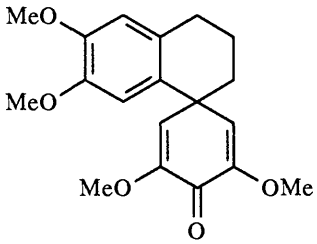
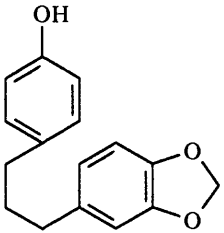
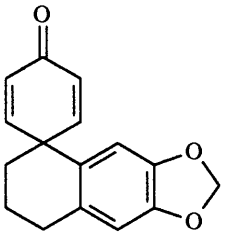
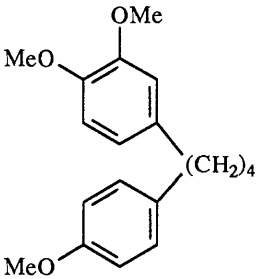
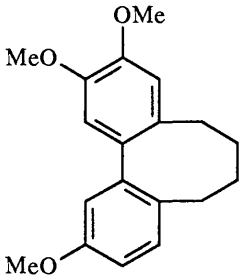
In acetonitrile, methoxybiphenyls are coupled in low yield, but almost quantitatively in dichloromethane–trifluoroacetic acid [135,136]. Yields are low in the first solvent because the cyclized products are more easily oxidized than their precursors and the oxidation products are not stable. In the presence of TFA, the cation radicals derived from the oxidation of cyclized **XXII** are stable and after reduction with zinc dust, for example, cyclized **XXII** may be isolated in high yield.

1,n-Bis-(3,4-dimethoxyphenyl)alkanes (**XXIII**, Y = –) cyclize almost quantitatively, when n = 1–4 (Table 7, numbers 1–6), but only in moderate yields when n = 6–10 and then intermolecularly [136,137]. The cyclic voltammograms of unsymmetrically methoxylated diphenylalkanes exhibit two oxidation potentials, at which either intramolecularly or intermolecularly formed products arise, permitting some conclusions to be drawn about the dimerization mechanism. These observations provide strong evidence that two radical

Table 7. Intramolecular Coupling

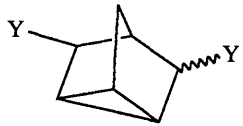
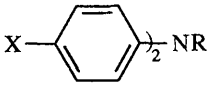
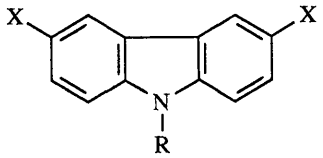
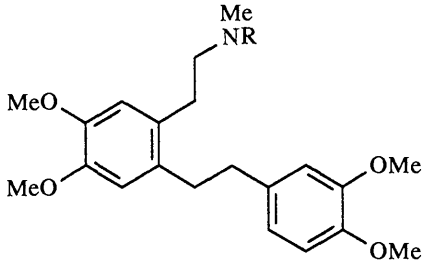
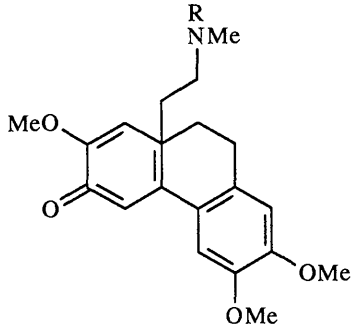
Number	Substrate	Conditions	Products	Yield (%)	Reference
1		CH_2Cl_2, TFA, $TBABF_4$, Pt		95	137
2		CH_2Cl_2, TFA, $TBABF_4$, Pt		95	137
3	Tetraphenylethylene	Pt, CH_2Cl_2, TFA, Bu_4NBF_4		92	138

(Continued)

4		MeCN, $TMABF_4$, Pt, 0.74 V (SCE)		85	139
5		Pt, MeCN, $NaClO_4$		75	139
6		Pt, CH_2Cl_2 TFA (3:1), $TBABF_4$		33	140

(Continued)

Table 7. (Continued)

Number	Substrate	Conditions	Products	Yield (%)	Reference
7	Norbornadiene	HOAc or MeOH, Et_4NOTos	 Y = AcO, CH_3O	*exo, endo* 14-16 *exo, exo* 15-18	142
8	 X = CH_3, t-Bu, Cl R = Et	MeCN, Et_4NClO_4		-	69
9a		MeCN, HBF_4, Pt, R = CO_2Et, 1.0 V (SCE)		87	145

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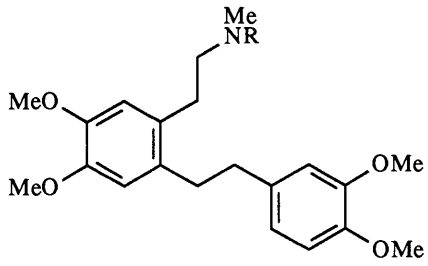
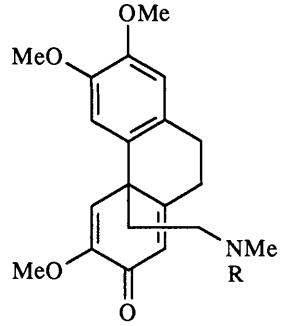
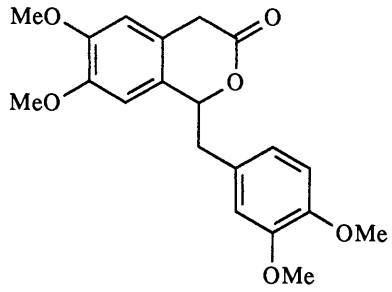
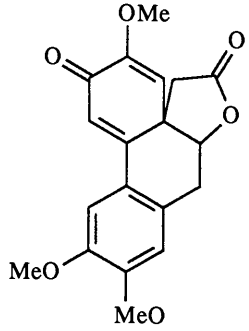
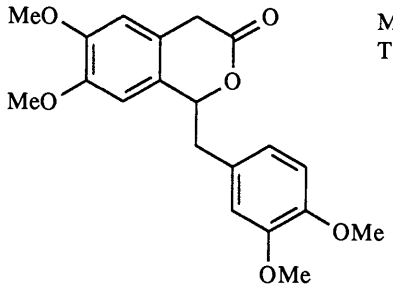
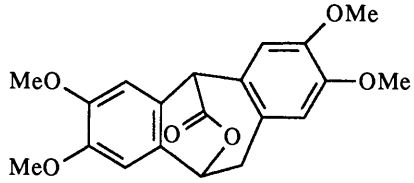
9b		$MeCN, HBF_4$, Pt, R = $COCF_3$, 1.3 V (SCE)		75	145
10a		CH_2Cl_2, TFA, $TBABF_4$, Pt		33	162
10b		MeCN, $TBABF_4$		20	162

(Continued)

Table 7. (Continued)

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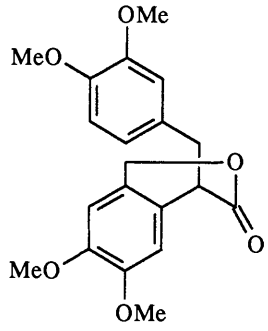
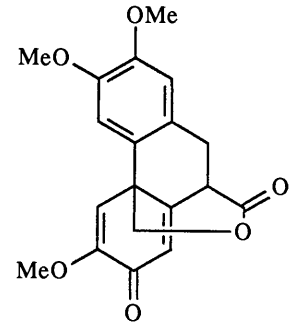
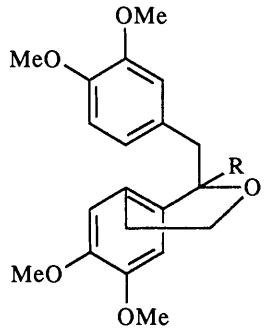
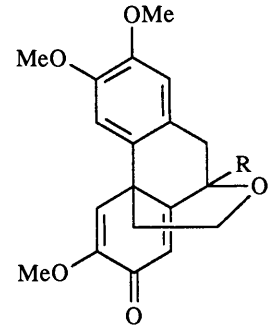
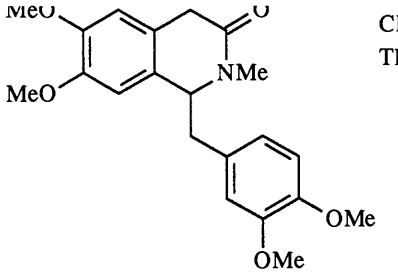
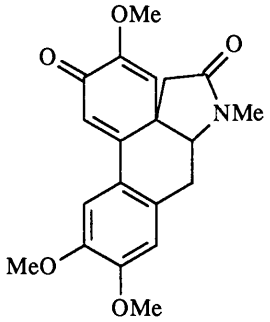
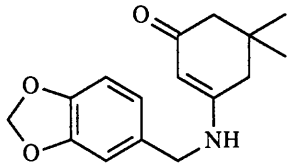
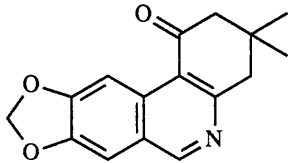
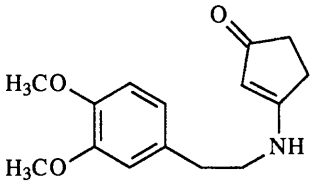
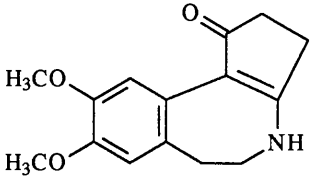
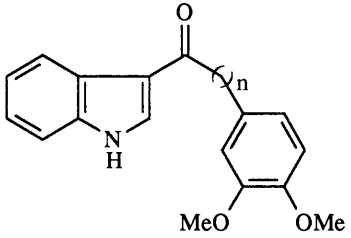
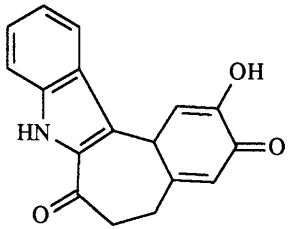
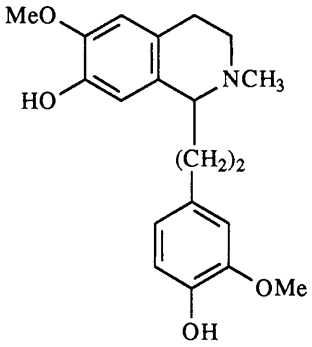
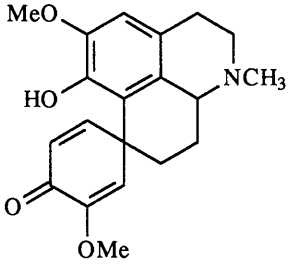
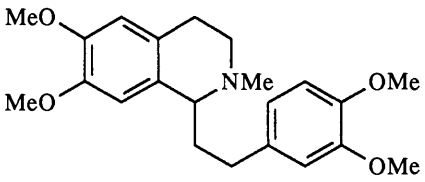
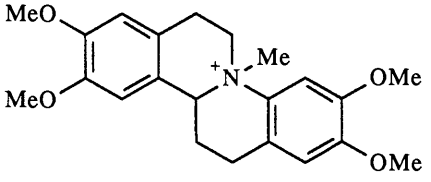
11		$MeCN, NaClO_4$, Pt		67	163
12		Pt, MeCN, HBF_4		R = H 26 R = CH_3 56	161

(Continued)

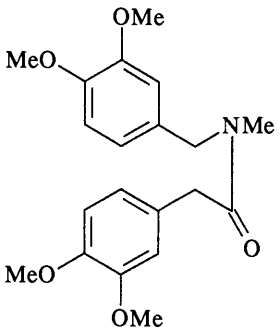
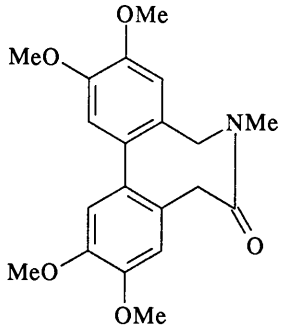
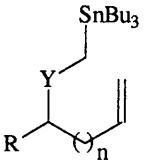
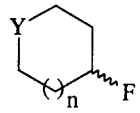
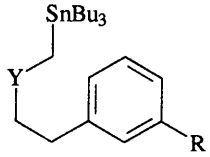
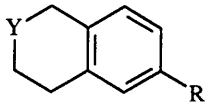
13		CH_2Cl_2, TFA, $TBABF_4$, Pt		40	162
14		MeOH, $NaClO_4$, C		45	164
15		MeOH, $NaClO_4$, C		43	164
16		C, MeCN, $NaClO_4$		62 (for n = 2)	166

(Continued)

Table 7. (Continued)

Number	Substrate	Conditions	Products	Yield (%)	Reference
17		H_2O, Et_4NClO_4, C		36	169
18		MeCN, $NaClO_4$, 1.2 V (SCE)		-	170

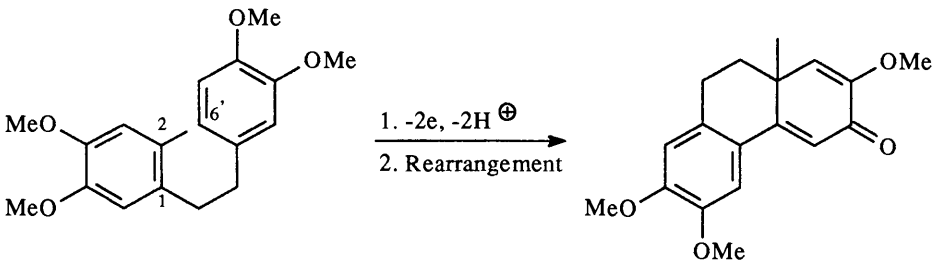
(Continued)

19		$MeCN$, $NaClO_4$, Pt, 1.1 V		45	174
20	 R = heptyl, cyclohexyl; Y = O, NCO_2Me; n = 1,2	CH_2Cl_2, Bu_4NBF_4 molecular sieve, C-anode	 cis/trans = 1.2 : 1 - 3 : 1	50-98	172b
21	 a: Y = O, R = H b: Y = O, R = F c: Y = NCO_2Me, R = H	CH_2Cl_2, Bu_4NClO_4		a: 55 b: 80 c: 54	172b

cations are necessary for aryl–aryl bond formation [140]. However, kinetic studies indicate a cyclization via path A, Eq. (13), followed by a rate-determining electron transfer [141]. Diarylalkanes substituted with a phenol ether group at one end and a phenolic group at the other end afford high yields of spirodienones (Table 7, numbers 4 and 5). This anodic cyclization can follow three mechanistic pathways.

Intramolecular couplings between nonconjugated double bonds being suitably disposed for transannular reactions have been carried out with norbornadiene (**XXII**, $n = 1$; Table 7, number 7) and bicyclo[2.2.2]octa-2,5-diene [142].

Substituted di- and triphenylamines lead to carbazoles (**XXII**, $n = 0$, Y = NR; Table 7, number 8). The yields are poor, however, and the cyclization is restricted to tertiary amines with the *para* position blocked by substituents not susceptible to substitution or elimination. The 2-methyltetramethoxybibenzyl derivative **XXIII** cyclizes in an anodic 2,6′-coupling reaction, with a subsequent dienone–phenol rearrangement, to give an 88–98% yield of the dihydrophenanthrene **XXIV** [Eq. (15)], which contains the essential structural elements of the B, C, and D ring of steroids [143].



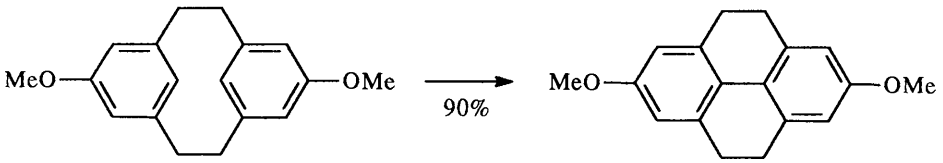
(XXIII) **(XXIV)**

(15)

With the corresponding dimethoxybibenzyl derivative, ring closure takes place without rearrangement to form a structure analogous to the A, B, and C ring of steroids [144], but the yield is only moderate (22%) because of the lower activation of the arene system. A remote substituent can strongly influence the occurrence of the subsequent rearrangement (Table 7, numbers 9a and b).

Tetraphenylethylene is coupled to 9,10-diphenylphenanthrene (Table 7, number 3). The corresponding coupling with tri- and diphenylethylene was unsuccessful. It was proposed that the initially formed cation radical disproportionates to a dication that couples to the observed product [138].

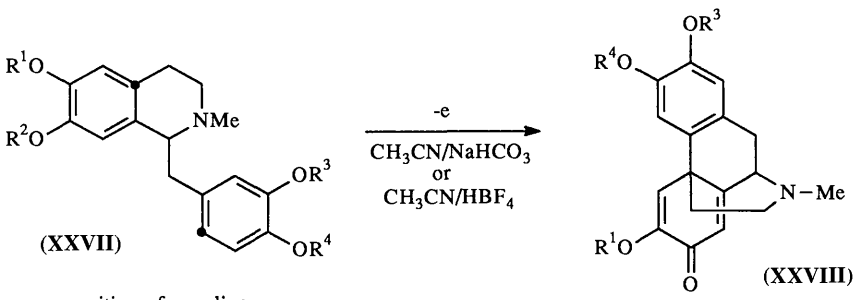
In the case of the [2.2]-*meta*-cyclophane (**XXV**), two anisyl radical cations couple in 90% yield to give the tetrahydropyrene derivative **XXVI** [Eq. (16)] [146]. **XXVI** can be further oxidized to a pyrene [147]. [2.2]-*Meta*-cyclophanes with other substituents than methoxy—for example, with CH_3, Br, CN, or NO_2—can also be cyclized [148].



(XXV) **(XXVI)**

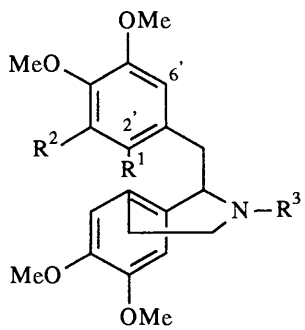
(16)

The anodic cyclization of benzyltetrahydroisoquinolines **XXVII** [Eq. (17a)] [**XXII**, $n = 2$, Y = –] to the morphinane skeleton is particularly interesting from the preparative point of view since the cyclization cannot be achieved so satisfactorily with chemical oxidants. **XXVIIIa** and **XXVIIIb** can be obtained in good yield in acetonitrile–sodium bicarbonate using a divided cell [149–153]; **XXVIIIc–f** can even be prepared in an undivided cell and in acidic electrolytes [155a,b], although under less mild conditions. The reaction has also been performed to prepare optically active 9-(*R*)-*O*-methylflavinantine [154]. Further oxidation of flavinantine leads to a specific hydroxylation at C10 together with a subsequent ring cleavage and reclosure to an oxohomomorphinane [155c].



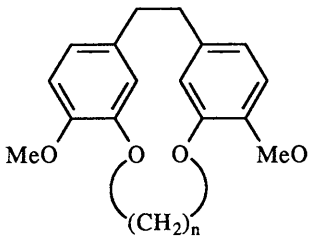
(17a)

a) $R^1=R^2=R^3=R^4=CH_3$ (52-85%)
b) $R^1=R^2=R^3=CH_3$, $R^4=PhCH_2$ (43-63%)
c) $R^1=R^2=R^3=CH_3$, $R^4=H$ (63%)
d) $R^1=R^2=R^4=CH_3$, $R^3=H$ (50%)
e) $R^1=R^2=CH_3$, $-R^3-R^4- = -CH_2-$ (80%)
f) $R^1=R^2=R^3=R^4=CH_3$ (70%)



(XXIX)

	R^1	R^2	R^3
a	Br	H	Me
b	Cl	H	Me
c	NO_2	H	Me
d	$NHCOCH_3$	H	Me
e	H	I	Me
f	H	Br	Me
g	H	MeO	Me
h	H	H	CHO
i	H	H	Me
j	H	H	CF_3CO



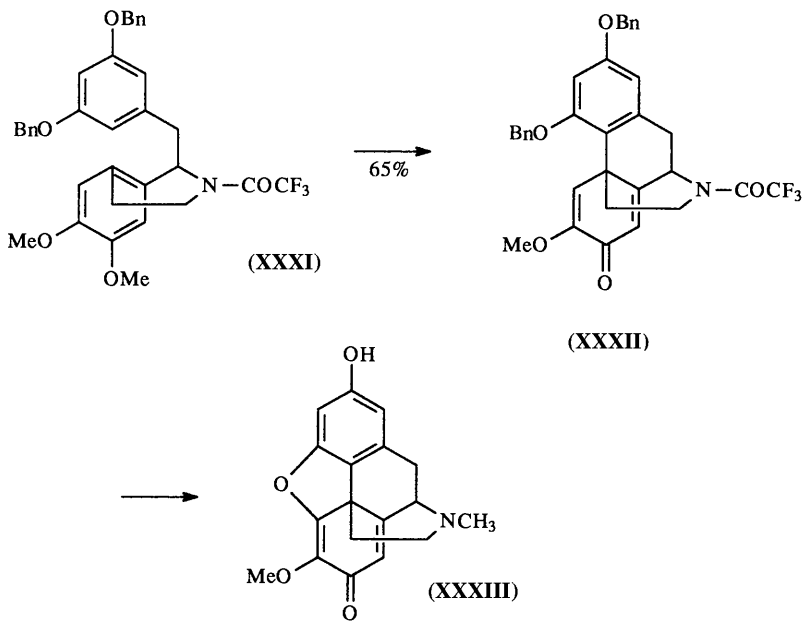
	n
a	6
b	4
c	3

(XXX)

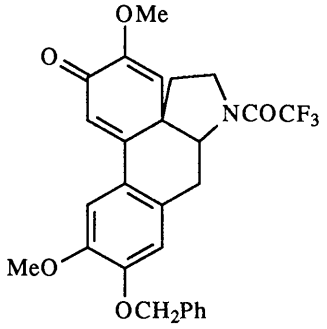
It is, however, a disadvantage that in **XXIXi** the -I-effect and the steric hindrance of the 5′-methoxy group induces a C2′–C5a coupling to the flavinantine type of compound and prevents the C6′–C5a coupling to the desired morphine type of compound. Even when the two dialkoxy-substituted phenyl rings are forced into an *ortho,ortho*-position as in **XXX**, no *ortho–ortho* coupling but an intermolecular dimerization occurs. When the methylene chain in **XXXb,c** becomes longer, intramolecular *ortho,para* coupling occurs [156].

Attempts to enforce the "morphine type" of coupling have so far been unsuccessful. **XXIXa** cyclizes at C2′ with debromination [153]. **XXIXb** [149,153] and **XXIXc,d** [157] lead to cleavage at C1; in **XXIXe,f** the C2′ ring closure is hardly hindered and I or Br is replaced in an *ipso* substitution [149,153]; **XXIXg**, however, in which the C2′ and C6′ coupling are identical, forms 35–55% of the cyclization product [151,153].

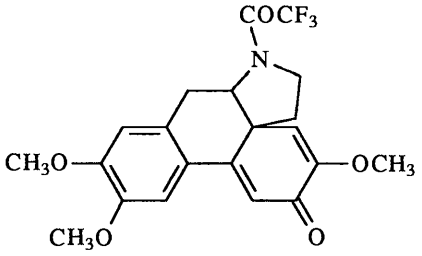
N-Acyl substituents considerably affect the formation of products; *N*-formyl (**XXIXh**) is cleaved at Cl, and *N*-trifluoroacetyl (**XXIXj** in 4′: OCH_2Ph instead of OMe) gives the dienone **XXXIV** in good yield [157].



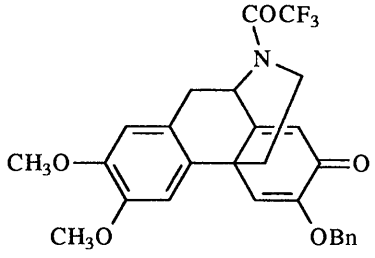
(XXXI) **(XXXII)** **(XXXIII)** (17b)



(XXXIV)



(XXXV)

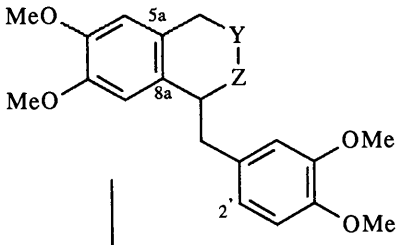


(XXXVI)

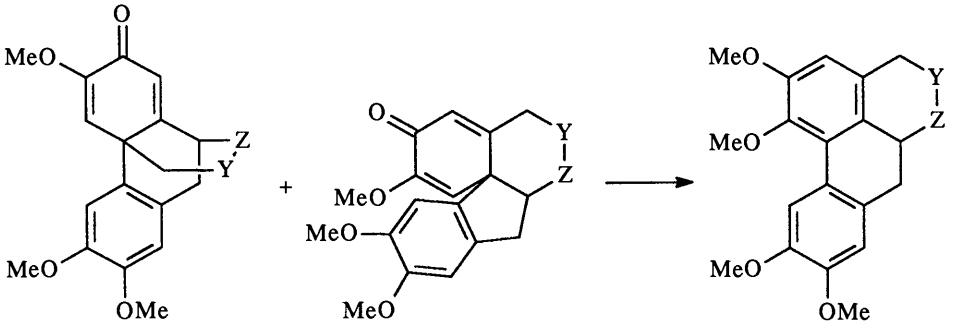
XXXI [Eq. (17b)], which also has two identical *ortho* coupling sites, can be cyclized in 65% yield to **XXXII**, which subsequently has been converted into 3-desoxythebain (**XXXIII**) [158].

The solvent exerts a strong influence on the product distribution. Starting from the same tetrahydrobenzylisoquinoline in MeCN, 82% **XXXV** are formed. In MeCN–MeOH the intermediate can be effectively trapped by methanolysis and 58% **XXXVI** are obtained [159]. A major mechanistic study seeking common denominators in the oxidations leading to **XXIV**, **XXVI**, and **XXVIII** has been published [152b]. A stereochemical study indicated that the yield in the cyclization is independent on the pseudoequatorial or pseudoaxial position of the benzyl substituent in the benzyltetrahydroisoquinoline [160].

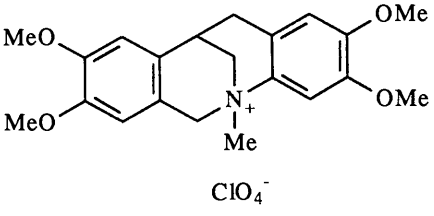
Carbon analogs (**XXXVII**, $Y = CH_2$, $Z = CH)_2$) of benzyltetrahydroisoquinolines [161] couple at C2′ and C5a in good yield to give **XXXVIII** [Eq. (18)] or at C8a to give **IXL**; in acidic electrolytes (CF_3CO_2H–CH_2Cl_2), **IXL** rearranges to give **XL**. A 4-benzyl-substituted tetrahydroisoquinoline afforded the tetracyclic structure **XLI**; the higher homolog, the 4-β-phenethyl derivative cyclized to a homoisoaporphine **XLII**. The results have been analyzed in terms of the Baldwin rules [165].



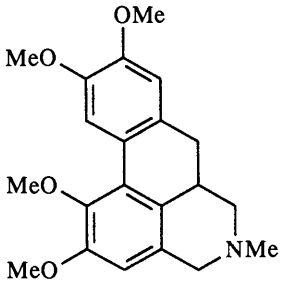
(XXXVII)



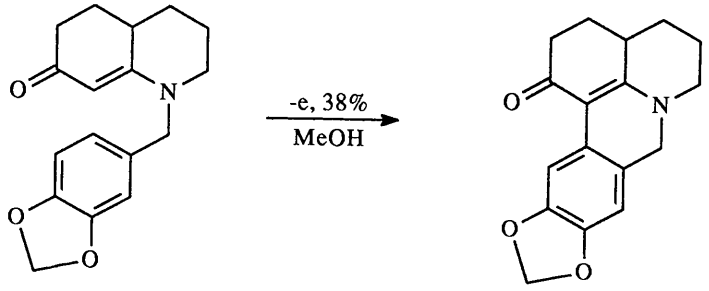
(XXXVIII) (IXL) (XL) (18)



(XLI)



(XLII)

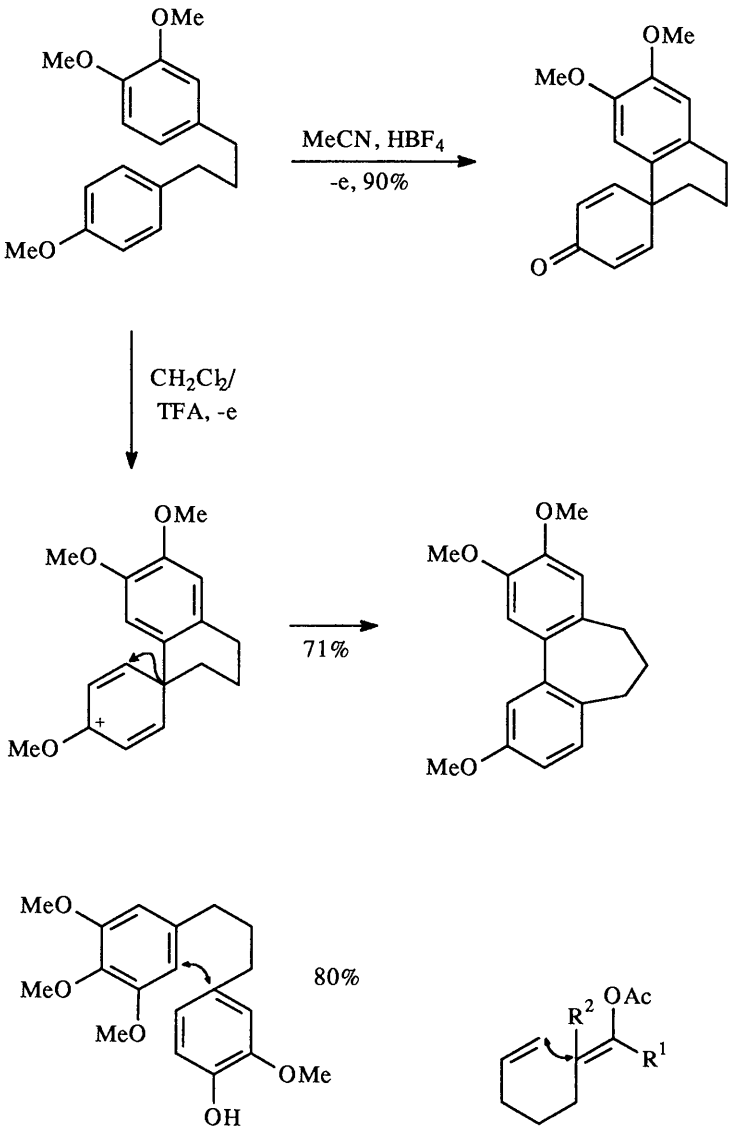


(19)

Oxygen analogs of benzyltetrahydroisoquinolines (**XXXVII**: Y = CO, Z = O) form in dichloromethane–TFA a spirodienone by C-6′,C-8a coupling; in acetonitrile a bridged lactone was obtained (Table 7, numbers 10a and b). The isomeric isochroman-3-one (Y = O, Z = CO) undergoes an intramolecular coupling between C-6′ and C-8a and migration of the 6′–8a bond to afford a γ-lactone (Table 7, number 11). Also benzylisochromanes (**XXXVII**: Z = O, Y = CH_2) afford in fair to good yields C-2′ to C-5a coupled diphenyl products (Table 7, number 12). For **XXXVII**: Y = CO, Z = NCH_3, a C-2′ to C-8a coupled product with subsequent rearrangement is found (Table 7, Number 13). A survey of anodic intramolecular coupling with multiple variations of **XXXVII** was undertaken [161]. The report offers mechanisms and a fairly complete overview of the area.

Benzyl- and 2-phenethylenaminoketones (**XXII**: Y = NR, n = 1, 2) can be cyclized in good yields to quinolines and benzazepines (Table 7, numbers 14 and 15). The cyclization has also been used to prepare a precursor of the alkaloid lycorane [Eq. (19)] [167]. In indoles the oxidation of the heterocycle must be suppressed by electron-withdrawing substituents. This is the case in 3-keto-substituted indoles. Although the α-phenyacetyl indole (Table 7, number 16, n = 1) undergoes no cyclization, which has been analyzed in terms of a geometrically unfavored transition state [165], the β-phenylpropionyl indole (n = 2) cyclizes. The radical cation first couples to a spiro intermediate, which undergoes oxidation, bond breaking, rearrangement, and tautomerization to the indolenine.

Unsymmetrical 1, 3-diaryl propanes (XXII, n = 3, Y = –), which bear phenolic hydroxyl groups, react to spirodienones, presumably via a phenoxonium ion (Table 7, numbers 4 and 5). Trimethoxy-substituted diphenylpropanes form different products depending on the reaction conditions. In MeCN–HBF_4 a spiro dienone is obtained [Eq. (20)] [140]; in dichloromethane TFA (3:1) a seven-membered ring is formed. The latter result is explained by the low nucleophilicity of the medium and TFA catalysis of the dienone–phenol-like rearrangement.



(20a)

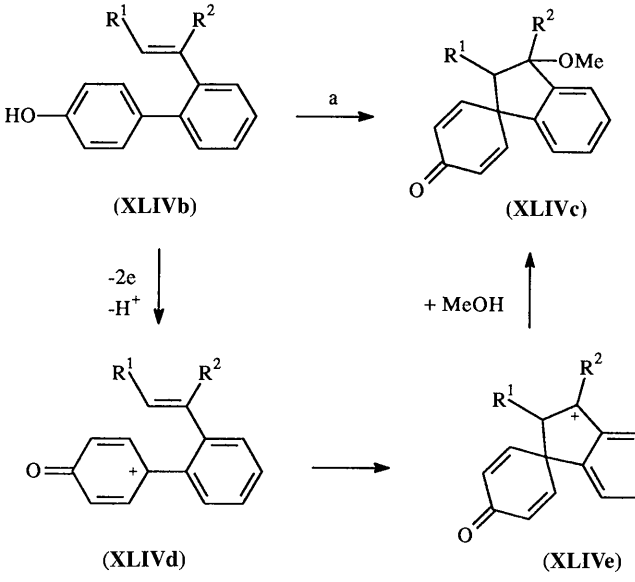
(XLIII) **(XLIVa)**

A 2-phenethyltetrahydroisoquinoline with hydroxyl groups as substituents leads to an *ortho*, *para*-coupled spiro compound (Table 7, number 17); with alkoxy groups a tetracyclic compound by nitrogen–aryl coupling is obtained (Table 7, number 18). The intramolecular aryl coupling of **XLIII** has been used in a synthesis of colchicine [171].

Unsaturated enol acetates (**XLIVa**) (**XXII**, $n = 3$, Y = –) have been cyclized to cyclohexenylketones [172a].

With the stannyl group as electroauxiliary, oxonium or *N*-acyliminium ions can be generated, which react in an electrophilic intramolecular addition or aromatic substitution to afford cyclic six-membered ethers or amines or their benzo analogues [Table 7, numbers 20 and 21] [172b]. Swenton has explored the dependence of yield

and selectivity in the intramolecular coupling of phenols and olefins [Eq. (20b)] on the substituents in the aryl ring and the olefin [172c,d]. Oxidation of the phenol **XLIVb**, deprotonation, and a further electron transfer lead to **XLIVd**, which undergoes an electrophilic addition to the double bond, and the resulting cation **XLIVe** is subsequently trapped by methanol.



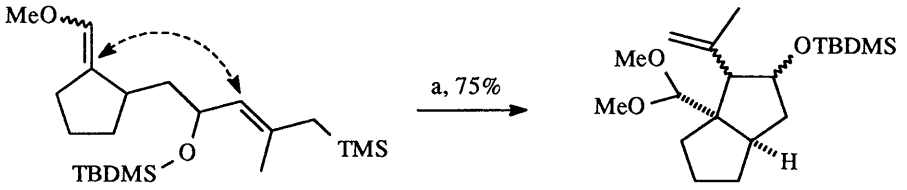
R^1	R^2	Yield(%
H	H	16
H	CH_3	85
H	Ph	65
CH_3	H	35
$-(CH_2)_3-$		69

(20b)

a: Pt anode, CH_3CN/MeOH/AcOH, $LiClO_4$

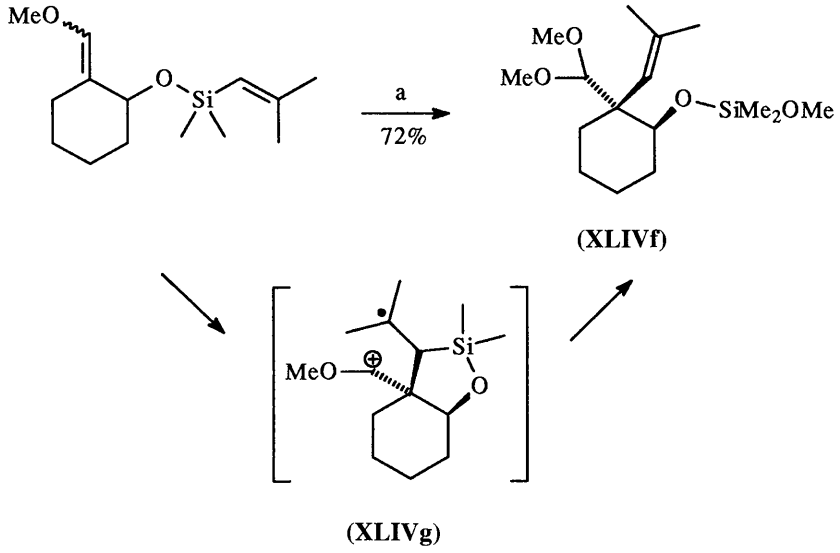
Aryl ethers were also coupled intramolecularly with enol ethers; when vinylsulfide was used as initiator of the coupling reaction the selectivity could be improved considerably [172e]. Additionally, the coupling to furan rings was studied, which led to advanced intermediates for the synthesis of bicyclic furan-containing natural products [172e].

The intramolecular coupling of enol ethers with enol ethers, styrenes, alkyl-substituted olefins, allylsilanes, and vinylsilanes was systematically studied by Moeller [172f]. Many of these coupling reactions turned out to be compatible with the smooth formation of quaternary carbon atoms [Eq. (20c)] [172g], which were formed diastereoselective and led to fused bicyclic ring skeletons having a *cis* stereochemistry [172i]. The cyclization is compatible with acid sensitive functional groups as the allylic alkoxy group. In the coupling of enol ethers with vinylsilanes, the results pointed to a mechanism where the oxidation led to a cyclized distonic radical cation with the positive charge located adjacent to the methoxy group and the radical β to the silyl group. A relatively low mass balance with the vinyl silane terminator could be resolved by switching to the vinylsiloxy group, whereby via the intermediate distonic radical cation **XLIVg** the product **XLIVf** was formed in 72% yield. This meant the transfer of the vinyl group with the stereoselective formation of a quaternary carbon atom [Eq. (20d)] [172h].



a : C-anode, 1 M $LiClO_4$, MeOH/THF, lutidine

(20c)

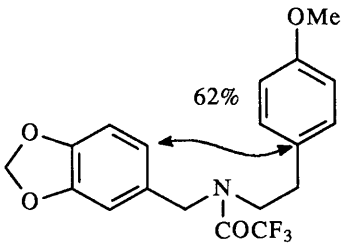


(20d)

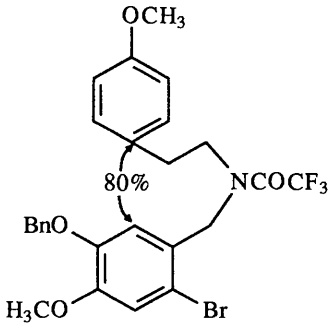
a: RVC anode, $LiClO_4$, MeOH/THF, 2,6-lutidine

Moeller has demonstrated in some cases that these reactions can be run without loss of selectivity and yield in a simple beaker with either a carbon rod or reticulated carbon as anode, without potential control and with a 6-V lantern battery as power supply [172i].

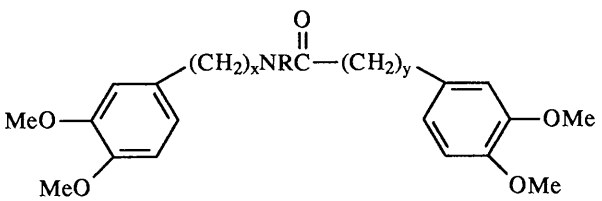
1,4-Di(methoxyphenyl)butane (**XXII**, $n = 4$, Y = –) forms in dichloromethane–TFA initially a seven-membered ring followed by rearrangement to the eight-membered ring and its dimerization (Table 7, number 6). The amide **XLV** (**XXII**, $n = 3$, $Y = NCOCF_3$) has been cyclized to a precursor of (+)-oxocrinine [168] and **XLVI** to a precursor of galanthamine [173].



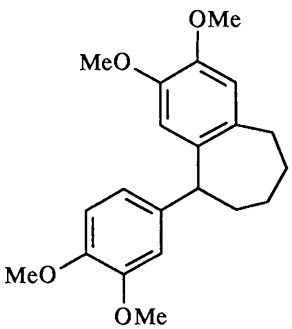
(XLV)



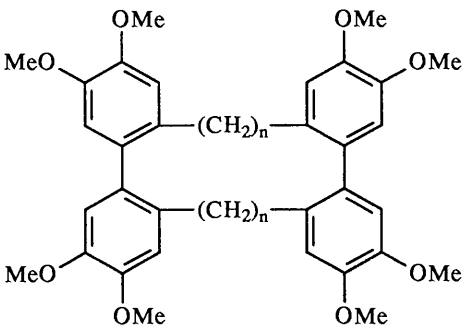
(XLVI)



(XLVII)



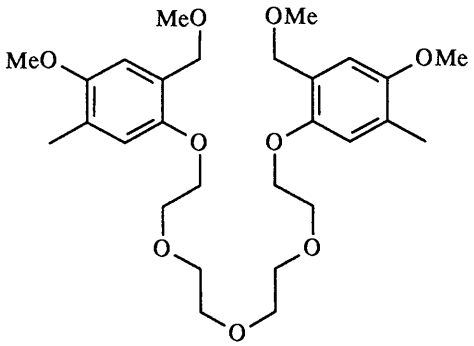
(XLVIII)



(XLIX)

Diarylamides (Table 7, number 19) and **XLVII** can be cyclized, when the amide is tertiary and the carbonyl and amino groups are not conjugated with the aromatic system (**XLVII**, x, $y \neq 0$) [174]. From the corresponding secondary amides only intermolecularly coupled products were obtained, which can be rationalized in terms of the preferred conformation of the amides. 1,5-(Bis(dimethoxyphenyl)butane (**XXII**: $n = 5$) forms a seven-membered ring **XLVIII** by a *para*-benzyl coupling [137]. With **XXII** ($n > 6$), coupling occurs intermolecularly and with partial subsequent cyclization to form up to 40-membered rings **XLIX** [175a].

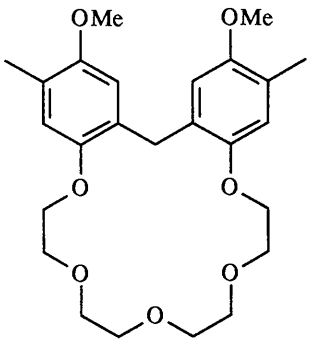
By dealkylative coupling of benzylic ethers mediated by the aromatic radical cation orange $CRET^{+\cdot}$, a novel crown ether, which contains a diarylmethane linkage, is obtained [Eq. (20e)] [175b].

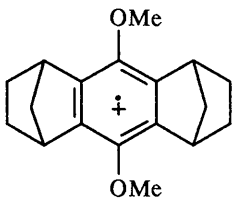


orange CRET$^{\bullet+}$

CH_2Cl_2, $NaPF_6$, 0°C, 100%

(20e)





orange CRET$^{\bullet+}$

E°_{Red} = 1.11 V vs. SCE

IV. COUPLING VIA RADICALS

A. Kolbe Dimerization

Radicals can be generated in preparative amounts and in an experimentally simple procedure by the use of Kolbe electrolysis. This reaction is discussed in detail in Chapter 14; For reviews see Refs. 176–182. The carboxylates are decarboxylated to radicals via $1e^-$ oxidation or to carbenium ions via $2e^-$ oxidation. The radicals couple or react with olefins to give "additive" dimers and/or monomers (see Sec. IV.C). Alcohols, amides, esters, alkenes, and rearranged products are formed from the carbenium ions. The radical route is favored by platinum anodes and also by those of vitreous or baked carbon [183a], glasslike hard carbon [183b], and also by a high current density, by an acidic electrolyte, in which only 5–10% of the acid is neutralized, by methanol as solvent, and finally by hydrogen- or electron-attracting substituents on the α-carbon atom of the carboxylic acid [184a].

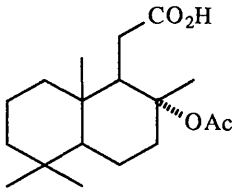
It has been shown that the metal-based oxidant hexachloro osmate (V) yields in some cases also decarboxylative coupling products [183c].

The Kolbe electrolysis of acetate to ethane and carbon dioxide was modeled for a parallel-plate reactor. Three zones were considered in the model: a turbulent bulk region, and a thin diffusion layer at each electrode [184b]. The same authors describe the electrolysis of gaseous acetic acid in a polymer electrolyte membrane (PEM) reactor. Platinized

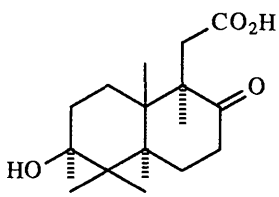
Nafion 117 is the PEM and functions simultaneously as electrolyte and separator. Current densities up to 0.4 A/cm^2 and current efficiencies up to 90% were obtained [184c].

Some representative Kolbe dimerizations are listed in Table 8.

If the retrosynthesis of a target compound leads to two symmetrical fragments, the Kolbe electrolysis is a favorable method for its synthesis. For example, the dimerization of **L** or **LI** is the key step in the synthesis of pentacyclosqualene [192] and of α-onocerin [193], respectively. Similarly, the precursor of a perhydrophenanthrene has been synthesized [194a].



(L)



(LI)

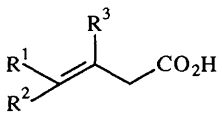
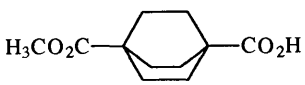
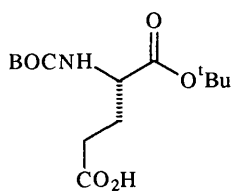
Methyl hydrogen azelate has been coupled to the $1,_{16}$-C_{16}-diester, which has been converted by acyloin condensation, deoxygenation, and 1,4-addition of a methyl group to homomuscone [189a]. Dimer fatty acid, which is obtained in a technical scale by clay-catalyzed, thermal dimerization from tall oil fatty acids, was coupled by way of the half ester in 38% yield to the diester $MeO_2C(CH_2)_{68}CO_2Me$ [189b].

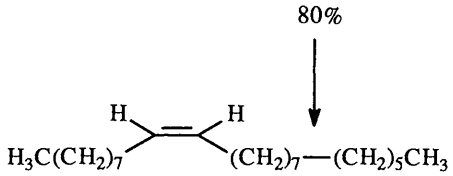
For the preparation of 2,7-diaminosuberic acid by Kolbe coupling of N-protected α-glutamic acid esters, the dependence of the yield on solvent, temperature, concentration of carboxylate anion, and protecting group has been investigated. The highest yield of protected dimer is obtained with Boc-Glu-OMe as starting material and MeOH/pyridine/NaOMe as electrolyte [194b].

Unsymmetrical compounds can also be prepared via mixed Kolbe electrolyses of different carboxylates (heterocoupling). The disadvantagous but unavoidable formation of symmetrical dimers can be suppressed to the formation of essentially one by-product if the cheapter carboxylic acid is used in a 5- to 10-fold excess. Hydrogenated carotenoids, saturated and unsaturated fatty acids, optically active ω-hydroxycarboxylic acids, and intermediates for the preparation of muscone and humulene have been obtained in this way [177b].

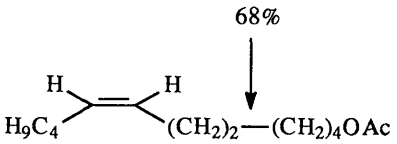
The method has recently been applied to the synthesis of pheromones [1a, 182a]. For example, muscalure (**LII**) has been synthesized in 80% yield [195]. Furthermore, the antagonist of muscalure, (*Z*)-11-heneicosene [195b], looplure (**LIII**) [196], brevicomin (**LIV**) [197], disparlure (**LV**) [198], the attractant of the German cockroach (**LVI**) [199], optically active **LVII**, a *Trogoderma* pheromone [200], and pheromones with a diene or triene structure, such as **LVIII** [201] (the arrows indicate the coupling position), have been prepared. In addition, alkyne carboxylic esters with different chain lengths can be obtained [202], which can be hydrogenated at will to either (*E*)- or (*Z*)-pheromones. Furthermore, useful intermediates for the synthesis of dicarba analogs of cystine peptides have been prepared from L-glutamate [203a] and chiral building blocks from enantiomerically pure β-hydroxybutyric acid derivatives [204a]. Orthogonally protected 2,5-diaminoadipic, 2,6-diaminopimelic, and 2,7-diaminosuberic acid derivatives bearing up to four different protecting groups have been prepared in one step by heterocoupling [203b]. A further selection of mixed Kolbe electrolyses is summarized in Table 9.

Table 8. Some Examples of the Kolbe Electrolysis of Carboxylic Acids

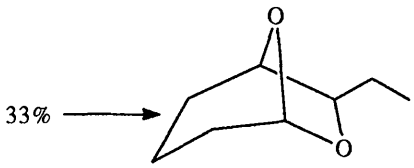
Carboxylic acid	Yield of dimers (%)	Reference
$H_3C(CH_2)_nCO_2H$, n = 5-15	60-90	177b
$RO_2C(CH_2)_nCO_2H$, n = 4-16	45-95	177b
$(CH_3)_2CH\text{-}CH(CO_2Et)CO_2H$	67	185
$AcO(CH_2)_nCO_2H$, n = 3-5	73-83	186
$F(CH_2)_nCO_2H$, n = 4-10	45-70	187
$EtCO(CH_2)_4CO_2H$	75	188
(Z)-$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$ (Oleic acid)	75	189a, 189b
(Z)-$CH_3(CH_2)_7CH{=}CH(CH_2)_{11}CO_2H$ (Erucic acid)	70	189b
$CH_3(CH_2)_5CH(OH)(CH_2)_{10}CO_2H$	56	189b
$CF_3(CF_2)_7CO_2H$	61	189b
$CH_3O_2C(CH_2)_7CO_2H$	80	189b
$R^1CO\text{-}CR^2R^3CO_2H$	35	190
F_2CClCO_2H	45	190
 R^1: octyl, ^{i}butyl, ^{i}propyl; R^2: H, Me; R^3: H	15-79	191a
	30	191b
	38	191c



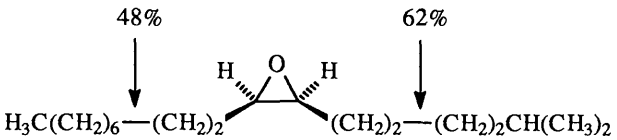
(LII)



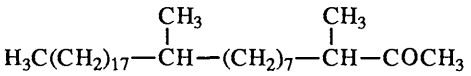
(LIII)



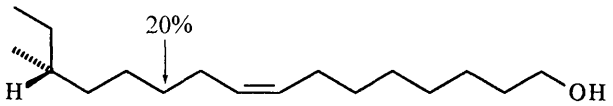
(LIV)



(LV)



(LVI)



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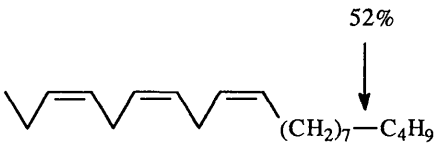
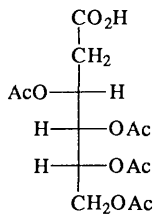
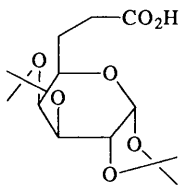
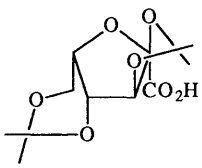
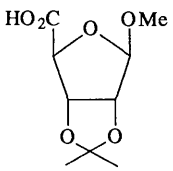


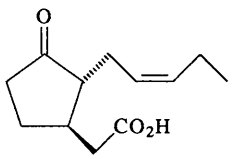
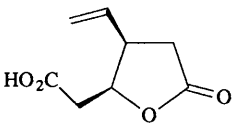
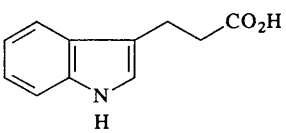
(LVIII)

Table 9. Examples of Kolbe Electrolysis of Carboxylic Acids

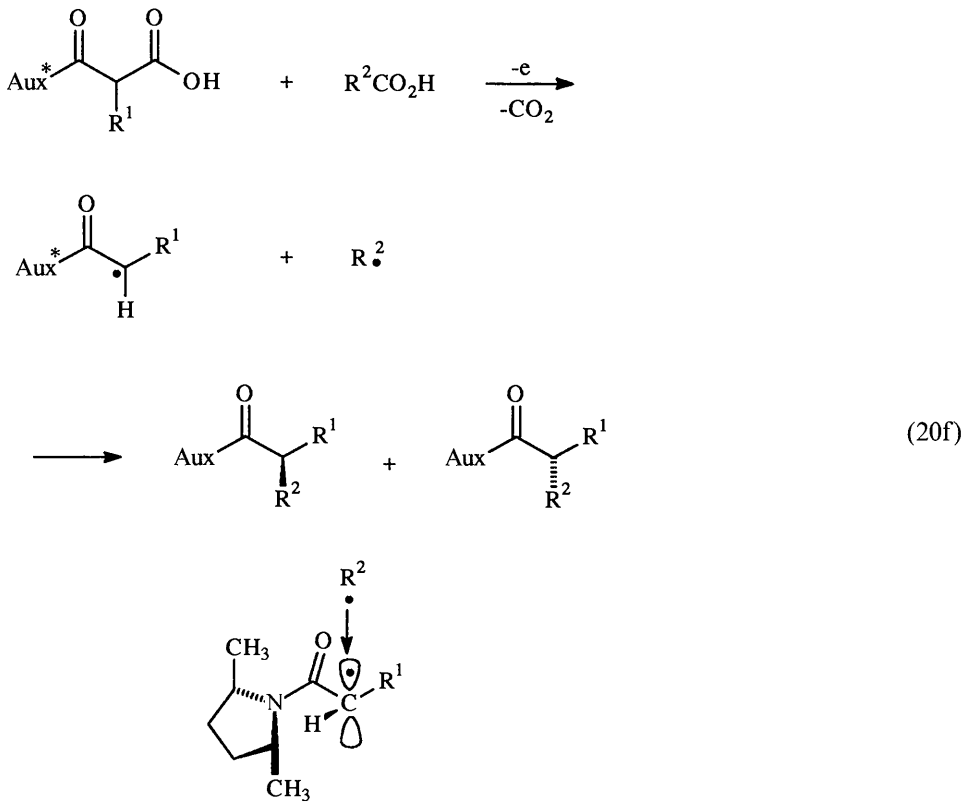
Carboxylic acid		Product	
A	B	A-B (%)	Reference
$MeO_2C(CH_2)_4CO_2H$	$H_3C(CH_2)_nCO_2H$ n = 2,4,8,12	12-48	205
$MeO_2C(CH_2)_2CO_2H$	$H_3C(CH_2)_7CH(CH_3)CH_2CO_2H$	35	206
$CH_3(CH_2)_2CH{=}CH(CH_2)_7CO_2H$	$HO_2C(CH_2)_6CO_2Me$	35	207
$EtO_2C(CH_2)_8CO_2H$	$Br(CH_2)_{10}CO_2H$	54	208
(E)-$C_2H_5CH{=}CHCH_2CO_2H$	$MeO_2C(CH_2)_3CO_2H$	59	209
CF_3CO_2H	$EtO_2CCH_2CO_2H$	46	210
CF_3CO_2H	CD_3CO_2H	68	211a
	$C_5H_{11}CO_2H$	69	211b
	$C_7H_{15}CO_2H$	54	
	$CH_3O_2C(CH_2)_7CO_2H$	49	
	$C_7H_{15}CO_2H$	70	211b
	$C_{13}H_{27}CO_2H$	51	
	(Z)-$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	46	
	$AcO(CH_2)_3CO_2H$	30	211c
	$C_{11}H_{23}CO_2H$	33	
	$Br(CH_2)_{10}CO_2H$	32	
	$C_7H_{15}CO_2H$	40	211c

(Continued)

Table 9. (Continued)

Carboxylic acid		Product	
A	B	A-B (%)	Reference
	$RO_2C(CH_2)_nCO_2H$ R = Me, Et, n = 4-7	10-43	211d
	$C_{12}H_{25}CO_2H$	40	211e
	RCO_2H R = C_2H_5, C_5H_{11}, C_8H_{17}, $C_{11}H_{23}$, $C_{15}H_{31}$	33-60	211f

The heterocoupling of carboxylic acids bearing chiral auxiliaries has been used to study the diastereoselectivity of the coupling of Kolbe radicals [204b]. For that purpose, 2-substituted malonic acid amides bound to seven different chiral auxiliaries were coelectrolyzed with different coacids [Eq. (20f)]. The yields in heterodimer ranged between 13 to 69%, and the diastereoselectivities between 20 and 86% *de*.



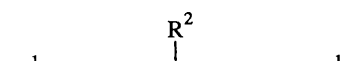
(20f)

(LIXa)

The most efficient auxiliary was the C_2-symmetrical chiral *trans*-2,5-dimethylpyrrolidine. The configuration at the stereogenic carbon atom of the major diastereomer agrees well with mechanistic conceptions developed for the radical addition of radicals substituted by chiral auxiliaries [204c]. According to these concepts the atoms C˙, C(= O), and N are located in a plane as shown in **LIXa**. The coupling from the *si* side is hindered by the 2-methyl group at the pyrrolidine ring, so that the coradical couples preferentially from the *re* side. The diastereoselctivity increases with the size of the coradical R^2 and the substituent R^1.

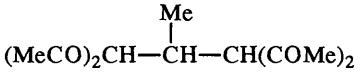
B. Coupling of Anions

In addition to the carboxylates, other anions can be dimerized at the anode, presumably via radicals. Anionized or enolized 1,3-dicarbonyl compounds and heteroanalogs of CH acids couple in satisfactory yields (Table 10, numbers 1–3).

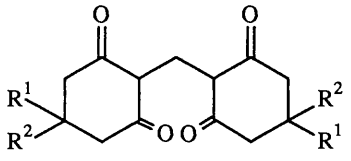


(LIX)

	R^1	R^2
a	Et	Me
b	Me	H
c	Et	H



(LX)



$R^1 = R^2 = Me$
$R^1 = H, R^2 = Ph$
$R^1 = H, R^2 = Me$

(LXI)

In the case of 1,3-dicarbonyl compounds, the solvent frequently interferes with the coupling reaction. So with diethyl sodio malonate in ethanol [212b], methanol [212b], dimethylacetamide [212b], or HMPTA [216], besides the dimer and the trimer, the compounds **LIXa–c** are obtained. They are presumably formed by oxidation of the solvent to the aldehyde and its condensation with the active methylene compound. No dimer was detected in the oxidation of sodio acetoacetate in ethanol, with the major product being **LX** [217]. Anodic oxidation of cyclic 1,3-diketones in aqueous methanolic sodium hydroxide does not yield the dimer but product **LXI**, formed by condensation of the starting compound with formaldehyde [218].

With some substrates, the yield is substantially improved with iodide as supporting electrolyte; an indirect electrolysis probably takes place here, with iodine as electrocatalyst [219a].

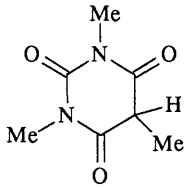
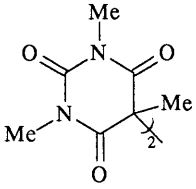
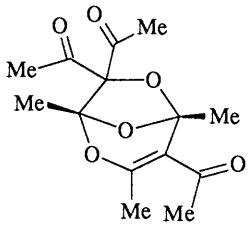
Mediated oxidations with NaBr, NaI of doubly activated methylene compounds CH_2XY (X = CO_2Me, CN, Y = CO_2Me) can be used to synthesize cyclopropane derivatives [219b]. Electrolysis of methylenemalonates in the presence of sodium iodide in an undivided cell results in 50–70% yield of stereoisomeric cyclobutanetetracarboxylates by first reductive dimerization at the cathode and subsequently mediated dimerization of the enolates at the anode [219]. In one of the rare examples, in which a useful product is obtained simultaneously at the working electrode and the counterelectrode (coupled or paired electrosynthesis), diethyl malonate dimerizes at the anode to give tetraethyl ethanetetracarboxylate and ethyl acrylate couples at the cathode to give diethyl adipate in yields of over 90% in each case [220]. Furthermore, anions of nitroaliphatic compounds are coupled to give vicinal dinitroalkanes (Table 10, number 4). Grignard compounds (Table 10, number 5) and borates (Table 10, number 6) couple to give alkanes, alkyne anions to give dialkynes (Table 10, number 7), sulfamides to give azoalkanes [224a], and dialkylamides to give tetraalkylhydrazines [224c].

The anodic oxidation of α-sulfonyl carbanions is shown to involve a coupling reaction between the electrogenerated radical and the parent anionic species. The relevance of this mechanism to transition metal oxidations of α-sulfonyl carbanions is examined [224d].

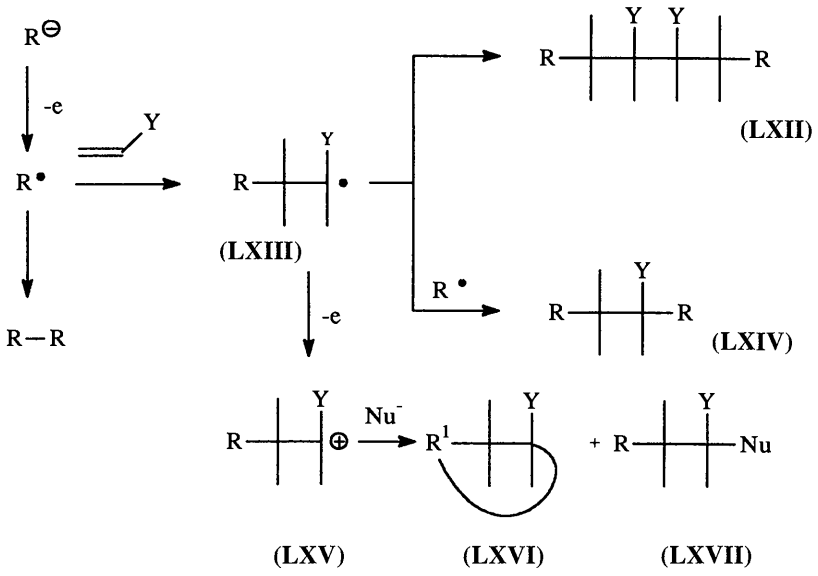
C. Oxidative Addition of Anions to Double Bonds

If anions R^- are oxidized in the presence of olefins, additive dimers (**LXII**) and substituted monomers (**LXIV**) are obtained [Eq. (21a), Table 11, and Ref. 1a]. The products can be

Table 10. Selected Examples of Coupling of Anodically Generated Radicals from Carbanions

Number	Carbanion or precursor	Conditions	Product	Yield (%)	Reference
1	$EtCH(CO_2Et)_2$	EtONa, MeCN	$[(EtO_2C)_2EtC\text{—}]_2$	55	213
2	Triethyl methanetri-carboxylate	NaOH, H_2O, acetone, EtOH	Hexaethyl ethanehexacarboxylate	50	212c, 214
3		pH 1, H_2O		69	215a
3a	$(MeCO)_3CH$	Et_3N, MeCN <10°C		92	215b
4	2-Nitrobutane	25% NaOH	3,4-Dimethyl-3,4-dinitrohexane	70	221
5	RMgBr (R = C_5H_{11}, $C_{18}H_{37}$, Ph)	Ether	R—R	54-60	222
6	R_3B R = C_5H_{11}-C_8H_{17}	MeOH, KOH	R—R	24-82	223
7	Ph—C≡C—H	THF, $LiClO_4$	$(Ph\text{—}C\equiv C)_2$	35	224b

rationalized by the following pathway: the radical R˙ obtained by a $1e^-$ oxidation from the anion R^- adds to the alkene to give the primary adduct **LXIII**, which dimerizes to give the additive dimer **LXII** with regiospecific head-to-head linkage of the two olefins, or couples with R˙ to give the additive monomer **LXIV**. If the substituent Y in the olefin can stabilize a carbenium ion, **LXIII** is oxidized to the cation **LXV**, which reacts intra- or intermolecularly with nucleophiles to give **LXVI** or **LXVII**.

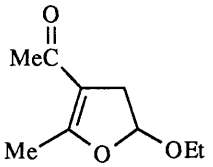
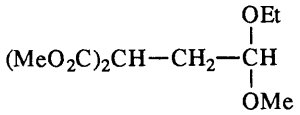
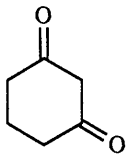
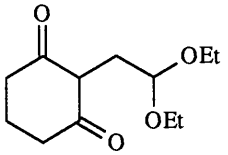
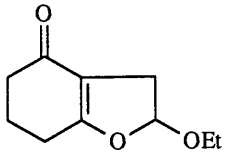
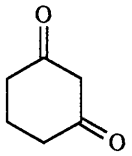
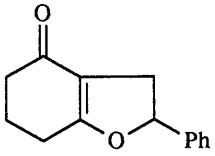


(21a)

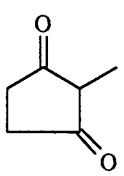
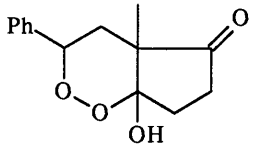
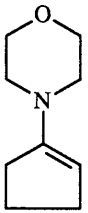
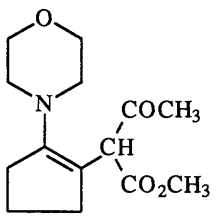
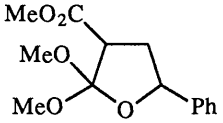
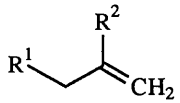
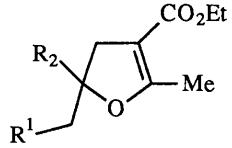
Satisfactory to good yields of adducts have been found for styrenes [Eq. (21a), Y = phenyl], conjugated dienes (Y = vinyl), enamines ($Y = NR_2$), and enol ethers (Y = alkoxy), particularly if they are unsubstituted at the β-carbon atom to Y. Nonactivated alkenes react less satisfactorily. In the oxidation of anionized 1,3-dicarbonyl compounds (Table 11, numbers 1–8) at potentials between 0.6 and 1.4 V (SCE) and in the presence of butadiene, only the additive dimer **LXII** is obtained; in the presence of ethyl vinyl ether only the disubstituted monomers **LXVI** or **LXVII** arise, but with styrene both types of products **LXII** and **LXVI** are formed. This result indicates that the primary adduct **LXIII** is oxidized rapidly between 0.6 to 1.4 V to the carbenium ion in the case of an ethoxymethyl radical (Y = OEt), and slowly in the case of an allyl radical (Y = vinyl).

With $Mn(OAc)_3$, generated by oxidation of $Mn(OAc)_2$ as mediator, a tandem reaction consisting of an intermolecular radical addition followed by an intramolecular electrophilic aromatic substitution can be accomplished [Eq. (21b)] [225b]. Further Mn(III)-mediated additions of 1,3-dicarbonyl compound to olefins are shown in Table 11 (numbers 8b,c, and 9a). Mediated by in situ generated Mn(III), methyl dibromoacetate, trichlorobromomethane, perfluoroctyl iodide, dimethyl bromomalonate, and active methylene compounds have been added via radicals to olefins [225d].

Table 11 Additions of Anodically Generated Radicals to Alkenes

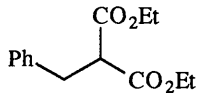
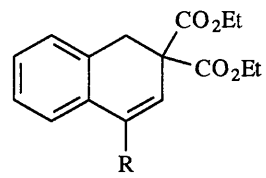
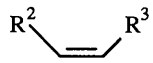
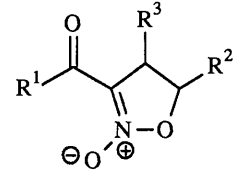
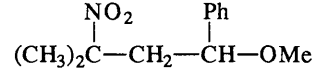
Number	Radical precursor	Olefin RCH=CYR'	Conditions	Product	Yield (%)	Reference
Anions of 1,3-dicarbonyl compounds						
1	MeO_2CCH_2COMe	$H_2C{=}CHOEt$	MeOH, MeONa, Pt		36	225a
2	$(MeO_2C)_2CH_2$	$CH_2{=}CHOEt$	MeOH, MeONa, Pt		37	225a
3		$EtOCH{=}CH_2$	EtOH, EtONa	 	79	226
4		$PhCH{=}CH_2$	MeCN, ET_4NOTos		85	227

(Continued)

5		$PhCH{=}CH_2$, O_2	MeCN, Et_4NOTos		79	227
6	$CH_3COCH_2CO_2CH_3$		CH_3ONa, MeOH		67	228a
7	$(MeO_2C)_2CH_2$	Styrene	MeOH, MeONa, Pt		40	225a
8a	$(MeO_2C)_2CH_2$	Butadiene	MeOH, MeONa, Pt	$[(MeCO)_2CH{-}CH_2{-}CH{=}CH{-}{-}CH_2{-}]_2$ + isomers	46	225a
8b	$CH_3COCH_2CO_2C_2H_5$	 R^1 = propyl pentyl, t-butyl R^2 = H, methyl	HOAc/EtOAc NaOAc, 0.1 eq. $Mn(OAc)_2$ C-anode		80-86	228b

(Continued)

Table 11 (Continued)

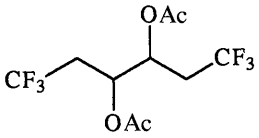
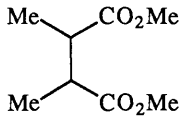
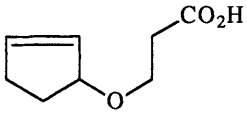
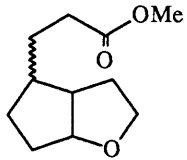
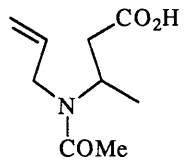
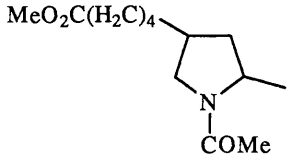
Number	Radical precursor	Olefin RCH=CYR'	Conditions	Product	Yield (%)	Reference
Anions of 1,3-dicarbonyl compounds						
8c		R—C≡CH R: C_6H_{13}, $(CH_3)_3Si$, Ph	KOAc/HOAc, 0.25 eq. $Mn(OAc)_2$ C-anode		40-91	228c
9a	$RCOCH_2NO_2$ R^1 = Ph	 R^2 = Bu, CH_2OAc R^3 = H	HOAc, Bu_4NBF_4 $Mn(OAc)_2$; 60°C C-anode		37-59	229a
Other anions						
9b	$(CH_3)_2CHNO_2$	Styrene	MeOH, MeONa, Pt		43	229b
10	nBuMgBr	Styrene	$(C_2H_5)_2O$, $LiClO_4$, Pt	$(nBu—CH_2—CHPh—)_2$	29	230

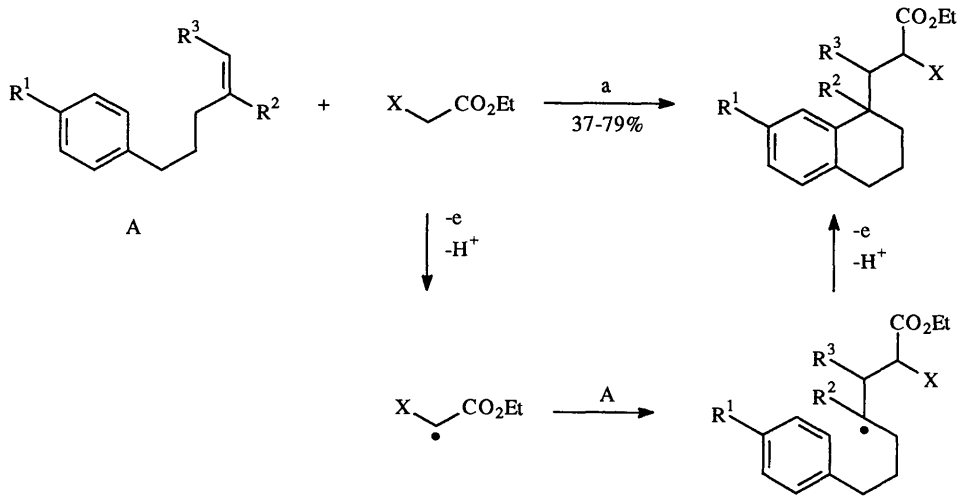
(Continued)

11	$(C_6H_{13})_3B(OMe)^-$	Butadiene	MeOH, MeONa, C	$(C_6H_{13}-CH_2-CH=CH-CH_2)_2$ $C_6H_{13}-CH_2-CH=CH-CH_2-C_6H_{13}$ $C_6H_{13}-CH_2-CH=CH-CH_2OMe$ + isomers	5 14	231
Carboxylates						
12	EtO_2CCO_2H	Butadiene	MeOH, Pt	$(EtO_2C-CH_2-CH=CH-CH_2)_2$ + isomers $EtO_2C-CH_2-CH=CH-CH_2-CO_2Et$	66 4	232
13	$MeO_2C(CH_2)_4-CO_2H$	Ethylene	MeOH, Pt	$MeO_2C(CH_2)_{12}CO_2Me$ $MeO_2C(CH_2)_{10}CO_2Me$	92-95	233
14	$MeO_2CCH_2CO_2H$	Vinyl ethyl, ether	MeOH, Pt	$[MeO_2C-(CH_2)_2-CH(OEt)-]_2$	35	234
15	$MeO_2CCH_2CO_2H$	Styrene	MeOH, Pt	$[MeO_2C-(CH_2)_2-CHPh-]_2$	38	232
16	$MeO_2C(CH_2)_4-CO_2H$	Butadiene	MeOH, Pt	$[MeO_2C-(CH_2)_4-CH_2-CH=$ $=CH-CH_2-]_2$ $MeO_2C-(CH_2)_4-CH_2-CH=CH-$ $-CH_2-(CH_2)_4-CO_2Me$	47 47	235
17	F_3CCO_2H	$CH_2=CH(CH_2)_2CH_3$	MeCN, NaOH, Pt	$CF_3-CH_2-CH(CH_2)_2CH_3$ (↓2)	40	236

(Continued)

Table 11 (Continued)

Number	Radical precursor	Olefin RCH=CYR'	Conditions	Product	Yield (%)	Reference
18	$CH_3CO_2^-$	Methacroleine	MeCN, H_2O, Pt	CH_3—$CH_2C(CH_3)CHO$ $\downarrow_2$	80	237
19	$CF_3CO_2^-$	Vinyl acetate	MeCN, H_2O, NaOH		24	238
20	$CH_3CO_2^-$	Dimethyl fumarate	MeCN, H_2O		80	239
21		$MeO_2C(CH_2)CO_2H$	5% MeONa, MeOH		41	242
22		$MeO_2C(CH_2)_4CO_2H$	5% MeONa, MeOH		53	243



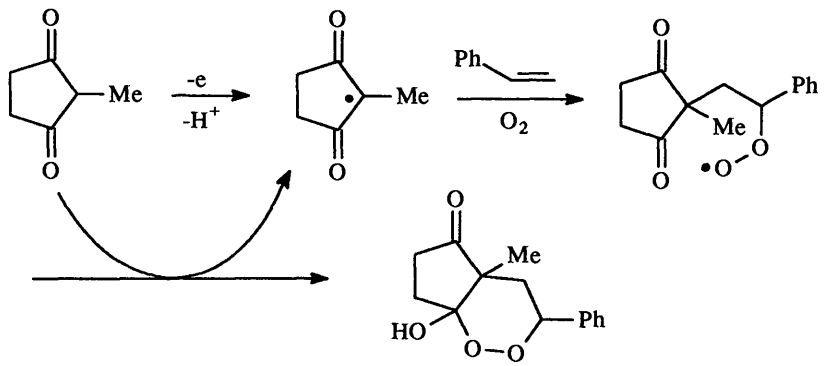
R^1 = H, F, Me, R^2 = H, Me, R^3 = H, Me, X = CN, CO_2Et

a: C-anode, NaOAc, HOAc/AcOEt (13:3), 0.2 eq. $Mn(OAc)_2$, 60°C

(21b)

Sorbic acid precursors have been obtained in larger scale and high current efficiency by a Mn(III)-mediated oxidation of acetic acid–acetic anhydride in the presence of butadiene. Cu(II) enhances the efficiency of this oxidation to isomeric acetoxyhexenoic acids. The reaction involves addition of the methylhydroxycarbonyl radical, generated by Mn(III) from acetic acid, to butadiene, further oxidation of the allyl radical by Cu(II) to the allyl cation, and subsequent acetolysis [225c].

In an electroinitiated radical addition, an olefin and oxygen can be added simultaneously to the 1,3-dicarbonyl compound [Eq. (22) and Table 11, number 5 [227].



(22)

Also other anions, such as the 2-nitropropanate anion, Grignard reagents, and borates, can be added to olefins (Table 11, numbers 9b, 10, and 11).

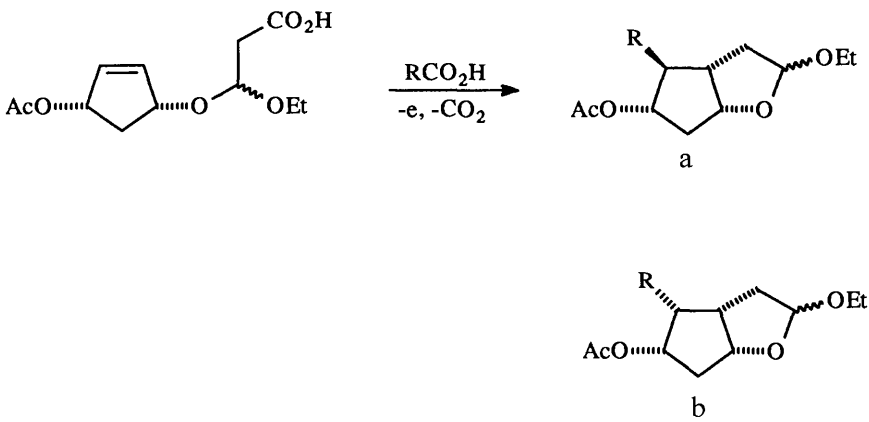
If carboxylates are subjected to Kolbe electrolysis in the presence of olefins, the generated Kolbe radicals add to the double bonds to afford mainly additive dimers

(Table 11, numbers 12–20). In vicinal disubstituted styrenes, upon addition of the Kolbe radical $MeO_2CCH_2\cdot$, the yields of adducts decrease with increasing size of the β-substituent: H = 42%, Me = 27%, Et = 11%, ^{i}Pr = 5%, ^{t}Bu = 2% [240a]. The ratio of additive dimer (**LXII**) [Eq. (21a)] to monomer (**LXIV**) can be affected to some extent by the current density *i*. With butadiene and ethyl oxalate (Table 10, number 12), the ratio of **LXII** to **LXIV** equals 15.6 for $i = 0.025\,mA\,cm^{-2}$, but decreases to 0.67 for $i = 0.66\,mA\,cm^{-2}$. Obviously, at low current densities the radicals R$^\cdot$ are trapped mainly by the olefin to give **LXIII**, a process that no longer dominates at a higher current density, which means at a higher radical concentration, so that then the heterocoupling to give **LXIV** is favored.

Upon electrolysis of trifluoroacetate in MeCN–H_2O–(Pt) in an undivided cell in the presence of electron-deficient olefins, additive dimers and additive monomers are obtained. The selectivity can be controlled by current density, temperature, and the substitution pattern of the olefin [240b].

Electrolysis of a methanol solution of methyl oxalate with ethylene under pressure yielded 70–90% of the dimethyl esters of succinic, adipic, suberic, and sebacic acids. Decrease in the ethylene pressure or increase of the current density led to a decrease in the higher esters in the product mixture [241]. The influence of mechanism and kinetic data on yields and selectivities in addition reactions of anodically generated radicals to olefins has been calculated and predictions have been tested in preparative electrolyses [244].

β-Allyloxy- and β-allylaminopropionates cyclize in a mixed Kolbe electrolysis (5-*exo-trig* cyclization) by intramolecular addition to form 3-substituted tetrahydrofurans and pyrrolidines (Table 11, numbers 21 and 22). This intermolecular addition has been used to synthesize a precursor of prostaglandin $PGF_{2\alpha}$ [Eq. (23a)] [245a].

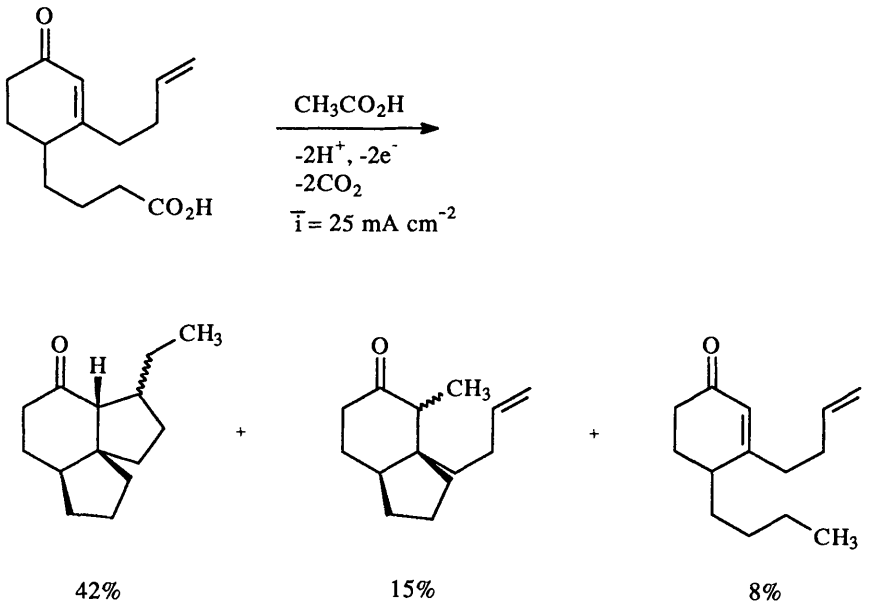


(23a)

R: $CH_3(CH_2)_7$, 54%, a:b 3.0:1
R: $PhMe_2SiCH_2$, 38%, a:b 4.3:1

A radical tandem cyclization, consisting of two radical additions and a heterocoupling reaction, has been achieved by coelectrolysis of unsaturated carboxylic acids with different coacids. This provides a short synthetic sequence to tricyclic products, such as

triquinanes [Eq. (23b)] [245b]. The selectivity for the formation of tricyclic, bicyclic, and monocyclic product could be predicted by applying a mathematical simulation based on the proposed mechanism.



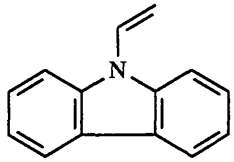
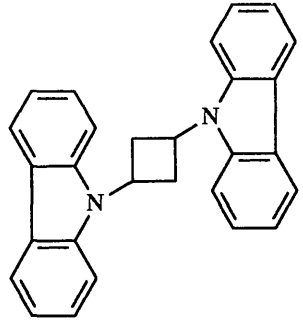
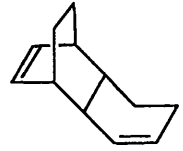
(23b)

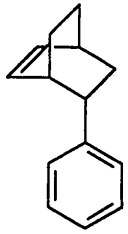
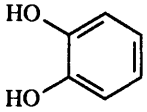
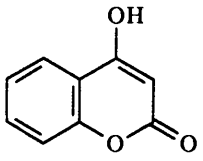
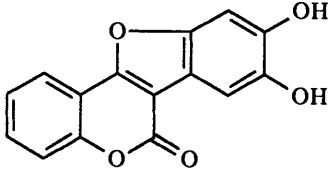
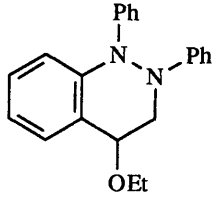
The coupling of an allyl or acyl moiety onto carbon atoms is achieved by anodic oxidation of α-heteroatom substituted organostannanes or *O,S*-acetals in the presence of allylsilanes or silyl enol ethers. The reaction probably involves carbocations as intermediates that undergo electrophilic addition to the double bond [245c].

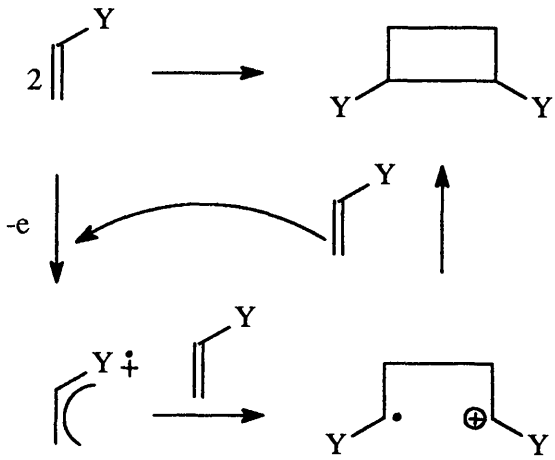
V. ANODICALLY INDUCED CYCLOADDITIONS

[4 + 2]- and [2 + 2]-cycloadditions can be induced by electron transfer. In a radical chain reaction the olefin is oxidized to its radical cation, which first undergoes an addition. The dimeric and distonic radical cation then accepts an electron from the olefin to undergo ring closure and to initiate a new cycle [Eq. (24a)] [246]. This way vinyl carbazole (Table 12, number 1) and 5,6-dimethoxyindene [247] have been cyclized. Indenone also reacts in an electrocatalyzed [4 + 2]- and [2 + 2]-cycloaddition with styrene derivatives [248a]. Furthermore, a series of dienes has been subjected to [4 + 2]- and [2 + 2]-cycloadditions with $Ar_3N^{+\cdot}$ as mediator (Table 12, numbers 2 and 3).

Table 12. Cycloadditions od Anodically Generated Intermediates

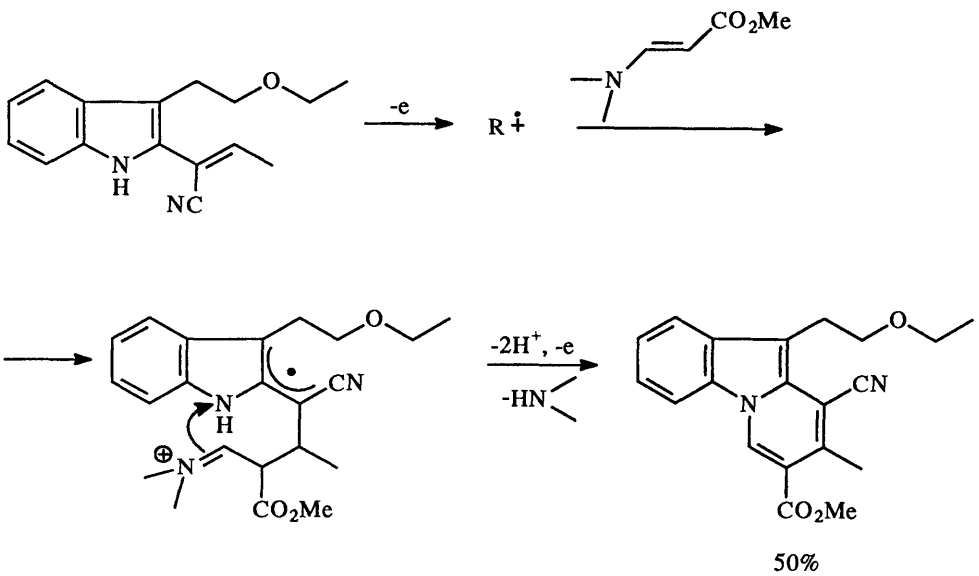
Number	Radical precursor	Olefin	Conditions	Product	Yield (%)	Reference
1			$Fe(NO_3)_3$, MeOH		80	246
2	1,3-Cyclohexadiene		MeCN, CH_2Cl_2 lutidine, C		24	249a

3	1,3-Cyclohexadiene	Styrene	MeCN, CH_2Cl_2 lutidine, C		33	249a
4			H_2O, NaOAc		95	250a
5	1,1,2-Triphenyl-hydrazine	Vinyl ethyl ether	MeCN, $LiClO_4$ Py, Pt		95	253



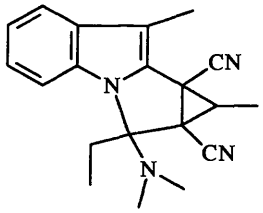
(24a)

[4 + 2]-Cycloadditions between 2-vinylindoles as heterodienes and acceptor substituted enamines can be induced by formation of 2-vinylindole radical cations either via anodic oxidation or photoelectron transfer. In this way pyridoindoles and indolonaphthyridines are formed in one step under complete regio- and stereochemical control [Eq. (24b)] [248b].



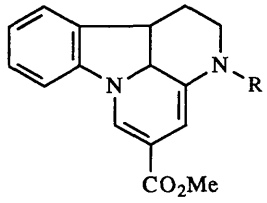
(24b)

Similarly, the cyclopropapyrroloindole **LXVIIa** has been obtained [248c].



(LXVIIIa)

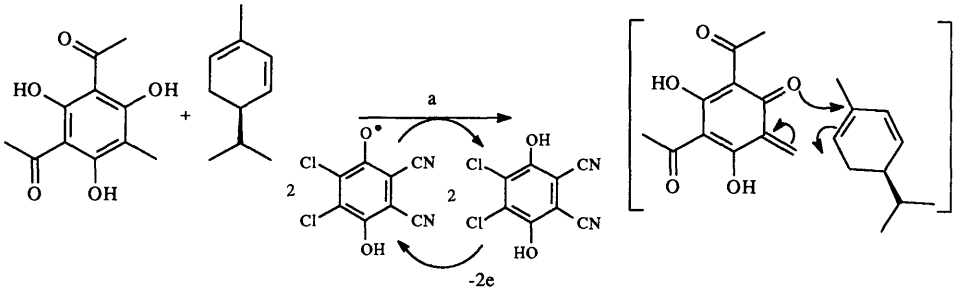
Using this methodology, the cytotoxic alkaloid canthin-6-one **LXVIIIb** has been synthesized in a short sequence with good overall yield [248d].



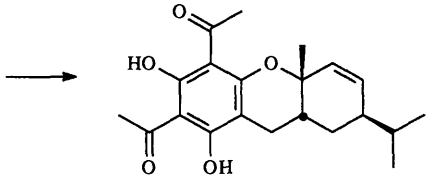
(LXVIIIb)

In other cases the cycloadditions are not electrocatalytic. The reactive intermediates are generated electrochemically and then react with the olefin to an adduct that stabilizes itself by reaction with a nucleophile or by deprotonation. This way *ortho*-phenols react with enols, presumably via an *ortho*-quinone as intermediate (Table 12, number 4).

In the synthesis of a Euglobal skeleton a quinone methide has been generated in situ by anodic oxidation mediated by DDQ. The cycloaddition with unactivated alkenes was promoted by the use of lithium perchlorate/nitromethane and a hydrophobic PTFE-coated electrode (Eq. 24c) [249b].



a : PTFE-coated Pt-electrode

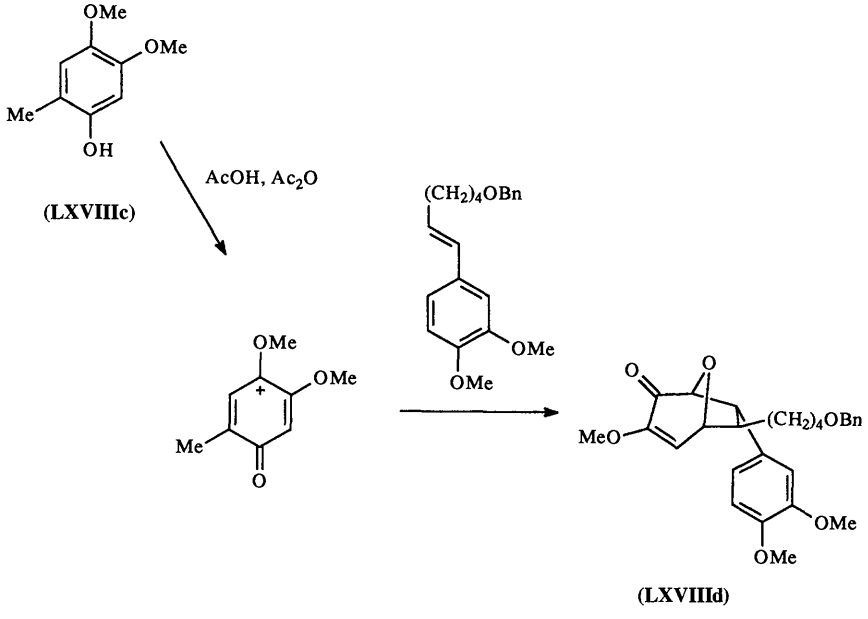


74%

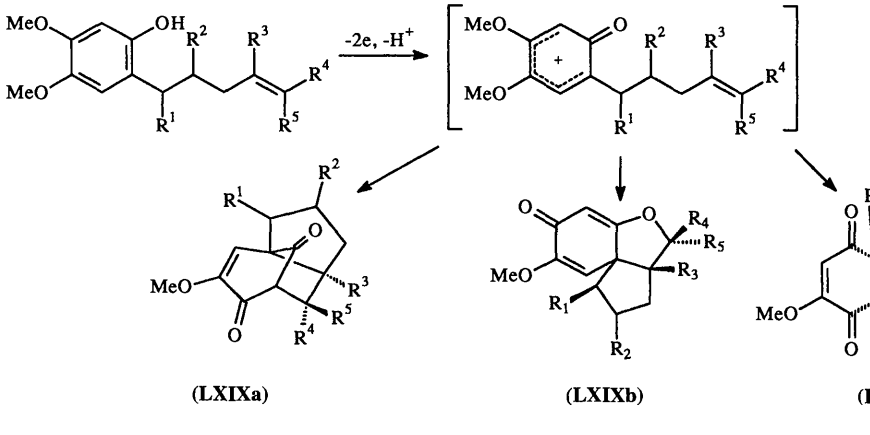
(24*c*)

A cyclohexadienyl cation is obtained from the oxidation of dimethoxyphenol (**LXVIIIc**), which undergoes a cycloaddition with a styrene derivative to afford the bicyclic compound **LXVIIId** in 80% yield [Eq. (25a)] [251].

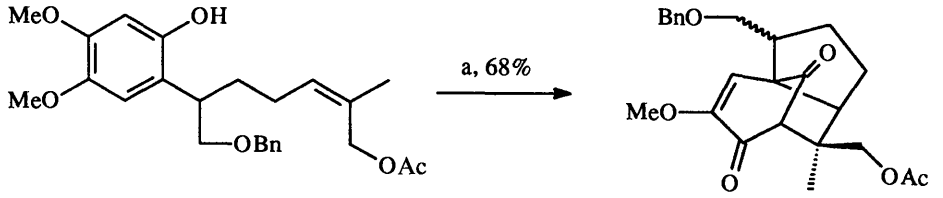
The intramolecular coupling of phenol derivatives with olefins is a very useful C,C-bond-forming reaction. Yamamura has shown that this reaction can lead to three different product types, **LXIX a–c** [Eq. (25b)] [250b]. The three pathways depended strongly on the configuration of the double bond and the nature of the functional groups attached to the double bonds. The different products can be formed quite selectively, as in Eq. (25c) [250c]. Correspondingly tricyclo[5.3.1.0(1,5)]undec-9-en-8,11-diones **LXIXd** and related skeletons have been obtained by an intramolecular cationic [5 + 2]-cycloaddition of substituted phenols initiated by anodic oxidation [250e]. These cyclization products must be regarded as promising synthetic intermediates for a number of sesquiterpenes. The synthetic possibilities have been nicely summarized with some retrosynthetic analyses of the target molecules by Moeller [250d].



(25a)

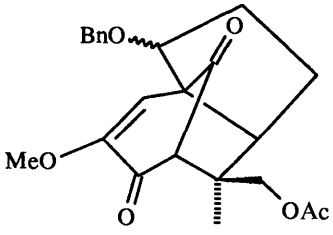


(25b)



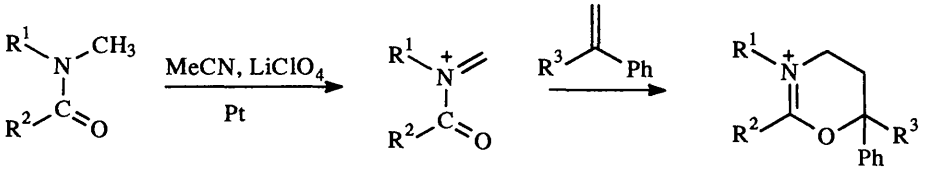
a : -e, Bu_4NBF_4, Ac_2O $\alpha/\beta = 5 : 2$

(25c)



(LXIXd)

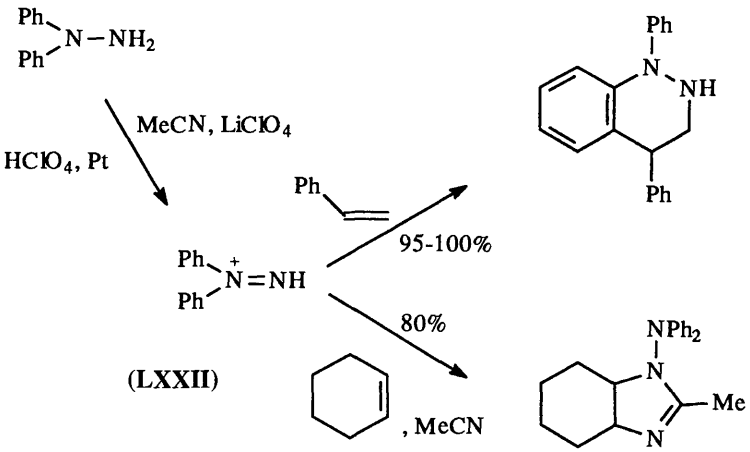
The electrolysis of *N*-methylamides (**LXX**) results in the formation of iminium intermediates that undergo a [4 + 2]-cycloaddition with olefins [Eq. (26)] [252] to afford heterocycles (**LXXI**) in 45–58% yield. 1,1-Diphenylhydrazine can be dehydrogenated to the diazenium ion (**LXXII**) [Eq. (27)], which undergoes cycloadditions with olefins [253].



(LXX) **(LXXI)**

R^1	R^2	R^3
Me	H	Ph
Me	Me	Ph
H	Me	H

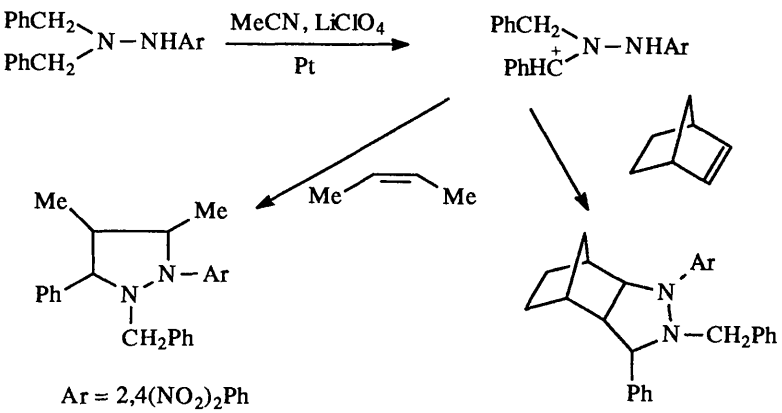
(26)



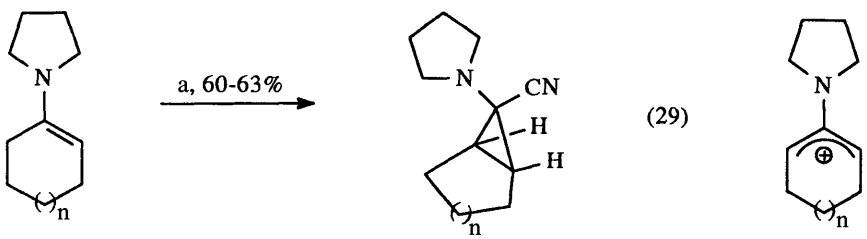
(27)

1,1,2-Triphenylhydrazine reacts in a similar way with enol ethers to cinnoline derivatives (Table 12, number 5). The electrooxidation of *N*-alkylhydrazines leads to an iminium ion, which can react with olefins to five-membered rings [Eq. (28)] [254]. The anodic oxidation of phenylhydrazones of benzaldehyde affords diphenylnitrilimines, which add to dipolarophilic compounds [255].

Anodic oxidation of enamines in NaCN–MeOH with iodide ion as mediator provides ring-fused cyclopropane aminonitriles with the nitrile group exclusively in *exo* position [Eq. (29)] [256]. This reaction is possibly an electrocyclic ring closure of an intermediate allyl cation **LXXIII**.



(28)



(29)

a: 0.3 eq. KI, 2.6 eq. NaCN, MeOH, n=1,2

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23
Cleavages and Deprotection

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I. INTRODUCTION

Electrochemical reactions resulting in cleavage of bonds are synthetically useful in many respects, for example, deprotection of functional groups and generation of reactive intermediates. The bond breakage may occur in concert with electron uptake or in a follow-up reaction. The main types of electrochemical cleavage reactions are described briefly in generalized terms in this section; in Secs. II through XVII the cleavage of the different types of bonds is discussed in more detail. Several of these reactions may be performed by direct as well as by indirect electrolysis.

Reductive cleavage of a bond may occur by addition of an electron to the antibonding orbital of a single bond; in most cases the electron transfer and the breakage of the bond are synchronous, a so-called dissociative electron transfer; only for very strong single bonds (e.g., C–F) may a certain lifetime be found for the initially formed radical anion. Owing to the stretching of the bond and the solvation of the developing ion in the transition state of the electron transfer, the free energy of activation of the reaction is high and requires a considerable overvoltage, and the rate of ET is relatively low. Electrode reactions of this type usually give drawn-out, irreversible voltammetric curves. Typical examples of such reactions are the cleavage of RX [R aliphatic, X a good leaving group such as halogen, NO_2^-, R_2S^+, R_3N^+, or R_3P^+; Eq. (1)], and RY–YR′ [Y = O, S, or Se; Eq. (2)]. The radical formed in the cleavage is usually further reduced.

$$R{-}X + e \longrightarrow R^{\bullet} + X^- \tag{1}$$

$$R{-}Y{-}Y{-}R + e \longrightarrow R{-}Y^{\bullet} + RY^- \tag{2}$$

On accepting an electron, aromatic and heteroaromatic compounds ArX (X being a good leaving group) usually form a radical anion of a certain lifetime. The reorganization energy λ connected with the electron transfer is much lower than for reactions (1) and (2) and the voltammetric curves are more easialy interpretable. This suggests that the electron is transferred primarily to the π-electron system. In some cases, especially with easily reduced compounds, the radical anion is stable, whereas the dianion cleaves, as in Eq. (4):

$$ArX + e \rightleftharpoons [Ar{-}X]^{\bullet -} \longrightarrow Ar^{\bullet} + X^- \tag{3}$$

$$Ar{-}X + e \rightleftharpoons Ar{-}X^{\bullet -} \xrightarrow{e} Ar{-}X^{2-} \longrightarrow Ar^- + X^- \tag{4}$$

Vinylic compounds, as in Eq. (5), and a certain carbonyl derivatives, as in Eq. (6), behave similarly, also with respect to having a low λ value. In Eq. (5), X is a good leaving group; in Eq. (6) Y is OR or NRR′:

$$>C{=}CRX + e \rightleftharpoons [>C{=}CRX]^{\bullet -} \longrightarrow >C{=}\dot{C}R + X^- \tag{5}$$

$$>C{=}\overset{+}{N}H{-}Y + e \rightleftharpoons [>C{=}NH{-}Y]^{\bullet} \longrightarrow >C{=}N^{\bullet} + HY \tag{6}$$

Compounds with suitably substituted carbon atoms α to an unsaturated center, such as a carbon–carbon double bond, an aryl group [Eq. (7)], or a carbonyl group [Eq. (8)], may lose the substituent at a less negative potential than required for the reduction of the

unsaturated center. In these cases it is not clear whether the electron is added to the σ bond or the π-electron system; for most benzyl chlorides the free energy of activation seems more like that of alkyl halides than that of aryl or vinyl halides. This suggests a dissociative ET.

$$ArCH_2X + e \longrightarrow ArCH_2^{\cdot} + X^- \tag{7}$$

$$\begin{matrix} -C- \\ \| \\ O \end{matrix}\!\!-CH_2X + e \longrightarrow \begin{matrix} -C- \\ \| \\ O \end{matrix}\!\!-CH_2^{\cdot} + X^- \tag{8}$$

Some cleavages occur via saturation of a double bond followed by elimination of HX; this is especially found in some substituted heterocycles [Eq. (9)], vinyl compounds [Eq. (10)], and acid derivatives [Eq. (11)]. The product of the elimination reaction may or may not be reduced further at the potential used to reduce the substrate.

$$\underline{\ulcorner C(X)=Y \urcorner} + 2e + 2H^+ \longrightarrow \underline{\ulcorner CH(X)-YH \urcorner} \longrightarrow HX + \underline{\ulcorner CH=Y \urcorner} \tag{9}$$

$$RR'C=CXY + 2e + H^+ \longrightarrow RR'\bar{C}-CHXY \longrightarrow RR'C=CHY + X^- \tag{10}$$

$$\begin{matrix} R-C-X \\ \| \\ Y \end{matrix} + 2e + 2H^+ \longrightarrow \begin{matrix} R-CH-X \\ | \\ YH \end{matrix} \longrightarrow R-CH=Y + HX \tag{11}$$

The reductive cleavage of two bonds and formation of a multiple bond in a concerted or nearly concerted reaction may occur when two good leaving groups are at vicinal atoms:

$$R-CHX-CHY-R' + 2e \longrightarrow RCH=CHR' + X^- + Y^- \tag{12}$$

Reactions (1) through (12) can be performed both by direct and by indirect electrolysis; the following reaction, Eq. (13), is indirect by nature. In reaction (13) hydrogen formed at a catalytically active cathode, such as platinum or Raney nickel, cleaves the bond; in Eq. (13) Y may be OH.

$$\begin{aligned} 2H^+ + 2e &\longrightarrow 2H^{\cdot} \\ 2H^{\cdot} + RY &\longrightarrow RH + HY \end{aligned} \tag{13}$$

A bond cleavage would also occur in an elimination reaction induced by an electrogenerated base (EGB, Chapter 30).

A C–H or Y–H cleavage, which involves a simple acid–base reaction or dissociation of an acidic compound and reduction of the protons thus formed to hydrogen at an electrode with a low hydrogen overvoltage and creation of a base or nucleophile, is not discussed here, (see Chapter 30) [1,2].

Oxidative cleavage may begin with a loss of an electron from a heteroatom or an anion. Removal of an electron creates a radical cation; in the absence of a suitable nucleophile or the possibility of losing a proton, the system may be stabilized by bond cleavage and formation of a double bond in a way similar to that found in mass spectrometry [Eqs. (14) through (17)]. Sulfur is more easily oxidized that nitrogen, which loses an electron more easily than oxygen.

$$RR'CH{-}Y{-}R'' - 2e \longrightarrow RR'C{=}Y + R''^{+} + H^{+}\ (Y = O, NR) \tag{14}$$

$$RR'C(YH){-}C(YH)RR' - 2e \longrightarrow 2RR'C{=}Y + 2H^{+}\ (Y = O, NR) \tag{15}$$

$$R{-}S{-}S{-}R - 2e \longrightarrow 2R{-}S^{+}\ (\text{may add to } C = C) \tag{16}$$

$$R{-}S{-}R' - e \longrightarrow R{-}S^{\bullet} + R'^{+} \longrightarrow (R{-}S{-}S{-}R + R{-}OH + H^{+}) \tag{17}$$

If the radical cation can lose a proton rapidly, the radical thus formed easily loses an electron to a cation, which may cleave or accept a nucleophile.

In Kolbe electrosynthesis the carboxylate ion loses an electron and then carbon dioxide [Eq. (18)]; this reaction is discussed in Chapter 14. A number of electrochemical reactions involve a cleavage of the bond between the central metal atom and one or more ligands. Such reactions are not discussed here.

$$R{-}COO^{-} - e \longrightarrow R^{\bullet} + CO_2 \longrightarrow \tfrac{1}{2}R{-}R + CO_2 \tag{18}$$

There are very few examples of cleavage initiated by loss of an electron from a C=C bond; however, after attack of a nucleophile on the initially formed radical cation, further loss of electrons may result in a cleavage analogous to that described in Eq (15). The special bonds in a cyclopropane ring may lose an electron with formation of a ring-opened radical cation:

$$(CH_2)_3 - e \longrightarrow {}^{\bullet}CH_2CH_2CH_2^{+} \tag{19}$$

II. CARBON–CARBON BOND

Electrolytic cleavage of a carbon–carbon bond may occur in the course of both cathodic and anodic reactions. During an uncontrolled anodic oxidation, many organic compounds end up as carbon dioxide and water, which involves splitting of C–C bonds, but only oxidations in which the reaction does not have the character of an extensive degradation are discussed here. The Kolbe reaction that involves a cleavage of a carbon–carbon bond has been discussed in Chapter 14.

A. By Reduction

Carbon–carbon single bonds may be cleaved when the two carbon atoms bear substituents that sufficiently stabilize the anions formed on the uptake of electrons to make them relatively weak bases. The reduction of ethanetetracarboxylate esters illustrates that; these esters are reducible at rather negative potentials in DMFf–10% water at a mercury cathode at 60–65°C with splitting of the central carbon–carbon bond [3]:

$$(ROOC)_2CR'{-}CR'(COOR)_2 + 2e \longrightarrow 2R'C^{-}(COOR)_2 \tag{20}$$

A similar cleavage occurs on reduction of 9,9′-bianthryl in DMF; in this case the radical anion is stable but the dianion undergoes bond rupture [4]. This reaction is an example of Eq. (4), whereas Eq. (20) is probably an example of Eq. (8).

The reduction of some aryltritylketones in aprotic, deoxygenated DMF [Eq. (21)] is of the same kind. The arylcarbon radical reacts with DMF and eventually forms diaryloxymethane. The primarily formed radical anion is stable on the time scale of cyclic voltammetry but cleaves slowly under preparative conditions. The cleavage is suggested [5] not to be the result of a slow disproportionation of the radical anion and cleavage of the dianion, but a slow splitting of the radical anion:

$$ArCOCPh_3 + e \longrightarrow [ArCOCPh3]^{\cdot-} \longrightarrow ArCO^{\cdot} + Ph_3C^- \qquad (21)$$

The radical anion of benzoylcyclopropane cleaves reversibly, but the ring-opened radical anion reacts with the substrate to dimers or trimers, whereas the radical anion of 2-phenyl benzoylcyclopropane cleaves irreversibly with formation, after further uptake of one electron, of 1,4-diphenyl-1-butanone [6].

Pinacols with at least one electroactive group α to the alcoholic function may be reduced. In protic media there occur cleavages of the C–O and the central C–C bonds with formation of a hydrocarbon; in strongly basic media the pinacol is cleaved by the base to the radical anion of the parent ketone [7,8]. The base may be generated electrochemically.

Cathodic reduction of some aryl-substituted α-diimines or α-diketones in DMF at the potential of the second wave in the presence of dioxygen results in splitting of the central carbon–carbon bond [9,10]. Possibly the dianion of the diimine, like the dianion of some pinacols, is unstable; the radical anions thus formed react with O_2 or $O_2^{\cdot-}$ to the isolated amides. In the case of α-diketones an attack of $O_2^{\cdot-}$ on the carbonyl group followed by cleavage is suggested [10]. Chalchones are similarly cleaved with attack both at the carbonyl group and at the double bond [11]. An oxidative cleavage of the C16–C21 carbon–carbon bond in catharanthine is used in the synthesis of anhydrovinblastine [12]; the reaction is discussed in Chapter 15.

Electrolytic cleavage of a carbon–carbon bond is found in certain aromatic nitriles in which the aromatic ring is π-electron deficient, due to the presence of either a heteroatom in the ring or an electron-attracting substituent on the ring. The driving force for the cleavage is the gain in resonance energy on reestablishing the aromaticity of the ring combined with the stability of the cyanide ion. Whereas 2- and 4-cyanopyridine in acid solution are reduced to aminomethylpyridines, the reduction in alkaline solution yields pyridine and cyanide ions [13,14]. Benzonitriles bearing electron-attracting groups like cyano or carbethoxy groups *meta* or *para* to the cyano group are also cleaved [15,16] with the loss of a cyanide ion.

The electrochemical removal of a cyano group in an aliphatic nitrile is dependent on the electrode material, solvent, and electrolyte; best results were obtained at a zinc cathode in DMF with Et_4NOTs as supporting electrolyte [17].

Reduction of $>C(Me)\text{-}CCl_3$ to $-CCl_2^-$ in 4-methyl-4-trichloromethyl-*p*-quinone-(1)-arylamine results in a loss of dichlorocarbene to a quinoid imine ring with formation of a substituted diphenylamine [18].

Another type of cleavage during electrolysis occurs as a slow step in the reduction of certain β-diketones in DMSO [19]; the primarily formed radical dimerizes to a pinacol that, catalyzed by the base generated during the electrolysis, is cleaved in a reverse aldol condensation to an α-diketone. 1,3-Diphenyl-1,3-propanedione is thus reduced in DMSO according to:

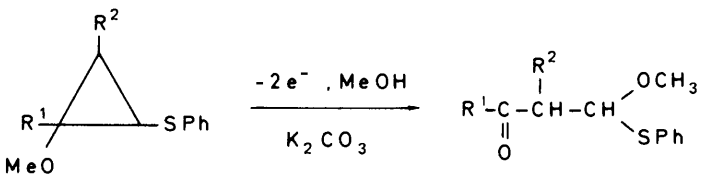
$$2C_6H_5COCH_2COC_6H_5 \xrightarrow{2e + 2HA} [C_6H_5\overset{|}{C}(OH)CH_2COC_6H_5]_2 + 2A^- \xrightarrow{[A^-]} C_6H_5COCOC_6H_5 + 2CH_3COC_6H_5 \quad (22)$$

The benzil is then further reduced to a radical ion.

B. By Oxidation

Cyclopropane rings may be opened on anodic oxidation; which bond is cleaved depends on the substituents and the experimental conditions. Thus 1-ethoxy-7,7-dichlorobicyclo[4.1.0]heptane [20] gives an anodic oxidation in methanol in the presence of lutidine at a carbon anode methyl 7,7-dichlorohept-6-enoate, whereas 7,7-dichloro-1-trimethylsilyloxybicyclo[4.1.0]heptane on oxidation in methanol at −13°C to −10°C in the presence of iron(III) nitrate [21] affords 2-methoxycarbonylcyclohexanone.

Anodic oxidation of 1-methoxy-2-phenylthiocyclopropanes (**I**) [22] in methanol in the presence of potassium carbonate proceeds with ring cleavage between C–1 and C–2; the product is a 2-[methoxy(phenylthio)methyl]-alkanone (**II**):

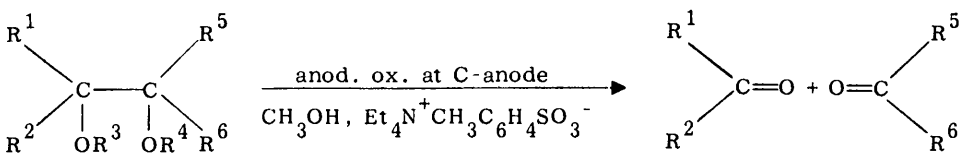


(23)

(**I**) (**II**)

A ring enlargement involving rupture of a cyclopropane ring on anodic oxidation is exemplified in the transformation of bicyclo[4.1.0]heptane-7-carboxylic acid in methanol to 3-methoxycycloheptene [23].

Vicinal glycols, their mono or dialkyl ethers, and β-diethylaminoalcohols can be cleaved at a carbon anode in methanol with TEA-OTs as supporting electrolyte to acetals or carbonyl compounds, as in Eq. (24). The anodic oxidation does not show any of the stereochemical limitations usually observed in the cleavage reaction by chemical oxidizing agents [24]. *Vic*-glycols may also be cleaved by indirect oxidation using a periodate–iodate system as mediator and lead dioxide as anode [25] or by direct oxidation at a PbO_2 electrode at pH 1.2 [26]. A similar oxidative cleavage of aziridines and 2-aminocycloalkanones may be achieved by electrogenerated "Cl^+" [27].

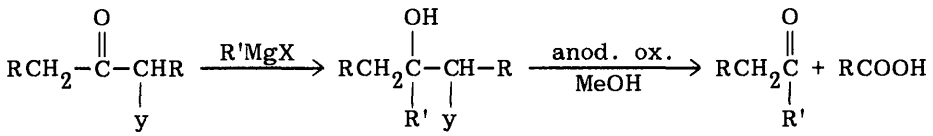


(24)

1-Alkenylarenes may be cleaved at the double bond by oxidation at a DSA or lead anode in methanol or ethanol containing CF_3COONa as electrolyte [28]; the reaction proceeds through an oxidative addition of RO^- to the double bond followed by cleavage to the dialkyl acetal in a reaction similar to Eq. (24).

Symmetrical ketones may be prepared by alkylation of methyl methoxyacetate with a metal-organic compound to a dialkyl methoxymethylcarbinol followed by anodic oxidation [29].

Unsymmetrical ketones can be obtained from symmetrical ketones by anodic oxidation of their enol ethers to the α-methoxy ketone (**III**) [29], reaction with R′MgX, and anodic oxidation of the glycol monomethyl ether. Alternatively, the ketone may be oxidatively aminated, alkylated at C=O, and oxidized (y = OCH_3 or NR_2):



(III)

(25)

Strangely enough, it has been observed that in the oxidation of the racemic and *meso* forms of 4,4′-dihydroxyhydrobenzoin at an anode of mild steel at pH 13.5, only the racemic form was oxidized at a measurable rate to *p*-hydroxybenzaldehyde, whereas the *meso* form was recovered unchanged [30].

Oxiranes may be ring opened in acidic methanol to α-methoxy alcohols, which can be cleaved anodically. This has been used to transform a propylene side chain to an aldehyde [31]. β-Hydroxyhydroxylamines may be cleaved to aldehydes and oximes on anodic oxidation at pH 8. [32]:

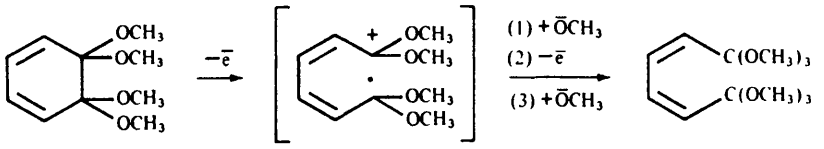
$$\mathrm{R{-}CHOH{-}CR'R''{-}NHOH} \xrightarrow[\text{pH 8}]{-2e-2H^+} \mathrm{RCHO + R'R''C{=}NOH} \tag{26}$$

One way of avoiding an extensive anodic degradation of organic compounds is to use acetone as a modifying medium, which is also well known from chemical oxidations, as with $KMnO_4$. Benzoin [33] is thus, in sulfuric acid–acetone containing some water cleaved mainly to benzaldehyde (35%) and benzoic acid (45%); a small amount of benzil (5%) and tar (10%) is also formed. Benzil is apparently not an intermediate, as only benzoic acid (67%) was obtained from oxidation of benzil under similar conditions [33]:

$$\mathrm{C_6H_5CHOHCOC_6H_5} \xrightarrow{-2e^- - 2H^+} \mathrm{C_6H_5CHO + [C_6H_5CO^+]} \xrightarrow{H_2O} \mathrm{C_6H_5CHO + C_6H_5COOH} \tag{27}$$

Vicinally tri- or tetramethoxy compounds may also be cleaved anodically. Thus 1,1,2-trimethoxycyclohexane obtained on electrooxidation of cyclohexanone enol ether may be oxidized to the acetal ester, $(CH_3O)_2CH(CH_2)_4\ COOCH_3$ [34].

Oxidation of resorcinol dimethyl ether [35] in methanolic KOH produces among other products 5,5,6,6-tetramethoxy-1,3-cyclohexadiene (IV), and hexamethyl *cis,cis*-orthomuconate (**V**); (**V**) could be obtained from (**IV**) in 77% yield on anodic oxidation, conceivably according to:



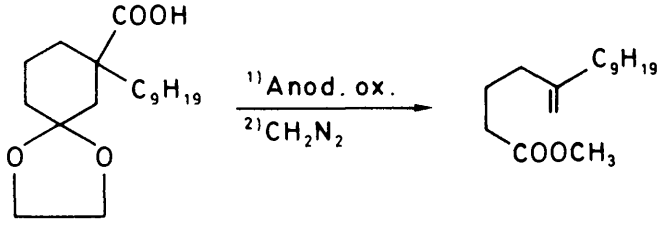
(28)

(IV) (V)

It is noteworthy that only the least stable *cis,cis* isomer is formed; this indicates that the intermediates are short-lived and/or adsorbed on the electrode during the fixation of the geometry of the product.

A Kolbe electrolysis of a vicinal decarboxylic acid, also referred to as anodic bis-decarboxylation, may be used for introducing a double bond; an example is the transformation of 2-aza-3-oxobicyclo[2.2.2]oct-7-en-5,6-dicarboxylic acid to 2-azabicyclo[2.2.2]octa-5,7-dien-3-one [36].

In a similar way, 1-nonyl-3-oxocyclohexanecarboxylic acid ethylene ketal (**VI**) has been ring opened [37] to methyl 5-nonyl-5-hexenoate (**VII**) by anodic oxidation at a C anode in methanol containing K_2CO_3:



(29)

(VI) (VII)

Ketones with branching in the α position may be anodically cleaved at a platinum electrode in CH_3CN–$LiClO_4$ [38]. A mechanism was proposed that involved generation of carbenium ion on α cleavage of the ketone radical cation, analogous to reactions in photochemistry and mass spectroscopy:

$$R_3CCOCH_3 \xrightarrow{2e^-} R_3C^+ + CH_3CO^+ \xrightarrow[H_2O]{CH_3CN} R_3CNHCOCH_3 + CH_3COOH \qquad (30)$$

Some reductively dimerized nitrogen heterocycles are oxidized anodically to their parent compounds with rupture of the C–C bond; thus the dimerized product from reduction of acridizinium may be oxidized to acridizinium [39].

III. CARBON–OXYGEN BOND

A. By Reduction

Reductive cleavage of a C–O bond requires activation of the bond; such activation can be obtained in different ways. Conjugated carbinols, like allylic and benzylic alcohols, π-electron-deficient heterocyclic carbinols, and α-hydroxyketones and the ethers of these compounds, may be reductively cleaved. Reductive elimination of two vicinal hydroxyl groups or derivatives thereof may also be possible. These reactions have been exploited in the electrochemical removal of protecting groups [40,41].

Unactivated aliphatic and aromatic hydroxyl groups may be reductively removed after esterification with a suitable inorganic acid whereby the hydroxyl group is transformed into a better leaving group. Thus the reduction of an aliphatic alcohol into an alkane may be done in a high yield by preparing the methanesulfonate of the alcohol and reducing it in DMF–Bu_4N^+ salt at a lead cathode at a rather negative potential [42]. Alternatively, the alcohol may be transformed into a reducible alkyl halide.

Esters of aromatic acids and alcohols are usually on reduction cleaved to aryl carboxylate and alkyl radical, which may be reduced to the anion and protonated to the hydrocarbon [43,44]. The influence of EGB should be considered when an acid is used as protecting group. Acyl derivatives of phenols as a rule cleaves between the carbonyl group and oxygen to phenolate and acyl radical, and may thus be used for protection of a phenol. The fate of the acyl radical is not clear; a dimerization to a diketone has been suggested [45,46]. Such a ketone would be more easily reduced than the ester and possibly attacked by the EGB [47]. The radical anion of some easily reducible esters (e.g., esters of 4-nitrobenzoic acid) cleaves very slowly, but the dianion usually cleaves fast [46].

Acylphosphonium salts, obtained by constant current electrolysis of Ph_3P in the presence of a carboxylic acid in CH_2Cl_2, are reduced with cleavage between the carbonyl carbon and the oxygen; when using Ph_3Ph^+ ClO_4^- as supporting electrolyte this cleavage has been used for the transformation of α-amino acids to α-amino aldehydes; paired electrolysis in MeCN containing R_3P and Et_4NBr may deoxygenate primary and secondary alcohols to alkanes [48].

Aromatic hydroxyl groups may be removed after transformation into an aryl diethyl phosphate, which can be electrochemically cleaved [49]:

$$\mathrm{ArOH} \longrightarrow \mathrm{ArOP(=O)(OEt)_2} \xrightarrow[\mathrm{DMF}]{2e^- + H^+} \mathrm{ArH} + {}^-\mathrm{OP(=O)(OEt)_2} \tag{31}$$

The radical anion of diphenyl ether [50] and of some substituted diphenyl and naphthyl ethers [51] have been found to cleave slowly in DMF to aryl radical and phenoxide ion.

1. Conjugated Carbinols

α,β-Unsaturated alcohols and their derivatives can be cleaved by direct electrolysis [52,53], electrocatalytically at a platinized platinum electrode in acidic medium [54,55], and by indirect electrolysis [56]. In protic medium, direct electrocatalytic reduction usually results in formation of the saturated alcohol or hydrocarbon, whereas indirect reduction using iodide as mediator [56] gives the alkene; in electrocatalytic reduction the rupture of the C–O bond precedes the saturation of the double bond. In aprotic medium (e.g., DMF), the primarily formed radical anion is cleaved with loss of the oxygen function.

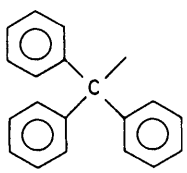
Indirect electrolysis of allyl alcohols can be performed at a mercury electrode at a rather positive potential [−0.2 V (SCE)], and high current densities may be used (10–20 A dm^{-2}). The first step is a transformation of the alcohol to an iodide; the double bond is shifted to the terminal position, even if it means breaking a conjugation with a phenyl ring [56]. A 20:1 mixture of 1-butene and 2-butene was obtained from crotyl alcohol:

$$\mathrm{CH_3CH{=}CH{-}CH_2OH} \xrightarrow[40-60°\mathrm{C,\ Hg}]{6\ N\ \mathrm{HCl,\ KI}} \mathrm{CH_3CH_2CH{=}CH_2} \tag{32}$$

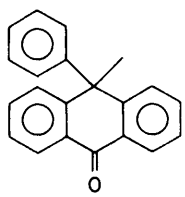
Allyl carboxylates can be reductively cleaved to carboxylic acids using a Pd^0 catalyst [57] and allyl ethers to phenols using a $Ni(bipy)_3$ catalyst [58]; both reactions may be used for deprotection. Propargyl acetates has been reductively cleaved to the corresponding allenes in the presence of a catalytic amount of $PdCl_2(PPh_3)_2/PPh_3$ in DMF. An *n*-value less than 2 suggested that PPh_3 acted as reducing agent through formation of an acetyltriphenylphosphonium salt, which was hydrolyzed to triphenylphosphine oxide [57].

Carbinols conjugated with aromatic systems, such as benzylic alcohols [59–62], trityl (**VIII**), tritylone (**IX**), and benzhydryl alcohols [59,62,63], and 9-hydroxy-9-phenylanthrone, heteroaromatic systems [64], α-hydroxy ketones [65–67], α-hydroxy acids, and their derivatives [68–70] can also be cleaved at potentials less negative than that of the activating group. Thus the radical anion of benzyl benzoate cleaves rapidly to benzoate and benzyl radical, which is reduced to the anion; protonation leads to toluene. In the absence of added proton donor, the base generated during the reduction (EGB) may cleave the ester to benzoate and benzyl alcohol [44].

The *N*-benzyloxycarbonyl group, which cannot be removed electrochemically in methanol, may be cleaved in DMF [40]. ψ-esters, such *o*-benzoylbenzoic acid ψ-ethyl ester, which is an acylated ketal of a benzophenone, may be reduced in an acetate buffer to a phthalide [71].



(VIII)



(IX)

All these systems may be used as protecting groups for alcohol functions, and the choice between them will depend, among other things, on the presence of electrophores in the protected molecule. It is usually possible to find a protecting system that is cleaved at a less negative potential than the electrophores in the protected system; otherwise, introduction of an electron-withdrawing substituent in the protecting group may be necessary. Resistance toward acid hydrolysis and a hydrogenation are considerations to be taken into account when choosing a suitable protecting group.

The relative abilities of the leaving groups in the cathodic cleavage of *p*-methoxycarbonylbenzyl carboxylates have been measured in a DMF acetate buffer. There seemed to be no recognizable correlation between the relative rate of cleavage and either the pK_a of the conjugate acid of the leaving anion or the peak potential in cyclic voltammetry [61].

In all these cases the electron is probably initially added to the π-electron system; the molecule is then stabilized by a follow-up reaction involving the expulsion of a negatively charged oxygen-containing species.

2. α-Substituted Alcohols

Reductive elimination of X and Y, as X^- amd Y^-, from $RR^1CX\text{-}CYR^2R^3$ or $RR^1CXCH_2CYR^2R^3$, where X^- and Y^- are reasonably good leaving groups, may lead to the formation of alkenes or cyclopropanes. Here some reductive eliminations are dis-

cussed in which X is an oxygen function and Y is oxygen or another heteroatom, regardless of whether C–Y is more easily cleaved than C–X.

Vicinal dioxalates are cleaved electrochemically to alkenes in DMF at a less negative potential (~ −1.2 V vs. Ag/AgI) than vicinal diacetates or diols [72,73]. Oxalic esters of monohydric alcohols give quasi-reversible peaks in cyclic voltammetry, whereas oxalates of vicinal diols give irreversible peaks. Oxalates of the diols may be formed through a rapid, base-catalyzed transesterification using diethyl oxalate, for example [74].

Cyclic sulfates of unactivated diols, such as 2,3-butanediol, are reduced in DMF/0.4 *M* Et_4NClO_4 at a mercury electrode at potentials less negative than the background reduction; 2-butene (*cis–trans*, 5:95) was formed in moderate yields, $n = 1$; minor amounts of several unidentified compounds were seen in GLC [75].

Phenyl-substituted oxiranes may be reduced in DMF akin to benzyl ethers by direct and indirect methods; the regioselectivity is slightly higher in the indirect reduction [76]. Benzoyloxiranes can be reduced in MeCN to aldoles; addition of acetic acid prevents a retroaldol reaction catalyzed by the EGB [77]. The ring opening is analogous to the reduction of 2-alkoxyacetophenone to acetophenone.

Highly aryl-substituted oxiranes can be reduced in DMF, partly to the alkene; the reduction potential is more negative than that of the resulting alkene, so the yield of alkene is moderate [75]. Oxiranes activated by an α-carbonyl group may be reduced to the β-hydroxyketone. Epoxypregnone is thus reduced to 16-hydroxypregnone in 75% aqueous ethanol containing a catalytic amount of hydrogen bromide [78].

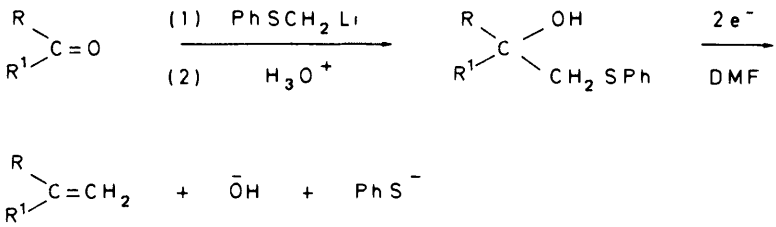
A slow cleavage of a benzylic C–O bond is observed in the reduction in DMF of 2-disubstituted 4-(4′-nitrophenyl)-1,3-dioxolanes and dioxanes; the hemiketal thus formed is hydrolyzed to the ketone so these compounds may be used as protecting groups for ketones. On preparative reduction besides ketone some side products, formed by attack by the EGB promoted substrate anion on DMF, were isolated [79].

2-haloethyl derivatives are reducible at different potentials, depending on the number and kind of halogens substituted at C–2. The reduction can be made in methanol with $LiClO_4$ as supporting electrolyte according to Eq. (33) [80]:

$$\begin{array}{l} \mathrm{PhCOOCH_2CCl_3} \xrightarrow{2e^-} \mathrm{PhCOOCH_2CCl_2^-} \xrightarrow[(H^+)]{} \\ \quad \mathrm{PhCOO^-} + \mathrm{CH_2{=}CCl_2} + \mathrm{PhCO_2CH_2CHCl_2} \\ \quad\quad 87\% \qquad\qquad\qquad 6\% \end{array} \tag{33}$$

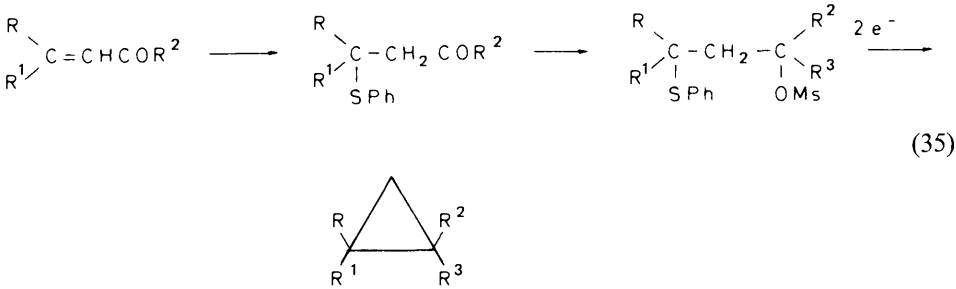
This kind of protecting group has been employed during a nucleotide synthesis using the triester method, in which the problem was the selective cleavage of one of the ester groups. The 5-trityl-protected nucleoside was first treated with 2,2,2-trichloroethylphosphoric acid dichloride and then with 2,2,2-tribromoethanol. On electrochemical reduction in acetonitrile the latter group could be removed selectively, whereas the detritylation could be done with 1% trifluoroacetic acid in methylene chloride [69].

The preparation of olefins by reductive elimination has been exploited in several cases. Thus the elimination of the hydroxyl and phenylthio groups from β-hydroxysulfides is a convenient route to olefins [81]:



(34)

A Michael addition of thiophenol to an α,β-unsaturated carbonyl compound, followed by sodium borohydride reduction or addition of a metal–organic reagent, gives a γ-phenylthioalcohol; electrochemical reduction in dry DMF of the methanesulfonate of this alcohol yields a cyclopropane and a small amount of alkene [81]:



(35)

Aldehydes may be prepared from the lower homolog or a ketone or ester by reaction with the anion of formaldehyde mono- or dithioacetal. The β-hydroxythioacetal may be reduced with elimination of a hydroxyl group and phenylthiolate. The resulting enol ether or thioenol ether can be transformed into an aldehyde on acid hydrolysis or reaction with mercuric chloride [82].

During the reduction of 2-phenylthio-1,2-diphenylethanol, the stilbene obtained by the reductive elimination is more easily reducible than the substrate; it is consequently reduced to its radical anion, which in a catalytic reduction with solution electron transfer reduces the substrate [83].

A transformation of an ester group into a vinylic group may be accomplished by reacting the ester with *p*-tolylsulfonylmethylmagnesium iodide followed by $NaBH_4$ reduction to the β-hydroxysulfones; cathodic reduction in DMF at a lead cathode produces the vinylic compound in good yield [84].

Aldehydes may be condensed with a nitroalkane and the resulting vicinal nitroalcohol reduced to an alkene after acylation of the alcohol [85].

The reduction of some β-hydroxysulfones depends on proton activity [86]; when the proton concentration is too high, the carbanion produced after uptake of two electrons is protonated and no elimination occurs. In aprotic media the electrogenerated base may lead to a retrocondensation reaction of the β-hydroxylsulfones to a sulfone and a ketone; for β-acetoxysulfones a base-catalyzed elimination may occur. The presence of a weak proton donor like phenol may thus be advisable in such cases.

1,2-Disubstituted alkenes can undergo reductive elimination to acetylenes; 1,2-diacetoxy-1,2-diphenylethylene may thus be reduced to diphenylacetylene in DMF at a mercury cathode [87]. In more protic media the diphenylacetylene is further reduced. A similar

cleavage occurs during the reduction of aromatic dithio and thiol esters to diarylacetylenes [88].

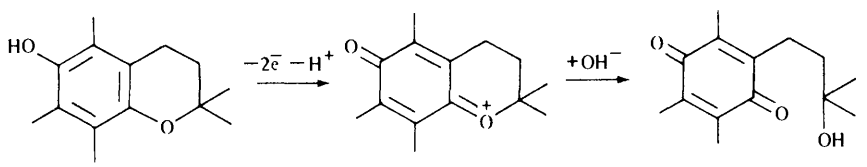
3. Nitroalkoxybenzenes

As described in Chapter 9, certain nitroalkoxybenzenes lose the alkyl group during reduction [89] owing to a nucleophilic attack by water. The mechanism of the loss during this reduction and during the oxidation of alkoxybenzenes is similar; in both reactions the essential intermediate has a quinonoid structure, which is attacked by water.

B. By Oxidation

It was an early observation [90] that both hydroquinone mono- and dimethyl ethers on anodic oxidation in dilute sulfuric acid yield quinone, which probably results from a nucleophilic attack by water on the primary oxidation product. Similarly, the oxidation of dimethoxydurene [91] in acetonitrile produced duroquinone rather than a side-chain oxidation product similar to that obtained from *p*-methoxytoluene.

A special reaction of this type is the oxidation of 2,2,5,7,8-pentamethyl-6-hydroxychromane (**X**) for which the following reaction was suggested [92] on the basis of polarographic data:



(**X**) (36)

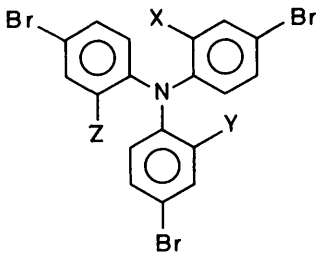
Later the reaction was proved by controlled-potential oxidation to be reversible in acetonitrile–acetic acid containing sodium acetate [93].

A suitable substituted acylated enol may be oxidized similarly; in the radical cation of such acylated enols the CO–O bond cleaves; the rate of cleavage is significantly higher in MeCN than in CH_2Cl_2 [94].

Benzyl alcohols [95] and ethers [96] may be oxidized anodically. This has been employed in an anodic removal of benzylic protecting groups. Anisyl ethers of the protected alcohols were preferred because of the relatively low oxidation potential of these ethers [1.65 V (SCE)] [97]:

$$CH_3OC_6H_4CH_2OR \xrightarrow[-2e^- - 2H^+ + H_2O]{\text{aq. } CH_3CN} CH_3OC_6H_4CHO + ROH \qquad (37)$$

The cleavage of *p*-methoxybenzyl ethers may be done indirectly using the stable cation radical of tris(*p*-bromophenyl)amine (**XIa**) as a mediator in acetonitrile containing some base (2,6-dimethylpyridine or $NaHCO_3$) [98, 99]; the reaction occurs under mild conditions. Benzyl ethers cannot be cleaved by **XIa**, but radical cations of more highly brominated triphenylamines (**XIb**, **c**, and **d**) can cleave these ethers [99]. It is thus possible to deprotect selectively groups that are protected by differently substituted benzyl groups by using different brominated derivatives of **XI**; the more bromine in the triphenylamine, the higher is its oxidation potential. Alternatively, metal-organic compounds such as dioxo-bridged binuclear manganese compounds, may be used as mediator in MeCN [100].



(XI)

a X = Y = Z = H
b X = Y = H Z = Br
c X = H Y = Z = Br
d X = Y = Z = Br

Protected carbonyl groups such as a 4-phenyl-1,3-dioxolane may be deprotected by indirect oxidation in MeCN containing pyridine with *N*-hydroxyphthalimide as mediator [101].

IV. CARBON–SULFUR BOND

A. Sulfonium Compounds

Sulfonium salts are electrochemically reducible in both aqueous and aprotic media with cleavage of a carbon–sulfur bond; the electrochemistry of sulfonium salts has been reviewed [102,103]. The mechanism of the reduction has been discussed in several papers.

Colichman and Love [104] assumed a one-step, two-electron cleavage to the sulfide and a carbanion, but later studies pointed to a cleavage after the uptake of one electron [105,106]. In trialkylsulfonium salts a dissociative electron uptake probably takes place, whereas in aryl dialkylsulfonium salts the reduction may be a sulfur–carbon bond breaking concomitantly with the electron uptake [106] or the sulfaranyl radical, formed by addition of an electron to the aryl π-system, may have a certain lifetime [107]. In favor of the former possibility, it is argued that the E_p values in CV are very sensitive to the electronegativity of the fragmenting radical.

The leaving group ability of different substituents in the reduction of sulfonium salts has been studied in water and MeCN [108] at a mercury electrode and in THF using potassium in graphite, KC_8 [107]. In water and MeCN [108], methyl is preferentially cleaved, which is in contrast to the findings for phosphonium or arsonium salts; in THF with electron transfer from KC_8, the following leaving group propensity was found [107]: benzyl > secondary > primary > methyl > phenyl.

Reduction of simple sulfonium salts in an aprotic solvent such as DMF at an Hg electrode at −20°C, gives a compound that has been described as an amalgam; at higher temperatures it decomposes [109]. The nature of these "amalgams" and the corresponding compounds obtained from quaternary ammonium compounds is discussed in Chapter 28.

Sulfonium salts undergo generally a coulometric two-electron reduction to sulfide and an anion; attempts to use the anion in a Michael condensation with acrylonitrile gave only moderate yields [110]. The formation of a basic anion may also be responsible for the formation of ylids [111,112,114] during the reduction of certain sulfonium salts. The reactions are probably, taking benzyldimethylsulfonium salt as an example:

$$PhCH_2\overset{+}{S}Me_2 + e^- \longrightarrow Me_2S + PhCH_2^{\bullet} \xrightarrow{e^-} Me_2S + PhCH_2^- \qquad (38)$$

$$PhCH_2\overset{+}{S}Me_2 + PhCH_2^- \longrightarrow Ph\overset{-}{C}H-\overset{+}{S}Me_2 + PhCH_3 \quad (39)$$

The formation of the benzyl radical, as in Eq. (38), is made likely by the finding of a small yield of 1,2-diphenylethane [111,112] and that 4-nitrobenzyldimethylsulfonium salts give good yields of 4,4-dinitrobibenzyl on reduction at a mercury cathode [113]. Arylsulfonium salts are cleaved more slowly than alkylsulfonium salts; in some cases a reversible ET is indicated by CV [114].

The indirect reduction of *t*-butyldimethylsulfonium perchlorate using the anion of 1,4-dihydro-1-methylpyridine as mediator to dimethyl sulfide and 4-*t*-butyl-1,4-dihydro-1-methylpyridine has been important for the understanding of electron transfer in the aliphatisk nucleophilic substitution [115].

The reduction products from triphenylsulfonium ions depend on the electrode material and the potential [116–118]. Electrolysis of tirphenylsulfonium bromide at a mercury electrode at the potential of the first wave quantitatively yields diphenylsulfide and diphenylmercury. No benzene or diphenyl is formed. At potentials more negative than the second reduction wave, diphenylsulfide and benzene are formed quantitatively, provided low substrate concentrations are used. With increasing substrate concentration the yield of diphenylmercury increases at the expense of benzene. Reduction in aqueous solution at an aluminum cathode produces diphenylsulfide and some benzene; addition of DMF increases the yield of benzene, as DMF is as a better hydrogen atom donor than water [117].

B. Thioethers and Sulfoxides

Unconjugated thioethers are not reducible in aqueous solution; in aprotic solvents alkyl aryl sulfides, ArSR, are reducible at relatively negative potentials (~ -2.5 V (SCE)) [118] with C–S cleavage to ArS^- and R·; the latter may be reduced further. Reduction of diphenylsulfide gives equal amounts of benzene and thiophenoxide ion:

$$C_6H_5SC_6H_5 + 2e^- + H^+ \longrightarrow C_6H_5S^- + C_6H_6 \quad (40)$$

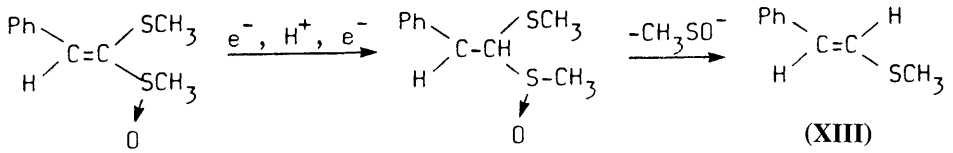
Phenacyl phenyl sulfide can be reduced in aqueous-alcoholic medium to acetophenone and thiophenol [119]; this is analogous to several other phenacyl derivatives; see Eq. (8). This reaction has been used to cleave some phenacylthio-substituted thiophenes by reduction at a mercury cathode in DMF containing 2 Eq. phenol [120].

A number of other groups can be used for the protection of thiols; benzyl thioethers of amino acids and peptides have been cleaved electrochemically at a platinum cathode in liquid ammonia [121], at mercury in MeOH–TMACl [122], and in DMF [123,124], and the trityl group has been used to protect cysteine; cysteine was recovered in 90% yield after reduction in DMF [124]. The 4-pyridylmethyl [125,126] and diphenyl-4-pyridylmethyl groups can be cleaved in acid solution [124] at a mercury cathode.

Reductive cleavage of β-ketosulfoxides is a practical way of preparing methylketones [127]; thus phenacylmethylsulfoxide, as in Eq. (41), gives acetophenone (74% yield) on reduction at a mercury cathode:

$$RC_6H_4COCH_2SOCH_3 + 2e + H^+ \longrightarrow RC_6H_4COCH_3 + CH_3SO^- \quad (41)$$

Reduction of (*E*)-1-methylsulfinyl-1-methylthio-2-phenylethene (**XII**) and 1-methylthio-*p*-tolylsulfonyl-2-arylethenes in acetonitrile with excess of phenol involves a selective cleavage of one C–S bond, resulting in formation of (*E*)-1-methylthio-2-phenylethene (**XIII**). The dependence of the CV curves on the phenol-substrate ratio and stereochemical considerations suggested [128,129] an ECEC reaction:



(**XII**) (**XIII**)

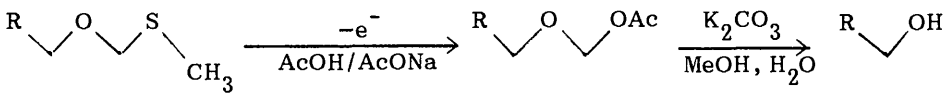
(42)

Reduction of the vinylic *gem*-disulfide (**XIV**) in the presence of CO_2 yields the carboxylated compound (**XV**) [130] described as an addition–elimination ECEC reaction.

(**XIV**) (**XV**)

Anodic oxidation of thioethers usually attacks the sulfur with formation of sulfoxides, sulfones, or sulfonates (Chapter 17). If R in ArSR is a good leaving group, oxidation in acetonitrile may lead to rupture of the C–S bond; $PhSCPh_3$ is thus oxidized [131] with formation of 48% PhS–SPh.

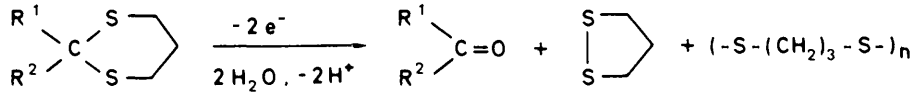
The methylthiomethyl group is used as a protecting group of hydroxy functions. A deprotection can be carried out by electrolysis in an undivided cell with Pt electrodes in AcOH containing NaOAc. The resulting acetoxymethyl ether can be hydrolyzed in weakly alkaline medium [Eq. (43)] to the hydroxy function [132]:



(43)

Electrooxidative desulfenylation of Michael-type thiol adducts of activated olefins may be performed in ethanol with TBABr as supporting electrolyte in an undivided cell at platinum electrodes. The activated olefin is formed in excellent yield; most of the sulfur is found as sulfinate [133].

gem-Disulfides can be oxidized anodically with cleavage of the carbon–sulfur bond [134–138]; in the presence of water a carbonyl group is formed. This has been utilized for the removal of the 1,3-dithian protecting group [136]; the 1,3-dithian derivative is oxidized anodically at a platinum electrode in aqueous acetonitrile according to:



(44)

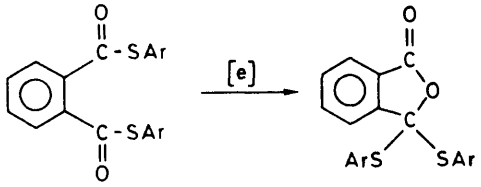
Esters of β-*t*-butylthioalcohols afford the acid on anodic oxidation in MeCN/H_2O [138].

Indirect anodic cleavage of 1,3-dithianes can be done using tris(*p*-tolyl)-amine as electron transfer agent in acetonitrile-$LiClO_4$ containing $NaHCO_3$; the yields of recovered carbonyl compound were almost quantitative [139,140]

C. Thiol Esters and Thiocyanates

Thiol esters are reduced at less negative potentials than carboxylic esters and can be cleaved in protic (e.g., methanol) [141] or aprotic [123, 142] media. Aroyl and benzyloxycarbonyl groups may thus be used for protection of sulfhydryl groups; in MeCN the radical anion of an arylthioic *S*-ester is usually cleaved to alkylthiolate and aryl radical; if it is relatively stable (minutes) it reacts eventually with oxygen with formation of an arylcarboxylate [43].

Cleavage of a C–S bond in the initially formed radical anion has been shown to be the first chemical step in the electrochemically induced rearrangement of *S*, *S*-diarylbenzene-1,2-dicarbothioates (**XVI**) to 3,3-bis(arylthio)phthalides (**XVII**) in DMF, as in Eq. (45). The reaction could be effected with 0.1 F mol^{-1} and was considered a kind of internal $S_{RN}1$ reaction [143].



(XVI) (XVII)

(45)

S-*tert*-butyl thioates can be deprotected by indirect electrochemical oxidation using bromide/bromine as mediator; the reaction probably goes through a bromosulfonium intermediate. By direct anodic oxidation, 4-methoxyphenylthiomethyl esters are readily converted to carboxylic acids. The initially formed radical cation cleaves on reaction with water to the acylated hemiacetal and further to the acid [144,145].

Triarylamine radical cations may also be used in an indirect electrochemical oxidative cleavage of thiol esters [142]:

$$R{-}CO{-}SR' \xrightarrow[MeCN/H_2O/Na_2CO_3]{Ar_3N^{+}} RCOOH + R'S{-}SR' \qquad (46)$$

Dialkyl, alkyl aryl, and diaryl trithiocarbonates are reduced in DMF to the radical anion, which loses a thiolate ion [146–148]. The rate of the cleavage was measured with CV; for substituted diphenyltrithiocarbonates, the rate constant of the cleavage was found to vary linearly with Hammett's substituent constant σ. The anion radicals of mono- and

dithiocarbonates having a carbonyl group were cleaved faster than those possessing a thiocarbonyl group.

Two types of electrode reactions were found in the reduction of thiocyanates. 2-Thiocyanatocacetophenones [119] are reduced in a two-electron reduction to the acetophenone and thiocyanate ion. In most other thiocyanates the reduction results in the loss of a cyanide ion; the half-wave potential is nearly independent of pH. Macroscale reductions at a mercury cathode yielded [149] the mercaptan.

D. Sulfones

Simple aliphatic sulfones, RSO_2R', are polarographically inactive both in protic and aprotic media; methylene disulfones are, however, reducible in DMF at potentials close to the decomposition potential of the medium. β-Disulfones and benzyl sulfones are rather acidic and may function as proton donors during the reduction, and their anions are generally not reducible [150]. Alkyl aryl sulfones and diaryl sulfones are reducible under protic and aprotic conditions [151–154]; during the reduction of long chain aryl alkyl sulfones the EGB may induce a β-cleavage, and in some cases dimerized products are observed [155]. The electrochemistry of sulfones has been reviewed by Chambers [103] and Simonet [156].

On reduction of alkyl aryl sulfones in methanol containing TMACl at a mercury electrode, the cleavage usually but not always [158,159] takes place between sulfur and the alkyl group [154–160] with formation of an arylsulfinic acid:

$$ArSO_2R + 2e + H^+ \longrightarrow ArSO_2^- + RH \tag{47}$$

The propensity to act as a leaving group in diaryl sulfones or alkyl aryl sulfones is benzyl ~ allyl > alkyl > phenyl [154–157]. In unsymmetrically substituted diaryl sulfones, both steric and electronic effects play a role; substituents in the *ortho* position promote cleavage of the neighboring C–S bond, probably by hindrance of the conjugation of the aromatic ring with the sulfone group. Thus, phenyl-2,4,6-trimethylphenylsulfone is reduced to 80% benzenesulfinic acid and 88% mesitylene [154] in methanol, and methyl-*o*-*tert*-butylphenyl sulfone is reduced predominantly (>90%) with aryl–sulfur cleavage [158].

The general rule for the electronic effects on the reductive cleavage seems to be that the aryl group with the strongest conjugation to the electron-attracting sulfone group would then promote a retention of the Ar–S bond; in the reduction of phenyl *p*-methoxyphenylsulfone in methanol [144], 16% anisole and 54% benzene are formed. Electron-attracting substituents would then be expected to promote splitting of the Ar–Sr bond; in this connection it is of interest that methyl 4-cyanophenyl sulfone, for example, is cleaved in aqueous ethanol at pH 9.3 at a mercury cathode to benzonitrile and methylsulfinic acid [161]. In accordance with that, arylalkylsulfones where the aryl is a π-electron-poor N-heterocycle form relatively stable radical anions, which are cleaved preferentially to alkylsulfinate and aryl radical. This gives a convenient route to alkylsulfinic acids and thus to alkylsulfones with two different alkyl groups [162a]. The electrochemistry of α,β-unsaturated sulfones is complicated by the electrogenerated base; isomerization to allyl sulfones and Michael addition of the sulfone anion to the substrate may occur [162b].

Substituted 1,2-bis(phenylsulfonyl)benzenes are cleaved in a one-electron reaction with loss of phenylsulfinate. The substituted aryl radical may react with formation of derivatives of dibenzothiophene and other products [163]. 1,4-Bis(alkylsulfonyl)benzenes

form in DMF a rather stable radical anion; fragmentation leads to 1-alkylsulfonyl-4-alkyl benzenes by *ipso* substitution and 4-alkylsulfonylphenoxy ions [159].

Surprisingly, bulky hexa(alkylsulfonyl)benzenes are reduced in CV in an irreversible reaction; it has been suggested that a conformational change of the radical anion is responsible for the observed irreversibility [164].

In the selective removal of an allylic benzenesulfonyl group in the presence of an unactivated benzenesulfonyl group, it was found that indirect electrochemical reduction employing suitable electrogenerated radical anions as reducing agents increased the selectivity [165].

Reductive cleavage of β-ketosulfones [166], $RCOCHR'SO_2R''$, in DMF at mercury is a practical way of preparing alkyl ketones; the primarily formed radical anion cleaved to a radical $RCOCHR'$ and a sulfinate ion $R''SO_2^-$. Since the anodic reaction was the oxidation of $R''SO_2^-$ to $R''SO_3^-$, an undivided cell could be used.

V. CARBON–NITROGEN BOND

A. By Reduction

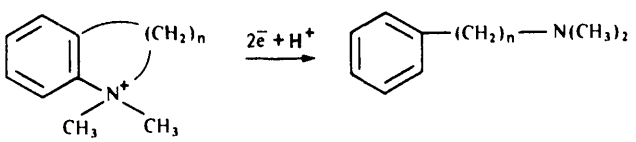
Quaternary ammonium compounds are widely used as supporting electrolyte, and their reduction is thus of considerable interest. It was demonstrated long ago [167] that anilinium salts with three *N*-alkyl groups are discharged at a lead cathode. Regardless of the nature of the saturated substituents on nitrogen, benzene and the corresponding tertiary amine were always obtained. These results show that in the discharge of the ammonium ion the bond between N and phenyl is particularly weakened; *N*-allyl and *N*-benzyl bonds are weakened even more. Dimethylallyl (or benzyl) anilinium ions yield in aqueous solution at a lead cathode propylene (or toluene) and dimethylaniline [168]:

$$[(CH_3)_2RNC_6H_5]^+ \xrightarrow{2e^- + 2H^+} C_6H_5N(CH_3)_2 + RH \tag{48}$$

The propensity of cleavage at a mercury cathode has been found to be benzyl > allyl > phenyl > alkyl.

In many cases it has been observed that reductive cleavage of quaternary ammonium compounds at lead is minor and that a Hofmann elimination is dominant; this is brought about by an electrogenerated base.

A useful preparation is the "Emmert cleavage." This is a reductive ring opening of anilinium salts in which one of the *N*-alkyl groups is simultaneously attached to the 2-position of the benzene ring (**XVIII**). The products are of the type **XIV** [169–170].



(49)

(XVIII) **(XIX)**

The yield of **XIX** ($n = 2$) is 90%; of **XIX** ($n = 3$), 88%; of **XIX** ($n = 4$), 90%. Tetrahydroisoquinolinium salts are not cleaved at the mercury cathode under ordinary conditions but are cleaved when NaI in liquid NH_3 is used [171].

The reduction of quaternary ammonium compounds having a phenyl, allyl, or benzyl substituent probably proceeds in a way similar to that of other compounds of the form ArX, $RCH{=}CHCH_2X$, or $ArCH_2X$, where X is a good leaving group, as in Eqs. (3) and

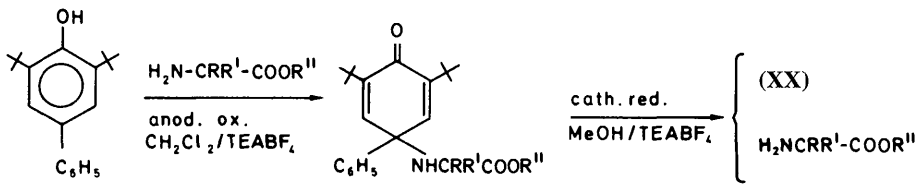
(7). Radicals seem to be intermediates in the cleavage; this is in accordance with the fact that a mixture of *meso*- and *d,l*- *1*-2,2-diphenylbutane is formed in the electrolysis of chiral *D*-α-phenylethyl-1-trimethylammonium nitrate in DMF [172] and that ESR spectroscopy reveals the presence of radical fragments in the reduction of dimethylbenzylanilinium salts [173].

Reduction in aprotic media of ammonium compounds having four aliphatic substituents at mercury or some other metals yields "tetraalkylammonium amalgam" or "tetraalkylammonium metals." This phenomenon is discussed in Chapter 28.

Protection of amino groups as carboxamides is generally not useful; however, benzyloxycarbonyl derivatives of primary and secondary amines may be reduced at vitreous carbon cathodes in DMF at very negative potentials, with cleavage to toluene and free amine in good yield (>80%) [174,175]. However, 4-nitrobenzyloxycarbonyl derivatives may be deprotected at 1.2 V (SCE); the cleavage of the initially formed radical anion is slow on the time scale of CV but sufficiently fast for a preparative-scale reduction.

The reduction of amides [176] to alcohols proceeds through a *gem*-amino alcohol, which loses either ammonia (or amine), forming an aldehyde, or water, forming an imine; the aldehyde is then reduced to the alcohol, whereas the imine forms an amine on reduction. The intermediate *gem*-amino alcohol, is also formed in the reduction of oxaziridines (Chapter 18) [177], and a similar *gem*-diamine during the reduction of amidines to amines [68].

3,5-Di-*tert*-butyl-4-oxo-1-phenyl-2,5-cyclohexadiene may be used as a protecting group in peptide synthesis; it can be introduced by electrochemical oxidation [178,179]:



(XX)

(50)

Several groups are useful for protecting amino groups, where the deprotection is a reductive elimination, Eq. (12), in which Y is an urethane and X a halogen [80,180]. Thus, for example, iodoethoxycarbonyl, trichloroethoxycarbonyl, and tribromoethoxycarbonyl are of practical importance in peptide synthesis.

Cleavage of C–N bonds has been described elsewhere, for example, the reduction of *gem*-dinitroalkanes to nitrite ion and nitroalkane anion [181,182] and *t*-nitroalkanes to nitrite and alkyl radical (Chapter 9) and the reduction of pyridylamines to picoline and ammonia (Chapter 18) [13,14]; a rare case of a reductive loss of a nitro group from a benzene ring in 1,2,4,5-tetrafluoro-3,6-dinitrobenzene has been reported [183]. Reduction of activated azides yields azide ion; phenacyl azide is thus reduced to acetophenone and azide [236].

The reduction of α-aminocarbonyl compounds [184–187] or α-aminonitriles [188] is similar to the reductive cleavage of the α-hydroxy compounds; the loss of amine occurs at a potential less negative than the reduction of the activating group.

If the amino group is β to the carbonyl group, a reduction takes place at the carbonyl group rather than resulting in a cleavage of the carbon–nitrogen bond; the polarographic

reduction of the β-aminoketone and the α, β-unsaturated ketone obtained by elimination of the amine may be used for following the kinetics of the elimination reaction [189,190].

Electrolysis of 4-aminobenzonitrile in DMF gave a yellow solution that, from the electron paramagnetic resonance (EPR) spectrum, was identified [191] as the radical anion of 4,4′-dicyanobiphenyl; a loss of amide ion is followed by dimerization of the neural radical.

A carbon-nitrogen bond is broken during a chemical follow-up reaction in many ring closures or ring contractions [192] of heterocyclic compounds in which a nucleophilic attack on an imine followed by an elimination of the amine or ammonia takes place. This is discussed in Chapter 18, in which is also mentioned the loss of ammonia from the primarily formed dihydro compound in the reduction of certain aminoheterocyclic compounds.

B. By Oxidation

Anodic oxidation of primary and tertiary [193] aliphatic amines in acetonitrile containing a small amount of residual water produced several compounds, including aldehydes. Tripropylamine is oxidized according to Eq. (51):

$$(CH_3CH_2CH_2)_3N \xrightarrow{-e^-} (CH_3CH_2CH)_3N^{+\cdot} \xrightarrow{-H^+} (CH_3CH_2CH_2)_2N\dot{C}HCH_2CH_3 \xrightarrow{-e^-}$$

$$(CH_3CH_2CH_2)_2\overset{+}{N}CHCH_2CH_3 \longrightarrow (CH_3CH_2CH_2)_2\overset{+}{N}{=}CHCH_2CH_3 \xrightarrow{H_2O} (CH_3CH_2CH_2)_2NH + CH_3CH_2CHO + H^+ \quad (51)$$

N-Methoxyphenyl-2-azetidinones may be deprotected under mild conditions by anodic oxidation in 1:1 MeCN–H_2O containing 1% $LiClO_4$. The dication is probably the species cleaved. The benzoquinone by-product may be extracted with 10% Na_2SO_3 [194]. β-Lactames protected by an *N*-(2,4-dialkoxyphenyl) group may be deprotected by anodic oxidation [195].

VI. CARBON–PHOSPHORUS BOND

Phosphonium compounds are reduced more easily than the corresponding ammonium compounds; the reduction results in a breakage of a carbon–phosphorus bond. The ease with which a group is cleaved from a phosphonium compound depends on several variables, primarily the electrode material, the potential, and the temperature [196–199].

At a mercury cathode the propensity for cleavage from a phosphonium salt in methanol increases in the sequence methyl < ethyl < *n*-butyl ~ phenyl < *tert*-butyl < allyl < benzyl; however, at a lead cathode the tendency for loss of an alkyl group from an alkyltriphenylphosphonium group is much higher than at a mercury cathode; ethyltriphenylphosphonium chloride is thus reduced in methanol at a mercury cathode to a 5:3 mixture of ethyldiphenylphosphine and triphenylphosphine, whereas 91% triphenylphosphine was isolated at a lead cathode [196].

A convenient synthetic procedure for the preparation [200] of mixed tertiary phosphines and quaternary phosphonium salts has been based on the preferential cleavage of

the benzyl group from P (and As). This method also provides a simple means for preparing phosphonium salts with four different ligands. The salts, after resolution into their optical antipodes, can be cathodically cleaved and thus provide optically active tertiary phosphines and of optically active tertiary arsines [201].

Reduction of alkyltriphenylphosphonium salts in aprotic media leads to the formation of ylids [202,203]. The formation of ylids as a result of the electrogeneration of bases (EGB) [204] is discussed in Chapter 30.

Triphenylphosphine is reduced in aprotic media; the results from polarographic, voltammetric, and preparative experiments point to the following radical mechanism [205].

$$(C_6H_5)_3P \xrightarrow{e} [(C_6H_5)_3P]^{\cdot -} \longrightarrow (C_6H_5)_2P^- + C_6H_5^{\cdot} \qquad (52)$$

Oxidation of the cleavage products leads to diphenylphosphonic acid and phosphine.

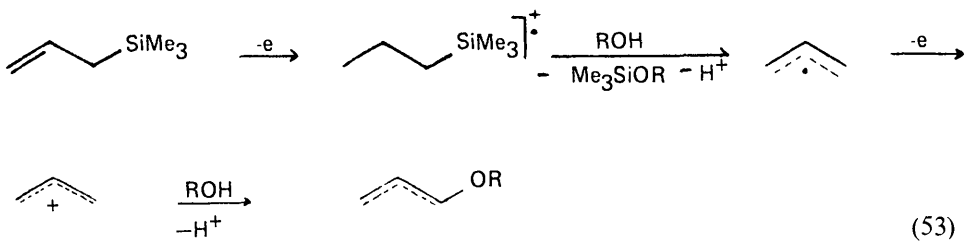
However, in DMF–$TBABF_4$, electrolysis of triphenylphosphine yielded butyldiphenylphosphine, tributylamine, and benzene and no biphenyl; a catalytic reduction involving $TBABF_4$ was proposed to take place during the reduction of triphenylphosphine [206]. Similar results were obtained from triphenylphosphine oxide.

Attempts to reduce triphenylphosphine oxide electrochemically to triphenylphosphine is difficult; in aprotic media a carbon–phosphorus bond is cleaved in preference to the phosphorus–oxygen bond [205,206].

Quaternary arsonium compounds are in general reduced at potentials 0.3 V less negative than those of the corresponding phosphonium salts [207]. The ease of cleavage of the different groups is mostly similar to that in the phosphonium compounds, but some differences are found.

VII. CARBON–SILICON BOND

Allyl and benzyl silanes may be anodically oxidized in the presence of an alcohol, a carboxylic acid, or water to the corresponding ether, ester, or alcohol [208]. The initially formed radical cation is believed to lose the silicon moiety by attack by the nucleophile on silicon:



(53)

Solvated electrons may cleave carbon–silicon bonds; thus electrolysis of Si_6Me_{12} in HMPA at −3.0 V yields the anion, $Si_6Me_{11}^-$. A small wave at −1.9 may be due to a direct reduction of Si_6Me_{12}; the necessary voltage drops during the electrolysis from −3.0 to −1.9 V [209].

Silyl substitution at a carbon adjacent to an oxygen causes a significant decrease in the oxidation potential of ethers and alcohols by stabilizing cations or cation radicals (β-silicon effect; Chapter 20) [210]; in some cases a similar effect is found for thioethers.

Anodic oxidation of ring-substituted aryl(trimethylsilylmethyl)-sulfides results in a cleavage of the carbon–silicium bond [211]. Oxidation of hexaalkyldisilanes in MeCN results in a cleavage of the Si-Si bond in a two-electron reaction [135].

The oxidation of allyl and benzyl silanes provides a method for "umpolung" of such organosilicon compounds.

VIII. CARBON–HALOGEN BOND

Reductions resulting in cleavage of a carbon–halogen bond have been discussed in Chapter 8. Here are mentioned only some cases in which halogens have been used as protecting groups.

Vicinal dibromides can be cathodically converted into olefins (Chapter 8). Their reduction potential is shifted to less negative values with increasing alkyl substitution. This may be used as a selective monoprotection of the less alkylated double bond in dienes. The diene is converted into the tetrabromide with bromine and subsequently deprotected by controlled potential electrolysis [212].

β-Halogenethyl groups have been used as protecting groups for several types of functional groups. The deprotection can be done electrochemically by direct [80,180] and indirect [213] electrolysis. Using a vitamin B_{12}-derivative as mediator, penicillin V β-bromoethyl esters can be deprotected to penicillin V under such mild conditions that the β-lactam ring is intact [213].

A special reaction of a halogen derivative is the 2F/mol reduction of 1,4-dichlorophthalazine which leads to phthalonitrile and involves the cleavage of the two C–Cl bonds and the N–N bonds; 1-chloro-4-methoxyphthalazine is reduced similarly (Chapter 18).

IX. OXYGEN–OXYGEN BOND

Compounds containing an oxygen–oxygen single bond are generally [214] polarographically reducible. Thus, hydroperoxides [215,216], peracids [217], acylperacids [218], ozonoides, and aldehyde and ketone peroxides [219] can be determined polarographically. The electrode reaction, which is a cleavage of the O–O bond, has not been widely used preparatively, although the half-wave potentials of the various types of peroxides are sufficiently different to permit a selective reduction of one type in the presence of others. The presence of many alkyl groups shifts the half-wave potential to more negative values because of the electron-donating power of these groups and their shielding of the reaction center. In methanol–benzene containing LiCl, the half-wave potential [218] of di-*tert*-butylperoxide is -1 V; dialkylperoxides, more negative than -2 V; *tert*-butylperoxy esters, -0.8 to -1.0 V; hydroperoxides, -0.6 to -0.9 V; diacylperoxides, ~ -0.1 V; and peracids, ~ -0.05 V. The half-wave potential of an organic peroxide is thus valuable in the elucidation of its structure.

Indirect reduction of *t*-butyl hydroperoxide by aromatic radical anions in DMF gives *t*-butoxy radicals which abstract hydrogen from DMF. The resulting *N,N*-dimethylaminocarbonyl radical may couple with the mediator [216].

X. SULFUR–SULFUR BOND

A. Disulfides

A sulfur–sulfur single bond may be cleaved either anodically or cathodically. A sulfur–sulfur bond is generally reducible and such compounds as di-, tri-, and tetrasulfides [220] and thiolsulfonates [221] are polarographically active.

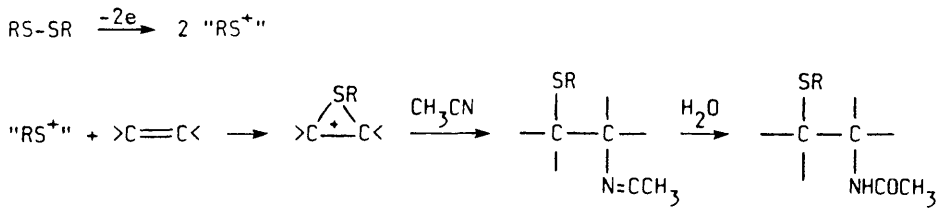
Disulfides are easily reducible to mercaptans; a high yield of thioglycolic acid [222] from dithiodiglycolic acid was obtained by reduction of 2 *N* sulfuric acid at a lead cathode at −0.55 V (SCE). This reduction is one of the few examples of a controlled potential reduction prior to the invention of potentiostats.

The rate constant of the heterogeneous electron transfer from a platinum electrode to aromatic disulfides in DMF is low, whereas the homogeneous electron transfer from suitable radical anions is much faster; these can be generated at potentials more negative than E^0 of the disulfides but less negative than their peak potentials [223].

Reactions of disulfides in the presence of alkylating or acylating agents give S-alkylated or S-acylated products in good yield [224]. If the reduction is done in the presence of oxygen, sulfinic acids may be formed [225].

Oxidation of diphenyldisulfide in a mixture of glacial acetic acid and concentrated hydrochloric acid at a platinum anode yielded benzenesulfonic acid; ethyl phenyl sulfide yields benzenesulfonic acid [226].

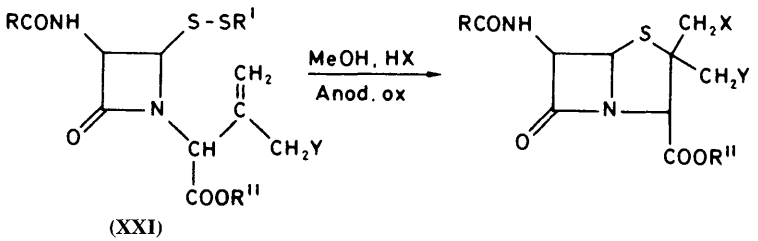
Oxidative cleavage of disulfides can be made by chemical and electrochemical means; thus anodic oxidation at platinum or carbon electrodes of different kinds of disulfides in the presence of alkenes in acetonitrile affords products of acetamidosulfenylation; with cyclic alkenes a high selectivity for *trans* addition is observed. The reaction may be formulated:



(54)

With terminal alkenes, the terminal sulfides are formed with high regioselectivity [227].

This reaction is employed in the ring closure, as in Eq. (55) [228], where **XXI** is anodically oxidized in methanol. It might be surprising that a five-membered ring is formed in preference to a six-membered ring; an episulphonium ion is probably formed as an intermediate.



(55)

(XXI)

XI. NITROGEN–NITROGEN BOND

Reductive splitting of a bond between a nitrogen atom and heteroatom occurs in many compounds of the type X=N–Y, where X may be carbon, oxygen, or nitrogen and Y may be oxygen or nitrogen [229]. This rule thus applies to cyclic and acyclic hydrazines, oximes, *p*-amino and *p*-hydroxyazobenzenes, triazines in acid solution, and *N*-nitrosamines in alkaline solution.

A. Hydrazones

Phenylhydrazones may be reduced to aniline and an amine in a four-electron reduction or to a hydrazine in a two-electron reaction, depending on pH. These results have been explained in Chapter 11.

A reduction route similar to that of phenylhydrazones [229] seems to be rather general for azomethine derivatives of hydrazine [229] as it s followed by cyclic and acylic phenylhydrazones, semicarbazones, azines, cyclic hydrazones, and acylated cyclic and acyclic hydrazones [231] under protic conditions; in DMF, acylated hydrazones of aromatic aldehydes are reduced with saturation of the C=N bond and cleavage of the N–N bond at a more negative potential [232]. The suggestion that the cleavage of the N–N bond precedes the saturation of the azomethine bond is also an essential part of the interpretation of many of the ring contractions of heterocyclic compounds (Chapter 18).

The preprotonation step is indicated from the polarographic data and from the fact that a quaternized hydrazone like benzaldehyde trimethylhydrazonium iodide, C_6H_5–CH=CH=$\overset{+}{N}\overset{+}{N}(CH_3)_3I^-$, is reducible in a four-electron reduction both in alkaline and acid solutions, whereas hydrazones are generally either nonreducible or reducible in a two-electron reduction in alkaline solution.

The cleavage of an N–N bond in *p*-hydroxyazobenzenes [233] may be regarded as a variant of the general scheme if the *p*-hydroxyazobenzene is considered reduced in its tautomeric form, the quinone monophenylhydrazone.

In aprotic media the rate of cleavage of the radical anion of *N,N*-dimethylhydrazones of arylaldehydes is a linear function of the reversible reduction potential of the hydrazone. The electrogenerated base may induce an elimination of amine to a nitrile [230].

Electrochemical oxidation of substituted hydrazones of benzaldehyde may result in cleavage of the nitrogen–nitrogen bond and formation of a benzonitrile [234] and oxidation products from the amine.

B. Hydrazides and Azides

Certain activated hydrazides [235], such as isonicotinic hydrazide, are reduced to the amides:

$$\overset{+}{H}NC_5H_4CONHNH_2 \xrightarrow{2e^- + 3H^+} \overset{+}{H}NC_5H_4CONH_2 + NH_4^+ \tag{56}$$

The reduction of isonicotinoyl azide also produces isonicotinic amide, and most other azides are similarly reduced according to Eq. (57) [236,237]:

$$R\text{–}\overset{-}{N}\text{–}\overset{+}{N}\equiv N \xrightarrow{2e^- + 2H^+} RNH_2 + N_2 \tag{57}$$

This reaction has been employed for the synthesis of saturated and unsaturated amino acids by cathodic reduction of azidocinnamic esters [237]. Reduction of azides in DMF in the presence of acetic anhydride yields diacetylated amines [237]. Azide groups in activated methylene groups may, however, be reduced to azide ion and methyl compound [236].

C. Triazines

Triazines are reduced to amines and hydrazines. It has not been proved for acyclic trizines whether the cleavage of the N–N bond precedes the saturation of the N=N bond, but in benzotriazoles [238] and benzotriazines (Chapter 18) [238], the first detectable intermediate contains the N=N bond even after cleavage of the N–N bond.

D. *N*-Nitrosamines

As discussed in Chapter 9, *N*-nitrosamines, O=N–NRR′, are reduced in alkaline solution with cleavage of the N–N bond according to Eq. (58) [239]:

$$O{=}N{-}NRR' \xrightarrow{2e^- + 2H^+} \tfrac{1}{2}N_2O + HNRR' \tag{58}$$

XII. OXYGEN–SULFUR BOND

Aliphatic sulfoxides are not cathodically reducible, but some give a catalytic hydrogen wave in acid solution [240]; at a lead cathode in alcoholic sulfuric acid diphenylsulfoxide [241] and dibenzylsulfoxide [242] have been reduced in fair yield to the sulfide. Methylphenylsulfoxide has been reduced in DMF or MeCN with phenol as proton donor at −2.3 V (SCE) to methylphenylsulfide [243].

Methyl benzenesulfenate has been reported [244] to be cleaved to thiophenol and methanol at −0.5 V (SCE) in aqueous buffer at pH 7; methyl 2-nitrobenzenesulfenate in DMF is reductively cleaved similarly [245].

Esters of arylsulfonic acids are generally reducible, and this has been employed for protection [40] of hydroxyl groups; the cleavage of tosylates [150,154, 246–249] and nosylates (esters of 4-nitrobenzenesulfonic acid) [250] has especially been studied.

The arylsulfonate esters, $Ar{-}SO_2{-}OR$, are reducible at rather negative potentials; the primarily formed radical anion can in principle cleave between Ar and SO_2, between SO_2 and OR, and between O and R. An O–R cleavage is unlikely in view of the observation that tosyl esters with optically active alcohols, in which the tosyl ester is at the chiral center, are electrochemically cleaved with retention of the configuration [246].

According to a simple MO theory it has been argued [251] that the Ar–SO_2 cleavage should predominate in protic media, whereas in aprotic media the anion radical would be reduced further to the dianion, which then decomposed. In general, the cleavage SO_2–O is predominant, as in Eq. (59), but some ArH is also observed [248,249]. It seems, however, that the cleavage of the C–S bond to give ArH and the cleavage of the S–O bond to give alcohol are not simple competitive reactions.

$$Ar{-}SO_2{-}OR + 2e \longrightarrow ArSO_2^- + RO^- \xrightarrow{H^+} ROH \tag{59}$$

It was found that the cleavage of the primarily formed radical anion was the rate-determining step in an indirect reduction of tosylates in DMF when R was aliphatic, whereas with R aromatic the cleavage was so fast that the homogeneous electron transfer from the reduced catalyst became rate-determining [249].

In the absence of protons the deprotection is complicated by nucleophilic attack of RO^- on the tosylate ester with formation of the ether, ROR [Eq. (60)]. This side reaction can be suppressed on addition of a proton donor, such as acetic acid. In that case aromatic radical anions cannot be used as catalyst and Ni(acacen) was used. The difference in yield of deprotected alcohol from direct and indirect reduction was insignificant [249].

$$Ar{-}SO_2{-}OR + RO^- \longrightarrow Ar{-}SO_3^- + ROR \tag{60}$$

Nosylates are reduced in two steps; the first reduction gives a rather stable radical anion at a potential characteristic of substituted nitrobenzenes [250]. In the second step (−1.2 to −1.7 V vs. SCE) a dianion is formed that cleaves rapidly at the S–O bond to give ROH and the arylsulfinate ion.

Bis(tosyloxy)benzene derivatives may be selectively cleaved; a tosyl group *ortho* or *para* to an electron-withdrawing group (e.g., an ester group) is cleaved preferentially to one in the *meta* position, whereas in derivatives of anisol, cleavage of the tosyl group *meta* to the methoxy group is preferred [252].

XIII. OXYGEN–NITROGEN BOND

The reduction of derivatives of hydroxylamine involves splitting of the N–O bond. It has been shown [229] that the cleavage of the N–O bond in oximes generally occurs prior to the saturation of the double bond. In alkaline solution at low temperature, however, some reduction of an aldoxime to a hydroxylamine takes place. A similar primary cleavage of an N–O bond is found in the reduction of amide oximes [229] and hydroxamic acids [236]. The reduction of oximes in acid solution has been formulated as Eq. (61):

$$RR'C{=}NOH \overset{H^+}{\rightleftharpoons} RR'C{=}\overset{+}{N}H{-}OH \xrightarrow{2e + 2H^+} RR'C{=}\overset{+}{N}H_2 + H_2O \xrightarrow{2e^- + 2H^+} RR'C\overset{+}{H}NH_3 \tag{61}$$

The hypothesis that oximes with a positive charge on nitrogen are reductively cleaved at N–O is supported by the observation that after quaternization, isoxazoles or 4,5-dihydroisoxazoles can be cleaved in neutral solution without reduction of the C=N bond [253]. As isoxazolines can be made conveniently from alkenes and oximes (through nitrile oxides), this is a convenient way of preparing β-hydroxyketones; the use of CPE makes it possible to tolerate substituents that are attacked by other reducing agents.

Nitrile-*N*-oxides are reducible at rather positive potentials to the nitriles; thus 2,4,6-trimethylbenzonitrile-*N*-oxide is reduced at −0.7 V at pH 6 in aqueous ethanol to the corresponding nitrile [254].

XIV. OXYGEN–PHOSPHORUS BOND

Triphenylphosphine oxide has been reported to be deoxygenated by reduction at a zinc cathode [255].

XV. SULFUR–NITROGEN BOND

The reduction of sulfonamides has been extensively studied in connection with the protection of amino groups [154, 246–250, 256–260]; the cleavage of *N*-tosyl groups probably follows Eq. (62):

$$\begin{aligned} &RR'NTs + e \longrightarrow RR'NTs^{\cdot -} \longrightarrow RR'N^{\cdot} + Ts^{-} \\ &RR'N^{\cdot} + e \longrightarrow RR'N^{-} \xrightarrow{+H^{+}} RR'NH \end{aligned} \tag{62}$$

In the presence of a suitable proton donor, $n = 2$ and Eq. (62) is followed; the yield of deprotected amine is usually good to excellent. The reduction potential at mercury or glassy carbon is rather negative (in DMF typically −2.3 to −2.4 V vs. SCE), and this must be taken into consideration if other reducible groups are present in the protected molecule.

In aprotic media complications of a different kind may arise. If the protected amine is primary, the resulting sulfonamide is fairly good proton donor that can protonate the resulting substituent amide ion, and $n = 1$ is found; on workup 50% of the sulfonamide is recovered [258]:

$$2RNH{-}Ts + 2e \longrightarrow RNH_2 + Ts^{-} + (RNTs)^{-} \tag{63}$$

When no hydrogen atoms are bonded to nitrogen the electrogenerated base (EGB), the amide ion, may still cause a side reaction, if one of the substituents on the nitrogen has an α-hydrogen. The EGB may induce a β-elimination with formation of an aldimine or ketimine, as in Eq. (64); the imine may be reducible at the potential used for cleavage of the sulfaonamide [258].

$$RR'CH{-}NR''{-}Ts \xrightarrow[-Ts^{-}]{2e^{-}} (RR'CHNR'')^{-} \xrightarrow{RR'CH{-}NR''{-}Ts} RR'CHNHR'' + RR'C{=}NR'' \tag{64}$$

The reduction of sulfonamides has been investigated in methanol [154, 246], DMF [247,249], and MeCN [248]; the reductive cleavage of *N*-tosyl amino acids and peptides has been studied in methanol at pH 11 at different electrodes; lead was the preferred material for deprotection [256,257].

To avoid the rather negative reduction potential necessary for reduction of benzenesulfonamides, the reduction of nitrobenzenesulfonyl derivatives of amines has been investigated. The radical anions of *N*, *N*-dibutyl-4-nitrobenzenesulfonamide and *N*-butyl-2-nitrobenzenesulfonamide were found to be stable in DMF at the time scale of CV; reduction of the radical anion to the dianion induced a rapid cleavage of the S–N bond with formation of the amine in good yield. The radical anion of *N*-butyl-3- or 4-nitrobenzenesulfonamide loses hydrogen and although cleavage takes place on further electron uptake, the yield of the deprotected amine was unsatisfactory. Therefore, the 4-nitrobenzenesulfonyl group was investigated as a protecting group for amino groups in amino acids; deprotection could be made in good yield by reduction at the potential of the second wave (about −1.1 V vs. SCE) of the protected amino acid in DMF [261].

Besides being used for the deprotection of amino acids and peptides, electrochemical cleavage has been employed in the synthesis of polyaza and polyaza–polyoxa ligands [259]; the deprotection may be performed by direct as well as by indirect electrolysis.

Indirect electrolysis using radical anions of aromatic hydrocarbons or Ni(acacen) as electron carrier has made it possible to determine the E^0 of some tosylamides in DMF and

also the rate of cleavage of the sulfonamide radical anions [249]. The results were similar to those for the tosylates; when the amine was aliphatic, the cleavage of the anion radical was the rate-determining step, whereas the homogeneous electron transfer from the electron donor became rate determining when the amine was aromatic.

A useful system for indirect electrolysis of sulfonamides was reported to be anthracene as mediator in the presence of ascorbic acid as proton donor [260].

In *N*-tosylcarboxamides there would be a competition in the reductive cleavage of the radical anion between the carbon–nitrogen bond and the nitrogen–sulfur bond; in DMF containing acetic acid the sulfinate is reductively split off. The yeld of deprotection is highest when a mercury electrode is used [262].

XVI. SULFUR-HALOGEN BOND

Both sulfenyl [263] and sulfonyl chlorides [142,264–267] are electrochemically reducible with cleavage of the sulfur-halogen bond.

The reduction of sulfonyl chlorides may lead to sulfinates [265–267], thiosulfonates [267], disulfides, and mercaptans depending on the conditions; in the presence of alkylating agents [266], sulfones or sulfides are among the products.

The sulfinate is the immediate product in the absence of a strong proton donor; under sufficiently acidic conditions reduction to mercaptans may take place. The thiosulfonate may be formed on thioacylation of the mercaptan or dismutation of the sulfinic acid; the thiosulfonate is reducible under the conditions employed, so the final product is the thiol.

XVII. SULFUR-PHOSPHORUS BOND

Electrochemical regeneration of triphenylphosphine from triphenylphosphine oxides may be performed by transforming the oxide to the sulfide with P_2S_5, methylating it into the phosphonium compound, and cleaving it electrochemically [268]:

$$Ph_3PO \longrightarrow Ph_3PS \longrightarrow Ph_3\overset{+}{P}SCH_3 \xrightarrow{2e^-} Ph_3P + CH_3S^- \tag{65}$$

Sulfophosphamides, $ArSO_2PPh_2$, are reduced more easily than the corresponding sulfonamides [269]; the radical anion is cleaved to sulfinic acid and phosphinyl radical, which is further reduced to the phosphine anion, Ph_2P^-. This anion, however, reduces the arylsulfinate to arylmercaptane according to:

$$Ph_2P^- + ArSO_2^- \longrightarrow Ph_2P(O)O^- + PhS^- \tag{66}$$

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24

Anodic Substitution and Addition

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I. INTRODUCTION

Anodic substitution reactions are common in organic electrochemistry. The overall reaction may be represented as in Eq. (1).

$$R{-}E + Nu^- \longrightarrow R{-}Nu + E^+ + 2e^- \quad (1)$$

The nucleophile [Nu^- (or NuH)] may include H_2O, ROH, OH^-, RO^-, $RCOO^-$, NO_3^-, SCN^-, $SeCN^-$, CH_3CN, NO_2^-, N_3^-, OCN^-, pyridine, halide ion, and CN^-; the electrophile [E^+] is most commonly H^+, but could be a carbocation or an alkoxonium ion. The case in which the electrophile is CO_2 (the Kolbe reaction) is treated in Chapter 14 and will not be dealt with here. Anodic substitution reactions therefore allow for a net substitution by a nucleophile, a reaction not easily achieved by ordinary chemical means. Specifically, this makes possible the direct formation of a C–O or C–N bond by substitution of a C–H bond. This is of considerable synthetic interest.

The mechanisms of anodic substitution reactions can be divided into direct and indirect processes.

In the direct process, oxidation of the organic substrate takes place at the anode with formation of a radical cation as the first step, as in Eq. (2), which is followed by reaction with a nucleophile and/or base present in the electrolyte [Eq. (3) and/or Eq. (4)]. The resulting neutral radical, **I** or **II**, is usually more easily oxidized than the starting material and undergoes further oxidation at the applied potential to a cation, **III** or **IV** [Eq. (5) or Eq. (6)], which in turn is converted to the final product, **V**, in a fourth step [Eq. (7) or Eq. (8)].

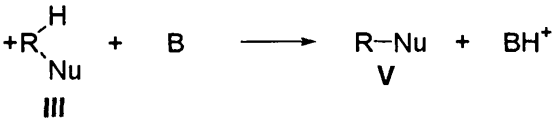
$$R{-}H \rightleftharpoons R{-}H^{+\bullet} + e^- \quad (2)$$

$$R{-}H^{+\bullet} + Nu^- \text{ (or NuH)} \rightleftharpoons \underset{\mathbf{I}}{\bullet R(H)Nu} \text{ (or } \underset{\mathbf{I'}}{\bullet R(H)NuH^+}\text{)} \quad (3)$$

$$R{-}H^{+\bullet} + B \rightleftharpoons \underset{\mathbf{II}}{R^\bullet} + BH^+ \quad (4)$$

$$\underset{\mathbf{I}}{\bullet R(H)Nu} \xrightarrow[\text{solution}]{\text{electrode, } -e^-} \underset{\mathbf{III}}{{}^+R(H)Nu} \quad (+R{-}H^{+\bullet},\ -R{-}H) \quad (5)$$

$$\underset{\mathbf{II}}{R^\bullet} \xrightarrow[\text{solution}]{\text{electrode, } -e^-} \underset{\mathbf{IV}}{R^+} \quad (+R{-}H^{+\bullet},\ -R{-}H) \quad (6)$$



(7)

(8)

The mechanism composed of Eqs. (2), (3), (5), and (7) is observed typically for nuclear substitution in aromatic compounds, whereas side-chain substitutions, for instance, typically proceed according to Eqs. (2), (4), (6), and (8). (For a more thorough discussion of the reactions between radical cations and nucleophiles, the reader is referred to the rich literature on this subject [1,2].) Essentially the same mechanistic pattern is found in oxidative substitution driven by high valent inorganic ions [3–6].

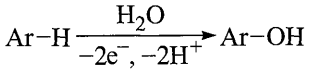
In an indirect process, the anode merely serves as a convenient source of an oxidant, such as Cl_2 by oxidation of Cl^- or $NO_3^{\cdot}$ by oxidation of NO_3^-, or an organic radical, such as methoxy radical from methoxide ion, which then attacks the organic substrate in a reaction similar to that taking place when the reagent is generated in any other way. The indirect processes also encompass reactions in which an organic compound is oxidized by an electrochemically generated oxidant, a so-called mediator, the reduced form of which is continuously reoxidized and therefore, in principle, needs only to be present in catalytic amounts.

In this chapter we emphasize reactions proceeding according to the direct mechanism, since in many cases the indirect processes do not differ in any important respects from analogous homogeneous processes. The subject has been reviewed extensively [7–13], and the reader is referred also to Chapters 15, 16, 17, 25, and 29 in this book.

II. FORMATION OF CARBON-TO-OXYGEN BONDS

A. Hydroxylation

The possibility of the direct introduction of a carbon-to-oxygen bond in a substitution process, for example, an anodic hydroxylation, is of considerable preparative interest, since in principle cheap starting materials could be used. Consequently, it would be possible to prepare phenols using only hydrocarbon, water, and electrical current in the process [Eq. (9)]. However, apart from the practical problems associated with this type of process, there are theoretical grounds why this reaction should not be feasible in general.

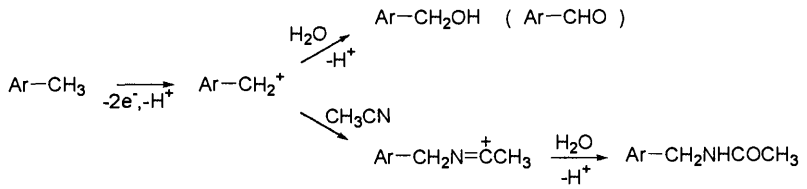


(9)

In this case the starting material is considerably more difficult to oxidize than the product; under comparable conditions benzene is oxidized at a potential ~ 1.3 V higher than phenol. Consequently, it is observed that the reaction usually cannot be stopped at the phenol stage, but proceeds to benzoquinone [14,15]. Similarly, the oxidation of 9,10-dihaloanthracenes leads to anthraquinone in an addition–elimination reaction [16]. However, the problem may to some extent be overcome if the degree of substrate conversion is kept low (e.g., the anodic oxidation of phenol to hydroquinone [17]) or if the oxidation product is continuously removed (e.g., the indirect oxidation of methylarenes

to the corresponding carbonyl compounds [18]). In other cases, such as the anodic hydroxylation of fluorenone to 2-hydroxyfluorene [19], the product partially survives further oxidation.

In nonaqueous solvents, water is an impurity that, on a preparative scale, even rigorous drying fails to remove completely [20]. Hydroxylation products are therefore common by-products. An example is the oxidation of alkylaromatic compounds in a nominally anhydrous solution of $NaClO_4$ in MeCN [Eqs. (10) and (11)], which gives mainly the product of acetamidation [21–23].

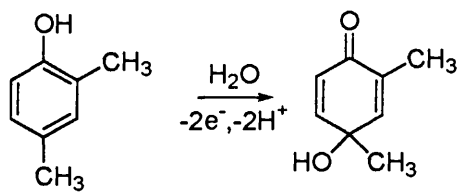


(10)

(11)

One of the side reactions gives the corresponding benzyl alcohol (and its oxidation product, the aldehyde). Related to these reactions is the anodic hydroxylation of 1-carbomethoxy-1,2,3,4-tetrahydrocarbazoles to the corresponding 1-hydroxy-1-carbomethoxy-1,2,3,4-tetrahydrocarbazoles in MeCN–H_2O mixtures [24].

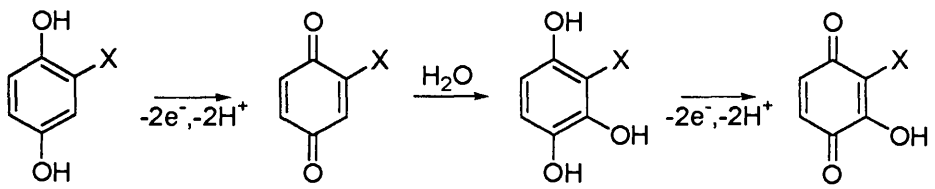
The anodic hydroxylation of phenols at PbO_2 in aqueous H_2SO_4 has been studied in detail [25]. Substitution is invariably at the 4-position to give benzoquinones; if the 4-position is already occupied, then 4-substituted-4-hydroxycyclohexa-2,5-dienones are formed, as in Eq. (12):



(12)

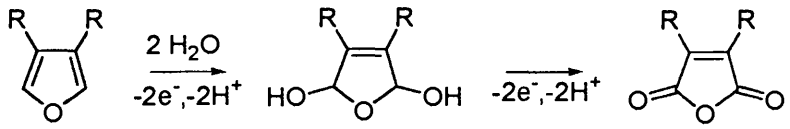
This particular reaction may sometimes be preparatively useful; for example; 4-allyl-phenols give good yields of 4-allyl-4-hydroxycyclohexa-2,5-dienones. Similarly, mesitylene is converted to 2,4,6-trimethyl-4-hydroxycyclohexa-2,5-dienone upon anodic oxidation in a mixture of H_2O, MeCN, and H_2SO_4 [26].

Anodic hydroxylation of quinones, substituted at the 2-position with an electron-withdrawing group, may be achieved at low potentials in aqueous solution [27]. In this case it is likely that nucleophilic attack is on the intermediate quinone:



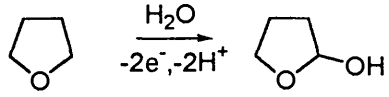
(13)

Anodic hydroxylation of furans provides a high-yield route to substituted maleich anhydrides [28]:



(14)

The introduction of a hydroxy group in an aliphatic compound already containing a simple oxygen function, such as an ether, does not affect the oxidation potential significantly. Consequently, the products of anodic hydroxylation of aliphatic ethers may survive the conditions necessary for the oxidation of substrate. For example, tetrahydrofuran has successfully been converted to 2-hydroxytetrahydrofuran by anodic oxidation in 1 *M* H_2SO_4 at Pt, as in Eq. (15) [29]. However, the hydroxylation of diisoalkyl ethers results in highly oxidized products such as ketones and acids [30].



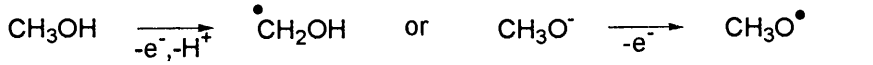
(15)

B. Alkoxylation

Alkoxylation may be achieved by anodic oxidation in an alcohol, often methanol (MeOH), containing a suitable electrolyte, such as KOH, NaOMe, NaCN, $NaBF_4$, or NH_4NO_3 [9–12,31,32]. Substrates that have been alkoxylated in this manner include aromatic compounds (both nuclear and side-chain alkoxylation has been observed), alkenes, ethers including vinyl ethers, enamines, *N*, *N*-dialkylamines, *N*-alkylsubstituted amides, and *N*-alkylsubstituted carbamates. In many cases alkoxylation by substitution is a side reaction only to concurrent alkoxylation by addition [7,9,11,33].

Methanolic electrolytes have been shown to undergo oxidation at lower potentials than many aromatic substrates, which may indicate that an indirect mechanism operates in the α-methoxylation of, for example, toluene, ethylbenzene, and cumene [34]. Further support for the indirect mechanism is indicated by the fact that α-methoxylation of tetralin in MeOH–NaCN takes place at potentials as low as 0.5 V versus SCE, whereas the half-wave potential, $E_{1/2}$, of tetralin must be around 1.9 V [35].

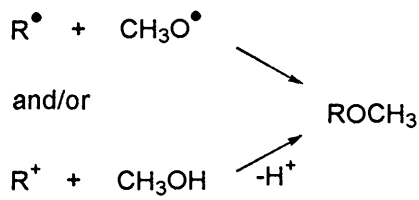
The nature of the anion present greatly affects the yield of α-methoxylation product, with the effectiveness decreasing in the series $F^- \approx ClO_4^- > CN^- \approx OH^- > Cl^- \approx CH_3O^- > Br^-$. The mechanistic possibilities are given in Eqs. (16)–(19).



(16)

(17)

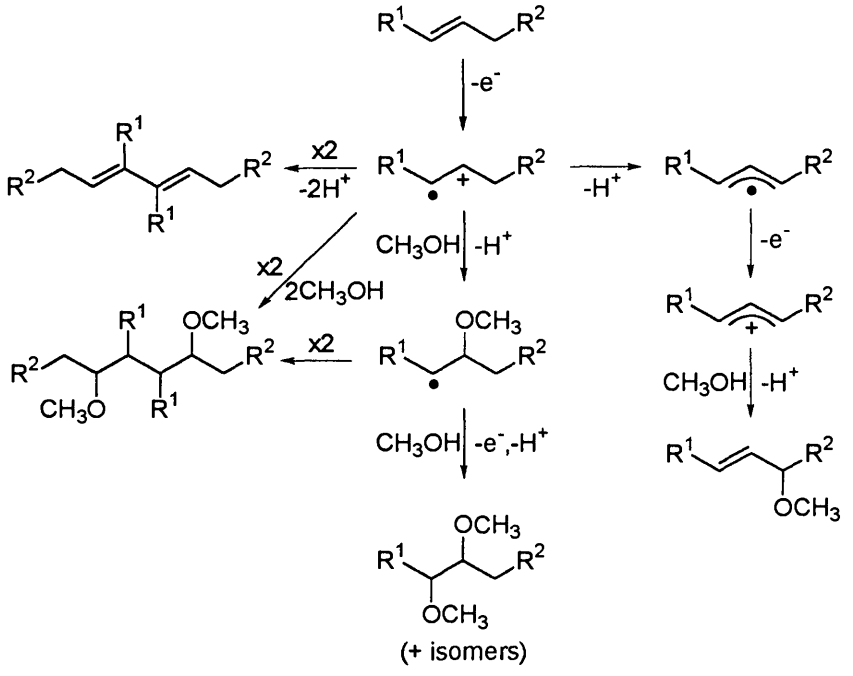
(18)



(19)

One would not expect F^- or ClO_4^- to be oxidized under the conditions used, which suggests that MeOH might be the electroactive species, forming a radical intermediate, which then functions as X˙ in Eq. (17). The radical ˙CH_2OH is the most likely candidate since the O–H bond in MeOH is much stronger than the C–H bond. In alkaline medium, MeO^- is probably the electroactive species, and MeO˙ would then be X˙.

Allylic methoxylation is often the result of anodic oxidation of alkenes and dienes in methanolic media [36–38]. Cyclopropanes behave similarly [39]. The reaction is usually accompanied by products of addition and combination, and the products may all be accommodated in the mechanistic scheme given in Eq. (20).



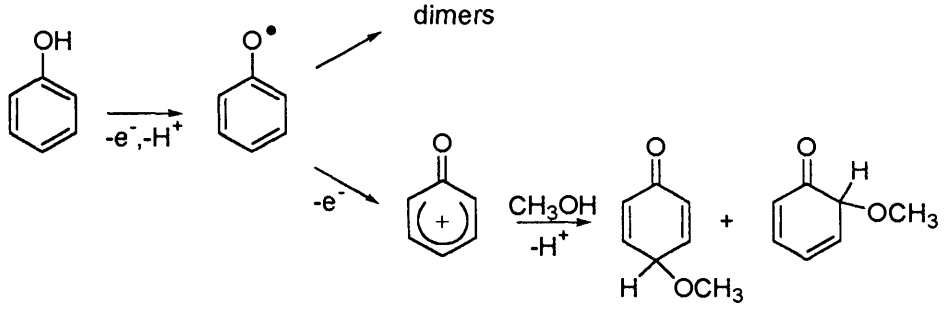
(20)

The yields of allylic methoxylation are only moderate (~ 25%) and compare unfavorably with the analogous allylic acetoxylation (described later) [40].

The anodic methoxylation of aromatic compounds such as naphthalene [41], anthracene [42], alkylbenzenes [31,43], phenols [44–46], anisoles [33,47–54] and other alkoxybenzenes [53], methoxynaphthalenes [33], methoxyanthracenes [50,54], inden-1-ones [55], *para*-substituted anilides [56] and heterocyclic compounds, such as furans [57], thiophenes [58], and pyrroles [59], has received considerable attention.

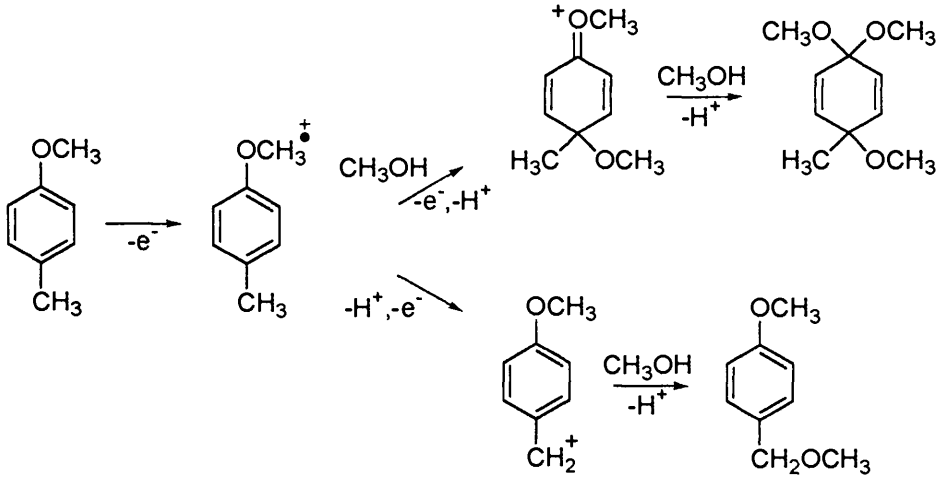
The products of methoxylation of phenols are usually further oxidized under the reaction conditions used [44–46]. Experimental conditions can be found, however, that in some cases allow selective formation of *para*-methoxylated dienones, *ortho*-methoxylated

dienones, or dimeric products. It is believed that methoxylation involves attack of MeOH on anodically generated phenoxylium ions, whereas dimeric products arise by combination of phenoxyl radicals:



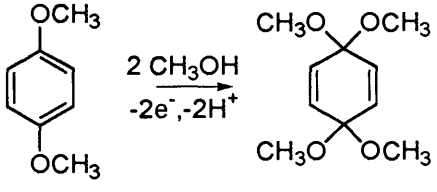
(21)

For the oxidation of alkylanisoles in MeOH containing various electrolytes [47] the current potential-curves support the scheme given, for *p*-methylanisole, in Eq. (22):



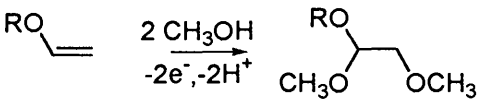
(22)

The oxidation of 1,4-dimethoxybenzene in MeOH to yield the corresponding quinone biketal [Eq. (23)] is the prototype example of the numerous related 1,4-addition reactions that may be accomplished electrochemically [33,47–54] (see Chapter 16).



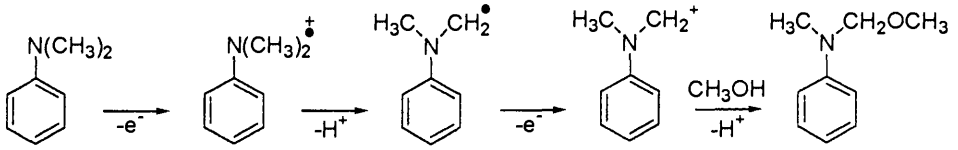
(23)

Additions similar to those reported for methoxysubstituted aromatic compounds are observed also for vinyl ethers, as in Eq. (24) [60,61], inden-1-one [55], furans [57], thiophenes [58], and pyrroles [59].



(24)

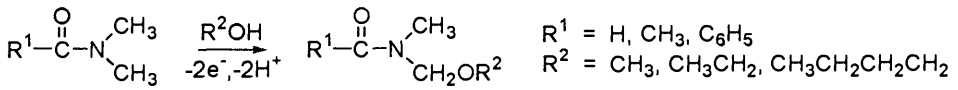
In contrast, the methoxylation of *N*, *N*-dimethylaniline in MeOH-KOH leads predominantly to side-chain substitution, as in Eq. (25) [62,63], most likely according to the following mechanism:



(25)

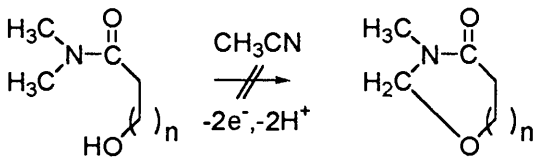
N, *N*-Dimethylbenzylamine [64,65], 2,4,6-tris(dialkylamino)-1,3,5-triazines [66], *N*-(2,2,2-trifluoroethyl)amines [67,68], and *N*-(2,2-difluoroethyl)amines [68] exhibit similar behavior. Methoxylation of enamines results in substitution at both the vinylic and the allylic positions [61].

Another reaction that has attracted considerable attention is the alkoxylation of *N*, *N*-dialkylamides and related compounds [69–85]. A typical example is the oxidation of *N*, *N*-dimethylamides [Eq. (26)] in ROH-NH_4NO_3 [70].

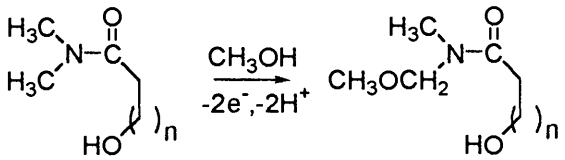


(26)

The use of a nitrate salt results in better yields and cleaner reaction than is observed with NaOR. A mechanism involving initial discharge of NO_3^- to form $NO_3^{\cdot}$, which then abstracts a hydrogen atom from one of the *N*-alkyl groups, is considered the most likely one in this case. When, for example, NaOMe is used as supporting electrolyte, the reaction most likely involves the substrate radical cation as the primary intermediate, followed by deprotonation and oxidation to the corresponding carbocation, which finally reacts with methanol. In this context it is of interest to notice that the intramolecular alkoxylation expected for the series of hydroxyamides shown in Eq. (27) did not take place in MeCN; only polymeric material was formed [71]. When the reaction was instead carried out in MeOH, only the "normal" methoxylation products were formed, as in Eq. (28). These, however, could easily be converted to the cyclized products by addition of acid.



(27)

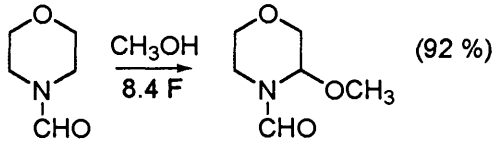


(28)

Numerous examples of the application of this synthetically useful reaction have been reported. Illustrative examples include the synthesis of eneamides and enecarbamates [72,73] and a large series of pyrrolidine, piperidine, and perhydroazepine derivatives [72,74–77].

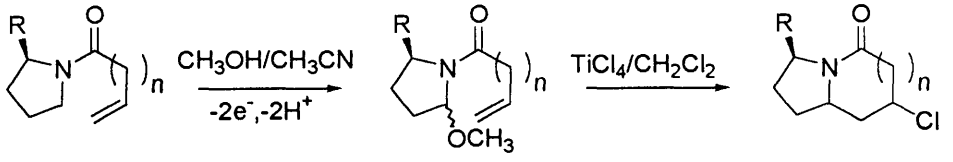
Attempts to methoxylate smaller ring systems like *N*-acetylaziridine and *N*-formylazetidine failed and resulted in ring-opened products [78].

Methoxylation lends itself well to operation on a relatively large scale [79–83]. For instance, several *N*-formyl derivatives have been anodically methoxylated on a 0.5-kg scale using a capillary gap cell with a graphite anode [80,82]. An example is given in Eq. (29). Polyalkoxylation of *N*, *N*-dimethylformamide (DMF) has also been achieved [81].



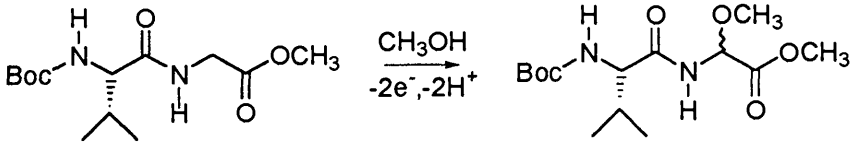
(29)

The selectivity and stereochemistry of the anodic methoxylation of the cyclic amides are noteworthy. First, *N*-formyl-2-methylpiperidine gives the 6-methoxysubstituted product in spite of the fact that loss of the proton in the 2-position would give a tertiary carbocation, which intuitively would be expected to be the more stable intermediate. Second, 4-substituted *N*-formylpiperidines give the corresponding 2-methoxy derivative with the methoxy group occupying an axial position [85]. Both these experimental facts were attributed to the steric constraints imposed by the *N*-formyl group. A good example of the selectivity is shown in Eq. (30); the methoxylated product could be cyclized to the bicyclic amide by reaction with $TiCl_4$ in CH_2Cl_2 [84].



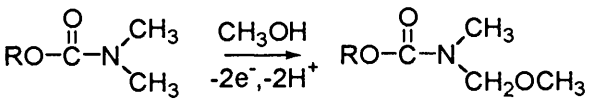
(30)

The anodic methoxylation of amides is not restricted to simple formic and AcOH derivatives, but has been performed also with peptides [Eq. (31)] [86], *n*-substituted carbamates [87–90], and cyclic derivatives such as *N*-methoxycarbonylpyrrolidines [90,91], *N*-methoxycarbonylpiperidines [90,92–95], and oxazolidin-2-ones [96–98].

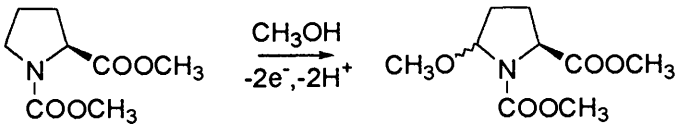


(31)

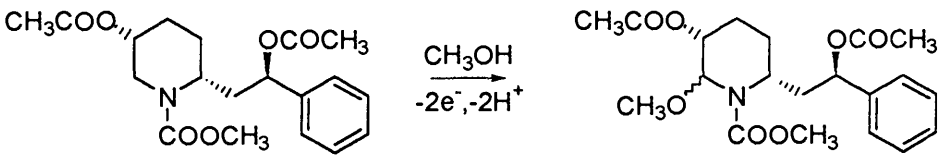
The prototype reaction [87] for methoxylation of a carbamate is shown in Eq. (32), and the applicability is further illustrated by the examples given in Eqs. (33) [91], (34) [93], and (35) [97]. It is seen that the stereochemical configuration of the starting material is preserved in all cases.



(32)



(33)



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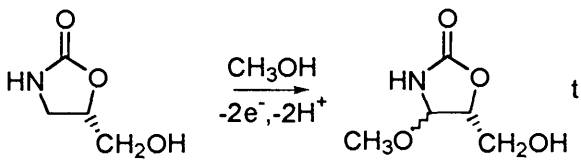
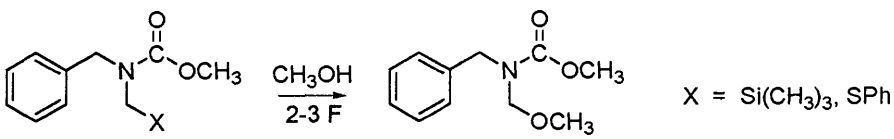


(35)

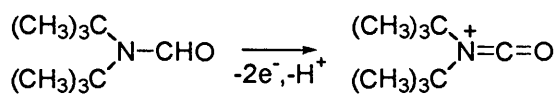
The presence of α-silyl [99] or α-phenylthio [100] groups activates carbamates toward oxidation by 500–600 mV and results in regioselective introduction of a methoxy group at the α-carbon carrying the activating substituent:



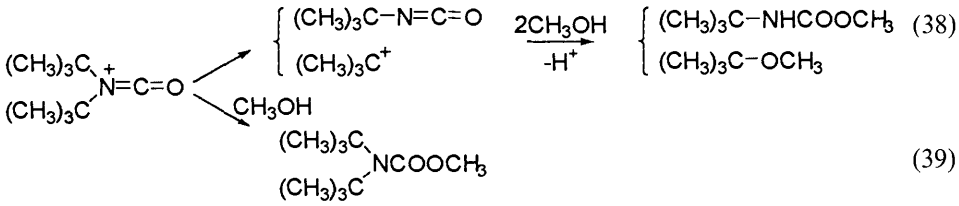
(36)

Sulfonamides and amidophosphates have been used as starting materials as well [101].

In all the examples given so far, the substrate carries at least one N-α-hydrogen atom. The anodic oxidation of fully substituted amides, like N, N-di-*tert*-butylformamide and N-formyl-2,2,6,6-tetramethylpiperidine, in MeOH would be expected to follow a different pathway. The products isolated after 12–14 F, methyl N-*tert*-butylcarbamate and N-methoxycarbonyl-2,2,6,6-tetramethylpiperidine, respectively [Eq. (37)] [102], indicated that the primarily formed substrate radical cation looses the formyl proton. Further oxidation of the neutral radical leads to the cation, which may either undergo cleavage, as in Eq. (38), or nucleophilic attack by the solvent, as in Eq. (39).



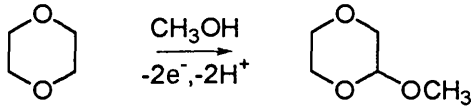
(37)



(38)

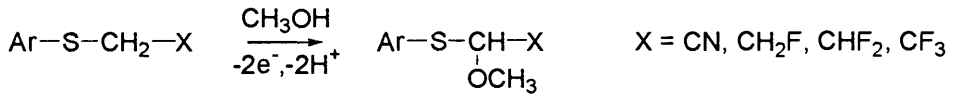
(39)

Saturated ethers, such as 1,4-dioxane, can be α-methoxylated by electrolysis in MeOH–NaOMe or MeOH–NH_4NO_3 in 10–30% yield [Eq. (40)] [103]. Yields are considerably higher, 45–70%, for the heterocyclic 1,3-benzodioxoles [104].



(40)

Related to these reacations is the anodic methoxylation of sulfides carrying an electron-withdrawing substituent, such as cyano [105], fluoromethyl [106], difluoromethyl [106], or trifluoromethyl [106–109] in the α-position [Eq. (41)]. Yields are typically between 50 and 90%. An analogous reaction has been reported for selenides carrying electron-withdrawing perfluoroalkyl or cyano substituents [110].



(41)

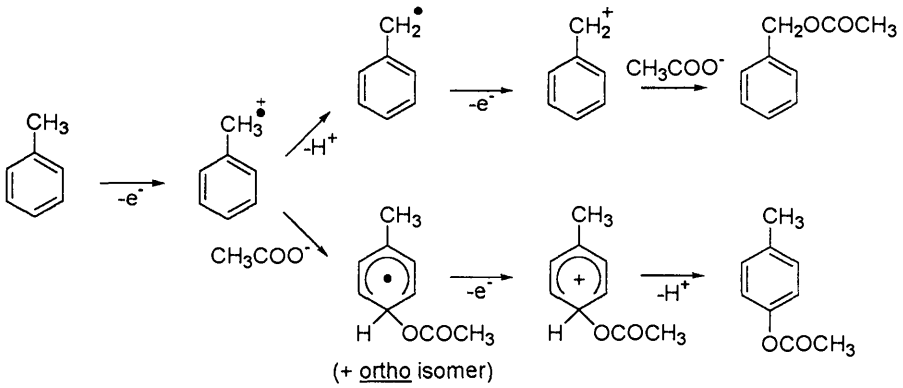
In analogy with what has been observed for carbamates (described earlier), the trimethylsilyl substituent in, for example, 1-phenylthio-1-trimethylsilylalkanes is easily replaced by methoxy during anodic oxidation in MeOH [111,112]. Similarly, the anodic oxidation of α,α'-bis(trimethylsilyl)xylenes in MeOH results in replacement of one trimethylsilyl group by methoxy [113].

C. Acyloxylation

Substitution by an acyloxy group can be accomplished by electrolysis of aromatic and alkylaromatic compounds [4,9–12,114], alkenes [40,115], benzyl ethers [116], alkyl aryl sulfides [107,117], or *N*-alkylsubstituted amides [70,75,118] in the presence of a carboxylate in a suitable solvent. For trifluoroacetoxylation (described later), a variety of relatively deactivated aromatic substrates or aliphatic compounds may be employed. The most commonly encountered process is acetoxylation, which takes place in AcOH or AcOH–Ac_2O. The supporting electrolyte in this case normally is NaOAc, although Me_4NNO_3, Bu_4NBF_4, $NaClO_4$, and others can be employed in certain cases. Other acyloxylations using carboxylates whose corresponding acids cannot be used as solvent have been performed in DMF [118] or MeCN [119,120].

Yields of acetoxylation products vary greatly [4,9–12,114,121], depending on the oxidation potential of the product(s) formed. As a general rule, they tend to be low in nuclear acetoxylation of aromatic compounds, and fair to good in acetoxylations at activated C atoms.

A characteristic feature of the reaction is that nuclear acetoxylation of aromatic compounds requires the presence of AcO^- [122], whereas acetoxylation of the other types of substrates takes place with either AcO^- or other anions present [40,70,123]. Both nuclear and side-chain acetoxylation may be rationalized according to the general mechanism given in Eq. (42).



(42)

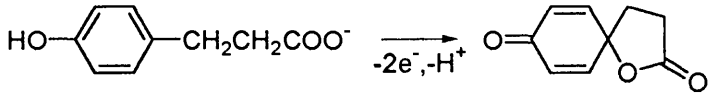
In the context of the direct mechanism, several perplexing features concerning nuclear and side-chain substitution of aromatic compounds have been highlighted [124-126], and in the search for explanations attempts have been made to estimate, by thermochemically based calculations, free energies of activation for reactions between radical cations and nucleophiles. Long-standing puzzles in this area include the dependence of the ratio of side chain/nuclear substituted products on the nucleophile; for alkylbenzenes, side-chain acetoxylation predominates in acetic acid (AcOH) unless AcO^- is present, when nuclear substitution becomes important.

The isomer distribution for anodic acetoxylation of a number of monosubstituted benzenes has been determined [122]. The reaction closely resembles ordinary electrophilic aromatic substitution processes, perhaps on the side of low-selectivity reactions. The isotope effect, k_H/k_D, for nuclear acetoxylation in anisole was found to be 1.0, whereas for α-substitution in ethylbenzene a value of 2.6 was observed. The interpretation of these values is not straightforward [126].

From a preparative point of view it is of interest to notice that selective nuclear substitution may be obtained when the oxidation is carried out in an undivided cell using a cathode made of Pd/C [114]. With this experimental setup, the side-chain acetoxylated product is reduced back to starting material at the cathode. The nuclear substituted product is unaffected and will accumulate during the electrolysis.

Aromatic compounds, in particular those carrying electron-withdrawing substituents, may be oxidized in the presence of CF_3COO^- with consequent trifluoroacetoxylation [127–134]. For compounds PhX, X may be $(CH_3)_3C$, COOMe, NO_2, CF_3, COMe, COPh, and CN; the trifluoroacetoxy derivatives produced by anodic oxidation in CH_2Cl_2–CF_3COOH–Et_4NBF_4 [123], in CF_3COOH–$NaOOCCF_3$ [128], or in CH_3NO_2–CF_3COOH [130] are hydrolyzed during workup to phenols. Yields of the phenols so produced are in the region 20–80%, and usually substantial amounts of the *meta*-substituted phenols are formed. For chlorobenzene, prolonged electrolysis in CF_3COOH–$NaOOCCF_3$, followed by hydrolysis, leads to good yields of the corresponding resorcinol and pyrocatechol derivatives [131].

A number of intramolecular acyloxylations have been reported [135–143], two examples of which are given in Eqs. (43) and (44).



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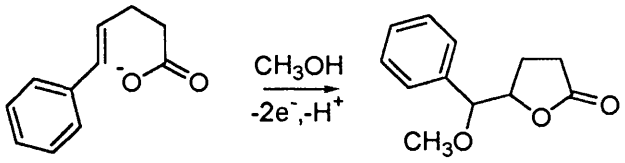
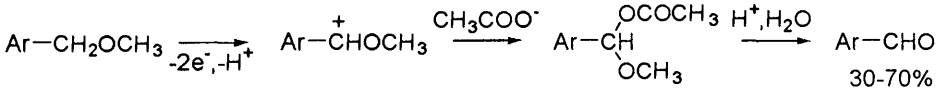


(44)

Acyloxylation of a number of benzyl ethers has been reported [Eq. (45)] [116]. A hemiacetal acetate is presumably formed and subsequently hydrolyzed during the workup procedure to give the aldehyde:



(45)

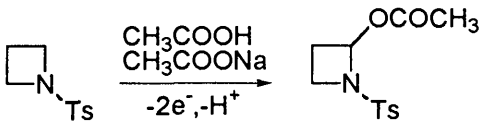
Aryl alkyl sulfides and selenides containing an electron-withdrawing substituent such as trifluoromethyl in the α- or β-position may be α-acetoxylated in good to excellent yields [107–109,144–146]. In the absence of the electron-withdrawing substituent the yields are usually poor [107,144] and give a mixture of the *S*-oxide and the α-acetoxylated product [117]. However, if the oxidation is carried out in boiling AcOH–Ac_2O–NaOAc the corresponding α-acetoxy derivatives may be obtained in almost quantitative yields [117]. Under these conditions the *S*-oxide, if formed at all, is converted to the desired α-acetoxy derivative in a Pummerer reaction parallel to the direct electrochemical acetoxylation. This illustrates that reactions that at room temperature give rise to mixtures of products may be synthetically useful when carried out at higher temperatures at which the thermodynamically more stable products are formed.

Acetoxylation of alkenes takes place in allylic position [40,115], concurrent with addition of acetoxy groups across the double bond or double-bond system. The mechanism is almost certainly analogous to that discussed previously for methoxylation [Eq. (20)]. Because AcO^- is difficult to oxidize, the anodic discharge of simple, unactivated alkenes may be achieved in its presence. Subsequent reactions of the cationic intermediates are not very selective, but several experimental parameters may be controlled and the method can compare well with the few competing chemical methods.

The oxidation of *n*-alkanes is possible in CF_3COOH containing R_4NBF_4, with the carbocations so formed being trapped to give secondary trifluoroacetates [147–150]. Anodic trifluoroacetoxylation of long-chain aliphatic ketones [151] or carboxylic acids [148] gives rise to mixtures of positional isomers. The substitution pattern for the ketones indicates that the reaction proceeds via intramolecular abstraction of a hydrogen atom from the 5-position by the carbonyl group. This reaction has been observed to take place during the oxidation of aliphatic ketones in MeCN (described later). The trifluoroacetoxylation of carboxylic acids is less selective, and the product distribution gives little indication of the mechanism.

The acyloxylation of *N*-alkylsubstituted amides has received considerable attention [70,75,118], from both the mechanistic and the preparative points of view. In electrolytes containing alkali metal carboxylates the direct mechanisms probably operates, whereas in the case where a nitrate salt is the supporting electrolyte an indirect mechanism involving hydrogen abstraction from the *N*-alkyl group by anodically generated $NO_3^{\cdot}$ is indicated. The same mechanistic problem is encountered in side-chain acetoxylation of alkylaromatic compounds in the presence of NO_3^- [123,152,153]. The method for large-scale substitution into *N*-formyl derivatives, which works so well for methoxylation, fails when applied to acetoxylation, probably because of the acid sensitivity of the products [80].

Similarly, 1-(*p*-tolylsulfonyl)azetidine is converted to the corresponding 2-acetoxy derivative by anodic oxidation in AcOH–NaOAc [154]:



(46)

D. Substitution by Nitrate Ion

Concurrent with side-chain acetoxylation of alkylaromatic compounds in AcOH–NH_4NO_3, formation of benzyl nitrates, $ArCH_2ONO_2$, is observed in about the same yield as the $ArCH_2OAc$ [123,152,153]. It seems likely that NO_3^- and AcOH compete as nucleophiles for an intermediate benzyl cation, although an indirect mechanism cannot be ruled out completely because of the complexity of the supporting electrolyte behavior [155].

III. FORMATION OF CARBON-TO-SULFUR BONDS: THIOCYANATION

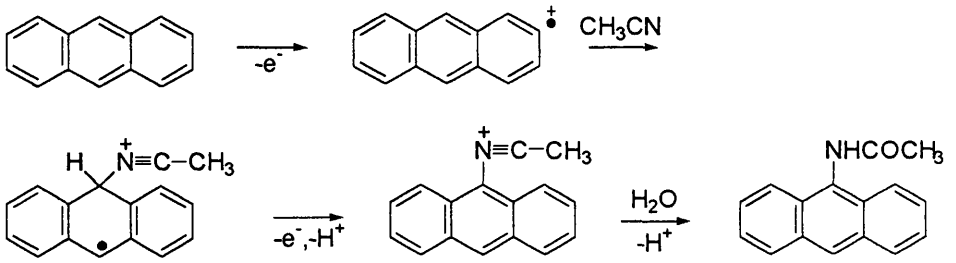
Phenols and aromatic amines are thiocyanated on electrolysis in an aqueous solution of SCN^- [13]. The reaction is indirect since there is compelling evidence that the thiocyanating reagent must be $(SCN)_2$, formed by anodic oxidation of SCN^- [156]. In MeCN solution oxidation of SCN^- and $SeCN^-$ in the presence of phenol of various aromatic amines leads to thiocyanation and selenocyanation in 55–80% yields 157 [109].

The direct reaction between a radical cation derived from an aromatic hydrocarbon (naphthalene) and SCN^- has been studied by mixing the salt $(C_{10}H_8)_2PF_6$ with a solution of Bu_4NSCN in CH_2Cl_2 at −78°C [158]. Two major products were isolated, 1-naphthylthiocyanate (kinetic control, 28%) and 2-naphthyl-*iso*-thiocyanate (thermodynamic control, 8%). The mechanistic details leading to this product distribution are not clear.

IV. FORMATION OF CARBON-TO-NITROGEN BONDS

A. Acetamidation

Anodic oxidation of anthracene in MeCN containing $(CF_3CO)_2O$ (to remove water and suppress hydroxylation) leads to the formation of the acetamidation product in 85% yield [159]. Results obtained by cyclic voltammetry supported the mechanism shown in Eq. (47).



(47)

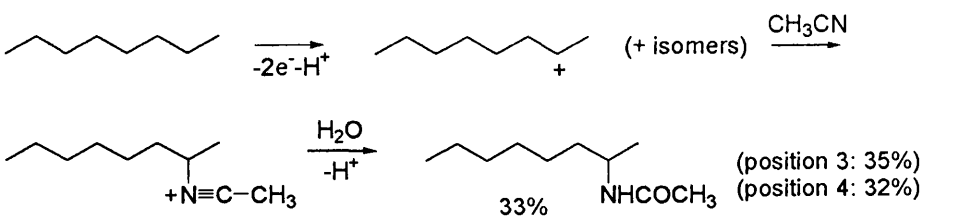
The rapid reaction of the anthracene radical cation with MeCN is nicely illustrated by the observation of an irreversible, two-electron oxidation peak in the voltammogram at +1.2 V versus SCE, whereas in CH_2Cl_2–$(CF_3CO)_2O$ the peak corresponds to a reversible one-electron oxidation process.

The acetamidation of alkylaromatics has been partly discussed [Eq. (11)]. Methyl-substituted benzenes are particularly good substrates for side-chain acetamidation, and they have featured in numerous product and mechanistic studies [9–12,21–23,160–162]; ethylbenzene and isopropylbenzene give other products predominantly [163]. Hexamethylbenzene has been a favored substrate for mechanistic investigations of acetamidation [160,164], and in this case there is evidence [165] that on the time scale of conventional cyclic voltammetry, proton loss is rapid from hexamethylbenzene radical cation but relatively slow from hexaethylbenzene.

At a Pt anode, aromatic carbonyl compounds undergo fairly efficient nuclear acetamidation in moist MeCN with Et_4NBF_4 as supporting electrolyte [129].

Alkenes undergo the combined addition of $NHCOCH_3$ and F when oxidized in MeCN containing $Et_4NF{\cdot}3HF$ [166,167] and of $NHCOCH_3$ and PhSe when oxidized in MeCN containing PhSeSePh [168]. It is of interest to notice that while fluoroacetamidation of cyclic alkenes results predominantly in *cis*-addition, selenoacetamidation gives the *trans*-isomer as the major product.

n-Alkanes can be oxidized in MeCN–R_4NBF_4 solutions (cf. Chapter 13). The observation of well-defined oxidation waves, the consumption of 2 F, and the formation of acetamides at secondary carbon atoms supports the mechanism outlined in Eq. (48) for *n*-octane [147]. In some cases prior cleavage of carbon–carbon bonds is observed, again in a manner that suggests a carbocation intermediate [Eq. (49)] [169].



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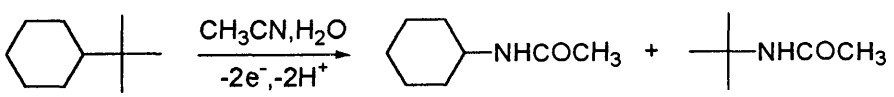
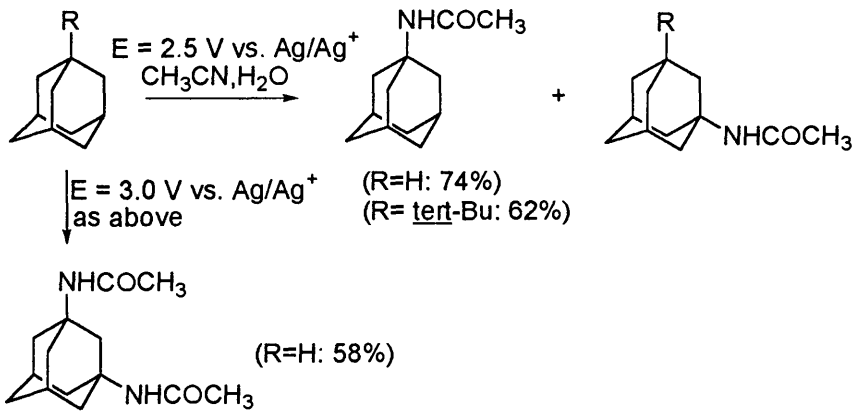


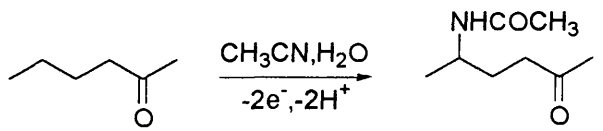
(49)

In the wake of the early work just described, several investigations of anodic acetamidation of polycyclic hydrocarbons were initiated; substituted adamantanes were much used in this work because of their availability and their relative ease of oxidation [170–174]. The results are generally explicable in terms of expected stabilities of intermediate carbocations and competition between proton loss and C–C bond cleavage. Difunctionalization of adamantanes is also possible using anodic acetamidation [Eq. (50)] [174].



(50)

Esters, ketones, and alcohols may also undergo substitution in MeCN [175–180]. Some of these substrates are oxidized in a region where oxidation of the electrolyte is concurrent, and, certainly for esters, it may well be that an indirect mechanism operates with necessary initial abstraction of hydrogen by a radical derived from the electrolyte [176]. Examples are given in Eqs. (51) and (52). In one case, the anodic oxidation of 2-octanone in MeCN containing $LiClO_4$, the reaction mechanism has unambiguously been demonstrated to involve specific abstraction of one hydrogen atom at C-5 by the carbonyl oxygen in a six-membered ring cyclic transition state, reminiscent of the first chemical step in the gas-phase McLafferty rearrangement [180].



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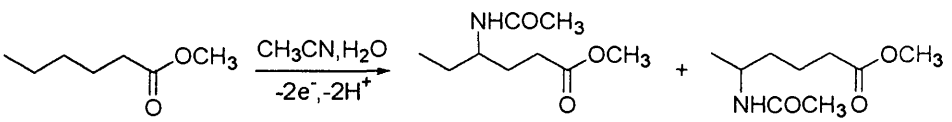
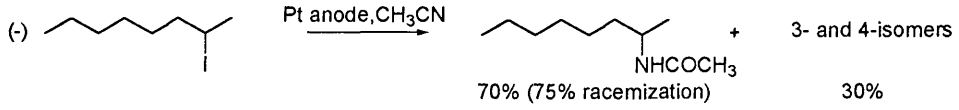


(52)

Acetamidation is also a result of the anodic oxidation in MeCN solution of carboxylates (cf. Chapter 14) and alkyl halides [170,181–185]. Much discussion and experimentation has centered on the likely mechanism of cleavage of the alkyl halides, particularly the iodides. From the extent of rearrangement of cations supposedly produced by alkyl iodide oxidation compared with that for the same cations produced by solvolysis of tosylates, it has been suggested that in electrolysis MeCN assists cation formation [182]. The S_N2

character of this process receives support from the 20% inversion observed for oxidation of optically active 2-iodooctane [Eq. (53)]. An alternative mechanism must, however, be considered and is based on the known anodic oxidation, at the potentials used for alkyl iodide cleavage, of iodine to an iodine(I) species [183]. The process given in Eq. (54), which is catalytic in iodine, is therefore plausible, given the initial generation of some iodine by direct cleavage.



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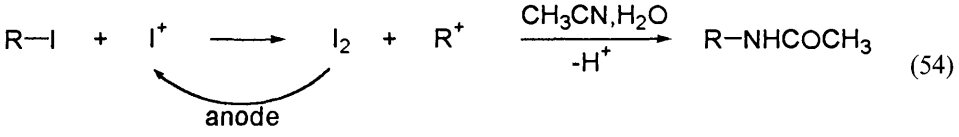
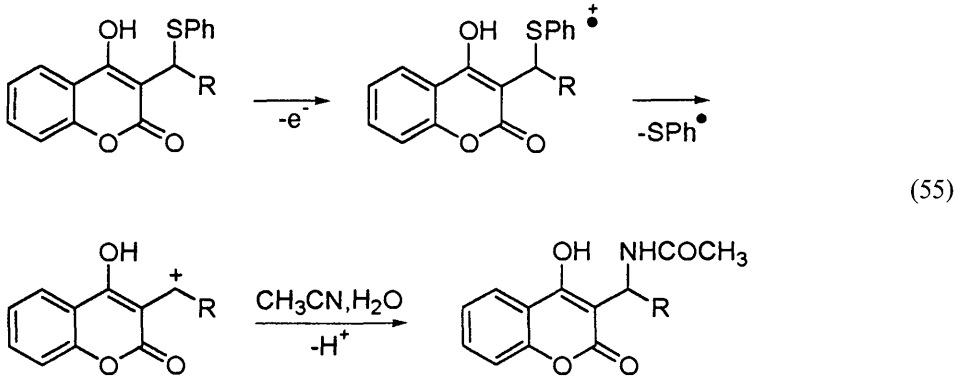


(54)

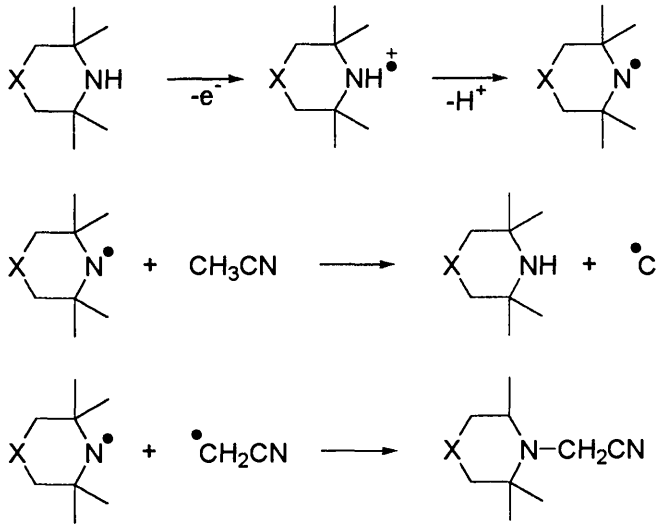
A Ritter-type reaction is also observed during the anodic oxidation of phenylthiomethane derivatives [186] of the type shown in Eq. (55), which summarizes the proposed reaction mechanism.



(55)

B. *N*-Cyanomethylation and Amination

The solvent MeCN may be incorporated in the product in an altogether different type of process, which leads to formation of substituted acetonitriles. For instance, the oxidation of 2,2,6,6-tetramethylpiperidine, or the corresponding morpholine, in MeCN–$NaClO_4$ under oxygen-free conditions leads to the formation of an aminoacetonitrile derivative [187]. The reaction was suggested to follow the mechanism given in Eq. (56).



(56)

Essentially the same mechanism has been proposed for anodic α-amination of tetrahydrofuran, which may be accomplished by oxidation of, for example, R_2NH or R_2NLi, in this solvent [188]. The best yields (70–80%) were observed when R_2NH was piperidine.

C. Nitration

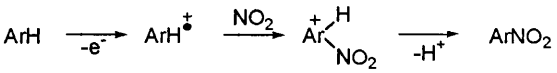
The formation of nitro compounds upon electrolysis of a suspension of an aromatic hydrocarbon in dilute aqueous HNO_3 has been known for a long time [189]. It has been interpreted in terms of formation of a high concentration of HNO_3 near the anode surface, in which region an ordinary electrophilic nitration process would take place. Studies on the anodic oxidation of NO_3^- in nitromethane [190] would seem to confirm this assumption; N_2O_5 is the oxidation product, probably formed via reactions (57) and (58). In aqueous solution this would lead to the formation of HNO_3.

$$2NO_3^- \xrightarrow[-4e^-]{} 2NO_2^+ + O_2 \tag{57}$$

$$NO_2^+ + NO_3^- \longrightarrow N_2O_5 \tag{58}$$

Similarly, the oxidation of N_2O_4 in, for example, concentrated HNO_3 or H_2SO_4 [191–193], MeCN [194], or sulfolane [195] has been shown to lead to nitrating mixtures containing NO_2^+.

Another mechanism of anodic nitration involves the generation of a radical cation in the presence of NO_2 [Eq. (59)]. This mechanism has attracted considerable attention [196–198] in the vivid discussion of electron transfer as a general step in conventional nitration, where in Eq. (59) the nitronium ion instead of the anode serves to oxidize the substrate to the radical cation state in the first step. Here it is sufficient to notice that, using naphthalene and methyl-substituted naphthalene radical cations as substrates in CH_2Cl_2–Bu_4NPF_6, it was shown [196] that the coupling reaction between $ArH^{\cdot +}$ and NO_2 is more selective than nitration by acetyl nitrate in $(CH_3CO)_2O$ or N_2O_4 in CH_2Cl_2.



(59)

The anodic oxidation of solutions of aromatic hydrocarbons and $AgNO_2$ in MeCN gives mononitration with a substitution pattern that is held to support initial formation of a radical cation [199]. Alkenes may similarly be oxidized in the presence of $AgNO_2$ and, depending on the alkene, nitro products are formed by substitution or addition. In probably the best example, coelectrolysis of anthracene and $AgNO_2$ at 1.3 V versus SCE gave 9-nitroanthracene in 47% yield (current efficiency 28%) and from 1,1-diphenylethylene, electrolyzed at 1.5 V, 1,1-diphenyl-2-nitroethylene was obtained in 40% yield. In each case 1 F was consumed. However, since NO_2^- is more easily oxidized than both anthracene and 1,1-diphenylethylene, it cannot be excluded that NO_2^- is oxidized at the anode to give NO_2/N_2O_4, in itself a good nitrating reagent in homogeneous medium [196]. Constant-potential electrolysis of 1,4-dimethoxybenzene in micellar solutions containing NO_2^- showed, however, that the nitration product, 2,5-dimethoxynitrobenzene, was only formed at potentials sufficiently high to oxidize both NO_2^- and 1,4-dimethoxybenzene. This was taken as evidence in support of a reaction including the coupling between the radical cation and NO_2 [200].

Aliphatic *gem*-dinitro compounds can be prepared by anodic oxidation of a nitroparaffin in aqueous alkaline solution in the presence of an excess of NO_2^- [201]. Yields are considerably better when Ag^+ is the oxidizing agent [202], so that an indirect oxidation process involving the generation of Ag^+ at an Ag anode was found to give excellent results [203].

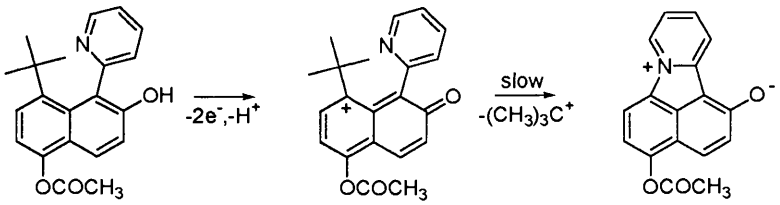
D. Substitution by Cyanate Ion

Both nuclear and side-chain substitutions of alkylaromatics by NCO^- have been observed [204]. Thus, electrolysis of anisole in MeOH–KOCN results in substitution of hydrogen by a methylcarbamyl group, via the isocyanate. The reaction has been pictured as a direct oxidation process. Yields are fairly low ($< 20\%$).

E. Pyridination

Nitrogen bases (e.g., amines) are not generally good nucleophiles for anodic substitution reactions, as they are themselves easily oxidized [2] (cf. Chapter 15). Pyridine bases, which are difficult to oxidize ($E_{pa} = 1.4$ V vs. Ag/Ag^+ [205]), provide exceptions. The vinylic proton of the very easily oxidized tris (*p*-methoxyphenyl)ethylene may be substituted anodically by pyridine to give the corresponding pyridinium ion [206] and, similarly, the oxidation of 1,2-dimethoxybenzene in MeCN containing pyridine resulted in formation the substitution product, 3,4-dimethoxyphenylpyridinium ion [207]. In contrast, the oxidation of 1,2-dimethoxy-4-prop-1-enylbenzene under the same conditions leads to the formation of a dipyridinum salt resulting from addition of pyridine over the side-chain C–C double bond [207]. This is analogy to the addition of pyridine over the 9,10-positions in anthracene derivatives [208–210]. Anodic pyridination of 2,6-di-*tert*-butyl-4-methylphenol in MeCN gives a mixture of the corresponding 4-pyridinated cyclohexadienone and the side-chain pyridinated phenol [46]. The anodic pyridination of Schiff's bases and *N*-methyl-4-methoxybenzanilide [211] has been reported and investigated in detail.

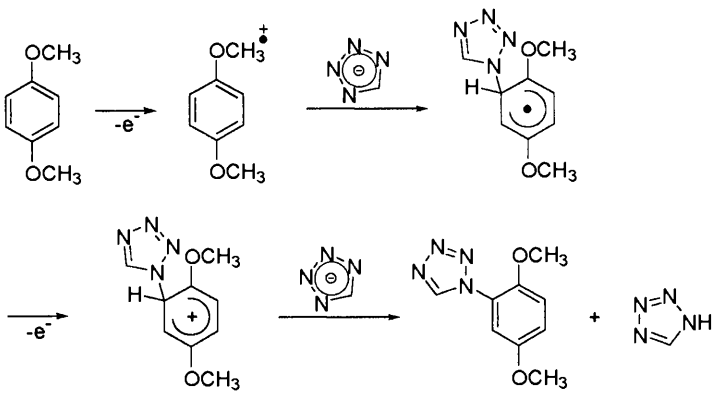
The reaction has been put to good preparative use for the formation in fair yields (~ 50%) of some heterocyclic zwitterions [Eq. (60)] [212]. This reaction also provides an example where the leaving group is a carbocation rather than a proton.



(60)

F. Substitution by *N*-Heterocyclic Compounds

Anodic oxidation of, e.g., 1,4-dimethoxybenzene in an undivided cell containing a tetrazole or triazole derivative together with the corresponding anion leads to the formation of the substituted product, presumably through the mechanism shown in Eq. (61) [213].



(61)

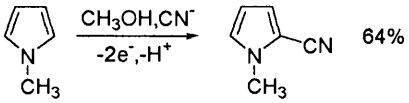
V. FORMATION OF CARBON-TO-CARBON BONDS

A. Cyanation

Anodic cyanation is a reaction of considerable preparative interest since it allows for the direct introduction of a cyano group into an aromatic ring [214–226]. Contrary to the situation in acyloxylation and alkoxylation, the product is more resistant toward oxidation than the starting material, due to the strong electron-withdrawing effect of the cyano group, and in principle good yields should be obtainable. The reaction is often run in MeOH–NaCN [214–219], which gives concurrent methoxylation [227]. This is avoided if MeCN–Et_4NCN is used [220]. An important advance is the use of emulsions with phase-transfer agents [222–225].

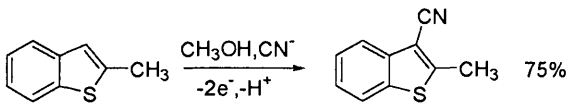
The reaction was initially believed to be a homolytic substitution reaction by anodically generated cyano radicals [214]. However, while significant oxidation of CN^- takes place at a potential as low as 0.5 V versus SCE, the cyanation process will occur only in the region around or above $E_{1/2}$ of the substrate. This strongly implies a direct mechanism [215,219,220] analogous to that for acetoxylation.

Isomer distribution for cyanation of aromatic compounds has been determined in a number of cases [217–220]. The selectivity of the cyanation reaction is higher than that of the anodic acetoxylation process. This high regioselectivity has been put to good use for the preparation of 2-cyanopyrroles and 2-cyanoindoles [226]:



(62)

If the 2-position is blocked, cyanation occurs at the 3-position. Similarly, cyanation of 1-methylpyrazole gives a mixture of the 4- and 5-carbonitrile [228]. The efficient substitution observed for many pyrroles, imidazoles [229], and indoles contrasts markedly the addition reactions observed for furans (cf. Chapter 16) and thiophenes [230]. However, this difference may only be apparent. At least for two of the cases already cited [226], it has been demonstrated [231] that the cyanosubstituted pyrroles arise as a result of elimination during workup of the 2,5-addition product originally formed. For benzo[b]thiophenes, cyanation leads predominantly to substitution products [232]:



(63)

The direct nature of attack of CN^- on radical cations of aromatic compounds has been demonstrated by CV [221]. The reversible one-electron oxidation of anthracene becomes irreversible in the presence of CN^-, and 2 F electrolysis gives a mixture of cyano and isocyano addition across the 9,10-position. Interestingly, it appears that cyanation of 9,10-diphenylanthracene gives the 9,10-diphenyl-9,10-dicyano-9,10-dihydroanthracene only [233].

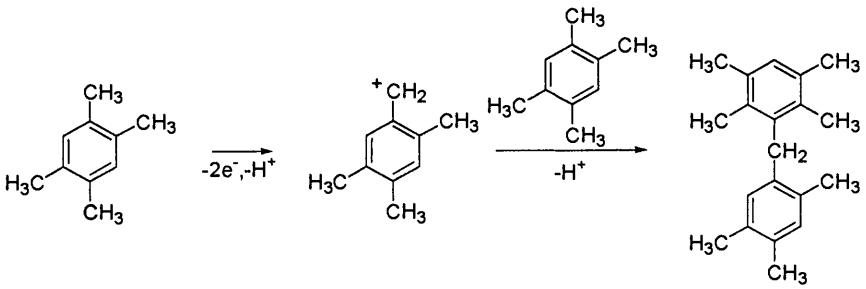
The best conditions for nuclear cyanation involve the use of emulsions, typically CH_2Cl_2–H_2O–NaCN, with a phase-transfer agent. This has been described in detail for the monocyanation of naphthalene and anisole with isolated yields in the region 50–70% [222,223]. For dimethoxybenzenes the yields are somewhat lower [223].

For *trans*-stilbene and *trans*-4,4-dimethoxystilbene, cyanation in an emulsion system gives for the former a mixture of addition and substitution products (including substitution of the vinylic protons), whereas for the latter substitution of the vinylic protons is the predominant reaction [225].

Alkylaromatic compounds do not give any side-chain substitution product under conditions that produce nuclear cyanation products [217–219] (discussed earlier). Anodic cyanation of *tert*-butylanisoles leads to mixtures of addition and substitution products [234].

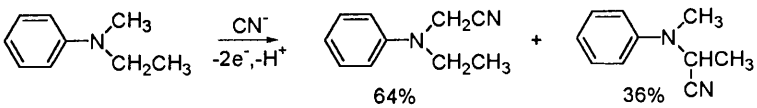
In most cases cyanation involves loss of a proton, but in some cases an alkoxyl group may be displaced with very good yields of substitution products [220,224]. Thus, 1,2- and 1,4-dimethoxybenzene undergo cyanation by displacement of one of the methoxy groups, presumably via an ECE-type mechanism [Eq. (42)]. On the other hand, anisole and 1,3-dimethoxybenzene do not undergo methoxyl displacement but instead give nuclear substitution in the usual manner. The presence of an activating group in the *ortho* and *para* positions thus seems essential for methoxyl group displacement. However, the selectivity is less pronounced when the reactions are carried out in aqueous micellar solution [235,236]. The fate of the displaced alkoxyl group is not always clear; the observation of aldehyde and alcohol among the products of anodic cyanation of 4,4′-dialkoxybiphenyls [224] and

the proven loss of benzyloxy radical from the radical cation of dibenzyl ether [237] support the mechanism shown in Eq. (64). The cyanation of the 4,4′-dialkoxybiphenyls [Eq. (64)] shows the use of emulsion systems to good advantage; the products include an important class of liquid crystals.



(64)

Tertiary amines are also substrates for the cyanation reaction [220,223,238–241], with substitution taking place at the carbon atom α to the nitrogen atom. In this case substitution often occurs preferentially at a primary carbon atom in mixed amines, such as *N*-ethyl-*N*-methylaniline [Eq. (65)]. This is not so for cyclic tertiary amines [Eq. (66)] [238].



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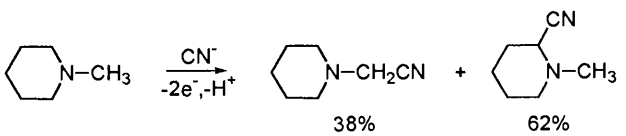
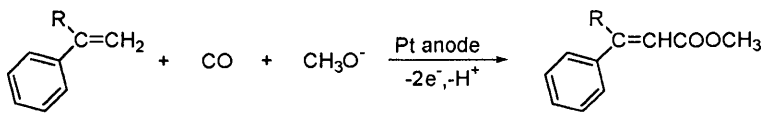


(66)

In this study, current–potential curves have been used to show that discharge of, for example, triethylamine occurs prior to the oxidation of the MeOH–NaCN electrolyte. Again, anodic cyanation in emulsion systems offers preparative advantage [223].

B. Carbomethoxylation

An unusual and interesting carbomethoxylation reaction occurs during electrolysis of an arylolefin in MeOH–NaOMe under CO pressure between two Pt electrodes [Eq. (67)] [242].

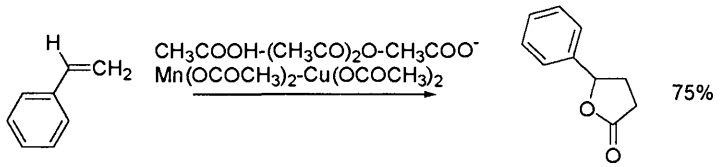


(67)

It has been shown that the Pt cathode dissolves to give a Pt(CO) complex. This is transformed at the anode to a carbomethoxy–Pt (CO) complex, which attacks the arylolefin to give the carbomethoxylation product.

Carbomethoxylation of styrene derivatives may also be effectively accomplished by oxidation in AcOH–Ac_2O–NaOAc mixtures containing small amounts of $Cu(OAc)_2$ and $Mn(OAc)_2$, with the latter serving as a mediator. However, under these conditions the reaction takes a slightly different course and leads predominantly to cyclized products as

illustrated by one [Eq. (68)] of the several examples reported [243]. Related to this reaction is the oxidation of 5-arylpent-1-enes in the presence of, for example, diethyl malonate [Eq. (69)] [244].



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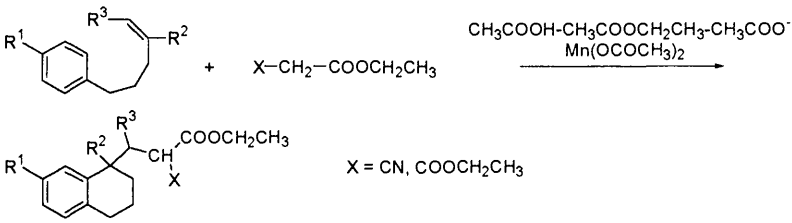
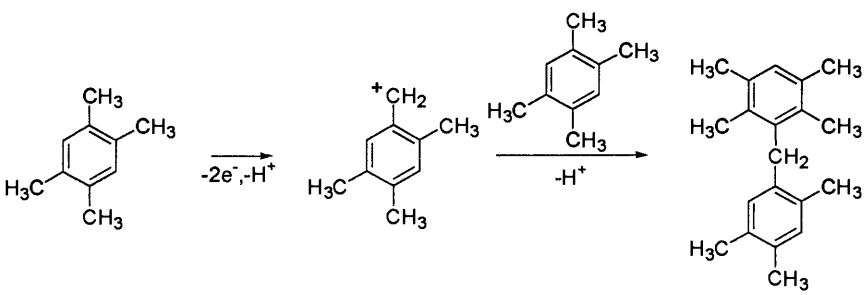


(69)

C. Inter- and Intramolecular Coupling with C–C Bond Formation

Reaaction conditions for anodic substitution may often be arranged so that the starting material is the most nucleophilic species present. Consequently, many synthetically useful inter- and intramolecular reactions may be so accomplished (cf. Chapter 22 for details of anodic coupling reactions).

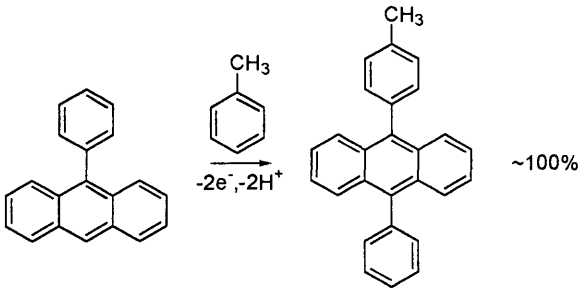
An obvious case is the oxidation of electron-rich hydrocarbons in nonnucleophilic media, typically CH_2Cl_2–R_4NBF_4 or CH_2Cl_2 mixed with strong acids such as CF_3COOH, CH_3SO_3H, or CF_3SO_3H [245,246]. The radical cations formed by one-electron oxidation either dimerize or attack the starting material; an example is given in Eq. (70). Such couplings have also been achieved using a large-scale capillary gap cell with a graphite anode [246].



(70)

Intramolecular coupling of aromatic systems based on this principle has been particularly fruitful. Phenols or aromatic ethers are usually involved: If the activation of the aromatic system is sufficient, the reactions do not require especially nonnucleophilic solvents. In the simplest case anisole may be anodically coupled in CH_2Cl_2–CF_3COOH to give, after workup in the presence of Zn dust, 4,4′-dimethoxybiphenyl in 60% yield [247].

Related to these coupling reactions is the reaction between an anodically generated radical cation, for example, derived from anthracene or 9-phenylanthracene, and a carbon nucleophile such as anisole, toluene or benzene [Eq. (71)] [248].



(71)

VI. FORMATION OF CARBON-TO-HALOGEN BONDS

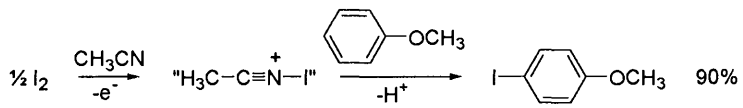
A. Fluorination

The virtually unique suitability of electrochemical methodology for preparing fluorinated compounds warrants the inclusion of a separate treatment on this subject (Chapter 25).

B. Chlorination, Bromination, and Iodination

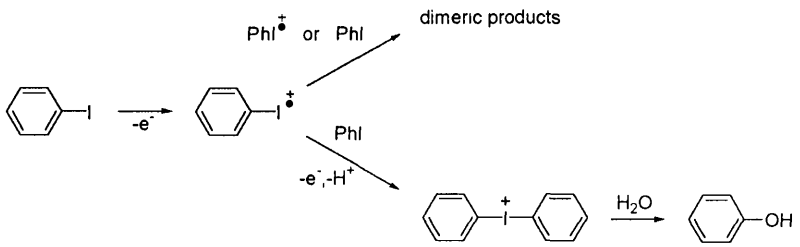
The oxidation of halide ions to molecular halogen is relatively easy; consequently, the mechanism of anodic halogenation, brought about by oxidation of organic substrates in the presence of halides is not always clear [249–254]. In many cases it may involve halogenation by anodically generated halogen. In other cases, where the substrate is easily oxidized, the halide has the role of a nucleophile and attacks a radical cation.

The oxidation of I_2 in MeCN produces a very reactive although ill-defined iodine (I) species [183,255]. The production of this species, in either MeCN or CH_2Cl_2 in the presence of a variety of substituted benzenes, results [255] in efficient iodination, as in Eq. (72).



(72)

Formation of a C–I bond is also the result of anodic oxidation of iodobenzene in the presence of benzene [256,257]. Two reactions are in competiton [Eq. (73)]; a careful investigation of the electrode kinetics supports the mechanism given and also allows optimization of conditions to the point where a 95% yield of the diphenyliodonium cation is obtained [257]. Hydrolysis of this species completes a route from benzene to phenol.



(73)

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25
Electrochemical Partial Fluorination

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I. INTRODUCTION

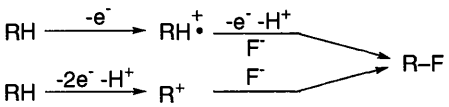
In contrast to electrolysis in anhydrogen fluoride, anodic fluorination of organic compounds can be achieved also in aprotic solvents (acetonitrile, dichloromethane, sulfolane, nitromethane, dimethoxyethane, etc.) in the presence of fluoride ions to provide mostly mono- and/or difluorinated materials [1–6]. Electrolyses are most often conducted at constant potentials slightly higher than the first oxidation potential of the substate by using a platinum or graphite anode. The choice of the combination of a supporting fluoride salt and an electrolytic solvent is most important to accomplish efficient partial fluorination because competitive passivation of the anode takes place very often during the electrolysis. Pulse electrolysis is in many cases effective in order to avoid such passivation. Therefore, difficult-to-oxidize fluoride salts, which do not cause the passivation of the anode and have strongly nucleophilic F^-, are generally recommended as the supporting fluoride salts. Thus, $R_3N \cdot nHF$ and $R_4NF \cdot nHF$ are most often used and even $R_4N \cdot BF_4$ salts are effective in some cases [2,3,6].

Particularly when HF supporting salts and low hydrogen overvoltage cathodes such as platinum are used, the discharge of protons (hydrogen evolution) occurs predominantly

at the cathode during the electrolysis. Therefore, a divided cell is not always necessary for the fluorination under such conditions.

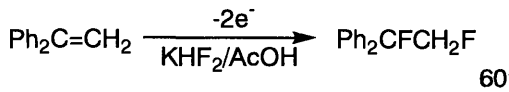
In aprotic solvent, F^- becomes more nucleophilic and HF a weak acid. However, the reactivity of F^- is quite sensitive to the water content of the electrolysis system because a hydrated F^- is a weak nucleophile [7,8]. Drying of both the solvent and electrolyte is therefore necessary to optimize the formation of fluorinated products.

Since the discharge potential of fluoride ions is extremely high (> 2.9V vs. SCE at Pt in acetonitrile [9]), an ECEC mechanism involving initial formation of a cation radical followed by attack of fluoride ions is often suggested:



(1)

In 1953, anodic fluorination of 1,1-diphenylethylene in $KH_2/AcOH$ was reported by Schmidt and Schmidt [Eq. (2)] [10]. This seems to be the first example of selective electrochemical fluorination. They also used liquid HF, MeCN, EtOH, or AcOH containing anhydrous HF [11], or even AgF as the fluorine source [12]. However, these electrolytic systems are not always effective and not widely applicable.

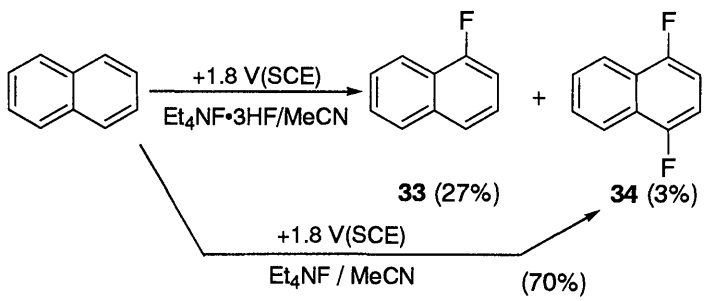


(2)

In contrast, Rozhkov and coworkers found that $Et_3N{\cdot}HF$ salt and $Et_4NF{\cdot}3HF$ were highly effective for conducting selective fluorination, particularly for nuclear fluorination of aromatic compounds (see Sec. II) [13]. This seems to be the first major breakthrough in anodic partial fluorination.

II. ANODIC FLUORINATION OF AROMATIC COMPOUNDS

In 1970, Rozhkov and coworkers reported the first example of anodic partial fluorination of aromatic compound [Eq. (3)] [14,15]. They found that anodic oxidation of naphthalene in $Et_4NF{\cdot}3HF/MeCN$ provided 1-fluoronaphthalene mainly, while the use of Et_4NF instead of $Et_4NF{\cdot}3HF$ led to the efficient formation of 1,4-difluoronaphthalene solely.

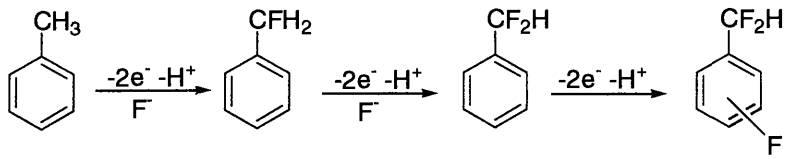


(3)

Since that time, anodic partial fluorination of various aromatic compounds such as anthracenes and substituted benzenes has been accomplished using various fluoride salts [1–3,13,16–18].

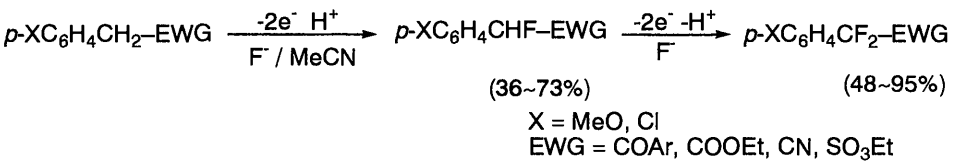
Recently, Momota and coworkers developed a new series of fluoride salts, $R_4NF{\cdot}nHF$ (R = Me, Et, and *n*-Pr; $n > 3.5$) that are useful in partial fluorination reaction [19,20]. These electrolytes are nonviscous liquids that have high electric conductivity and stability. As a result, anodic partial fluorination of arenes such as benzene, mono-, di-, and trifluorobenzenes, and fluorotoluenes was successfully carried out at high current densities by employing these fluoride salts in the absence of solvent with good to high current efficiencies (66–90%) [21–23]. Nonconducting polymer films often form at anode surfaces when ordinary fluorides salts are used as supporting electrolytes and fluorine sources. Howver, such film formation is reduced considerably when these new supporting fluoride salts are used.

Generally, anodic benzylic substitution reactions take place readily. However, anodic benzylic fluorination does not always occur. The major competitive reaction is acetamidation when MeCN is used as a solvent [24–26]. In contrast to these cases, triphenylmethane is selectively monofluorinated in 80% yield [27]. When $Et_4NF{\cdot}nHF$ ($n = 3,4,5$) is used in the absence of MeCN, anodic fluorination of toluene and monofluoromethylbenzene provides mainly mono- and difluoromethylbenzenes, respectively [22]. On the other hand, difluoromethylbenzene affords only products fluorinated in the benzene ring [Eq. (4)] [28].



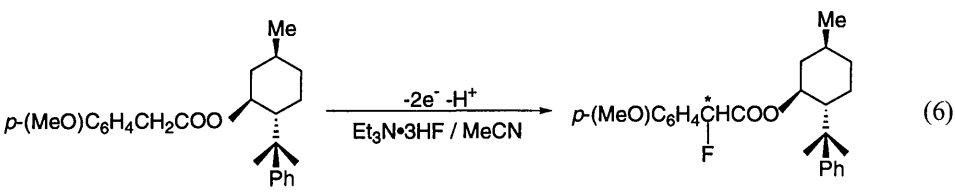
(4)

Laurent and coworkers found that anodic benzylic mono- and difluorination proceeds selectively when the benzylic position is substituted by electron-withdrawing groups (EWG) [Eq. (5)] [29,30]. In these cases, *p*-methoxy or *p*-chloro substituents on the benzene ring are necessary for the operation of efficient fluorination. In their absence, benzylic acetamidation becomes a major reaction. The use of sulfolane as a solvent instead of MeCN leads to higher yields of fluorinated products owing to the absence of competing acetamidation [31].



(5)

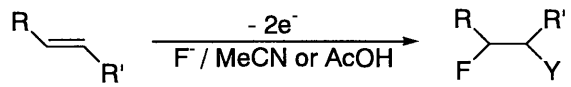
Diastereoselective anodic fluorination of phenylacetate having a chiral auxiliary has also been reported [Eq. (6)] [32].



(6)

III. ANODIC FLUORINATION OF OLEFINS

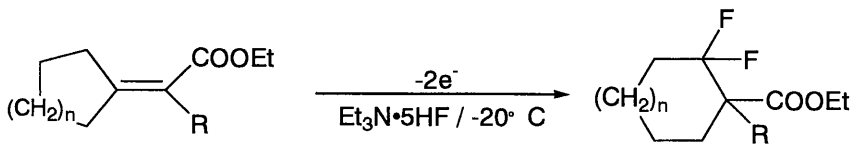
Anodic oxidation of olefins in the presence of fluoride ions provides mono- and/or difluorinated products [Eqs (2) and (7)] [10,33,34]. Butadiene gives a 1:2 mixture of 1,2- and 1,4-adducts [35]. Anodic fluorination of vinyl sulfides such as 2-(phenylthio)styrene provides vicinal difluorides [36].



(7)

Y = F⁻, NHCOMe, OAc

1-Phenylhexene undergoes stereoselective difluorination and fluoroacetamidation upon anodic oxidation in MeCN, while the difluorination predominates in the less nucleophilic solvent CH_2Cl_2 [26]. Electrochemical fluoroacetamidations of 1-alkylindene were investigated by Laurent's group. The stereoselectivities with respect to F/alkyl and F/MeCONH introduction were found to be mainly *trans* and *cis*, respectively [37]. In contrast, Yoneda and coworkers found that anodic oxidation of cyclic unsaturated esters in $Et_3N{\cdot}5HF$ resulted in fluorination induced ring expansion to provide 2,2-difluorocycloalkanecarboxylates [38]:

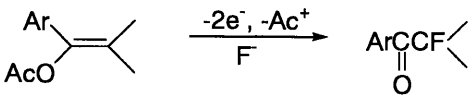


(8)

n = 1~3
R = H, CH_3, COOEt

Yield = 32~71%

Also, α-fluoroketones were prepared from α-acetoxystyrene and 1-acetoxy-3,4-dihydronaphthalene [39,40]:



(9)

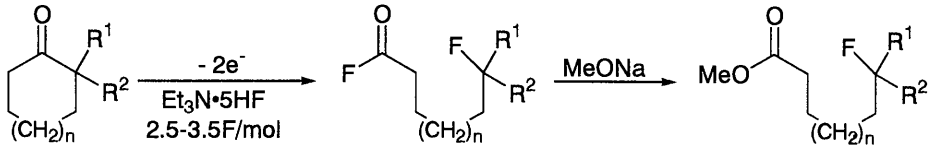
44~63%

IV. ANODIC FLUORINATION OF CARBONYL COMPOUNDS

Selective anodic fluorination of aldehyde and cyclic ketones can be successfully carried out in $Et_3N{\cdot}5HF$ to give the corresponding acyl fluorides and fluoroacyl fluorides, respectively, in good yields, as shown in Eqs. (10) and (11) [41]. In these reactions, fluoride salts such as $Et_3N{\cdot}3HF$ lead to lower yields, reflecting the fact that this salt is discharged prior to oxidation of the carbonyl compounds.

$$\mathrm{RCHO} \xrightarrow[\mathrm{Et_3N{\bullet}5HF\ /\ MeCN}]{-2e^-\ -H^+} \mathrm{RCF(=O)} \tag{10}$$

R = *t*-Bu, C_7H_{15}, C_6H_{11} : 66~85%



$R^1 = R^2 = Me$, n = 0~2 (80%)
$R^1 = Me$, $R^2 = Cl$, n = 1 (86%)

(11)

V. ANODIC FLUORINATION OF CHALCOGENO COMPOUNDS

Fuchigami's group and Laurent's group independently found that electron-withdrawing groups, such as fluoroalkyl, ester, and cyano groups, markedly promote anodic α-fluorination of sulfides, as in Eqs. (12) and (13) [42–46].

$$\mathrm{PhSCH_2Rf} \xrightarrow[\mathrm{Et_3N{\bullet}3HF\ /\ MeCN}]{-2e^-\ -H^+} \mathrm{PhSCHFRf} \tag{12}$$

Rf = CF_3 (62%); CF_2H (53%); CFH_2 (60%)

$$\mathrm{R^1SCH_2R^2} \xrightarrow[\mathrm{Et_3N{\bullet}3HF\ /\ MeCN}]{-2e^-\ -H^+} \mathrm{R^1SCHFR^2}$$

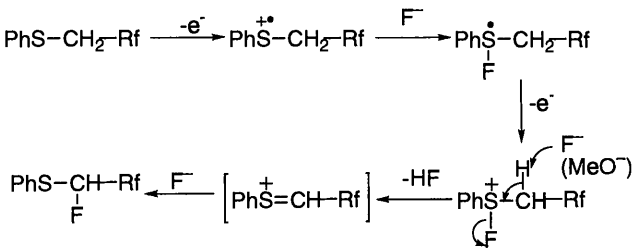
(~88%)

R^1 = Ph, *p*-MeC_6H_4, $PhCH_2$, C_7H_{15}
R^2 = CF_3, CF_2H, CFH_2, H, CH_3, CN, COOR, COR, $CONR_2$, $PO(OEt)_2$

(13)

The anodic fluorination is highly regioselective and widely applicable, even though α-thio-substituted esters have several positions susceptible to substitution by a fluorine. A fluorine is introduced exclusively α to the ester group, and no fluorination of the *p*-tolyl, benzyl, or heptyl groups is observed [Eq. (13)] [46]. As shown in Eq. (12), the electron-withdrawing ability of the fluoroalkyl group does not affect the efficiency of anodic monofluorination of sulfides. This is in sharp contrast to the anodic methoxylation of fluoroalkylsulfides [47]. Even simple alkyl phenyl sulfides devoid of an electron-withdrawing group undergo fluorination in ethereal solvents such as THF and DME to provide monofluorinated products in moderate yields [45].

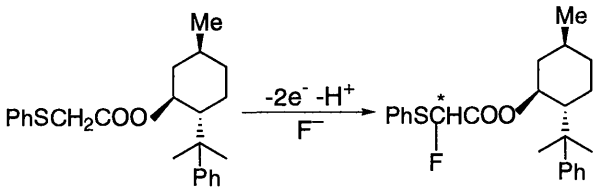
Fuchigami and coworkers have proposed a Pummerer-type mechanism via the fluorosulfonium cation for the anodic fluorination of sulfides [Eq. (14)], based on the comparative study of anodic methoxylation and fluorination of fluoroalkyl sulfides [43,45].



(14)

Simonet and coworkers similarly performed regioselective anodic α-monofluorination in an $Et_3N{\cdot}3HF$/MeCN solution of alkyl aryl sulfides having an electron-withdrawing group on the aromatic ring [48].

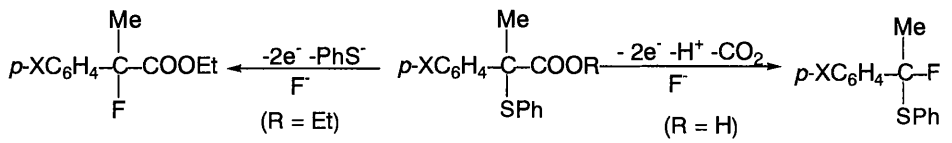
The diastereoselective anodic fluorination of α-phenylsulfenyl acetates has been studied using various chiral auxiliaries [Eq. (15)] [49]. The diastereoselectivity is affected by supporting fluoride salts, and $Et_4NF{\cdot}3HF$ leads to better selectivity relative to $Et_3N{\cdot}3HF$ or $Et_3N{\cdot}2HF$.



16% *d.e.* ($Et_3N{\bullet}3HF$); 18% *d.e.* ($Et_3N{\bullet}2HF$);
28% *d.e.* ($Et_4NF{\bullet}3HF$)

(15)

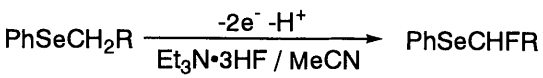
It is interesting that anodic fluorination of α-thio α-arylesters and α-thioacids provides different types of fluorinated products [Eq. (16)] [50].



X = Cl, MeO, Me_2CHCH_2

(16)

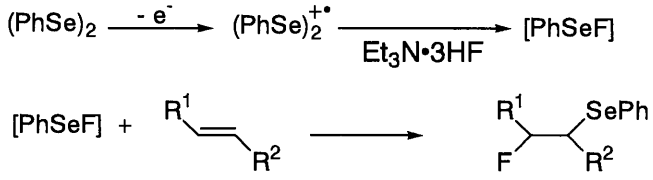
Anodic monofluorination of selenides bearing electron-withdrawing cyano and ester groups can be performed in an undivided cell, while the fluorination of α-selenoamide requires an anion-exchange membrane diaphragm [51]:



R = CN, COOEt, $CONH_2$ (60~70%)

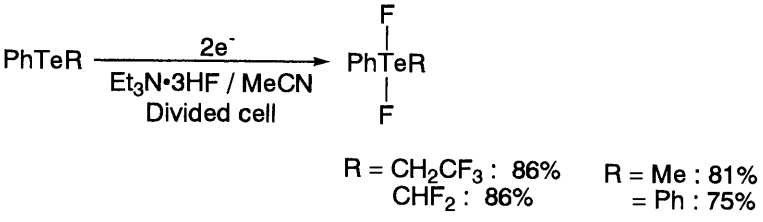
(17)

Uneyama and coworkers reported electrochemical generation of "PhSeF" for fluoro-selenation of alkenes and alkynes and recycling of the selenenylating reagent [52]:



(18)

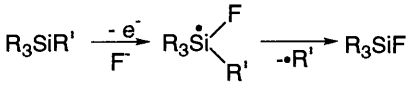
Anodic oxidation of organotellurium compounds in the presence of fluoride ions results in difluorination at the tellurium atom selectively in excellent yields and with high current efficiencies [53]:



(19)

VI. ANODIC FLUORINATION OF OTHER HETEROATOM COMPOUNDS

Anodic oxidation of tetraalkylsilanes in the presence of fluoride ions provides the corresponding fluorosilanes derived from cleavage of the C–Si bond, as in Eq. (20) [54]. The proposed intermediates are the pentacoordinate silyl radicals, which eliminate the most stable alkyl radical to give the corresponding fluorosilane. Becker and Shakkour found that anodic oxidation of cyclic peralkylsilanes results in the formation of α, ω-difluorosilanes via Si–Si bond cleavage, as in Eq. (21) [55].



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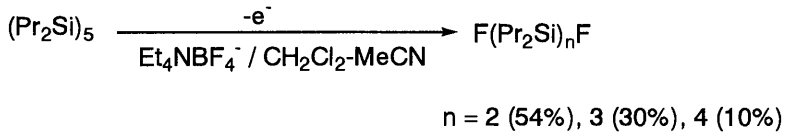
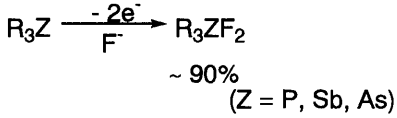


(21)

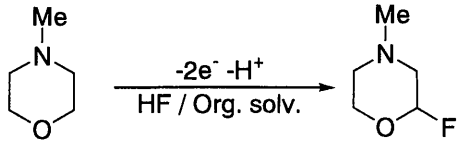
Anodic oxidation of organic compounds containing group 15 elements in the presence of fluoride ions provides the corresponding fluorinated products [Eq. (22)] [56–61]. Fluorination occurs at the heteroatoms selectively.



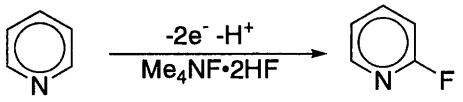
(22)

VII. ANODIC FLUORINATION OF HETEROCYCLIC COMPOUNDS

Though partially fluorinated heterocycles are focus of much biological interest, limited examples of selective anodic fluorination of heterocycles have been reported [Eqs. (23-27)] [62–66]. These processes are limited to nitrogen- and oxygen-containing heterocycles, and the yields are generally quite low. In addition, no successful anodic fluorination of sulfur-containing heterocycles has been reported up to 1991.



28% (23)



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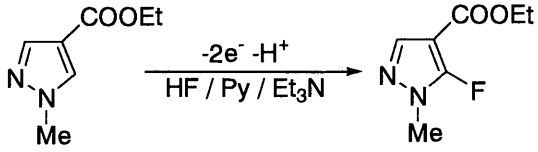

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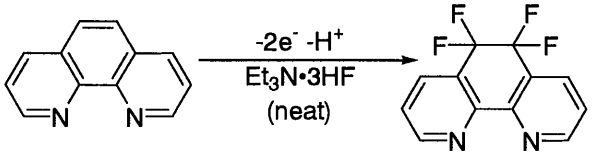
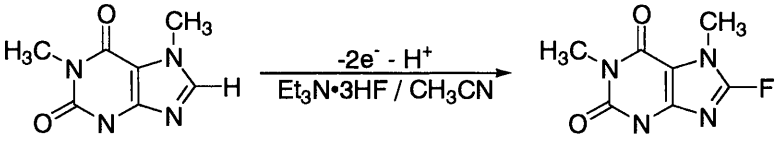


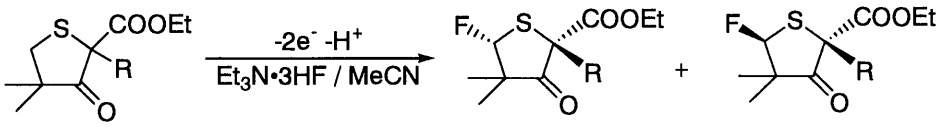
34% (26)



40% (27)

Fuchigami and coworkers have developed conditions for highly selective anodic fluorination reactions of various heterocyclic compounds including sulfur-containing heterocycles, as discussed later [3,6].

Anodic fluorination of 4-thianones [67] and 4,4-dimethyl-2-ethoxycarbonyl-3-thiolanones [68] in $Et_3N{\cdot}3HF$/MeCN provides the corresponding monofluorinated products in moderate to good yields:

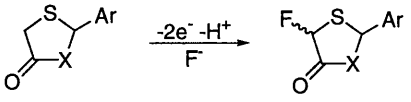


R= Me (74%; *trans/cis*: 74/25)

R= Bzl (71%; *trans/cis*: 61/39)

(28)

Highly regioselective anodic monofluorination of 2-aryl-4-thiazolidinones can be performed by using pulse electrolysis in $Et_3N{\cdot}3HF$/MeCN [Eq. (29)] [69]. However, this electrolytic system is not suitable for anodic monofluorination of 2-substituted 1,3-dithiolan-4-ones and 1,3-oxathiolan-4-ones owing to severe passivation of the anode. In contrast, $Et_4NF{\cdot}4HF$ provides monofluorinated products selectively [Eq. (29)] [70,71]. In these cases, benzylic fluorination does not take place at all, although anodic benzylic substitution easily takes place in general. The high regioselectivity can be explained in terms of facilitation of deprotonation of radical cation intermediate of the substrates by the electron-withdrawing carbonyl group (i.e., kinetic acidity control).



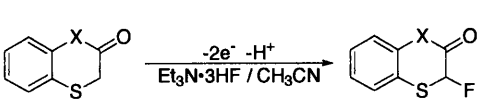
X = N, Ar = Ph (84%; *trans/cis* : 57/43) (in $Et_3N{\cdot}3HF$ / MeCN)

X = O, Ar= Et (86%; *trans/cis*: 53/47) (in $Et_4NF{\cdot}4HF$ / MeCN)

X = S, Ar= n-Pr (78%; *trans/cis*: 52/48) (in $Et_4NF{\cdot}4HF$ / MeCN)

(29)

N-Substituted 2*H*-1,4-benzothiazin-3(4*H*)-one derivatives undergo selective anodic fluorination very efficiently in $Et_3N{\cdot}3HF$/MeCN [Eq. (30)] [72]. In contrast, anodic oxidation of 3*H*-1,4-benzoxathian-2-ones in $Et_3N{\cdot}3HF$/MeCN gives poor yields of fluorinated products owing to strong passivation of the anode. However, use of $Et_4NF{\cdot}mHF$ ($m = 3,4$)/MeCN suppresses the passivation and leads to good to excellent yields on pulse electrolysis [Eq. (30)] [73]. The increases observed in the yields and current efficiencies are mainly attributable to much higher oxidation potential of $Et_4NF{\cdot}4HF$/MeCN compared with that of $Et_3N{\cdot}3HF$/MeCN.



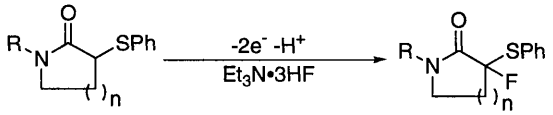
57

X = NMe: 68%, Ni-Pr: 88%, NCOPh: 77%

X = O : 80% ($Et_4NF{\cdot}4HF$), 54%($Et_4NF{\cdot}3HF$), 5% ($Et_3N{\cdot}3HF$)

(30)

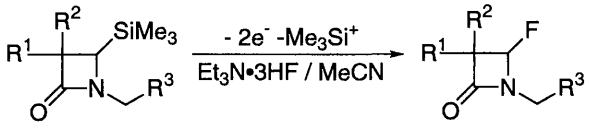
Various α-phenylthio lactams including β-lactams can be also anodically fluorinated efficiently [Eq. (31)] [72,74]. However, seven-membered lactams does not give fluorinated products.



(31)

n= 0 : R = n-Bu (92%); c-Hx (84%)
n= 1: R= Me (85%); c-Hx (84%)
n= 2: R= Me (69%)
n= 3: R= Me (0%)

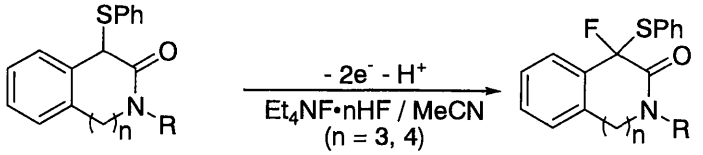
Suda and coworkers reported anodic fluoro desilylation of β-trimethylsilyl-β-lactams [Eq. (32)]. In this reaction, the good leaving trimethylsilyl group assisted the regioselective fluorination.



(32)

$R^1 = R^2 = H$, $R^3 = Ph$: 80%, Pr : 78%
$R^1 = H$, $R^2 = CH_3CH_2O(Me)CH$, $R^3 = Ph$: 75%

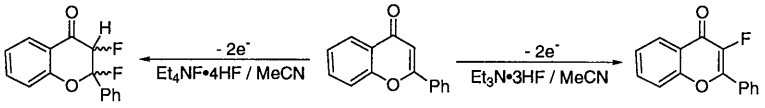
Highly regioselective, anodic monofluorination of oxinodole and 3-oxo-1,2,3,4-tetrahydroisoquinoline can be achieved by using $Et_4NF{\cdot}nHF$ ($n = 3,4$) [Eq. (33)] [76,77]. Although three kinds of benzylic carbons exist in a molecule [$n = 1$ in Eq. (33)], the fluorination takes place at the 4-position exclusively.



(33)

n = 0, R = Ph, *p*-Tol : 50-64%
n = 1, R = CH_2Ph : 71%

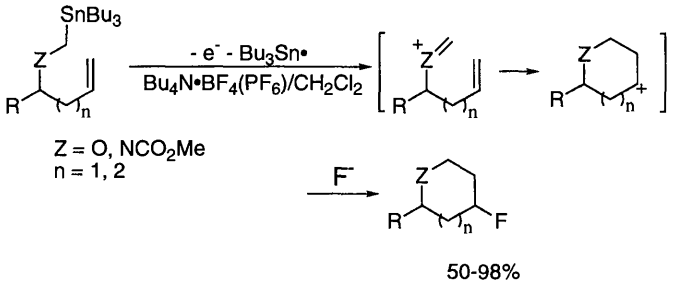
Recently, Laurent and coworkers reported that anodic fluorination of thioflavone provided mono- and/or trifluorinated products depending on the applied potential [78]. On the other hand, Fuchigami and coworkers found that anodic fluorination of flavones by using $Et_3N{\cdot}3HF$ provides mainly 3-monofluoroflavones, while the use of $Et_4NF{\cdot}4HF$ leads to formation of 2,3-difluoroflavones preferentially, as in Eq. (34) [79].



(34)

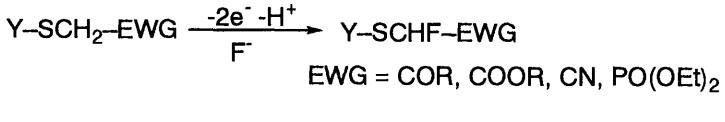
68% (*cis/trans* = 2)
58%

Yoshida and coworkers found an example of an anodic process involving direct displacement of tributylstannyl group with fluorine. They extended this fluorination process to accomplish unique cyclization fluorination [Eq. (35)] [80]. Similar fluorocyclization methods based on the use of an organothio group instead of the stannyl group have been developed [81].



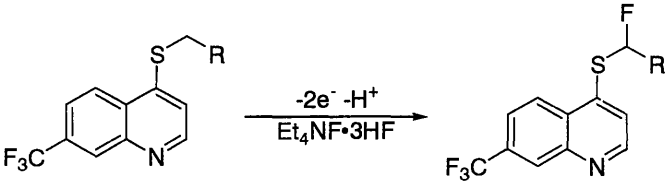
(35)

Anodic monofluorination of the side chain of various heterocyclic compounds has been systematically studied [82–84]. The active methylenethio group attached to heterocycles is selectively fluorinated to give the corresponding α-fluorinated products in moderate to good yields [Eqs. (36) and (37)] [82–87]. In these reactions, the choice of solvent and supporting fluoride salt is of great importance in order to achieve efficient fluorination reaction [84–87].



(36)

Y = 2-pyridyl, 4-pyrimidinyl : 55~76% (in Et_3N•3HF / MeCN)
Y = 2-Benzothiazolyl, 51~82% (in Et_4NF•3HF / DME)
Y = 2-Benzoxazolyl : 17~39% (in Et_4NF•4HF / DME)

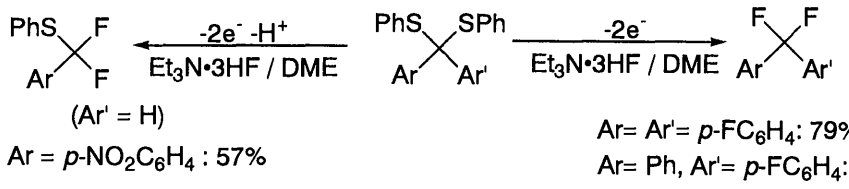


R = $COCH_3$: 96% (in DME), 28% (in MeCN)
R = H : 63% (in DME)

(37)

VIII. ANODIC *gem*-DIFLUORINATION

Organic compounds containing a difluoromethylene group are of great interest in biochemistry since this functionality is isopolar and isoteric with an ether oxygen. *gem*-Difluorinated products were obtained directly from sulfides bearing an electron-withdrawing group using difficult-to-oxidize Et_4NF·HF [88]. On the other hand, anodic desulfurization of dithioacetals of ketones in the presence of Et_3N·3HF provides the corresponding *gem*-difluoro compounds while dithioacetals of aromatic and aliphatic aldehydes give *gem*-difluoro thioethers [Eq. (38)] [89].

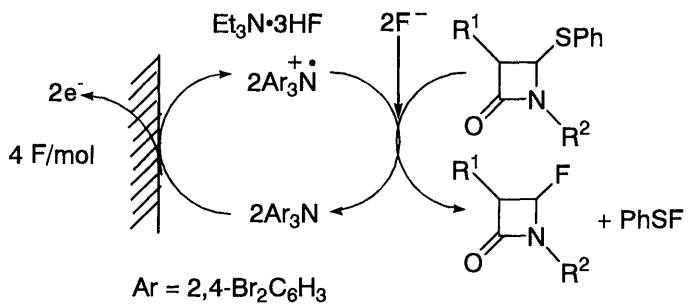


(38)

In contrast, anodic oxidation of hydrazones in the presence of fluoride ions provides mainly monofluorinated products, and *gem*-difluorinated products are formed in low yields [90].

IX. INDIRECT ANODIC FLUORINATION

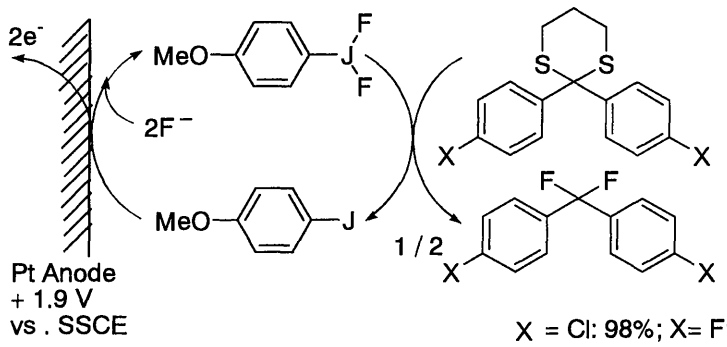
As mentioned earlier, passivation of the anode due to the formation of nonconductive polymers on the anode takes place commonly during anodic oxidation of organic substrates in the presence of fluoride ions. For example, as shown in Eq. (38), anodic oxidative difluorodesulfurization of dithioacetals does occur; however, the current efficiencies are low due to this passivation phenomenon [89]. In order to prevent such passivation, Fuchigami and coworkers have developed an indirect electrochemical method using various mediators [91–95]. Thus, Br^+/Br^- and triarylamine redox mediators have been shown to be effective for selective mono- and difluorodesulfurization of dithioacetals, respectively [91]. Furthermore, triarylamine has recently been shown to be a highly effective mediator for monofluorodesulfurization of β-lactams [Eq. (39)] [95]. In the absence of triarylamine, severe passivation of the anode takes place during anodic fluorination.



(39)

Although hypervalent iodobenzene difluorides are selective fluorinating reagents, their preparation is not straightforward and these reagents are not stable. Fuchigami and coworkers have found that anodic oxidation of *p*-substituted iodobenzenes in the presence of fluoride ions provides the corresponding iodobenzene difluorides in high yields [92]. These workers also demonstrated that selective indirect anodic *gem*-difluorodesulfurization of dithioacetals can be successfully carried out using a catalytic amount of iodo-

benzene in the presence of fluoride ions [Eq. (40)] [92]. Double mediatory systems using iodobenzene and chloride ions are also effective for this *gem*-difluorodesulfurization even at a much lower oxidation potential compared with the single mediatory system [93]. In this reaction, anodically formed hypervalent iodobenzene chlorofluoride acts as an oxidizing reagent.



(40)

Recently, Yoneda's group has also demonstrated that the iodobenzene difluoride mediator is also effective for α-fluorination of β-dicarbonyl compounds using $Et_3N \cdot 5HF$ as the supporting salts [96].

X. CONCLUSIONS

In contrast to chemical fluorination methods using hazardous and/or costly reagents such as F_2, $FClO_3$, CF_3OF, XeF_2, Et_2NSF_3 (DAST), *N*-fluoropyridinium salts, and *N*-fluorotriethylenediamine derivatives (selectfluor), anodic partial fluorination can be carried out under mild conditions and does not require any hazardous reagents. Although there are still many problems to solve, anodic fluorination is a promising procedure for the preparation of partially fluorinated organic substances.

ACKNOWLEDGMENTS

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26

Stereochemistry of Organic Electrode Processes

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I. INTRODUCTION

Stereochemistry is one of the most interesting and important fields in organic chemistry and has brilliantly advanced to date. Although organic electrochemistry has rapidly developed since the 1960s, its stereochemical aspect has advanced very slowly. One of the earliest works concerning the stereochemistry of an electrochemical reaction may have been made by Clemo and Smith [1]: They reduced *p*-dimethylaminobenzaldehyde at a cathode in aqueous sulfuric acid and separated one of the two diasteromeric glycols as a product. Although the stereochemistry of this kind of reductive dimerization of carbonyl compounds was afterward studied extensively and made considerably clearer, many of later workers who investigated other reactions did not pay much attention to the stereochemistry of their products.

However, in the last 20 years, the sitution seems to be changing, since many convenient and useful techniques for stereoisomeric analysis have been developed and have become familiar not only to organic chemists but also to electrochemists.

An electrochemical reaction is a unique oxidation–reduction that takes place in a unique heterogeneous interface between an electrode and an electrolytic solution, as is described later in detail. Therefore, the stereochemical feature of electrochemical reaction must be also unique. However, there is a problem. Generally, it is not easy to rationalize simply and clearly a stereochemical course involved in a given electrochemical reaction on the basis of experimental results and theoretical considerations, since the manner of stereocontrol is very complicated in general. Thus, despite a number of rules, it is not easy to predict stereochemical results in advance. Although it is likely that this problem will be solved in the near future, fortunately it is not so difficult to improve the stereochemical results empirically (optimization) from the point of view of stereoselective synthesis. Nearly one thousand original papers published in the past and some general [2–11] and topical [12–27] reviews should be very helpful for this type of investigation.

II. STEREOCONTROL IN ELECTROCHEMICAL REACTION

A. Steric and Polar Factors

Substrate and/or intermediate species absorb on an electrode surface and orient themselves so that their least hindered sides face the electrode unless there is another effect, such as a polar one. This may be the simplest steric factor governing the stereochemistry of reactions. There may also be more complicated steric effects that result in conformational or configurational change of the species, since the electrode on which the species adsorb strongly may behave as if it were a very bulky substituent. For example, visualize a substituted cyclohexane molecule (Fig. 1). The substituent must be preferentially in the equatorial position in a free state (**I**), but it may be in the axial position in an adsorbed state (**II**), if the electrode effectively gives more steric hindrance than the substituent.

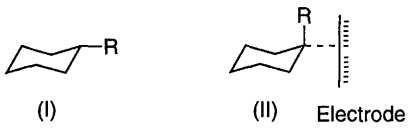
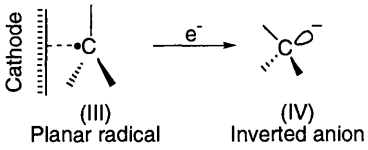


Figure 1. Steric interaction of adsorbed substituted cyclohexane with an electrode.

In addition to the steric interaction of adsorbed species with the electrode, the species can sterically interact with the other species adsorbed on the electrode surface.

An electrode interface has a layered structure in which a nonuniform electric field (potential slope) is generated by polarization of the electrode. An extremely strong electric field of around $10^8\,V\,cm^{-1}$ in the innermost layer, the so-called electron transfer layer, which is very thin, 10 Å or less, might cause a variety of polar effects. Since not only the electron transfer step but also adsorption and some of the chemical steps involved in an electrolytic reaction take place in the electron transfer layer, the electrochemical reaction should be strongly influenced by polar factors. The orientation of polar adsorbed species, such as ions and dipoles, is electrostatically influenced, and consequently the stereochemistry of their reactions is also controlled by this kind of electrostatic factor.

A conformational or configurational change may also occur at the electrode interface. For example, when a planar radical (**III**) receives one electron from a cathode to give the corresponding anion, the original configuration of the radical may be inverted by such a strong electric field to give the inverted anion (**IV**), as shown in Eq. (1):



(1)

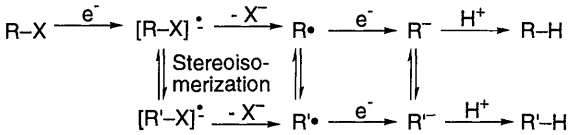
B. Conformational and Configurational Stabilities

The stereochemistry of reactions is controlled by conformational and configurational stabilities of intermediate species in the transition state. Therefore, the stereochemical course of reactions must be discussed on the basis of the interemdiates and reaction mechanism that have been presumably clarified by electrochemically and organic chemically reasonable ways. However, on the contrary, it is also likely that a stereochemical result makes the mechanism more clear. In this sense, a stereochemical study can be useful as one method for analyzing the mechanism.

Anyway, it should be noted that the conformational and configurational stabilities of the species in an electrode interace may be quite different from those in free states, owing to the peculiar steric and polar factors. In a given situation, the conformation or configuration at the electrode interface may be the reverse of that in the free state.

The relation between the rate of each reaction step and the steric stability of the intermediate species must also be considered to rationalize the stereochemical results. Consider the electrochemical reduction [Eq. (2)] of an alkyl halide (R-X) to the corresponding alkane (R-H) via a radical anion $[(R\text{-}X)^{\cdot -}]$, radical (R·), and anion (R^-) mechanism (ECEC). The order of configurational stability may be $R\text{-}H > (R\text{-}X)^{\cdot -} > R^- > R\cdot$ in general, but the stability of R· is not always lower than that of R^- when the adsorption of R^- is weakened by electrostatic repulsion by the cathode. The situation is more compli-

cated when the stereoisomerization of the intermediates must be considered. For instance, if the reaction rate of an unstable intermediate is high enough, its isomerization can actually be neglected. In contrast, the isomerization of other intermediates with very low rates cannot be neglected even though they may have considerable stability.



(2)

C. Thermodynamic and Kinetic Control

It is important in a mechanistic discussion of stereochemical results to know whether the stereochemistry of products is kinetically or thermodynamically controlled. However, in many reports this point is ignored; moreover, only a few reports have mentioned the thermodynamic equilibrium ratio of stereoisomeric products. The former point can be examined not only by experiment but also by computational molecular calculation, but it may not always be easy to determine the ratio. For the latter, much more attention to the stereochemical literature must be paid by electrochemists engaging in stereochemical studies.

D. Stereoselective Synthesis

The most important problem from a synthetic aspect is how to increase the stereoselectivity of a desired product. For this purpose, empirical procedures seem to be more useful at present than theoretical or mechanistic ones, because the manner of stereocontrol in electrochemical reactions is too complicated, as described earlier. It has been well known that stereochemical results are affected by a variety of conditions, such as electrode material, electrode potential, current density, supporting electrolyte, solvent, additive, and temperature. Modification of electrodes is also useful for changing stereochemical results.

It is strongly desired that theoretical considerations be used much more in designing electrochemical stereoselective synthesis in the near future. Therefore, in this chapter the theoretical and mechanistic problems of the stereochemistry of electrochemical reactions are discussed, as well as stereoselective synthesis.

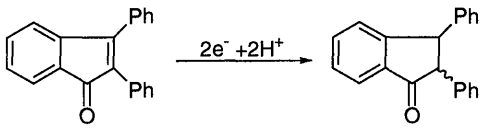
III. STEREOSELECTIVE AND STEREOSPECIFIC ELECTROREDUCTION

A. Olefinic Compounds

1. Hydrogenation to Alkanes

Since olefin molecules can have stereoisomers (*cis* and *trans*; *Z* and *E*), the interesting stereochemistry, which is not only stereoselectivity but also stereospecificity, of their hydrogenation should be observed when the products also have stereoisomers (*d*, *l* and *meso*; *threo* and *erythro*). However, only in a few works could stereospecificity be observed. Dimethylmaleic and dimethylfumaric acids are reduced at a mercury cathode to form *d*, *l* and *meso* α, α'-dimethylsuccinic acids, respectively. This is direct evidence that this hydrogenation proceeds through *trans* addition of hydrogen.

1,2-Disubstituted cyclic olefins give the corresponding stereoisomeric (*cis* and *trans*) products in the hydrogenation, but studies from the aspect of stereoselective synthesis have been rarely reported [28]. However, Sarrazin and Tallec [29,30] reported remarkable stereochemical results in the hydrogenation of some 2,3-disubstituted indenones to the corresponding indanones at various pH values and indicated a tentative interpretation of the results. The most remarkable result was obtained using 2,3-diphenylindenone, as shown in Eq. (3). This suggests that the hydrogenation proceeds through the *cis* addition in a strongly acidic medium but with *trans* addition in approximately neutral media.



(3)

100% (*cis*/*trans*: ∞) in 0.25 M H_2SO_4
100% (*cis*/*trans*: 0) at pH 4.7-9.3

Utley and coworkers [31,32] reported that the stereoisomeric ratio (*cis*/*trans*) of 1,4-disubstituted cyclohexanes formed by the hydrogenation of the corresponding activated cyclohexenes at a mercury electrode depended on solvents and proton sources, and discussed the stereochemical mechanism in detail. On the other hand, according to Lessard and coworkers [33,34], the hydrogenation at a Raney nickel electrode always provides the *trans* isomers in excess.

Then hydrogenation of conjugated dienes can also have stereochemical features; however, only few synthetically [35] or mechanistically [36–38] valuable studies have been reported.

A characteristic nature of the cathodically initiated copolymerisation of isoprene maleate was found [39]. The cathodic polymerization afforded a copolymer with an alternting structure with 1,4-isoprene units only and the ratio *cis*-1,4/*trans*-1,4 = 7); chemical polymerization led to a mixture of alternating block and cyclic structures. Stereoregularity has been found in a few studies of the electropolymerization of vinyl compounds.

Peters and coworkers [40] reported that some *trans*-monoolefins were found as by products in the reduction of a long-chain accumulated diene with a chloro group at the ω-position.

2. Hydrodimerization

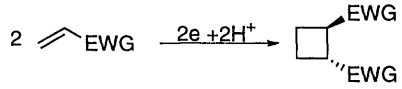
a. Intermolecular Dimerization. The intermolecular hydrodimerization of olefins gives stereoisomeric (*d*, *l* and *meso*) products. Moreover, the stereospecificity can be discussed by using stereoisomeric (*cis* and *trans*; *Z* and *E*) olefins.

Baizer and coworkers established the most brilliant industrial electroorganic synthesis of the hydrodimerization of acrylonitrile to adiponitrile. They extended this hydrodimerization to a variety of activated olefins and in some cases [41–43] paid attention to the stereochemistry of products. However, their stereochemical data were not enough to discuss the stereochemical course of the reaction. Afterward, an attempt was made to provide a working hypothesis in the hydrodimerization of cinnamates by considering an orientated adsorption of radical anion intermediates on a cathode surface, but this was not persuasive because of a lack of experimental data on the stereochemistry of both the starting olefins and products. Recently Utley and coworkers [44–46] have reported stereochemical data of hydrodimers derived from a variety of cinnamic acid esters with chiral alcohol components.

Simonet and coworkers [47–49] also reported in detail the stereochemistry of hydrodimers derived from activated olefins. The *d*, *l* dimers were predominant in most cases; however, the remarkable substituent effect was not enough explained.

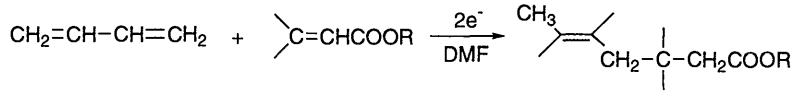
Some fundamental studies were made earlier. It was found that the hydrodimerization of an α, β-unsaturated ketone (enone) was at least partially stereospecific, with the *d*, *l* dimer formed from the *trans*-enone and mainly the *meso* dimer formed from the *cis*-enone. Kanetsuna and Nonaka [50] also examined both the stereoselectivity and stereospecificity of the hydrodimerization in detail. It was indicated that either the reaction mechanism or the stereochemical course is changed by the nature (protic or aprotic) of the reaction media. Particularly, the latter is greatly influenced by the manner of adsorption of an anion radical intermediate on the cathode. It was also postulated to explain the experimental results that the radical anion is adsorbed at the β-position, where the radical *p* electron is delocalized and the adsorption is affected by the nature of the media.

Lund and coworkers [51] reported interesting stereochemical results in the reductive dimerization-cyclization of benzylidenemalononitrile, but the reaction pathway was not stereochemically clarified. Recently, it has been clearly demonstrated by some workers [51–54] that the reductive cyclodimerization of activated olefins in aprotic media affords the *trans*-1,2-disubstituted cyclobutanes as shown in Eq. (4).



(4)

Although the cross-reductive coupling between different activated olefins could also afford the formation of stereosiomeric (*threo* and *erythro*) products, no study has been reported so far. However, it was reported that acrylates gave almost predominantly the corresponding *trans*-unsaturated carboxylic acids (**V**) by reduction in the presence of butadiene [Eq. (5)] [55]. This reaction may be valuable from the aspect of stereoselective synthesis.



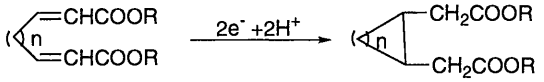
(5)

(V)

Nedelec and coworkers [56] reported highly stereoselective and stereospecific cross-coupling of activated olefins with stereoisomeric vinyl halides via nickel-catalyzed electroreduction.

The hydrodimerization of non-activated olefins at a platinum electrode affords the corresponding *d*, *l*-isomeric products in excess (> 80%) [57].

b. Intramolecular Cyclization. Since the development of the hydrodimerization of activated olefins in aqueous solutions containing R_4N^+, some workers have paid attention to the stereochemistry of reductive intramolecular cyclization of diolefins as well as the intermolecular dimerization of monoolefins. The reaction is presented in Eq. (6), where the *trans*-cyclized products are always predominant [58–66]. These resutls seem interesting from the aspect of the stereoselective synthesis of cyclic compounds, although the stereochemical course of each reaction has not been made clear in most cases because of uncertainty about the stereochemistry of the starting diolefins.

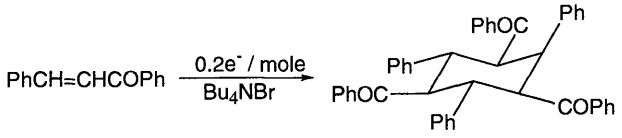


n = 1-4 37 - 87% (*cis* / *trans* : 0-0.93) (6)

It is noticeable that the *cis–trans* ratio of the reaction products is influenced strongly by proton donor and cathode material [60]. The ratio and the yield increase when a stronger proton donor is used. This may suggest that the protonation of the anionic intermediate is a key step in either cyclization or stereocontrol. The fast protonation of the configurationally unstable anionic species results in the predominant formation of the less stable *cis* products.

Benzene-1,2-diacrylate gave a quite different type of stereosiomeric cyclized product, which originated from two molecules of the starting diacrylate, along with a normal intermolecular hydrodimer in the *meso* form [62,63]. A dissymmetric diolefin was also found to give a mixture of stereosiomeric cylization products, but the ratio of isomers could not be determined [64].

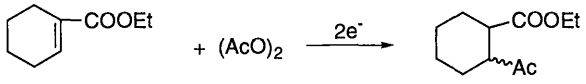
A unique cathodically initiated intermolecular cyclization of α,β-unsaturated ketones was reported by Fournier and coworkers [65,66]. An unsaturated ketone (**VI**) gave nonstereoselectively two stereosiomeric hydrodimers, consuming 1 F mol^{-1} when electrolyzed at a mercury cathode in a dry DMF solution of $LiClO_4$; in a Bu_4NBr solution of cyclized trimer (**VII**) was obtained as the sole product by passing a catalytic amount of electricity. The configuration of **VII** is as shown Eq. (7). The dimer and trimer are formed through a sort of cathodically initiated radical oligomerization, but the detailed mechanism has not been clarified.



(VI) (VII) 64% (7)

c. Cross-Coupling and Cyclization. Reductive cross-coupling of olefins with anionic and radical species formed by electroreduction of other molecules is also important from both synthetic and mechanistic aspects.

d. Acylation with Acetic Anhydride. Shono and coworkers [67] reported that the reduction of ethyl 1-cyclohexenecarboxylate (**VIII**) in an anhydrous acetonitrile solution containing tetraethylammonium tosylate in the presence of acetic anhydride afforded the *cis* and *trans* products (**IX**) in good yield and moderate stereoselectivity:



(VIII) (IX) (8)

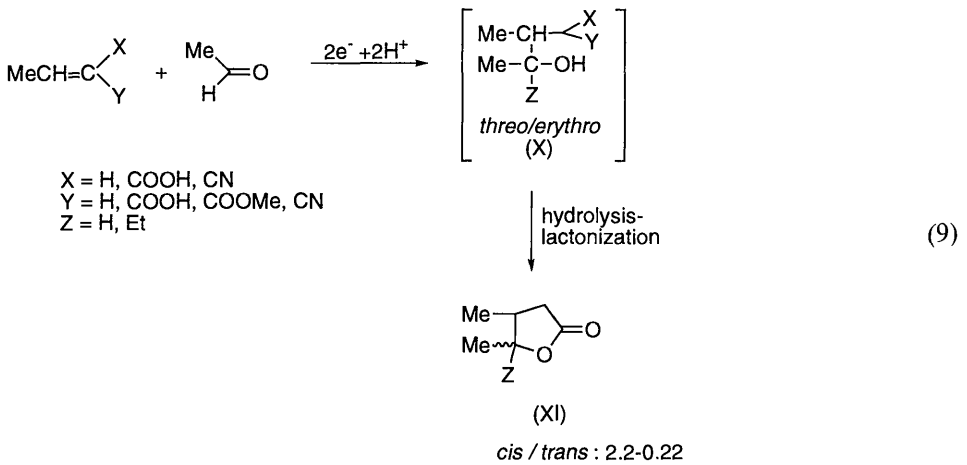
74% (*cis* / *trans* : 0.32)

Lund and coworkers [68,69] also extended this reaction to a variety of activated olefins, but in most cases the acylation occurred with either low stereoselectivity or low product selectivity.

e. Carboxylation with Carbon Dioxide. It is well known that olefins, when reduced in the presence of carbon dioxide, are dicarboxylated in high yields, but poor stereoselectivity was found.

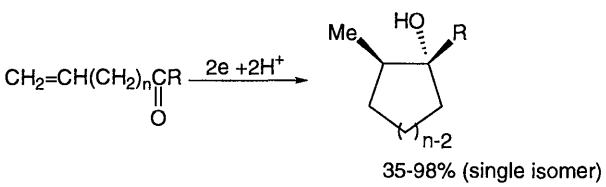
f. Cross-Coupling with Carbonyl Compounds. The electroreductive cross-coupling of olefins with carbonyl compounds, which are initially reduced to radical or anion intermediates to attack the olefins, is synthetically useful. The stereochemistry of this type of intermolecular reaction has lately been examined less [70–72] than that of intramolecular cyclization [73–77].

Kanetsuna and Nonaka [70] examined in detail the stereochemistry of final cyclic products (**XI**) derived by hydrolysis from initially formed cross-coupling products (**X**) of crotonic acid derivatives with dissymetrical carbonyl compounds as in Eq. (9). The *cis–trans* ratio of **XI** varied in a wide range from 2.2 to 0.22 depending on the molecular structure of the starting compounds and electrolytic conditions. Stereochemistry around the C–C bond formed by the coupling reaction was discussed in this case and in the coupling of 1-cyclohexenecarboxylic acid derivatives with a symmetrical ketone (acetone). The stereochemistry of the C–C single bond to the corresponding olefinic double bond was examined [71]. In the latter case, the *cis–trans* ratio of the products also varied, but the less stable *cis* products were always predominant. This results can be helpful for discussing stereocontrol in this reaction. In fact, Kanetsuna and Nonaka [71] discussed the stereochemical course based on these results.



(9)

g. Cyclization of Olefinic Carbonyl Compounds. The stereochemistry of intramolecular cyclization of olefinic carbonyl compounds has been extensively studied [73–76,78,79]. Particularly in the case of unactivated olefins with carbonyl functions, which are reduced more easily than the C=C double bonds, the stereoselectivity is so high that only a single isomer is formed [78,73]:

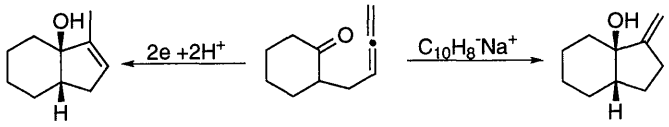


(10)

Compared with unactivated olefins, activated olefins with carbonyl groups are reductively cyclized with slightly lower stereoselectivity [75,79–82].

The reductive cyclization of unsaturated carbonyl compounds can also be achieved by using chemical reducing reagents, such as Al-amalgam, $MgTiCl_4$, and $NaNH_3$, but in general not only chemical yields of cyclized products but also stereoselectivity are lower than those of the electroreductive cyclizations.

Pattenden and Robertson [76] reported a very interesting cathodic reduction of a variety of terminal allenic ketones that were cyclized highly stereoselectivity through the *exo* mode, producing five-membered rings. It is particularly notable that the products formed in the electrochemical and chemical (sodium naphthalenide) reductions are structural isomers, but with the same configuration:



(11)

A quite different type of reductive cyclization of olefins with 1,4-dihaloalkanes was stdied stereochemically [77]. In this case the reaction is initiated by the reduction of the C= C double bonds.

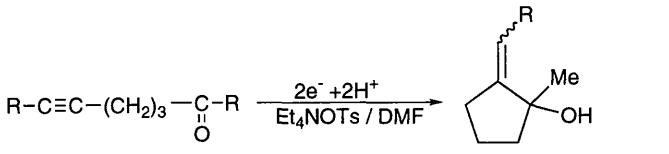
B. Acetylenic Compounds

The stereochemical feature of electrolytic hydrogenation of acetylenes to the corresponding olefins changes drastically with electrolytic conditions, such as supporting electrolyte, solvent, and cathode material [83–88].

Kita and Nakajima [89] found that the *cis–trans* ratio of 6.3 of 2-butene formed from 2-butyne at a palladium black cathode was not influenced by neither cathode potential nor pressure. On the other hand, Nonaka and coworkers [90] examined the *cis–trans* ratios of dimethyl 2-butenedioate formed from dimethyl acetylenedicarboxylate on a palladium black cathode and catalytic hydrogenation at various pH levels and found that an increase in pH resulted in a decrease in the ratio in both the electrolytic and catalytic hydrogenations, but the former was less strongly influenced by pH. They also performed similar comparative studies with olefins and ketones from a stereochemical aspect.

The stereochemistry of olefins formed from acetylenes at a mercury cathode in R_4N^+ salt solution is sometimes greatly affected and in a complicated manner by experimental conditions [40].

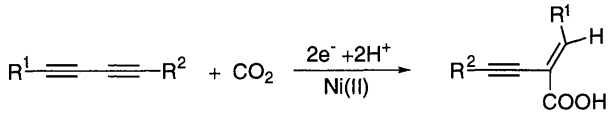
Shono and coworkers [91] reported an interesting reductive cyclization of acetylenic ketones (**XII**) [Eq. (12)]. The cyclized products (**XIII**) were formed in good yields with some stereoselectivity. Perichon and coworkers [92] also reported that the reductive cross-coupling of 1,3-diynes with carbon dioxide gave exclusively the corresponding *cis* addition products in the presence of a Ni(II) complex, as shown in Eq. (13).



(12)

(XII)

(XIII)
53-60% (*E*/*Z*: 0.5)



(13)

C. Aromatic Compounds

Aromatic hydrocarbon nuclei can be hydrogenated partially or completely under various electrolytic conditions. Hydrogenation of *o*-phthalic acid to dihydrophthalic acid is industrially important (Chapter 32). *o*-Phthalic acid is efficiently hydrogenated at high hydrogen overvoltage cathodes, such as mercury and lead in acidic solutions, to give almost exclusively *trans*-dihydrophthalic acids [93–97].

In contrast to phthalic acid, benzene nuclei without electron-withdrawing substituents, such as a carboxyl group, are hydrogenated by using hydrogen-active cathodes in acidic solutions. For example, *o*-methylphenol is stereoselectively hydrogenated on an Rh/C cathode to give *cis*-2-methylcyclohexanol [42–83% yields (*cis–trans* ratio 2.3–6.7)] as the major isomer [98].

Naphthols are hydrogenated to the corresponding decanols. β-Naphthol gives *trans*-2-decanol (70% yield) in an acidic solution [99], whereas α-naphthol is hydrogenated in HMPA to *cis*-1-decanol (47% yield) [100]). The latter is regarded as a hydrogenation induced by cathodically generates solvated electrons.

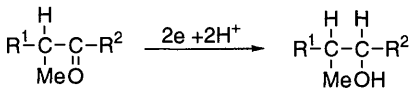
D. Carbonyl Compounds

The stereochemistry of the cathodic reaction of carbonyl compounds has been extensively studied from synthetic and mechanistic aspects. In this section the reaction is discussed in three parts: hydrogenation to alcohols, hydrodimerization to pinacols, and cross-dimerization with unsaturated compounds.

1. Hydrogenation to alcohols

a. Acyclic Carbonyl Compounds. A set of stereochemical studies of the reduction of 1,2-diphenyl-1-propanone to the corresponding diasteromeric (*threo* and *erythro*) alcohols has been reported [101]. Diaz and coworkers [102] determined that both isomers were formed at a *threo–erythro* ratio of 0.45. They also suggested that such a low stereoselectivity would be due to proton exchange at the α-position of radical anion intermediates formed by the first one-electron transfer.

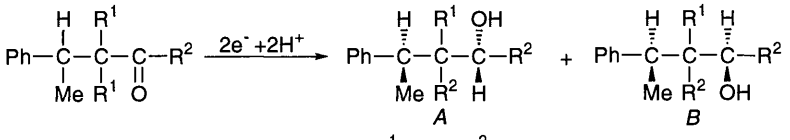
Nonaka and coworkers [103] reduced racemic ketones at a mercury cathode and found that the stereochemistry of the products was affected greatly by the molecular structure of the starting ketones and the pH of the electrolytic solutions used [Eq. (14)]. Note that when R^1 = cyclo-Hex and R^2 = Me, the *anti*-Cram isomer was formed as a major product. This suggests that stereochemical interaction between cathode and intermediates contributes to stereocontrol in the reaction. In addition, considering the equilibrium *threo–erythro* ratios of the alcohols, it is concluded that the stereochemistry of the reaction in kinetically controlled. The stereochemical course of the reaction was discussed in detail, and it was suggested that key points for the stereocontrol are the adsorption step of the starting ketone on the cathode surface and the configurational stability of one-electron transferred intermediates (radical anions) at the cathode interface. This reduction is also interesting for stereoselective synthesis [104].



(14)

R^1 = Ph, R^2 = Ph; 8-91% (*threo/erythro* : 0.2-0.7)
R^1 = Ph, R^2 = Me; 3-82% (*threo/erythro* : 1.3-1.4)
R^1 = c-Hex, R^2 = Me; 3-7% (*threo/erythro* : 0.5-0.9)

A similar study using another type of starting ketones was reported by Nonaka and Kusayanagi [105] [Eq. (15)] and the stereochemical course was discussed.

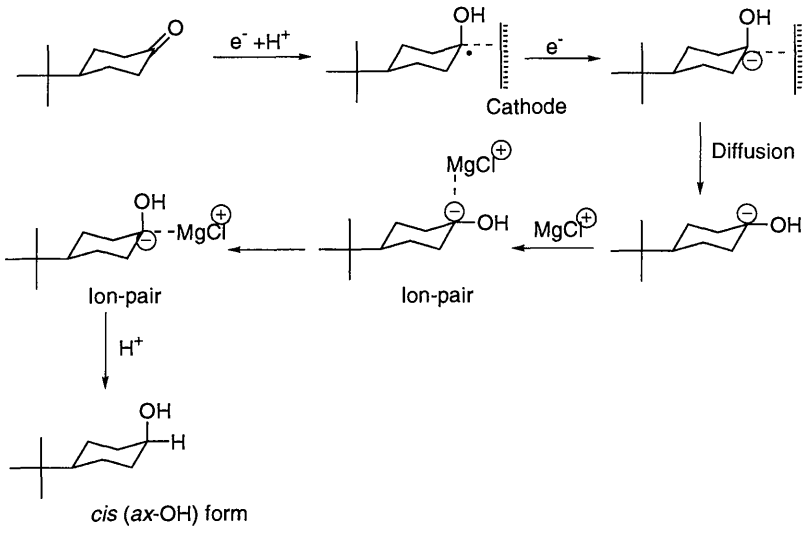


(15)

R^1 = Me, R^2 = Ph; 75-100% (*A/B* : 0.64-0.76)
R^1 = Me, R^2 = Me; 1-7% (*A/B* : 0.80-0.87)
R^1 = H, R^2 = Ph; 12-100% (*A/B* : 1.13-1.44)

Quite different stereochemical results were obtained when hydrogen-active cathodes, such as platinum and palladium blacks, were used instead of mercury [90] in the reduction given in Eq. (14).

b. Cyclic Carbonyl Compounds. Most of the stereochemical studies on the hydrogenation of cyclic carbonyl compounds to the cyclic alcohols have been performed using substituted cyclic cyclohexanones and cyclopentanones [90,106–116]; the stereochemistry of the cyclic alcohols formed is discussed by examining the *cis–trans* geometry and/or *ax–eq* conformation of the hydroxyl groups. The stereoselectivity of the reaction varies drastically depending on such conditions as pH, solvent system, proton donor, cathode material, cathodic potential, supporting electrolyte cation, and temperature. In one case, 100% stereoselectivity for a stereoisomeric cyclic alcohol is achieved; in other cases, another isomer is formed in 100% stereoselectivity. However, it is not easy to clarify the stereochemical course of the hydrogenation of monocycloalkanone systems, except for *t*-butylcyclohexanones, because the conformation of the intermediates is not fixed. A *t*-butyl group substituted on a cyclohexane ring is always in the equatorial position. Therefore, for instance, it can be reasonably explained that the less stable *cis*-4-*t*-butylcyclohexanol with an *ax*-OH is formed predominantly in electrolytic solutions containing bulky cations, such as $MgCl^+$ and $ZnClO_4^+$, which make tight ion pairs with carbanions [109,110]:



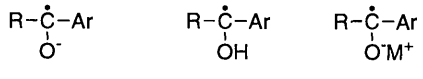
(16)

Since polycyclic systems are also conformationally fixed, their stereochemical course may be rationalized [108,110,116–118].

2. Hydrodimerization to Pinacols

a. Intermolecular Dimerization. A number of reports of the hydrodimerization of aromatic carbonyl compounds have been published and a basic concept of stereocontrol was established [119–156]. The stereochemistry (*d, l* and *meso*) of pinacols is generally controlled by steric and nonsteric interactions between two radicals (illustrated in Fig. 2) coupling with each other, but not by interaction with the cathode [139], because electrochemical hydrodimerization gives almost the same stereochemical results as nonelectrochemical hydrodimerization in homogeneous media. The radicals **XIV**, **XV**, and **XVI** are formed by one-electron transfer in neutral, acidic, and aprotic media, respectively. The steric interaction is brought about by a steric hindrance (repulsion) between substituents of the radicals and nonsteric interactions are attributed to hydrogen bonding (attraction) and electrostatic force (repulsion). These stereocontrolling factors are influenced by various reaction conditions, and consequently the stereochemistry of a reaction can be influenced in very delicate and complicated ways.

Some interesting results have been reported on this subject. Although most stereochemical investigations of hydrodimerization have been performed using aromatic carbonyl compounds with unsubstituted and substituted phenyl groups, some examples dealing with other aromatic groups have appeared [141–144,154–156]. The hydrodimerization of



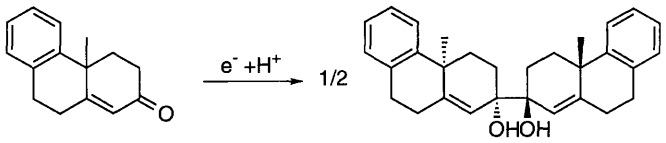
(XIV) (XV) (XVI)

Figure 2. Ketone-derived intermediate species.

simple aliphatic carbonyl compounds generally proceeds with very low yields, and no stereochemical study has been reported so far.

Some α,β-unsaturated carbonyl compounds are stereoselectively hydrodimerized to give the corresponding unsaturated glycols in various yields [146–151] (Chapter 22).

Since the olefinic part of the α,β-unsaturated carbonyl compounds is conjugated with the carbonyl group, the original geometry of the olefinic part is not always retained in the radical anion intermediates (**XIV**, **XV**, and **XVI**). Consequently, the stereochemistry of the final products is expected to be complicated [157]. Additionally, the stereochemistry may become more complicated for other reasons, particularly in the case of cyclic unsaturated carbonyl compounds. Touboul and Dana [145,148] analyzed six stereoisiomeric glycols formed from a variety of substituted tetrahydro-2*H*-phenanthrones and discussed the stereochemical course of the reaction. For example, racemic and optically active **XVII** gave the six and three possible isomers, respectively, of which **XVIII** was the major product over a wide range of pH:



(17)

(XVII)

cis-threo-cis (Major)
(XVIII)

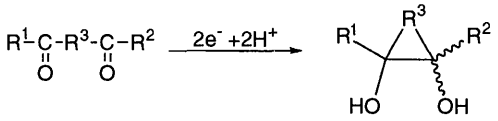
In the hydrodimerization of 2,3-dimethylindanone, 11 hydrodimers, including 8 stereoisomers, were analyzed [150]. The stereochemistry of hydrodimers formed from 2-methylindenone in an oxygen-saturated DMF solution would also be complicated, but it is known only that the stereochemistry around the central C–C bond is a *threo* form [151]. Another complication in the stereochemistry of a hydrodimer was observed in the dimerization of benzoin at a mercury-plated copper cathode in a basic aqueous ethanol solution: A single stereoisomeric hydrodimer was formed [152].

Although the stereochemistry of hydrodimers is greatly affected by the structure of the starting carbonyl compounds and electrolytic conditions, the less stable *d,l* isomers from simple aromatic carbonyl compounds are very rarely formed in *d,l–meso* ratios higher than 1.5 in the hydrodimerization. Rusling and Zuman [142] reported that 4-pyridylcarboxaldehyde gave the hydrodimer in the *d,l–meso* ratio of 1.92 in a strongly alkaline solution. Furthermore, Smith and Utley [153] found that benzaldhyde was hydrodimerized at a mercury cathode in dry DMF solution of Bu_4NBF_4 to give the *d,l–meso* ratio 14; the addition of β-cyclodextrin drastically decreased the ratio to 0.33.

Indirect electroreduction using a redox mediator sometimes gives quite different stereochemical results than direct reduction [158,159].

The stereochemistry of hydrodimerization of aliphatic carbonyl compounds has very rarely been studied. It was reported that an aliphatic ketone gave an almost equal quantity of the isomeric hydrodimers at a mercury cathode [160].

b. Intramolecular Cyclization. Some aromatic diketones have been stereoselectively hydrocyclized under various electrolytic conditions, which influenced strongly stereochemistry of the cyclic diols formed [161–165]:



$R^1 = R^2 = C_6H_5$, R^3 = CHMe; 80% (*cis/trans* : ?) [123]
$R^1 = R^2 = C_6H_5$, $R^3 = CMe_2$; 80% (*cis/trans* : ∞) [123]
$R^1 = C_6H_5$, R^2 = Me, R^3 = CHMe; 80% (*cis/trans* : 1) [123]
$R^1 = R^2 = C_6H_5$, $R_3 = (CH_2)_3$; 80% (*cis/trans* : ∞) [8]
$R^1 = R^2 = 4\text{-}HOC_6H_4$, $R^3 = (CH_2)_3$; 82-89% (*cis/trans* : 0.9-24.3) [8]
$R^1 = R^2 = 4\text{-}HOC_6H_4$, $R^3 = (CH_2)_4$; 64% (*cis/trans* : ∞) [8]

(18)

In one case where unsymmetrical diketones were used [165], the stereochemical course of the reaction could be explained. The reduction of 1-acyl-8-benzoylnaphthalenes afforded predominantly the corresponding *cis* and *trans*-1,2-acenaphthenediols in strongly acidic and alkaline media, respectively. The preferable formation of the *cis*-diol is rationalized as due to cyclization through intramolecular coupling of the biradical intermediate, while the *trans*-diol is formed by intramolecular nucleophilic addition of the benzylic carbanion intermediate to its unreacted acyl group.

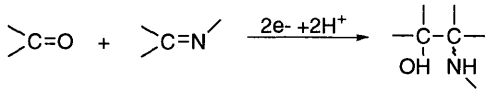
Only one example of a stereochemical study of the hydrocyclization of an aliphatic carbonyl compound has been reported, but the stereoselectivity is extremely low [166].

3. Cross-Dimerization with Unsaturated Systems

In most cases of cross-dimerization between carbonyl and unsaturated groups in the previous section, there has been an ambiguous point on whether the carbonyl or unsaturated group is first reduced to give a reactive intermediate. Hence, the stereochemical course of the reaction was not sufficiently discussed. In this section, the stereochemical course of cross-dimerization, in which it has mechanistically been clarified that the carbonyl groups are reduced to give the corresponding radical or anion intermediate species (XIV–XVI) that react with the unsaturated bonds such as C=C, C=N and C≡N is discussed in detail.

a. Cross-Dimerization with C=C Bonds. Cathodic coupling of ketones with allylic alcohols was reported by Shono et al. [167] to take place at a carbon fiber cathode with high diastereoselectivity due to interaction (hydrogen bonding) between two hydroxyl groups of the starting alcohols and the ketone-derived intermediate species (**XIV**, **XV**). It was also found that the reduction of nonconjugated aromatic ketones at metal cathodes gave the corresponding *cis* isomes of intramolecularly cyclized products in high stereoselectivity [168], similar to the reduction shown in Eq. (10).

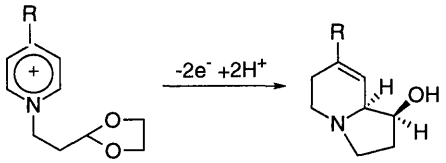
b. Cross-Dimerization with C=N Bonds. Reductive cross-dimerization of ketones with C=N compounds, such as oximes, hydrazones and nitrones, takes place diastereoselectively [169,170]:



(19)

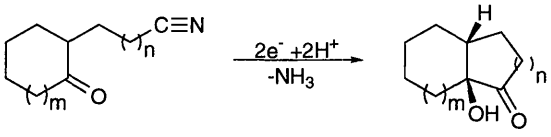
Intramolecular cyclization products are also stereoselectively formed in the reduction of compounds having carbonyl and C=N groups [170. Schäfer and coworkers [171]

reported diastereoselective cathodic cyclization of 1-(3-oxoalkyl)pyridinium salts to indolizidine derivatives, as in Eq. (20).



(20)

c. Cross-Dimerization with C≡N Bonds. α-Cyanoalkylated cyclic ketones are reductively cyclized to corresponding bicyclic hydroxyl ketones, which have *cis* structures with respect to the adjacent OH and H groups, as in Eq. (21) [172,173].

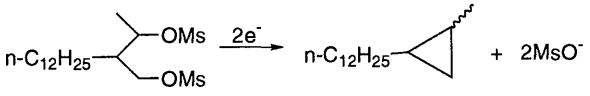


(21)

E. *Vic*-Oxygen Compounds

Some classes of *vicinal* oxygen-functionalized compounds are reduced to give stereoisomeric products [174–180]. Cathodic reduction of benzil in acidic and neutral solutions led to the formation of *cis* and *trans*-stilbenediols. The *cis–trans* ratio could be determined by trapping the chemically unstable stilbenediols as the O,O′-dimethyl derivatives during electrolysis in the presence of dimethyl sulfate [175]. The *cis* isomer, as expected, was always predominant.

Shono and coworkers [176] found that 1,3-dimethanesulfonates of 1,3-diols underwent electroreductive cyclization in dimethylformamide (DMF) containing R_4N^+, giving stereoselectively the corresponding cyclopropanes in a good yield:



(22)

76% (*cis/trans*: 0.33)

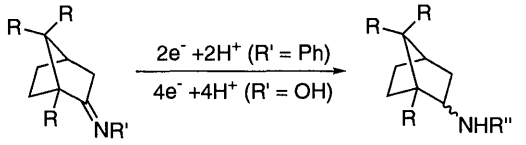
Nonaka and coworkers [177,178] found that a stereoselective one-electron reductive elimination reaction of cyclic sulfates of 1,2-diols proceeded to provide the *trans*-olefins and disulfate dianions of the parent diols. This reaction may be not only stereoselective but also stereospecific. An epoxide was also stereoselectively and regioselectively reduced to the monoalcohol [179,180].

F. Nitrogen Compounds

1. Imines and Immonium Compounds

Cyclic imines are hydrogenated highly stereoselectively. A typical example, the hydrogenation of the Schiff base of aniline with camphor, was reported by Fry and Reed [Eq. 23)] [181]. An unsubstituted analogue with norcamphor gave a little less stereoselectivity. The electrohydrogenation gives the same stereochemical results as the sodium reduction in ethanol, but platinum-catalyzed hydrogenation gives different stereochemical results.

Bicyclic oximes also give the corresponding amines with high stereoselectivity, but in a manner different from the bicyclic imine of Eq. (23); the stereochemical feature of the electrochemical reduction is the same as that of the $LiAlH_4$ reduction, but opposite that of the sodium reduction [182].

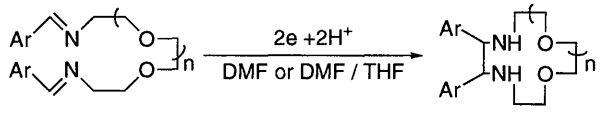


(23)

R = Me, R' = Ph R = Me, R" = Ph; *exo / end* : 0
R = H, R' = OH R = H, R" = H; *exo / end* : 0.01
R = Me, R' = OH R = Me, R" = H; *exo / end* : ∞

An acyclic *vic*-diimine was hydrogenated at a mercury cathode to give a mixture of the *d*, *l*- and *meso*-diamines in 70% yield [183]. Imines can be stereoselectively hydrodimerized to 1,2-diamines in a manner similar to the hydrodimerization of carbonyl compounds to pinacols [184,185].

Kise and coworkers found an efficient intramolecular hydrodimerization of aromatic diimines using a lead cathode providing 1,4-diazacrown ethers, as in Eq. (24) [186,187]. The stereoselectivity greatly depended on the ring size of the products and solvents used.



(24)

n = 0, Ar = Ph; *cis/trans* : 0
n = 1, Ar = Ph, 1-Furyl; *cis/trans* : 0.053
n = 2, Ar = Ph; *cis/trans* : 0.33
n = 5, Ar = Ph; *cis/trans* : 0.67-1.5

Substituted cyclic immonium salts are also electrochemically hydrogenated in aproptic solvents to give stereoselectively the isomeric cylic amines [188]: The stereoselectivity is influenced by solvent and supporting electrolyte. Immonium cations can be hydrodimerized with a certain class of bromo compounds [189] with some stereoselectivity.

Benzaldehyde reacts with electrogenerated superoxide ion to provide solely *trans*-stilbene via a carbene intermediate [190].

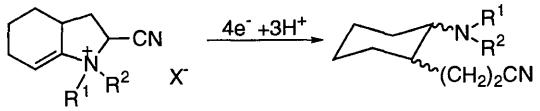
2. Azacylopropane and Azo Compounds

The azacylopropane ring of mitomycin C was opened in methanol electrochemically, but the stereoselectivity of the methoxyamine formed was low [191].

3. Quaternary Ammonium Compounds

Quaternary ammonium cations are cathodically decomposed in aprotic solvents to generate radicals that couple with each other to give the isomeric dimers. Such radicals seemed to be free from steric interaction with the cathode because the stereoisomeric ratio of the dimers was almost equal to that of the same product obtained by a well-known free-radical process in a homogeneous medium [192].

Iverson and Madsen [193] reported a synthetically interesting electroreductive ring-opening reaction of cyclic quaternary ammonium salts. The stereochemistry of products is greatly affected by pH:



$R^1 = R^2 = Me$; 0-82% (*cis/trans* : 0.2-10.1)
$R^1, R^2 = (CH_2)_4, (CH_2)_2O(CH_2)_2$
$X = Cl, ClO_4$

(25)

4. Others

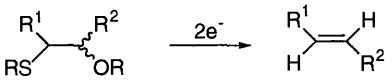
Trans-azobenezene was detected by Raman spectroscopy as an adsorbed species on a silver cathode in the reduction of nitrobenzene [194]. Hydroxylamine intermediates derived from the electroreduction of γ-nitroketones undergo intramolecular cyclization, and the cyclized products are further reduced to isomeric pyrrolidines [195].

Knittel [196] found that electroductive acetylation of benzoyl azide led to the isolation of both rotational isomers of *N*-acetylbenzamide formed.

A stereospecific nature of the cathodically initiated anionic polymerization of isocyanates in DMF containing Bu_4N^+ has been mentioned [16].

G. Sulfur Compounds

Sulfur compounds (**XIX**, RS = SPh, O_2SPh) with oxygen functions at the β-positions are reductively desulfurized to give the corresponding *trans*-olefins, regardless of the original stereochemistry of *threo/erythro*, as in Eq. (26) [197–199]. The reaction is highly stereoselective but not stereospecific. Methyl styryl sulfoxide and sulfone are also desulfurized in the presence of *t*-BuBr to give *E*-PhCH = CHCMe$_3$ [200].

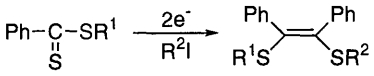


(XIX)

(26)

Some ring-opening reactions of cyclic sulfur compounds to olefins proceed stereoselectively via desulfurization. 1,2-Diphenylthiirene dioxide is reduced with elimination of sulfur dioxide, giving *trans*-stilbene in 30% yield [201].

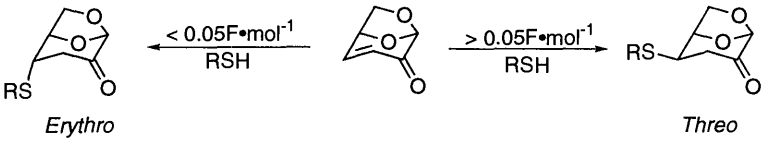
The reductive coupling of dithiobenzoate esters results in the predominant formation of *Z*-1,2-dialkylthio-1,2-diphenylethylenes in good yields when alkyl halides are added after completion of the electrolysis [Eq. (27)] [202]. A reaction mechanism via a dianion intermediate is postulated, but the stereochemical course has remained ambiguous.



(27)

Shono and coworkers [203] reported a synthetically useful reductive cyclization reaction of γ-hydroxyphenylsulfides leading to the formation of stereoisomeric cyclopropanes, but the iosmer ratio was not determined. Ethylene bis-dithiobenzoate is also reductively cyclized in dry acetonitrile containing methyl idodie to give nonstereoselectively *d, l*- and *meso*-dithiane derivatives in good yield [204].

Cathodically initiaited Michael addition of thiols to levoglucosenone provides *threo* or *erythro* addition products selectively depending on the amount of charge passed [Eq. (28)] [205].



(28)

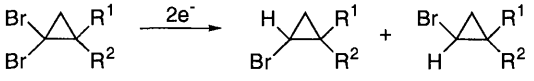
H. Halogen Compounds

Various stereoselective and stereospecific reductions of halogen compounds have been reported.

1. Cyclic Halides

a. Cyclic Monohalides. Only a few reports on the stereochemisty of reduction of monohalides, except chiral halides (see Sec. V), have appeared so far. Tallec and coworkers [206] found that the reduction of *cis*- and *trans*-cyclopropyl bromides proceeds stereospecifically in a Bu_4N^+ solution. On the other hand, in an ammonium (NH_4^+) salt solution the opposite stereochemistry of the products is observed.

b. Monocyclic gem-*Dihalides.* 1-Substituted-2,2-dibromocyclopropanes (**XX**) are stereoselectively reduced to the corresponding diastereomeric monobromides (**XXIa** and **XXIb**) in good yields, as in Eq. (29) [207]. Although the stereochemistry of the monobromides formed is strongly influenced by the substituents (R^1 and R^2) of **XX** and electrolytic conditions, such as pH, supporting electrolyte in aqueous ethanol, and cathode potential, **XXIa** (*erythro*-type isomer) is always predominant.



(XX) (XXIa) (XXIb)

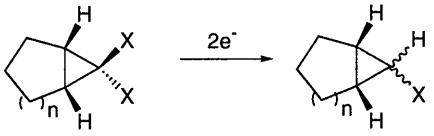
R^1 = H,	R^2 = Ph;	XXIa/XXIb : 1.6–5.3
R^1 = Me,	R^2 = Ph;	XXIa/XXIb : 1.1–4.6
R^1 = Me,	R^2 = COOH;	XXIa/XXIb : 1.9–6.1
R^1 = Ph,	R^2 = COOH;	XXIa/XXIb : 1.0–10.1
R^1 = Ph,	R^2 = COOEt;	XXIa/XXIb : 0.9–1.8

(29)

A similar diasteroselective reaction has been found in the reduction of 3-substituted 4,4-dichlorosuccinimides [208]. The stereochemistry of the products in an acidic medium is opposite to that in an alkaline medium.

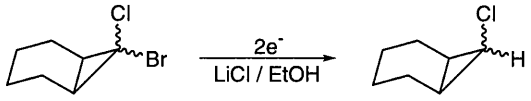
c. Bicyclic gem-*Dihalides.* Bicyclic *gem*-dihalocyclopropanes (**XXII**) always give predominantly the corresponding *endo*-monohalocyclopropanes (**XXIII**), which seem to be formed by the reduction of the less-hindered *exo*-halogen against the cathode in an adsorbed state [Eq. (30)], although the isomeric ratio varies with the molecular structure of **XXII** and electrolytic conditions, such as solvent and supporting electrolyte [209,210]. Similarly, cathodic reduction of bicyclic *gtem*-dibromocyclopropane (**XXII**) in the presence of chlorotrimethylsilane provides *exo*-silylated isomer selectively (*exo*/*endo* : 1.4 ~ 5.3) [211]. It is noticeable that an *exo*-bromo-*endo*-chlorocyclopropane (**XXIVa**) normally gives the *endo*-chloride (**XXIVa**) as a major isomeric product, but the *endo*-bromo-*exo*-chlorocyclopropane (**XXIVb**) gives the *exo*-chloride (**XXVb**), and a mixture of **XXIVa** and **XXIVb** gives both isomers in an equal amount under the same conditions, [Eq. (31)]. Considering that alkyl bromides in general are more easily

reduced than chlorides, this suggests that the reduction of *gem*-dihalocyclopropanes may occur at either halogen atom rather than only on the less hindered *exo*-halogen.



(XXII) (XXIII) (30)

n = 2, X = Br *endo / exo* : 1.1–5.0
n = 2, X = Cl *endo / exo* : 1.9–∞
n = 4, X =Br *endo/exo* : ∞



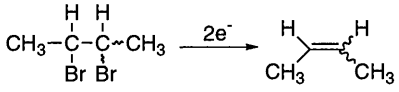
(31)

exo-Br, *endo*-Cl (XXIVa) XXVa (*endo/exo* : 2.6)
endo-Br, *exo*-Cl (XXIVb) XXVb (*endo/exo* : 0.38)
XXIVa + XXIVb XXVa + XXVb (*endo/exo* : 0.97)

Similar stereochemical studies also have been made in detail using *gem*-dihalonorbornanes and also bicyclic monohalides [212–214].

2. Acyclic Polyhaloalkanes

It was found that *vic*-dihaloalkanes were highly stereospecifically reduced at a mercury cathode to the corresponding olefins in high yields, Eq. (32) [215]. The resulting electrochemistry suggests that the elimination of halogen atoms from the *trans*-periplanar conformation is strongly preferred. The detailed stereochemical course of the reaction was discussed by Brown and coworkers [216]. the stereospecific reduction of α, α'-dibromosuccinates to fumarates and maleates was also reported earlier [217].



dl 90-95% (*cis/trans* : 29–∞)
meso 95% (*cis/trans* : 0) (32)

It is known that pyridinium tribromide converts olefins with specific *anti*-dibromination. Therefore, the *vic*-dibromides thus obtained can be cathodically reduced to the original olefins without geometrical changes of molecular structure [218]. This stereospecific bromination–debromination may be useful as an olefin protection–deprotection method.

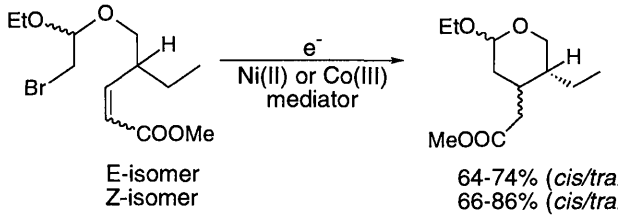
Monomeric and polymeric *N*-alkylpyridine-4-carboxylates serve as redox mediators for the indirect electroreduction of *vic*-dihalides to *trans*-olefins [219,220].

1,1,2,2-Tetrachloroalkanes also give stereoselectively the corresponding 1,2-dichloro-olefins in which the *E*-(*trans*)-isomers are the major product [221]. Trichloromethylmethanols are reduced with electrogenerated chromium(II) ion to give *Z*-monochlorovinyl compounds in good yields [222]. When a carboxyl function is at the α-position, the *E*-double bond is predominantly formed.

3. Acyclic Halo-Olefins

Monohalonmaleic and -fumaric acids and their esters are reductively dehalogenated with complete retention of the original molecular geometry in a wide range of pH, with the exception that bromomaleic acid gives mixtures of maleic and fumaric acids at pH 0.6–5.8 [223,224]. *Cis*- and *trans*-3-iodo-3-hexenes are also similarly deiodinated in DMF, but the stereospecificity is lower [225]. *meso*-2,3-Dibromosuccinic acid is also debrominated to give fumaric acid selectively at all pH. On the other hand, the racemic acid is reductively converted to fumaric or maleic acid as major products depending on pH. However, diethyl *meso*- and *racemic*-2,3-dibromosuccinates always give diethyl fumarates [226].

Indirect electroreductive cyclization of η-bromo-α,β-unsaturated esters using Co(III) or NI(II) redox mediator provides six-membered ring products stereoselectively, as in Eq. (33) [227].



E-isomer
Z-isomer

64-74% (*cis/trans* : 0.25)
66-86% (*cis/trans* : 0)

(33)

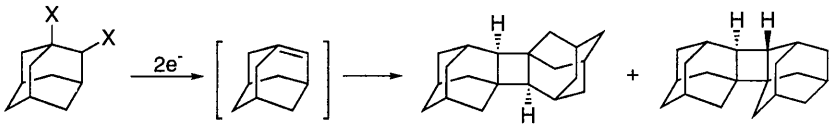
4. Intermolecular Dimerization

a. Monohalides. Kanetsuna and Nonaka [228] reported that ethyl α-chlorophenylacetate was reductively dimerized and the *d, l–meso* ratio (0.4–1.4) of diethyl 2,3-diphenylsuccinate was influenced by the cathode material. A similar study was also reported by Rampazzo and coworkers [229–232]. They found that an excess of *d, l*-isomers derived from α-bromo-*p*-halogenophenylacetates decreases in the order of the F, Cl, and Br substitutents in the phenyl group [230]. 3-Halo-6-nitro-5-cholestenes [233], aroyl chlorides [234,235], and benzylic halides [236,237] are also stereoselectively dimerized.

b. Polyhalides. Stereoselective dimerization of a *gem*-dihalide was achieved in direct and indirect electroreduction. α,α-Dibromotoluene was reductively dimerized by a Cr(II)/Cr(III) redox mediator to stilbene (*cis/trans* : 0.18) [238]. Similar results were obtained by direct cathodic reduction [237]. On the other hand, indirect cathodic dimerization of benzal chloride using a Co(II) (Salen) mediator gave a slightly excess of *cis*-stilbene (*cis/trans*: 1.1) [239]. α,α,α-Trichlorotoluene also gives 1,2-dichlorostilbene (*cis/trans*: 1) [221].

A *vic*-dihaloadamantane undergoes the intermolecular reductive dimerization via unstable adamantene species to give stereoisomeric products in 80–90% yields, as in Eq. (34) [240]. Cathodic reduction of α,α'-dibromo-1,2-dialkylbenzenes in the presence of dienophiles (maleic anhydride, etc.) and hinderd dienophiles provides diels–Alder adducts stereoselectively [241,242]. In this reaction, the dienophiles play a duel role as mediators

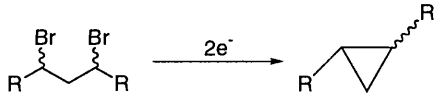
and dienophiles. Cathodic reduction of α,α'-dibromo-1,2-dialkylbenzenes in the absence of dienophiles gives stereoisomeric dimerization products [243].



(34)

5. Intramolecular Cyclization

The *d, l*- and *meso*-2,4-dibromopentanes are reductively cyclized, but neither the stereoselectivity nor stereospecificity is high [244,245]. A cyclic dibromide also gives a similar result [246]. On the other hand, 1,3-dibromo-1,3-dimethoxycarbonylpropane gives the corresponding *trans*-cyclopropane with high stereoselectivity [247]:



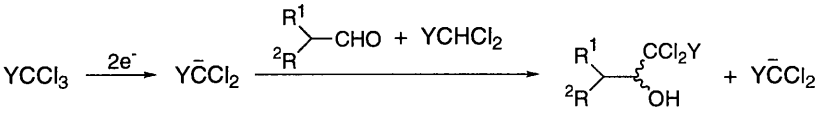
dl or meso :	R = Me;	Hg/DMSO : 84–91% (*cis / trans* : 0.8–1.1) [208]
Unknown :	R = COOMe;	Pt/THF: 60–74% (*cis / trans* : 0.25) [188]
Unknown :	R = COOMe;	Pt/DMF : (*cis / trans* : 0.07) [188]

(35)

The reduction of α,α'-dihaloketones may lead to the formation of stereoisomeric cyclopropanones, but their stereoselectivity could not be examined because of their instability under electrolytic conditions [248,249]. On the other hand, α,α'-dihalophosphinates were found to give stereoisomeric olefins via unstable oxyphosphiranes, but the stereoselectivity was low [250]. A similar result was also obtained in the reduction of α,α'-dibromodibenzylsulfone [251].

6. Others

1,2-Dihalonorbornanes gave stereoisomeric mixtures of reductive adducts with furan via reactive norbornene species [252]. Shono and coworkers [253,254] reported the diastereoselective addition of cathodically generated dichloromethyl anion to α-branched aldehydes including α-amino aldehydes. The reaction proceeds catalytically:



Y = Cl, COOMe; R^1, R^2 = Alkyl, Aryl : 25-89% (*syn/anti* : 5-∞) [194]

Y = Cl, COOMe; R^1, R^2 = OAc, : 52-76% (*syn/anti* : 0.05-0.50) [194]

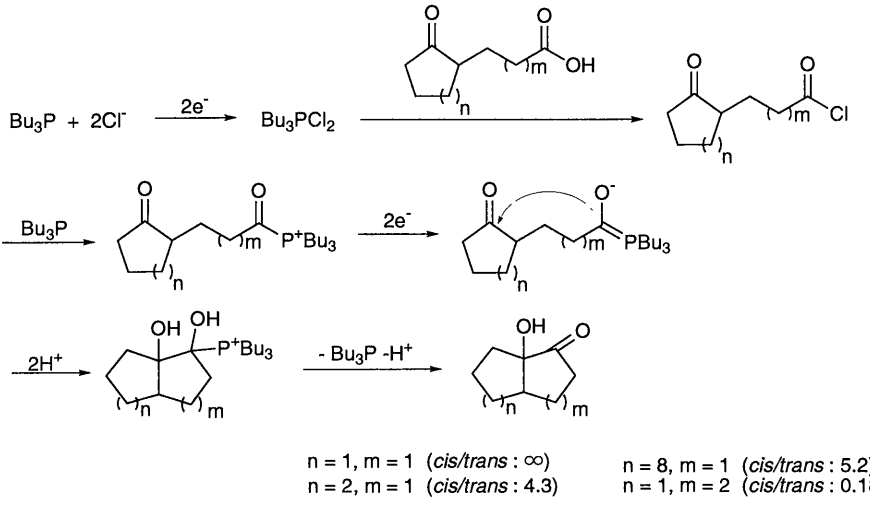
Y = COOMe; R^1= Alkyl, R^2 = NRCOOMe : 39-66% (*syn/anti* : 0-0.8) [195]

(36)

I. Other Heteroatom Compounds

Only a few stereochemical studies of electroreduction of compounds containing heteroatoms other than oxygen, nitrogen, sulfur, and halogens have been reported so far.

Ohmori and coworkers found a stereoselective preparation of α-hydroxybicycloalkanones from cyclic ketoacids by the electrolysis in the presence of Bu_3P in an undivided cell, as in Eq. (37) [255]. The stereoselectivity depends on the ring size of the starting cyclic ketoacids.

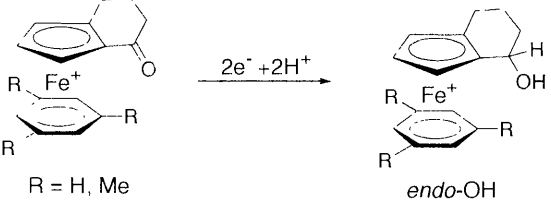


(37)

Cathodically generated methyldiphenylgermyl anion having a Bu_4N^+ reacts with phenylacetylene to afford predominantly (*Z*)-2-methyl (diphenyl)germylstyrene. this is in sharp contrast to the same addition of methyldiphenyllithium giving the (*E*)-isomer preferentially [256].

J. Organometallic Compounds

Stereoselective electroreduction of some organometal complexes has been reported. The reduction of α-oxotetramethylene-cyclopentadienyl-iron$^+$-η^6-benzenes in an acidic solution occurs specifically from the *exo* side to give only the *endo*-alcohol, as in Eq. (38); in alkaline solution the corresponding stereoisomeric (*d*, *l* and *mso*) pinacols are formed but the stereochemistry has not been determined [257].



(38)

Arewgoda and coworkers [258] reported a cathodic preparation of a stereoisomer of $(CF_3)_6C_6CO_2(Co)_2[P(OMe)_3]_2$ complex.

IV. STEREOSELECTIVE AND STEREOSPECIFIC ELECTROOXIDATION

A. Carboxylic Acids

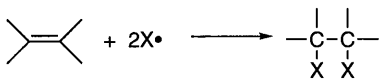
1. Kolbe-Type Reaction

a. Dimerization. The stereochemistry of Kolbe dimerization products has been studied [259–264], see also Chapter 14. Hawkes and coworkers [263] mentioned the stereochemistry of three stereoisomeric dimers from 4-*t*-butylcyclohexanecarboxylic acid; Kanetsuna and Nonaka [264] found that the ratio of the isomeric dimers from ethyl phenylmalonate was not influenced by the kind of anode material.

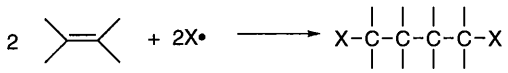
Kolbe cross-dimerization has also been studied stereochemically mainly from a practical aspect with the aim of preparing stereoisomeric long-chain olefins from saturated and unsaturated carboxylic acids [265,266]. The stereoisomeric ratio (*Z*/*E*: 2.4–10.1) is influenced by current density (100–250 mA cm^{-2}) and temperature (−16 to 60°C). Although the pure *Z* acid was used as the starting material, the product was not the pure *Z* olefin but a mixture with the *E* olefin. This indicates that stereoisomerization around the double bond at the γ-position can occur in the Kolbe-type decarboxylation. Hawkes and coworkers [263] also reported that cross-coupling between acetic and 4-*t*-butylcyclohexanecarboxylic acids proceeded nonstereoselectively.

b. Radical Addition to Olefins. The following four types of addition reactions of anodically generated radicals X·(RCCO· and R·) from RCOOH have been stereochemically studied:

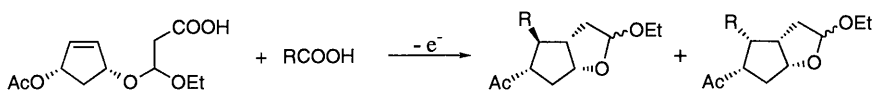
1. Addition of two X· to one olefin molecule, as in Eq. (39) [267–269].
2. Addition of two X· to two olefin molecules, as in Eq. (40) [267]. This addition reaction prefers activated olefins.
3. Intramolecular addition in unsaturated carboxylic acids, as in Eq. (41) [270,271].
4. Addition of two X· to one diene molecule, as in Eq. (42) [272].



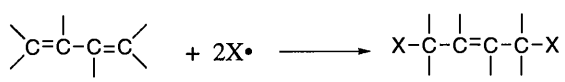
Z/*E* *dl*/*meso*, *erythro*/*threo* (Acyclic); *cis*/*trans* (Cyclic) (39)



Z/*E* *dl*/*meso*, *erythro*/*threo* (40)



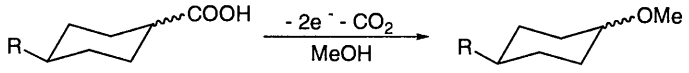
R = Me, 52%, 2.7 : 1 [208]
R = $(CH_2)_2COOMe$, 56%, 3 : 1 [208] (41)



Z/*E*, *E*/*Z* *E*/*Z* (42)

2. Non-Kolbe-Type Reaction

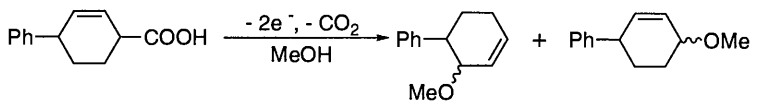
a. Monocarboxylic Acids. Carboxyl groups of cyclic monocarboxylic acids are anodically exchanged by nucleophiles, such as methoxide ion, to give stereoisomeric products [263,273–275]. 4-Substituted cyclohexanecarboxylic acids give the stereoisomeric methoxylated products, as in Eq. (43) [265]. The reaction is nonstereospecific. Pyrrolidine-2-carboxylic acids are also methoxylated in high yields, and the stereoselectivity is generally low [273–275].



R = *t*-Bu, *trans* : 10.5-27.1 % (*cis* / *trans* : 0.3-0.4)
R = *t*-Bu, *cis* : 30.8% (*cis* / *trans* : 0.3)
R = Ph, *trans* : 13.2% (*cis* / *trans* : 0.5)

(43)

Utley and Yates [276] reported an interesting stereochemistry and regiochemistry of methoxylated prdoucts derived from 4-phenylcyclohexene-2-carboxylic acid:



(44)

26% (*cis* / *trans* : 0.4) 49% (*cis* / *trans* : 1.5)

Stereoisomeric (*exo* and *endo*) bicycloalkane carboxylic acids are stereospecifically methoxylated, hydroxylated, and amidated [277,278]. cyclic monocarboxylic acids are also anodically decarboxylated to give stereoselectively cycloalkenes in high yields [279,280].

Substituted cyclopropanecarboxylic acids undergo a ring-opening reaction under conditions for anodic methoxylation and give stereoisomeric products [281,282].

b. Dicarboxylic Acids. 1,2-Dicarboxylic acids give stereoselectively but nonstereospecifically olefins [283,284]: the *d, l*- and *meso*-α, β-diphenylsuccinic acids gave *trans*-stilbene as the sole isomeric product in 63 and 36% yield, respectively [283]. However, anodic oxidation of perhydrodiphenic acids results in the stereospecific formation of lactones [285].

B. Acetoxylation

Acetoxylation occurs in either of the following ways: (1) nucleophilic attack of acetate ion on cationic intermediates formed by loss of electrons, or (2) radical attack by the acetoxy radical generated by loss of an electron from the acetate ion.

1. Olefins

Diacetoxylation of monoolefins sometimes proceeds stereoselectively and/or stereospecifically [8,286–291]. The stereoselectivity is influenced by the structure of the starting olefins and electrolytic conditions. the 1,2- and/or 1,4-diacetoxylation of conjugated dienes occurs stereoselectively, but the stereoselectivity of the latter is generally low [292,293].

2. Benzyl and Allyl Compounds

The stereochemistry of acetoxylation at benzyl positions of substituted indanes and acenaphthenes was investigated in detail [294–296]. the *cis–trans* ratio of diactoxylated products is significantly larger in the anodic than in chemical processes.

It has been reported that the anodic acetoxylation at allylic positions procees with high stereoselectivity (88–93%), as does microsomal acetoxylation (88–93% stereoselectivity). A chemical method with perbenzoic acid gives selectivity as low as 74–80% [297].

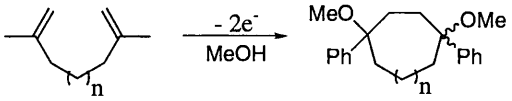
3. Cyclopolyenes

Cyclooctatetraene gave stereoisomeric (*cis* and *trans*) bicyclo[4,2,0]octane-7,8-diols and their diacetates in water and acetic acid, respectively [298,299], and the anodic acetoxylation of anthrancene resulted in the predominant formation of *trans*-9, 10-diacetoxy-9,10-dihydroanthracene [300].

C. Methoxylation

1. Olefins

Acyclic olefins are stereoselectively and sometimes stereospecifically dimethoxylated [301,303]. Anodic oxidation of 1,5- and 1,6-dienes in methanol provides the corresponding 1,4-dimethoxylated six- and seven-membered rings, and the *trans*-isomers are predominantly formed in both cases, as in Eq. (45) [304].



(45)

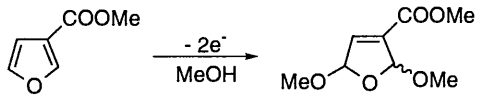
n = 0 : 64% (*cis* / *trans* : 0.04)
n = 1 : 52% (*cis* / *trans* : 0.04)

The anodic dimethoxylation of simple cyclic olefins, such as cyclohexenes, results in the predominant formation of *trans*-dimethoxycyclohexanes [303,305]. However, Barba and coworkers [306] reported that the stereochemistry of 1,2-dimethoxy-1,2-dihydroacenaphthene derived from acenaphthene is drastically influenced by the anode material. Palasz and Utley [307] have reported that *N*-acetylpiperidines are methoxylated via the enamide intermediate species formed by the oxidation. 1,3-Dienes are also 1,4-dimethoxylated in low stereoselectivity [293]. The anodic methoxylation of α-pinene proceeds similarly to the acetoxylation, resulting in the formation of two sets of stereoisomeric products [308].

2. Furans

Since furans are anodically 2,5-dimethoxylated in high yields to give the corresponding *cis*- and *trans*-2,5-dimethoxy-2,5-dihydrofurans, which are regarded as equivalents to the *E* and *Z* unsaturated 1,4-dicarbonyl compounds, this anodic methoxylation is important and useful in synthetic chemistry.

The stereochemistry (*cis* and *trans*) of the methoxylated furans has been examined [309]. In most cases the *trans*-isomers are the major products.



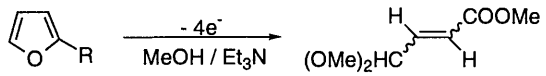
(46)

100% (*cis* / *trans* : 0.37)

2,5-Dimethylfuran was also anodically cyanomethoxylated in the presence of cyanide ion to give 2,5-dimethyl-2-methoxy-5-cyano-2,5-dihydrofuran in a *cis–trans* ratio of 1.46–2.89, which varied with the type of aromatic additive in the anolyte [310].

2-Furylacetic acid derivatives are primarily 2,5-dimethoxylated; an elimination of methanol leads to stereoisomeric olefins (**XXVI**) [311] as in Fig. 3.

The further oxidative methoxylation of 2,5-dimethoxydihydrofurans in situ leads to the stereoselective formation of ring-opened olefins [312–316]. A typical xample [312] is in Eq. (47):



(47)

R = COOH, CHO, CH_2OH, CH_2OAc 84% (Z / E: 0.04) in NH_4Br

24-87% (Z / E: ∞) in Et_4NClO

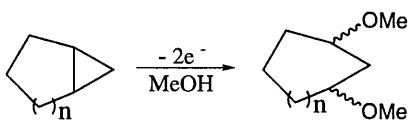
3. Aromatic Compounds

Aromatic hydrocarbons can also be anodically dimethoxylated to give the *trans*-dimethoxy dihydro derivatives in high or moderate stereoselectivity [317–319].

4. Others

Benzyl and allyl positions may be stereoselectively monomethoxylated or sometimes hydroxylated [320,321].

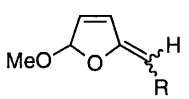
Bicyclic cyclopropyl compounds are anodically dimethoxylated to give stereoisomeric (*cis* and *trans*) cyclopropane ring-opened products, as in Eq. (48) [322]. Shono and coworkers [323] reported a different type of ring-opening reaction of a cyclobutyl compound through anodic methoxylation. They also found that anodic oxidation of borneol and isoborneol in methanol resulted in a rearrangement to provide methoxylated stereoisomeric products with the same *endo–exo* ratio, as in Eq. (49) [324]:



(48)

n = 1 : 35% (*cis* / *trans* : 1.3)

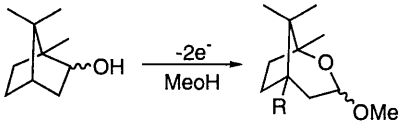
n = 2 : 21-23% (*cis* / *trans* : 1.1-1.3)



R = CN, COOMe, COOEt, COOH

(XXVI)

Figure 3. Anodic methoxylated products derived from 2-furylacetic acid derivatives

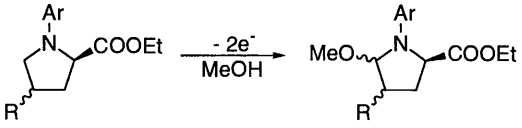


(49)

end or *exo* 72-74% (*end/exo* : 32)

Rearrangement of complicated polycyclic compounds may also be induced by anodic methoxylation [325–328]: The product yields are not high, but high stereoselectivities are obtained in most cases.

The α-positions of cyclic amides may be stereoselectively methoxylated, as in Eq. (50) [329]:



(50)

R = *trans*-OH : COOEt : 60% (*cis/trans*-MeO : COOEt : 2.2)
R = *cis*-OAc : COOEt : 50% (*cis/trans*-MeO : COOEt : 1.9)

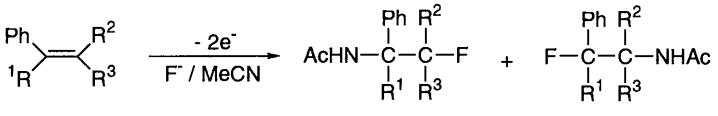
Noyori and Kurimoto [330] have found an interesting anodic ether exchange reaction of aryl glycosides. They described that this is a rate example of $S_{ON}1$-type transformation reaction, but the reaction may be EGA (electrogenerated acid)-catalyzed. The reaction is also stereoselective but not always stereospecific.

D. Acetamidation

The anodic acetamidation of olefins proceeds smoothly in wet acetonitrile containing suitable nucleophiles leading to stereoisomeric products.

1. Haloacetamidation

The stereospecificity, stereoselectivity, and regioselectivity of the fluoroacetamidation of a variety of olefins have been studied in detail from synthetic and mechanistic aspects by Laurent and coworkers, as in Eq. (51) [331–334]. The significant stereochemical results observed may be rationalized by considering coplanar adsorption on the anode of carbonium cation intermediates derived from the olefins.



(51)

$R^1 = R^2 = H$, $R^3 = Ph$: 29% (*erythro / threo* :0.28) 0% [250]
$R^1 = R^3 = H$, $R^2 = Ph$: 45% (*erythro / threo* :0.25) 0% [250]
$R^2 = H$, $R^1 = R^3 = Me$: 29% (*erythro / threo* :3.00) 0% [250]

Stereoselective chloroacetamidation [335,336] and iodoacetamidation [337] have also been reported.

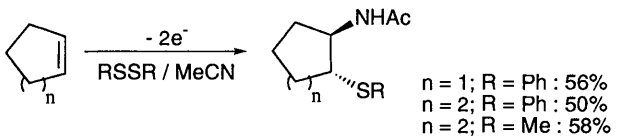
2. Nitroacetamidation

Bloom and coworkers [338] reported in detail the stereochemistry and regiochemistry of the nitroacetamidation of conjugated dienes that were electrolyzed in acetonitrile contain-

ing N_2O_4 as a precursor of electrogenerated nitronium ion at an anode. The reaction proceeded efficiently in most cases.

3. Thioacetamidation

Bewick and coworkers [339,340] found that the anodic thioacetimidation of cycloalkenes occurred highly stereoselectively in acetonitrile containing disulfides:

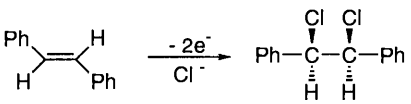


(52)

E. Other Addition Reactions to Olefins

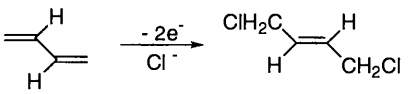
1. Halogenation

Olefins can be anodically dihalogenated, sometimes with very high stereoselectivity. Laurent and coworekrs [333] reported the difluorination of 3-*t*-butylindene, but the stereoselectivity was not high. On the other hand, the dichlorination of olefins, dienes, and acetylenes is highly stereoselective and gives almost exclusively single stereoisomers of products, as in Eqs. (53) through (55) [336,341]. The bromination also gives single stereoisomers of *vic*-dibromo compounds [342–344]. No study of the stereochemistry of anodic iodination has been reported.



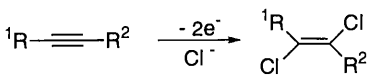
meso 65% [254]

(53)



trans 51% [257]

(54)



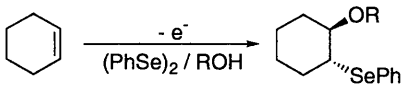
trans

(55)

$R^1 = HOCH_2$, Ph(HO)CH; $R^2 = H$: 60-70% [254]
$R^1 = R^2 = Ph$: 40% [254]

2. Cyanation, Thiocyanation, and Carboxylation

Anodic dicyanation and dithiocyanation of olefins have been reported, but the stereochemistry of the products has not been examined [345,346]. The selenoalkoxylation of olefins, such as cyclohexene [Eq. (56)], cyclopentadiene, and indene, proceeds highly stereoselectively and regioselectively to give *trans* products in high yields [347].



(56)

R = H, Me, Ac 96-98%

F. Intermolecular and Intramolecular Reactions of Olefins and/or Aromatics

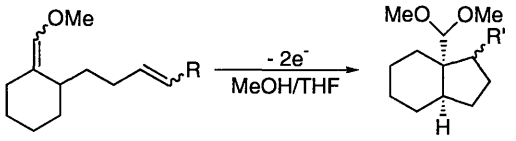
1. Dimerization

Olefins [348] and aromatics [349] are oxidatively dimerized to give stereoselectively dienes and biaryls (rotamers), respectively.

Some types of EGA-catalyzed dimerizations, which proceed stereoselectively, have been reported [288,350–353]. Maleic anhydride is stereoregularly polymerized by anodic initiation to give mainly *cis*-poly(vinyleneketoanhydride) [353].

2. Crossed Coupling

Moeller and coworkers [355–358] studied intramolecular anodic coupling of bisalkyl and bissilyl enol ethers, and enol ethers having a vinylsilane or allylsilane group. They found that *cis*-isomers about the ring juncture were preferentially or predominantly formed:



(57)

R = Me_3SiCH_2 R' = CH_2=CH : 70% (*cis/trans* : ∞) [273]

R = MeO R' =$(MeO)_2$CH : 65% (*cis/trans* : ∞) [273]

Anodically generated phenoxy cations, *o*-quinones, and *o*-quinone methides react with olefins to give bicyclic and tricyclic annelated compounds stereoselectively [359–366].

3. Other Reactions

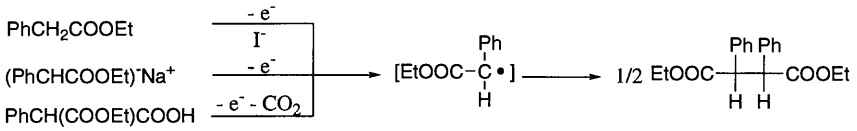
Some interesting stereoselective anodic reactions of unsaturated hydrocarbons have been known, although the stereoselectivity is not always high [367–369]. The reaction seems to proceed via radical cations of the diene. Ando and coworkers [368] investigated in detail the stereochemical consequence of anodic (probably EGA) catalyzed oxygenation of stereoisomeric (*syn* and *anti*) di-*t*-butyl(bicyclo[3,3,1]non-9-ylidenes) compared with the stereochemistry of the photosensitized oxygenation.

G. Active Hydrogen Compounds (Carbon Acids)

Only few studies of the stereochemistry of anodic oxidative dimerization of active hydrogen compounds (carbon acids) and their salts (carbanions) have been reported.

Kanetsuna and Nonaka [264,370] compared the stereochemistry of diethyl 2,3-diphenylsuccinate formed in the oxidation of (1) ethyl phenylacetate (in the presence of iodide ion), (2) its sodium salt, and (3) ethyl phenylmalonate [Eq. (58)]. A phenylethox-

ycarbonylmethyl radical may be a common intermediate in these three reactions and undergo coupling to form the succinate.



(58)

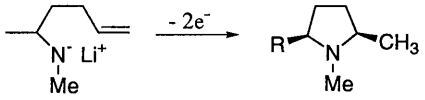
(1) 9-46% (*dl / meso* : 0.7-1.0) [201,288]
(2) 1-4% (*dl/meso* : 1.4-1.8) [201]
(3) 4-17% (*dl/meso* : 0.9-1.0) [201]

In similar studies, Matsumura and coworkers later found that iodine-mediate anodic oxidation of methyl phenylacetate anion having Bu_4N^+ counterion provided the corresponding succinate in good yield and with high *d*, *l*-selectivity (*d*, *l*/*meso*: 3.5) [371].

H. Heteroatom Compounds

1. Nitrogen Compounds

A few reactions of nitrogen compounds interesting from a stereochemical aspect have been reported. Tokuda and coworkers [372] reported the stereochemically clear result that lithium alkeynylamides undergo a highly stereoselective cyclization by anodic oxidation to give *cis*-1-methyl-2,5-disubstituted pyrrolidines in reasonable yields, as in Eq. (59). The cyclization seems to proceed via neutral amino radicals.



cis

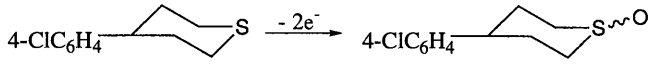
(59)

R = Me, Et, 4-MeC_6H_4, 4-$MeOC_6H_4$: 31-52%

It has been also found that ditosylates of α, ω-diamines are anodically cyclized in methanol containing halide ions to give stereoisomeric *N*-tosyl-2-methoxy-2-tosylaminopyrrolidines (or piperidines) [373].

2. Sulfur Compounds

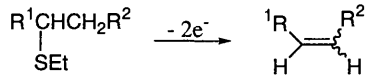
Stereoselective anodic methoxylation [374] and ring-opening reaction of thiophenes leading to olefin formation [375] have been reported. Anodic oxidation of saturated cyclic sulfur compounds has also interesting stereochemical features. Kimura and coworkers [376] reported that a 4-substituted thiane was stereoselectively oxidized to the *trans*-thiane oxide, which was always the major product, although the iomeric ratio was affected by electrolyte and solvent used [Eq. (60)]. The oxidation of 2,5-substituted-1,3-dithianes to the *cis*- and *trans*-4-substituted-1,2-dithiolanes is stereoselective but not stereospecific [377].



(60)

ca. 50% (*cis/trans* : 0.08-0.52)

Kimura and coworkers [378] have also reported that electrooxidative desulfenylation of Michael-type thiol adducts of α, β-unsaturated esters, ketones, and also nitriles resulted in the formation of *E*- and *Z*-olefins as major products, respectively:



(61)

R^1 = Me, Ph; R^2 = COOEt, COOMe, COMe : 24-98% (*Z*/*E* : 0)
R^1 = Me, Pr; R^2 = CN : 28-67% (*Z*/*E* : 1.1-2.0)

3. Silicon Compounds

Yoshida and coworkers [379] found that stereoisomeric mixtures of 1-trimethylsilyl-1,3-dienes are oxidized in methanol to give trimethoxylated *trans*-olefins as single stereoisomer.

Anodic oxidation of 1,2-bis(trimethylsilyl)-1,2-diphenylethane in methanol afforded 1,2-dimethoxy-1,2-diphenylethane (*d*, *l*/*meso*: 10) [380]. γ-Acyloxyvinylstannanes undergo copper mediated anodic homocoupling to afford 1,3-dienes without isomerization. Thus, optically active 1,3-dienes were prepared anodically from optically active alkenylstannanes [381].

The stereoselective EGA-catalyzed reaction of trimethylsilyl enolates and dimethylacetals has also been reported [382].

I. Organometallic Compounds

Stereoselective synthesis of organometallic complexes has been achieved in the oxidative addition of aryl halides to triethylphosphine nickel(0) complexes, leading to the exclusive formation of *trans*-aryl nickel(II) halide complexes [383]. Electron-transfer reactions on the Fe of *cis*- and *trans*-$[\eta\text{-}C_5H_5Fe(CO)SR]_2$ occur stereospecifically with no stereoisomerization on changing the oxidation state of the Fe [384,385]. In the electrochlorination of a ligand (R) of the $\eta\text{-}C_5H_5Fe(CO)R$ complex, the stereochemistry is retained [386].

V. ASYMMETRIC REDUCTION AND OXIDATION

A. Reaction of Chiral Compounds

Electrochemical reactions that occur at chiral centers and also give chiral products are mentioned here.

1. Reduction of Halides

Cathodic reduction of chiral (optically active) haloalkanes to the chiral alkanes has been studied mainly from a mechanistic aspect. The configurational change (retention and inversion) during the reduction is discussed.

The reduction of chiral 1-substituted 1-halo-2,2-diphenylcyclopropanes at a mercury cathode to the chiral cyclopropanes has been reported by some workers [387–389].

The reduction of chiral open-chain halides has been also reported. Nonaka and coworkers [390] investigated the reduction of a chiral chloroalkane and attempted to rationalize the stereochemical course of the reaction by considering the configurational

stability of the radical intermediate species at the cathode interface. Optically pure(+)-(1*R*, 2*R*)-1,2-dimethylcyclopropane was obtained in the reductive intramolecular cyclization of (+)-(2*S*, 4*S*)-2,4-dibromopentane [245].

Maran [391] investigated electroreduction of optically active 2-bromo-*N*-phenylpropanamide giving optically active *N*-phenyl-2-hydroxypropanamide and *cis*-1,4-diphenyl-3,6-dimethyl-2,5-dioxopiperazine.

2. Reduction of Alcohols and Amines

Alcohols and amines are generally not reducible. Only certain alcohols and amines can be reduced to the corresponding alkanes.

Optically active *O*-benzoylatrolactic acid and its methyl ester were reduced to 2-phenylpropionic acids with almost complete loss of optical activity [392]. On the other hand, Nonaka and coworkers [393] found that 1-(2-pyridyl)alkanols were reduced to 2-alkylpyridines with configurational retention in acidic medium; 1-(4-pyridyl)alkanols gave racemic 4-alkylpyridines. The stereochemical course was discussed considering perpendicular adsorption of pyridylalkanol molecules on the cathode and the configurational stability of carbanion intermediates.

Electroreductive deprotection of tosylates and sulfonamides of chiral alcohols and amines, respectively, was achieved without racemization [394,395].

3. Reduction of Onium Compounds

Optically active quaternary arsonium [396,397] and phosphonium [398] salts are electroreductively decomposed to tertiary arsines and phosphines, respectively, with retention of configuration. Since the tertiary products can be converted again into different quaternary salts with alkylating regents, this decomposition reaction may be useful for transformation between a variety of optically active quaternary salts [397].

4. Oxidation of Carboxylic Acids

Carboxylic acids with a chiral center at the α-carbon give racemic Kolbe dimers [399,400]. Addition products of radicals derived from such carboxylic acids to olefins are also racemic [401]. Racemization is also observed in anodic methoxylation of carboxylic acids [402]. These facts may suggest that Kolbe rdicals interact so weakly with the anode surface that their configuration cannot be stabilized during the reaction. However, it can also be stated that the radicals interact sterically with the anode so that the geometry of the dimers is influenced by the anode material (see Sec. IV).

β-Chiral carboxylic acids give optically active dimers with high optical purity [403,404].

It is interesting that anodic methoxylation and subsequent chemical alkylation of optically active *N*-protected α-amino acids with one more chiral center affords the final products in high optical purity, although the diastereomeric purity of the intermediate methoxylated products does not seem to be so high [405,406]. Intramolecular asymmetric induction may occur in the chemical alkylation step.

5. Oxidation of Heteroatom Compounds

Shono and coworkers [407] reported that an α-chiral alcohol was converted into the corresponding chloride by diphenylsulfide-mediated anodic reaction. Anodic cyclization of α-amino acids in methanol was also reported [408].

Ohtani and coworkers [409–413] found photocatalytic one-step synthesis of L-proline and L-pipecolinic acid from L-ornithine and L-lysine using aqueous semiconductor suspensions.

B. Asymmetric Synthesis

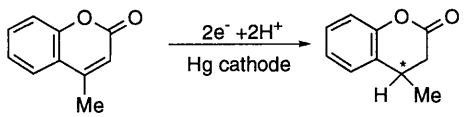
Asymmetric synthesis is a very important area in organic chemistry. However, it must be noted that electrochemical asymmetric synthesis has been immature compared with chemical, catalytic, and enzymatic methods, although much effort has been made since the first report in this area by Grimshaw and coworkers [414] in 1967.

Although the history is short, a number of papers have been published and some methodologies have already been established. Particularly in recent years, new methodological developments have been successful. This point was reviewed by Nonaka [19] and Bersier [11].

1. Use of Chiral Electrode Adsorbants

In most studies, optically active alkaloids have been used as asymmetry inducers in this method.

Asymmetric reduction of activated olefins has been performed using prochiral cumarin derivatives [414–416]. A maximum asymmetric yield reported was 17%, as in Eq. (62) [415], and an asymmetry induction mechanism has also been discussed [416]. Later, Schäfer and coworkers carried out similar enantioselective electroreduction of various 4-substituted cumarins by systematic variation of the electrolysis conditions, and they obtained optical yields as high as 67% [Eq. (62)] [417–419]. Computational chemistry using semiempirical AM1 demonstrates that *si*-protonation of the intermediate anion by protonated yohimbine to form the (*R*)-isomer is energetically favored [418,419].



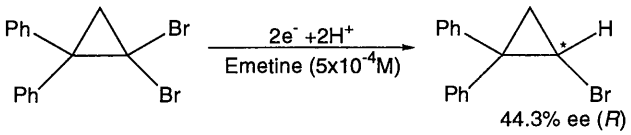
(62)

alkaloid = sparteine (0.07 equiv); pH = 5.4: 17% ee (*R*) [415]
alkaloid = yohimbine (0.01-0.05 equiv); pH = 2-3: 47-67% ee (*R*) [417-419]

The asymmetric reduction of prochiral ketones to chiral alcohols has been extensively investigated [420–428], and a maximum asymmetric yield of 48.4% has been reported using 2-acetylpyridine [421].

The asymmetric reduction of C=N double bonds has been investigated using prochiral oximes [427–431]. The maximum asymmetric yield is 18% [428].

gem-Dihalides are also asymmetrically reduced to chiral monohalides [432–434], and a maximum asymmetric yield of 44.3% has been reported [Eq. (63)] [433]:



(63)

Not only asymmetric yields of products but also their absolute configurations vary drastically with cathode potential, supporting electrolyte, solvent, pH, cathode material,

concentration, and other factors that influence adsorption [435–438]. It may sometimes be a disadvantage in asymmetric synthesis that a reaction is too sensitive to variations in conditions. There have also been attempts to replace alkaloids with other inducers, such as optically active amino acids [439].

2. Use of Chiral Supporting Electrolytes

This method was applied to the asymmetric reduction of ketones [440–444] and imines [439,445]. Maximum asymmetric yields reported for the former and the latter are 20% [441] and 8.95% [445], respectively. A higher asymmetric yield (20.6%) was obtained in the hydrodimerization of a ketone [444]. It is a problem that lower asymmetric yields are obtained using much larger amounts of asymmetry inducers, which must play the role of supporting electrolyte.

3. Use of Chiral Media

Seebach and Oei [446,447] reported the asymmetric hydrodimerization of acetophenone (a maximum asymmetric yield of 6.4%) in a chiral cosolvent. The use of small amounts of chiral crown ethers was attempted; however, no significant asymmetric induction was observed [443]. It is interesting that in the presence of β-cyclodextrin, head-to-tail coupling of acetophenone leads to optically active dimeric monoalcohol (ca. 24% ee), whereas the head to head coupling gives optically inactive pinacols [448,449].

4. Use of Chiral Oxidant

Recently, electrochemical Os-catalyzed asymmetric dihydroxylation of olefins with Sharpless's ligand has been developed by Amundsen and Balko [450] and by Torii and coworkers [451,452].

5. Use of Chiral Modified Electrodes

The use of chiral modified electrodes (see Chapter 27) may be the most promising method for electrochemical asymmetric synthesis because of (1) use of extremely small amounts of inducers, (2) low sensitivity to reaction conditions, (3) variety of kind, and (4) possible application of both cathodic and anodic reactions, although there are some problems to be solved.

a. Chemically Modified Electrodes (CME). Miller and coworkers [453,454] found that prochiral carbonyl compounds were reduced to chiral alcohols on a cathode chemically modified with (*S*)-phenylglycine. This may be the first example of a chemically modified electrode. The maximum asymmetric yield obtained was 14.5% in the reduction of 4-acetylpyridine. A similar electrode modified with (+)-camphoric acid was used for the oxidation of *p*-tolyl methyl sulfide to the sulfoxide in 2.5% asymmetric yield [455]. However, no asymmetry induction could be observed in the reduction of carbonyl compounds on other modified cathodes with α-chiral amines [456].

b. Electrodes with Irreversibly Adsorbed Inducers. Osa and coworkers [457] developed a chiral Raney nickel electrode on which (*S*, *S*)-(−)-tartaric acid was irreversibly adsorbed and applied it to the asymmetric reduction of carbonyl compounds. A maximum asymmetric yield of about 20% was obrained in the reduction of methyl acetoacetate.

c. Polymer-Coated Electrodes. Nonaka and coworkers [458–463] prepared a variety of electrodes coated with optically active poly(amino acids) and applied them to

both asymmetric reduction and oxidation. Maximum asymmetric yields in the reduction and oxidation were 43% [458] and 93% [463], respectively. The reproducibility of asymmetric yield in the sulfide oxidation was not high when poly(amino acids) prepared from different lots were used [19,464].

Osa and coworkers [405,466] developed a graphite felt electrode modified with 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO) and applied it to enantioselective, electrocatalytic oxidative coupling of naphthol, naphthyl ether, and phenanthrol in the presence of (−)-sparteine as a base. The enantioselectivity of the coupling products were as high as 98%.

d. Clay–Metal Chelate-Coated Electrodes. Yamagishi and Aramata [467] prepared a clay-coated electrode that incorporated optically active tris(1,10-phenanthroline)ruthenium (**II**) into the montmorinite thin film. In the oxidation of sulfides, a maximum asymmetric yield of 20% was obtained.

e. Intercalated Graphite Electrodes. Simonet and coworkers [468] prepared a new type of chiral electrode by forming a lamellar compound ($CnNR_4$*) of graphite and optically active ammonium compounds by electrochemical intercalation. This electrode resulted in a maximum asymmetric yield of 9.3% in the reduction of phenyl *t*-butyl ketone to the alcohol.

6. Intramolecular Asymmetry Induction

Intramolecular asymmetric induction has also been used in electrochemistry as in the reduction of optically active alcohol esters or amides of α-keto [469,470] and unsaturated [471] acids and oximes [472] and in the oxidation of olefins [473]. A maximum asymmetric yield of 81% was obtained in the reduction of (*S*)-4-isopropyl-2-oxazolidinone phenylglyoxylate [470]. Nonaka and coworkers [474,475] found that amino acid *N*-carboxy anhydrides were polymerized with various electrogenerated bases as catalyst to give the poly(amino acids) with high chirality in high yields. Conductive chiral poly(thiophenes) prepared by electropolymerization can be used for chiral anion recognition [476].

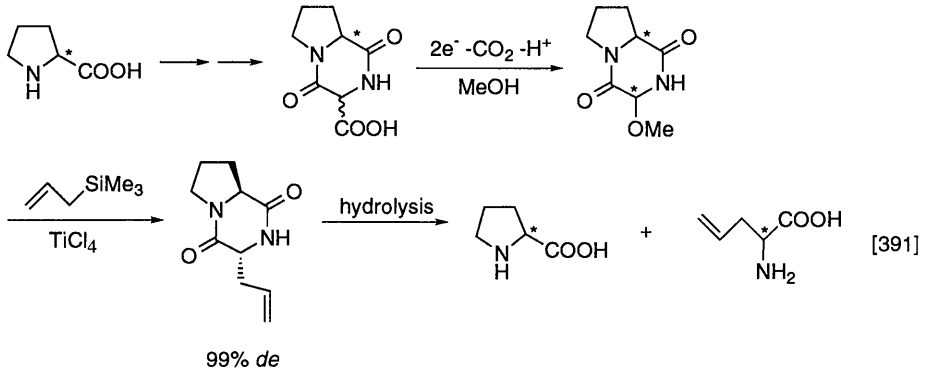
In simulation of the intramolecular asymmetric reduction using chiral but optically inactive (racemic) substrates, such as ketones [103,104] and *gem*-dihalopropanes [477], asymmeric yields higher than 80% could be obtained. It was also found that the intramolecular asymmetric reduction could be improved in asymmetric yield by using an optically active supporting electrolyte [445,478,479].

Electrochemical diasteroselective substitutions based on intramolecular asymmetric induction are highly useful for asymmetric synthesis. Recently, many studies focused on this subject have been done.

Electroreductive asymmetric alkylation [480,481] and electrooxidative asymmetric fluorination [482,483] of chiral substrates have been reported.

Moeller and coworkers [484] found that electrochemical cyclization (anodic intramolecular alkoxylation) of optically active dipeptides proceeded highly diasteroselectively.

Recently, Steckhan and coworkers [485,486] have reported that anodic methoxylation of chiral 5-methyl- and 5-chloromethyl-2-oxazolidinones followed by Lewis acid-catalyzed allylation provides 4-allyl products highly diastereoselectively. Similarly, anodic methoxylation of cyclic dipeptides and dipeptolides derived from chiral α-amino acid [487] or α-hydroxy acid [488] provides useful chiral synthetic building blocks, as in Eq. (64). α-Alkoxylation of lactic amide derivatives was also reported [489]. However, the diastereoselectivity was low.



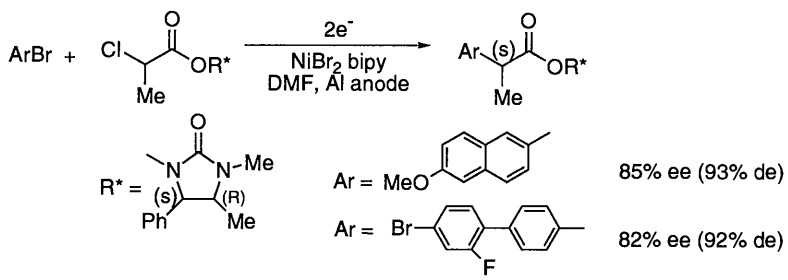
(64)

3,3,3-Trifluoropropylsulfides having a methoxy or an ester group at the 2-position undergo anodic α-methoxylation efficiently in the presence of fluoride ions. The diasteroselectivity of the products is moderate [490,491].

Kise and coworkers [492] reported electroreductive intramolecular hydrocoupling of diimines derives from chiral 1,2-diamines giving enantiomerically pure piperazines. They also prepared enantioselectively 3,4-diphenyladipate by electroreductive intermolecular hydrocoupling of chiral *N-trans*-cinnamoyl-2-oxazolidones [493].

Schäfer and coworkers [494] reported interesting diasteroselective cross-coupling of anodically generated radicals bearing chiral amide groups.

A highly asymmetric induction in the nickel-catalyzed electroreductive couplings of aryl halides with α-chloropropionic acid derivatives was reported by Nedelec and coworkers [Eq. (65)] [495].



(65)

7. New Asymmetic Induction Methods

Recently, asymmetric electroreduction methods based on new principles have been developed.

a. Electroenzymatic Reduction. Electroenzymatic asymmetric reduction of activated olefins was achieved by the methylviologen-mediated indirect electroreduction in the presence of enolate reductase [496]. (*E*)-2-Phenylsuccinic acid gave (*R*)-2-methyl-3-phenylpropionic acid in 96% ee. Electromicrobial asymmetric induction has also been proposed. Similar electroenzymatic reduction of ketones and aldehydes using alcohol dehydrogenase provided almost optically pure chiral alcohols in high yields [497]. Highly asymmetric electroreduction of 3-ketoesters using Baker's yeast was similarly achieved [498]. Electroenzymatic synthesis is reviewed in Chapter 27.

C. Optical Resolution

Electrochemical optical resolution of racemic mixtures is achieved by using enantiomer-differentiating oxidation or reduction.

Komori and Nonaka [499] reported the first example of an electrochemical enantiomer-differentiating reaction: When racemic 2,2-dimethyl-1-phenyl-1-propanol was oxidized at a poly(L-valine)-coated anode, 43% optically pure (*S*)-(−)-2,2-dimethyl-1-phenyl-1-propanol was recovered as an unreacted part. Yamagishi and Aramata [500] also found electrooxidative optical resolution of a racemic $Co(1,10\text{-phenathroline})_3^{2+}$ complex by a chiral clay-coated anode, and Yoshinaga and coworkers [501] electroreductively resolved racemic $Co(acetylacetonato)_3$ by using optically active supporting electrolytes.

Recently, Osa and coworkers [502] have reported highly enantioselective electrocatalytic oxidation of racemic monoalcohols using a TEMPO-modified graphite felt electrode in the presence of (−)-sparteine. Optically almost pure *R*-isomeric alcohols remained unreacted. Highly enantioselective lactonization of racemic diols was also achieved by using the same TEMPO-modified electrode to give (*S*)-isometric lactones [503].

On the other hand, Hisaeda and coworkers [504] found that the vitamin B_{12}-mediated electroreductive optical resolution was accompanied by rearrangement: Electroreduction of racemic 3-bromo-2-methoxy-2-phenylpropionate using a hydrophobic vitamin B_{12} mediator afforded ethyl (*S*)-2-methoxy-2-phenylpropionate in 55% ee, while a novel hydrophobic vitamin B_{12} modified by introducing a 1,3-phenylene diacetyl moiety into the peripheral site around the corrin's B ring, a so-called strapped hydrophobic vitamin B_{12}, provided the corresponding *R*-enantiomer in 26% ee.

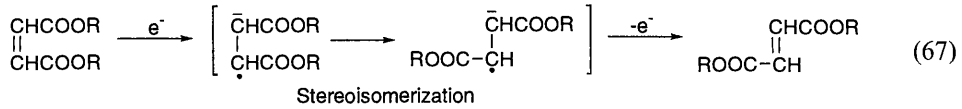
Enantioselective electrodialysis of *N*-α-acetylryptophans through molecularly imprinted polymeric membranes has also been reported [505]. Highly efficient electroenzymatic optical resolution of diols and ketones has been achieved using a polymer-coated graphite felt electrode immobilizing all mediatior components including alcohol dehydrogenase [506–508].

VI. ELECTROCHEMICAL STEREOISOMERIZATION

As shown in Eq. (66), a stable stereoisomer (A) can be converted into another stable isomer (B) through electrochemical oxidation–reduction or reduction–oxidation, if a stereoisomeric unstable intermediate (A^n) is rapidly stereoisomerized to an isomeric intermediate (B^n). Such an electrochemical stereoisomerization can sometimes be observed under cyclic voltammetric conditions; for preparative isomerization reactions, AC electrolysis at a suitable frequency or undivided cell electrolysis may be useful.

$$A \xrightarrow{\pm ne^-} [A^{\pm n} \xrightarrow[\text{Stereoisomerization}]{} B^{\pm n}] \xrightarrow{\pm ne^-} B \qquad (66)$$

a. Cis-to-Trans *Isomerization.* Yeh and Bard [509] observed the isomerization of dialkyl maleates to the fumarates through a reduction–oxidation by cyclic voltammetry and rotating ring-disk electrode techniques:



(67)

Electrochemically induced *cis*-to-*trans* postitional stereoisomerization of ligands has been found on oxidation-reduction of several types of octahedral complexes of groups VIIB metals [510–519]. The key step is isomerization of cationic *cis*-intermediates formed by one-electron oxidation.

b. Tub-toChair Isomerization. COT ligands in COT-cobalt complexes undergo a tub-to-chair conformational isomerization induced by electrochemical reduction–oxidation via an unstable planar COT^- or COT^{2-} [520–526].

c. A-to-B-Form Isomerization in Bianthrones. The A form of bianthrones is isomerized to the B form by both electrochemical reduction–oxidation and oxidation–reduction via unstable anionic and cationic species with the bifolded structures, respectively [12,527–536].

VII. STEREOISOMERIC EFFECTS ON THERMODYNAMICS AND KINETICS OF ELECTRODE PROCESSES

It is sometimes observed that stereoisomers have different oxidation and reduction potentials and electron transfer rates. Such phenomena are effectively utilized for clarification of reaction mechanisms and analysis of stereoisomers.

A. Cathodic Processes

1. Hydrocarbons

Polarographic studies of stereoisomeric α, β-diactivated olefins have been made since early times [537,538]. Generally, half-wave potentials $E_{1/2}$ of the first wave of the *trans*-isomers may be slightly less negative than those of the corresponding *cis*-isomers, although the behavior of the second waves and limiting current is not simple. Kita and coworkers [539] reported in a kinetic study that the electron transfer rate of a *cis*-isomer is several times larger than that of the *trans*-isomer.

The *Z*-isomers of monoactivated olefins may be more easily reduced than the *E*-isomers in aqueous solutions, but no significant differences are observed in nonaqueous media [540–543].

2. Halogen Compounds

The less stable *ax*- and *exo*-monohalo derivatives of mono- and bicycloalkanes, respectively, have remarkably less negative $E_{1/2}$ than their *eq*- and *endo*-halo isomers. In the reduction of acyclic *vic*-dihalo compounds, it is not easy to find a clear tendency in the stereoisomeric results; in cyclic *vic*-dihalides a regularity can be found, particularly a very interesting law, that there is a pronounced dependence of $E_{1/2}$ on the torsion dihedral angle between the two C–Br bonds of *vic*-dibromides. Such a significant difference in $E_{1/2}$ values between stereoisomers of *vic*-dihalides is applicable to stereoisomeric analysis [544,545]. A significant difference in $E_{1/2}$ was found between *cis*- and *trans*-1,2-dihalo olefins [224,546]: The *trans*-isomers are more easily reduced. Lund and coworkers [547] reported an interesting kinetic phenomenon in the single-electron transfer from vinyl

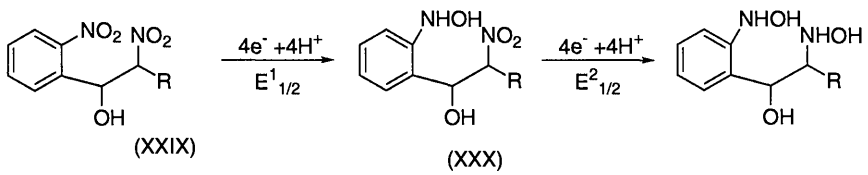
anions generated by indirect electroreduction of stereoisomeric (*cis* and *trans*) vinyl bromides.

3. Carbonyl Compounds

An interesting stereoisomeric effect was reported in the reduction of a formyl group [548] (Fig. 4). Compound **XXVII** is reduced more difficultly than **XXVIII** owing to an interaction between the formyl group and the double bond or to a difference in the reaction rate of the *ax*- and *eq*-substituents; the semicarbazones of **XXVII** and **XXVIII**, however, do not show any difference because the bulky azometine groups of the both compounds are always equatorial.

4. Nitrogen Compounds

Stereoisomeric (*erthryo* and *threo*) *o*-nitro-α-(nitromethyl)-benzylalcohols (**XXIX**) undergo a two-step electroreduction, as in Eq. (68) [549]. The first-wave $E_{1/2}$ values of *erythro*-**XXIX** are less negative by 10–50 mV than those of the *threo*-isomers; the second-wave $E_{1/2}$ values of the former ones are more negative than those of the latter. Since the configuration of intermediate **XXX** should be the same as that of **XXIX**, this is stereochemically interesting.



(68)

The $E_{1/2}$ of *cis*-azocyclohexane is less negative by about 200 mV at $2 < pH < 9$ than that of the *trans*-isomer, but they are almost equal in aprotic media [550]. On the other hand, aromatic azo compounds show a quite different behavior. Isomeric (*cis* and *trans*) azobenzenes are reduced at the almost same potential at $pH < 11$ because of a fast *cis*–*trans* isomerization during the first stage of the reduction, but at $pH > 11$ the *cis* isomer is reduced at a less negative potential than the *trans*-isomer [551].

5. Organometallic Compounds

2-Substituted cyclohexyl mercury halides form carbanions on reduction. A significant difference between the $E_{1/2}$ values of *cis* and *trans* forms may be rationalized as due to differences in the conformational stability of carbanions formed or in some charge-dipole interaction in the transition state leading to the carbanions [552].

The *trans*-isomers of (η^6-stilbene)$Cr(CO)_3$ and (η^6, η^6-stilbene)$[Cr(CO)_3]_2$ have less negative $E_{1/2}$ values than the *cis*-isomers [553]. A similar difference of $E_{1/2}$ is also observed in the reduction with conformational change of *cis* and *trans*-diiodocyclohexane [554].

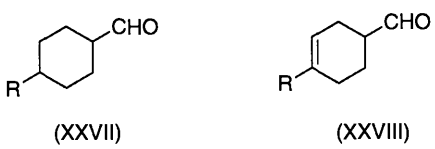


Figure 4. Stereoisomeric effect in the reduction of a formyl group.

B. Anodic Processes

1. Hydrocarbons

Arnold and Wong [555] have reported that the oxidation potentials of *cis* and *trans*-1,2-diphenylcyclopropanes have simple linear correlations with both their ionization energies and charge transfer adsorption energies with tetracyanoethylene as an acceptor. Similar correlations have been observed in *cis*- and *trans*-2,3-diphenyloxiranes.

2. Alcohols

Nonaka and coworkers [556] compared the anodic oxidation rates of *ax*- and *eq*-hydroxyl groups of a variety of cyclic alcohols. *ax*-Alcohols with no substituent at the 2-positions are more easily oxidized than the *eq*-alcohols; for 2-subsituted alcohols the situation is reversed. This is rationalized as due to a different contribution of adsorption of the isomers on the anode.

cis-cyclic diols are much more easily oxidized with chemical oxidizing reagents, such as chromic and periodic acids, than the *trans*-diols. A similar trend has recently been reported in the indirect oxidation [557]. However, such a significant difference is not observed in the anodic oxidative cleavage [558–560]. It is interesting to note that *cis- and trans*–1,2-cyclohexanediols give adipaldehyde and adipoin, respectively, at a platinum anode, but a lead dioxide anode only adipaldehyde is formed from both diols [559]. 2-Aminoalcohols are also anodically cleaved to give the corresponding carbonyl compounds as main products, along with some amounts of by-products [560,561]. Masui and coworkers [561] reported that *threo*- and *erythro*-amino alcohols were oxidized at equal potentials to give a somewhat different product selectivity.

3. Other Heteroatom Compounds

Nelsen and coworkers [562] detected conformational equilibria in *eq, eq*- and *ax, eq*-*N, N′*-disubstituted cyclic hydrazines from their oxidation potentials. The anodic oxidation reactions of *trans*- and *cis*-1,3-diisopropy-1-2,4-bis(diisopropylamino)-cyclodiphospha(III)azanes are quite different [563]: The *trans* isomer is reversibly oxidized at 0.53 V (SCE) forming a stable cation radical; the *cis*-isomer undergoes a completely irreversible oxidation at a more positive potential because an unstable radical cation is formed. Evans and coworkers studied structural changes associated with electron transfer reactions of $W(\mu^5\text{-}C_5(CH_3)_5)(CH_3)_4$ and related compounds [564,565]. Yoshida and coworkers found a linear correlation on plotting the oxidation potentials of α-silylated ethers, where the rotation around the C–O bond is restricted, against the HOMO energy-torsion angle (Si–C–O–C) curve estimated by MO calculation [566].

The oxidation potential of 2-*endo*-methylthio-6-*endo*-substituted norbornanes is strongly influenced by the substituents because of 2,6-space interaction, but there is no such influence in teh 6-*exo*-substituted isomer [567–569].

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27
Electroenzymatic Synthesis

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I. INTRODUCTION

Biocatalysts like isolated enzymes or whole cells have found widespread application in organic synthesis during the last two decades [1]. The interest in these biocatalysts stems from the fact that complex organic compounds can be generated with high chemo-, regio-, and enantioselectivity at ambient temperature in mostly aqueous media and therefore often cause less ecological problems [2]. Numerous applications in asymmetric synthesis [1,3], C–C bond formation, synthesis and derivatization of carbohydrates [4,137], glycoside formation [5], peptide synthesis and protective group strategy [6], and redox reactions [7,8] have been reported. Until now, preparative synthetic applications of isolated enzymes have been concentrated on hydrolytic reactions. More recently, C–C bond-forming reactions found increasing attention.

The synthetic application of redox enzymes (oxidoreductases), especially in the field of enantioselective reductions and chemo-, regio-, and stereoselective oxidations, is very important [7,8] and covers a wide range of processes, as listed:

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1. Reductions catalyzed by alcohol dehydrogenases: formation of chiral enantiomerically pure alcohols from carbonyl compounds.
2. Reductions catalyzed by lactate dehydrogenase: formation of chiral α-hydroxy acids from α-keto acids.
3. Reductions catalyzed by glycerol dehydrogenase, sorbitol dehydrogenase, mannitol dehydrogenase, and aldose reductases: formation of polyols from carbohydrates.
4. Reductions catalyzed by amino acid dehydrogenases: formation of α-amino acids from α-keto acids.
5. Reductions catalyzed by enoate reductase: enantioselective hydrogenation of α, β-unsaturated enoates and comparable compounds.
6. Oxidations catalyzed by monooxygenases: Oxygenations of C–H and C=C bonds forming alcohols, epoxides; enantioselective Baeyer-Villiger oxidations of ketones to chiral lactones and of sulfides to chiral sulfoxides; nuclear and side-chain hydroxylation of aromatic compounds.
7. Oxidations by dioxygenases: *cis*-hydroxylation of aromatic double bonds.
8. Oxidations catalyzed by oxidases: regio- and stereoselective oxidations of polyols; oxidations of carbohydrates; oxidations of hydroxy steroids; oxidations of alkyl phenols to form chiral *p*-hydroxybenzylic alcohols; hydroxylation of phenols; oxidation of amino acids to keto acids.
9. Oxidations catalyzed by $NAD(P)^+$-independent dehydrogenases: stereoselective alcohol oxidation.
10. Oxidations catalyzed by $NAD(P)^+$-dependent dehydrogenases: formation of chiral lactones from *meso*-diols; stereoselective formation of ketones from polyfunctional alcohols; regioselective oxidations of steroids.
11. Oxidations catalyzed by aldehyde oxidases: oxidation of aldehydes to carboxylic acids.

But the application of redox enzymes is also connected with intrinsic problems. The difficulty with redox enzymes in synthetic processes is based on the fact that this class of biocatalysts is dependent on freely dissociated (like NADH, NADPH, pteridin) or enzyme-bound (like FMN, FAD, thio-tryosine, PQQ, or cytochrome) cofactors, respectively, prosthetic groups (Fig. 1) in stoichiometric amounts to shuttle the redox equivalents from the enzyme to the substrate.

To solve this problem, oxidoreductases are usually not used in their isolated form, but via fermentation techniques using microorganisms in which the cofactor regeneration components are integrated. Using this method, however, the solutions obtained at the end of the fermentations are composed of many different compounds such as the residual substrates and products of the growth step and the by-products resulting from other enzymes that are contained in the microorganism. Besides, large amounts of biomass are produced. As a consequence, complex and costly separation and purification steps are necessary to obtain the product in a pure form. Thus, the high intrinsic selectivity of oxidoreductase is not well exploited by fermentation techniques [9].

The use of isolated enzymes, therefore, has great advantages. However, for the preparative applications of isolated redox enzymes, especially for continuous processes, effective and simple methods for the continuous recycling of the active cofactors have to be available. In addition, such systems have to be stable over long times and the separation of the product must be simple to render technical processes economically feasible. Until now, this problem has been generally solved by coupling of the synthetic enzyme with a

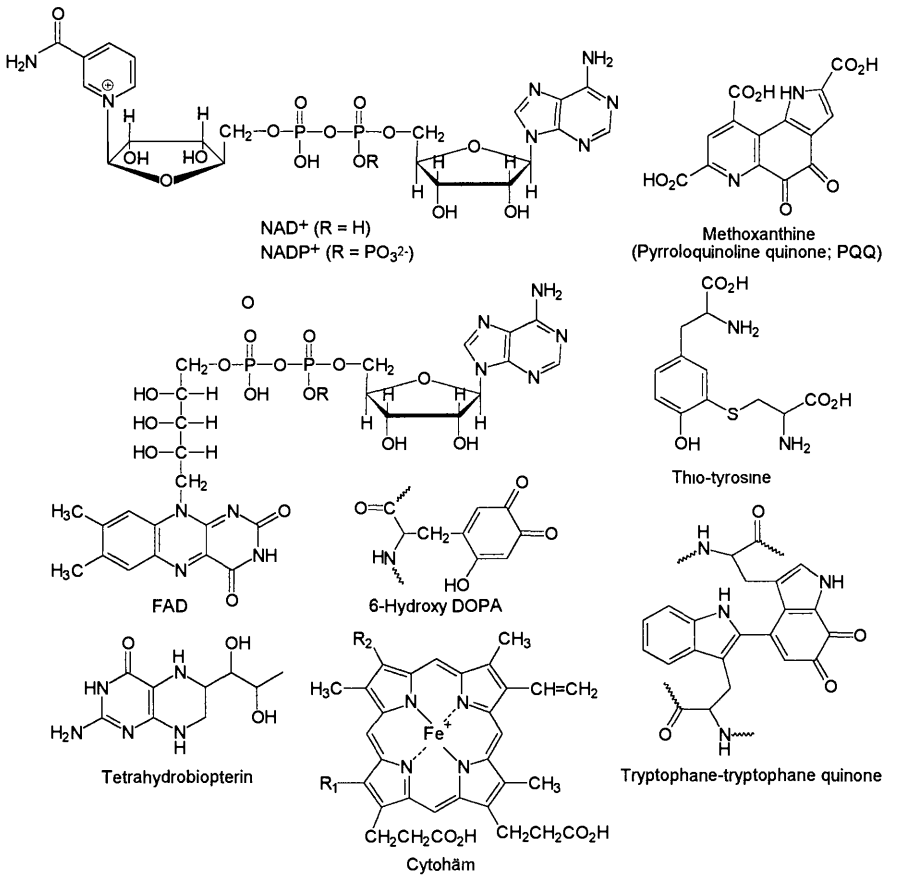


Figure 1. Cofactors and prosthetic groups in dehydrogenases, oxidases, and monooxygenases.

chemical [10] or more often an enzymatic regeneration using a second regeneration enzyme (enzyme-coupled regeneration) (Fig. 2) [11].

Thus, besides a production enzyme for the transformtion of the substrate into the product, a regeneration enzyme (sometimes the production enzyme also acts as regeneration enzyme) together with its cosubstrate in usually high concentrations is also necessary to reactivate the cofactor of the production enzyme. The additionally formed couple–product then has to be separated from the desired product. In some cases, such enzyme-coupled regeneration systems are highly developed. This is in particular the case for NAD(P)H-dependent enzymes where formate dehydrogenase is used as a regeneration

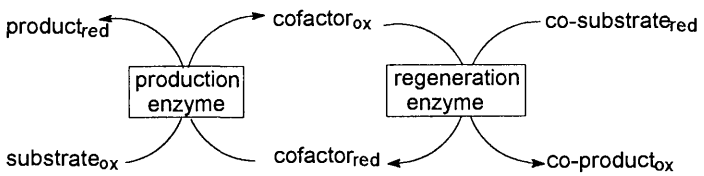


Figure 2. Principle of an enzyme-coupled cofactor or enzyme regeneration system for an enzymatic reduction process.

enzyme [12]. However, these systems can be complicated and not stable enough for synthetic purposes. This is especially true for the chemical regeneration using reducing or oxidizing agents. For example, in the chemical regeneration of NAD^+ using FMN and oxygen, which was developed by Jones [10,13,14], a large excess of FMN as redox catalyst and high concentrations of the cofactor had to be applied. Even then, only slow turnover frequencies have been observed. In a comparative study by Lee and Whitesides [15] a very low bimolecular reaction rate between FMN and NADH; $0.2\,M^{-1}\,s^{-1}$, was observed.

Therefore, it would be extremely interesting to use the reagent-free electrochemical procedure to regenerate the cofactors. In this case, not only can the cosubstrate be replaced by the electrons but also the regeneration enzyme should not be necessary anymore. Such a system is, at least in principle, much simpler and easier to develop for a continuous process than the enzyme-coupled regeneration. Until recently, this method was mostly applied by biosensors [16]. But recently, this economically and ecologically promising methodology has found increasing interest also for preparative processes [9,17,18] and a large research program even for the development of electroenzymatic processes for commodity-scale products has been introduced by the government of the United States.

The goal of this chapter is to present the present concepts and the present status in the field of electroenzymatic redox reactions for the synthesis of complex organic compounds. The large field of analytical applications of bioelectrochemical systems for example in biosensors will not be covered. However, it should be pointed out that analytical studies and applications present very useful information in the search for synthetic developments.

Because of their large protein structures, enzymes can usually only slowly exchange electrons with the electrode. Therefore, at least in the case of redox-active prosthetic groups, a redox catalyst has usually to be added to accelerate the turnover by speeding up the electron exchange between the enzyme respectively the cofactor and the electrode. However, sometimes the direct electron transfer to and from a redox enzyme can be performed by activation of the electrode surface using promoter molecules or by certain electrode modifications by the enzymes [20].

II. PRINCIPLES OF REDOX-CATALYTIC ENZYME ACTIVATION AND COFACTOR REGENERATION

As pointed out before, to couple the redox enzyme to an electrode, a redox catalyst usually has to be applied that shuttles the electrons between the electrode and the protein (Fig. 3) (indirect electrochemical processes [19]). In certain cases, the transfer of the redox equivalents between the mediator and the cofactor also has to be catalyzed by an enzyme (see later discussions).

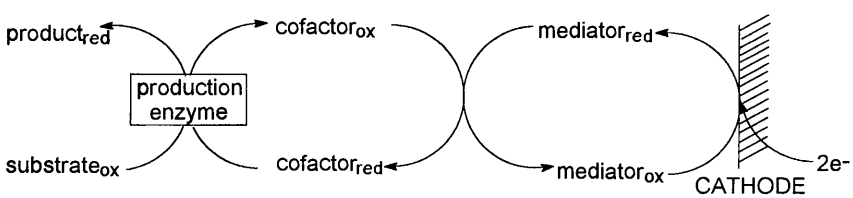


Figure 3. Principle of an indirect electrochemical cofactor or enzyme regeneration system for an enzymatic reduction process.

The redox catalyst has to fulfill the following conditions:

It must be stable toward side reactions in both redox states.
Its activation at the electrode (electrode reaction) must occur at potentials at which neither the enzyme nor the substrate or the product is electroactive.
Its heterogeneous electron exchange with the electrode must be fast.
Its homogeneous redox reaction with the enzyme or, respectively, the prosthetic group must be fast and selective.

In certain cases, promoter molecules that cover the electrode surface can be used to couple the enzyme electronically to the electrode so that electron exchange is made possible [20]. However, the long-term stability and the current density necessary for preparative applications are questionable.

For preparative applications, especially in the case of continuous processes, means for the recovery of the valuable enzymes, the cofactors, and the redox catalysts in the reactor must be developed. One attractive possibility is the immobilization of the enzyme and sometimes also the cofactor and the redox catalyst at the electrode surface. However, the formation of enzyme-modified electrodes has also some practical drawbacks:

1. The long-term stability of such a system is usually limited and needs time-consuming optimization.
2. The reaction between the mediator and the enzyme and the reaction between the enzyme and the substrate are of heterogeneous nature and develop diffusional problems. To minimize them, strongly swelling films should be applied so that substrate, product, and mediator can easily diffuse in and out.
3. The number of active sites in such an electrode modification is limited. therefore, thicker films with good swelling properties should be used.
4. A loss of enzyme activity of a modified electrode can usually not be recovered, while in the homogeneous approaches the addition of more enzyme activity is unproblematic.

Some of these problems have been discussed for alcohol and glucose dehydrogenase immobilized on a porous graphite felt electrode in combination with the direct electrochemical regeneration of NAD^+ at the necessary considerable high overpotential [21]. In the case of the enzymatic oxidation of alcohols using horse-liver dehydrogenase in combination with the indirect electrochemical regeneration of NAD^+ using a ferrocene derivative as redox catalyst and diaphorase to speed up the process, Osa has bound all components to the graphite felt electrode surface via a polyacrylic acid layer (Fig. 4) [22,112]. Here, the problems of a larger scale application are very obvious, as the process is quite slow and has a very low productivity.

In contrast, a very stable and efficient electrode modification has been obtained by Pletcher and Bartlett [23]. In this case, a high-surface-area reticulated vitreous carbon electrode has been modified by electropolymerization of aniline, thereby further increasing the surface area. Horseradish peroxidase (HRP) was immobilized on this electrode by cross-linking with glutaldehyde and 1,2-diaminobenzene. The immobilization of the enzyme led to a strongly enhanced lifetime of the enzyme.

The use of electrochemically polymerized films to immobilize enzymes at electrode surfaces was reviewed by Bartlett and Cooper up to 1992 [24]. While a large variety of studies have been performed mainly using poly(pyrrole) as the conducting polymer, many problems still have to be solved, particularly with respect to the question of the speed of

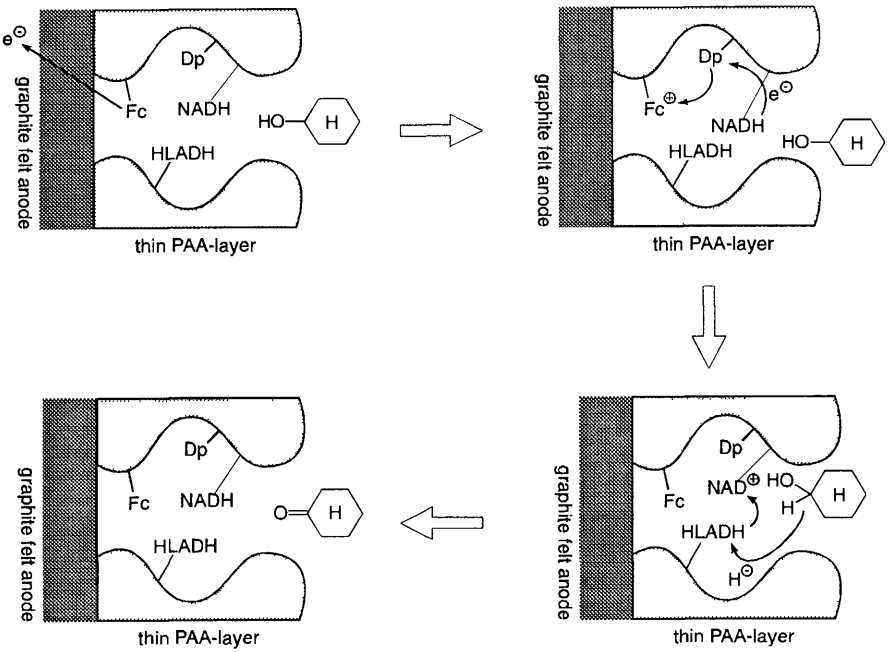


Figure 4. Carbon felt electrode modified with poly-acrylic acid (PAA) under coimmobilization of HLADH, ferrocene derivatives, diaphorase (Dp), and NADH for the indirect electrochemical regeneration of NAD^+ for enzymatic alcohol oxidation [22,112].

electron transfer that can be obtained between the protein and the conducting polymer. Other examples of immbolization procedures are given in the following sections.

The immobilization of the enzyme, the redox catalyst, and sometimes also the cofactor can also take place at a solid support different from the electrode so that the components can be recovered within a solid-bed reactor (a column filled with the enzyme-containing particles) or by a filter plate or membrane. The immobilization of enzymes at solid supports or by the formation of cross-linked enzyme crystals can sometimes also enhance the enzyme stability. This concept has the advantage of the ease of separation but the disadvantage of diffusional limitations due to the heterogeneity of the reactions between the enzyme and the substrate and the cofactor or the redox catalyst. Additionally, the number of available redox centers is usually limited.

A third possibility is the application of an ultrafiltration or dialysis membrane with a molecular weight cutoff such that the enzyme can not penetrate it. This approach can be combined with the use of redox catalysts and cofactors with increased moleculear weight by binding them to soluble polymers. Steckhan has called this procedure *homogeneous immobilization*. Hereby, diffusional limitations are avoided and the number of active redox centers can be kept high. However, for the separation, ultrafiltration membranes have to be applied and the low-molecular-weight components have to be bound to water-soluble polymer backbones like polyethylene glycol or poly(*N*-vinyl-pyrrolidone) without losing their activity. The application of a homogeneous system, as explained before, is considered to be the most direct and easiest approach for the realization of a continuous synthetically and technically applicable electroenzymatic

process. Using electrodes with high active surface areas, like graphite felt or reticulated vireous carbon, in combination with a capillary disc stack cell design; high turnovers and good space–time yields could be obtained. This concept has been successfully applied in the continuous electroenzymatic oxidation of *p*-hydroxyalkylphenols to give chiral *p*-hydroxybenzyl alcohols using FAD-dependent enzymes in combination with polyethyleneglycol-bound ferrocenes using an electrochemical enzyme–membrane reactor. By proper adjustment of the residence time, either the end products or the intermediate products of the enzymatic reactions can be obtained while side reactions can be suppressed [17,25–31]. Similarly, alcohol dehydrogenases can be applied for reductions and oxidations using the indirect electrochemical regeneration of either NAD(P)H or $NAD(P)^+$ as reported later. A membrane-enclosed electroenzymatic process has also been used for the formation of L-lactate from pyruvate or for L-2-hydroxybutyrate from α-ketobutyrate using methyl viologen as a low-molecular-weight mediator, lipoamide dehydrogenase (diaphorase) as the cofactor regeneration enzyme (described later), and L-lactate dehydrogenase as production enzyme. Both enzymes are separated from the rest of the solution by a dialysis membrane [32].

III. ELECTROENZYMATIC REDUCTIONS

For enzymatic reductions with NAD(P)H-dependent enzymes the electrochemical regeneration of NAD(P)H always has to be performed by indirect electrochemical methods. Direct electrochemical reduction, which requires high overpotentials, in all cases leads to varying amounts of enzymatically inactive NAD dimers generated due to the one-electron transfer reaction. One rather complex attempt to circumvent the problem of NAD dimerization is the combination of the NAD^+ reduction by electrogenerated and regenerated potassium amalgam with the electrochemical reoxidation of the enzymatically inactive species, mainly NAD dimers, back to NAD^+ [33]. The consequence is that only indirect electrochemical process can be applied for a selective and efficient NAD(P)H regeneration (see Fig. 5). Three pathways seem to be possible:

1. If one-electron transfer redox catalysts are used as mediators, the problem of NAD dimerization also occurs. The dimerization can only be prevented if an additional regeneration enzyme is applied, which must be able to accept two electrons in two steps from the mediator and then to transfer one electron pair to $NAD(P)^+$. This is the case if the flavo enzymes ferredoxin-$NADP^+$-reductase (FNR) [34,35,43,46], lipoamide dehydrogenase (diaphorase) [32,35,49], enoate reductase [36], or the so-called "VAPOR" enzymes (viologen-accepting pyridine nucleotide oxido-reductases) [37,52] are used as regeneration enzymes in combination with methyl viologen (*N*, *N*-dimethly-4,4-bipyridinium dichloride) as one-electron mediator. A different approach uses hydrogenases for the catalysis of the direct electrochemical reduction of NAD^+ on a platinum cathode without hydrogen evolution [9,38].
2. The problem of cofactor dimerization can potentially be avoided, if electrochemically regenerable redox catalysts are found that can transfer a hydride ion selectively to the 4-position of $NAD(P)^+$.
3. Similarly, also a redox catalyst that transfers two electrons in one step could prevent the dimerization of the cofactor.

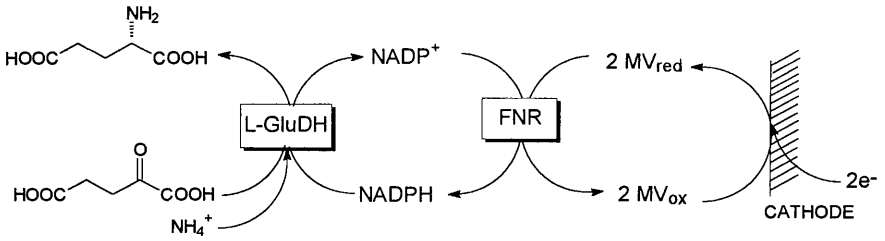


Figure 5. Methyl viologen-mediated electroreductive amination of α-ketoglutarate using ferredoxin–NADP–reductase (FNR) as the regeneration enzyme and L-glutamate dehydrogenase (L-GluDH) as the production enzyme [35].

A. Reductions with NAD(P)H-Dependent Dehydrogenases

1. Enzyme-Coupled Indirect Electrochemical Regeneration of NAD(P)H

Usually, viologens have been used as one-electron transfer agents in combination with FNR to produce NADPH by an indirect electrochemical way [34,35,43,46]. This approach was first applied by Whitesides for the generation of L-glutamate from α-ketoglutarate (Fig. 5). The transformation taking place at a tungsten cathode was complete after 7 days with a total turnover number (TTN) for NADPH of 1000 resulting in an overall turnover frequency of 6/h. The current yield was practically quantitative [35].

Also ferredoxin itself (from spinach leaves) can be used as mediator system for FNR, if special conditions are applied. Ferredoxin is an electron-transfer protein with an iron–sulfur cluster as redox center, and its surface is negatively charged in neutral solution. Electron transfer therefore can be promoted, if the electrode surface is positively charged, for example, in the presence of bivalent metal ions [39], or by adsorbed or bound viologens [40]. Similarly, ferredoxin does not given an electrochemical response in a buffer solution at an In_2O_3 electrode; however, a well-defined redox reaction was observed in the presence of small amounts of positively charged poly peptides like poly-(L-lysine) or poly-(L-serine) [41] as promoters. The heterogeneous electron ransfer rate constant was $> 5 \times 10^{-3}$ cm s^{-1} and the formal redox potential −0.6 V (vs. Ag/AgCl) at pH 7 [42]. Using this system in the presence of FNR, NADPH was effectively produced from $NADP^+$. Ferrodoxin was more efficient than the otherwise used viologens. This indirect electrochemical NADPH production could be combined with an NADPH-dependent production enzyme. For example, in combination with malic enzyme, pyruvate was carboxylated by carbon dioxide to form malic acid with a current efficiency of 90% on a very small scale (Fig. 6) [43].

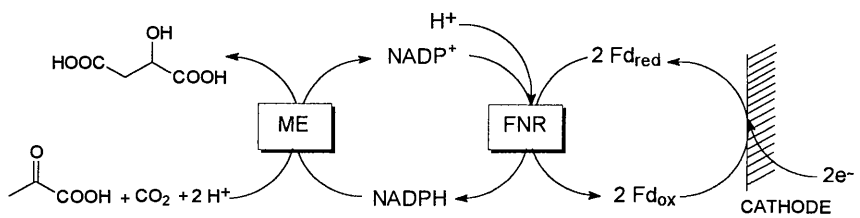


Figure 6. Ferredoxin (Fd)/Ferredoxin–$NADP^+$–reductase (FNR) mediated enzymatic carboxylation of pyruvic acid to form malic acid catalyzed by the NADPH-dependent malic enzyme (ME) [43].

Lipoamide dehydrogenase (diaphorase) can act as electron accepting and transferring enzyme for the formation of NADH using electrogenerated and regenerated viologen radical cations as one-electron donors (Fig. 7). This system was applied to the synthesis of D-lactate from pyruvate using D-lactate dehydrogenase as production enzyme. Both enzymes were immobilized on poly(acrylamide). The transformation was 94% complete after 9 days with a TTN of 940 for NADH and a quantitative current yield. The turnover frequency for NADH reached an overall value of 5/h. The activities of the flavoenzymes toward NADH regeneration were found as follows: LipDH (yeast):LipDH (pig heart):FNR $= A : B : C = 1 : 4 : 7$. The activity of FNR toward the NADPH regeneration is a factor of 5 higher than that for NADH, while the activity of LipDH is only 10% of that for the NADPH regeneration [35].

This system works especially well if the production enzyme, like horse liver alcohol dehydrogenase, is coimmobilized with lipoamide dehydrogenase at the electrode surface [44]. Yoneyama applied such a system not only for the reduction of formaldehyde, acetaldehyde, and acetone [45], but also for the enantioselective reduction of 1-phenyl-2-propanone using either lipoamide dehydrogenase or ferredoxin-NADP reductase for the viologen mediated NAD(P)H regeneration. The production of 15 μmol was obtained at a turnover frequency of 1.7 TN/h [46].

In a mirror-image reaction to the enzymatic oxidation catalyzed by HLADH, with the indirect electrochemical regeneration of NAD^+ using lipoamide dehydrogenase (diaphorase) as the regenerating enzyme and ferrocenes as mediators at an all-components-immobilized graphite felt electrode shown in Fig. 4, Osa [47] also developed an all-components-immobilized graphtie felt/poly(acrylamide(PAA) electrode for the electroenzymatic reduction of ketones. In this case, a Nafion-immobilized viologen was used as a one-electron mediator that shuttles the electrons to the PAA-immobilized diaphorase. This enzyme transfers the reducing equivalents to the oxidized and immobilized cofactor, allowing the formation of 1,4-NADH and avoiding the NAD dimerization by direct one-electron transfer. The immobilized alcohol dehydrogenase then catalyzes the reduction of racemic 2-methyl- and 3-methylcyclohexanone, leading to a kinetic resolution under formation of the corresponding alcohols in high current yield and high enantiomeric excess. The same is true for the remaining cyclohexanones.

Fry has used a similar system for the enzymatic reduction of pyruvate to L-lactate. In this case, the one-electron transfer redox catalyst, methyl viologen, and the lipoamide dehydrogenase are coimmobilized within a Nafion cation-exchange layer on the surface of a reticulated vitreous carbon electrode. As production enzyme, L-lactate dehydrogenase (LDH) was employed [48], which was later stabilized considerably in the form of cross-

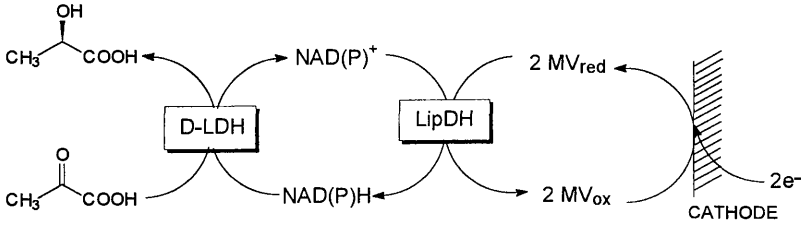


Figure 7. Methyl viologen-mediated electroreductive formation of D-lactate using lipoamide dehydrogenase (LipDH) as regeneration enzyme and D-lactate dehydrogenase (D-LDH) as the production enzyme [35].

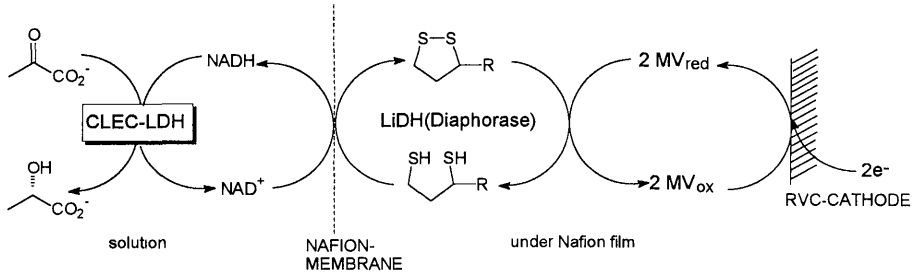


Figure 8. Methyl viologen-mediated electroenzymatic reduction of pyruvate to D-lactate using lipoamide dehydrogenase (LiDH) and cross-linked enzyme crystals of D-lactate dehydrogenase [49].

linked enzyme crystals (CLEC) (Fig. 8). A total turnover number (TTN) of 368 turnovers for NAD within 25 days (0.6 TN/h for NAD) has been reached [49].

In a different approach, instead of methyl viologen, the organic disulfide dithiothreitol was cathodically reduced to give the bis-thiol, which consecutively reduces the disulfide bridge within the lipoamide of the lipoamide dehydrogenase. This is followed by the NADH regeneration by the reduced LipDH in combination with the production of enzyme L-lactate dehydrogenase for the production of L-lactate from pyruvate. Both enzymes were immobilized within a poly(acrylamide) gel [50].

It has also been pointed out that electrogenerated $FMNH_2$ in combination with diaphorase can also act as mediator for the NADH regeneration in an uphill reaction [51].

In another approach, Yoneyama used electrogenerated and regenerated 1-phenylethanol as reducing equivalent for the alcohol dehydrogenase-catalyzed regeneration of NADH. In this system, the production enzyme and the cofactor regenerating enzyme are identical. A production of 2–4 μmol was reached at turnover frequency of 1.7 TN/h or less (Fig. 9) [46].

The VAPOR enzymes are flavoenzymes and can be isolated from therophilic bacilli. They accept viologen radical cations as reducing agents and are especially valuable because they allow regeneration of all four forms of the pyridine nucleotides NADH, NAD^+, NADPH, and $NADP^+$ according to Fig. 10 [37,52].

Coimmobilization of the viologen and the VAPOR enzyme at the surface of a carbon cathode can be used for the electrochemical production of NADH from NAD^+ at a rate of 9 nmol h^{-1} cm^{-2} [37,53].

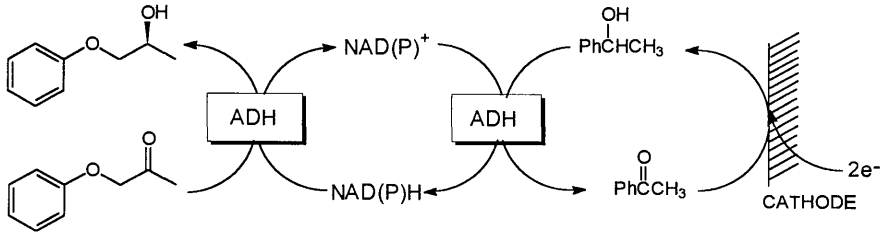


Figure 9. Acetophenone-mediated electroenzymatic reduction of 1-phenoxy-2-propanone to (*S*)-1-phenoxy-2-propanol using lipoamide dehydrogenase (LiDH) or ferredoxin-NADP reductase (FNR) and an alcohol dehydrogenase [46].

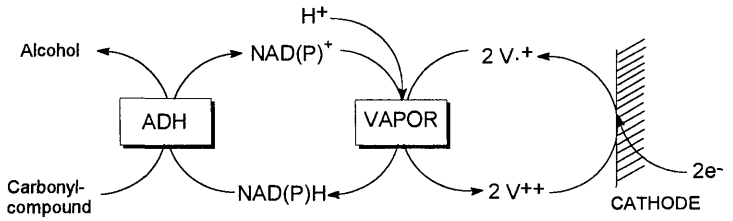


Figure 10. Application of VAPOR enzymes for the indirect electrochemical NAD(P)H regeneration.

In a different approach, instead of using a production enzyme together with an NADH-regenerating enzyme, baker's yeast was used to take over both objectives. Thus 3-keto esters were electrochemically reduced to give the optically active 3-hydroxy esters in the presence of baker's yeast and NAD^+ using a viologen as redox catalyst to shuttle the electrons from the cathode to the yeast cells which then catalyze the NADH formation and the enzymatic reduction. In such an approach, usually the permeation in and out of the yeast cells is a limiting factor [54].

A promising technique uses NAD-dependent hydrogenases to catalyze the electron transfer between a platinum cathode and NAD^+. This approach was applied to the synthesis of lactate from pyruvate [9,38,55] or L-glutamate from α-ketoglutarate in an analytical thin-layer cell with 50 µl volume at a potential of −0.7 V vs. SCE (Fig. 11). Within 1 h, a 44.8 m*M* concentration of the product was obtained at a turnover frequency of 448/h [56].

2. Indirect Electrochemical NAD(P)H Regeneration Without a Regeneration Enzyme

To be able to regenerate NAD(P)H by an indirect electrochemical procedure without the application of a second regeneration enzyme system, the redox catalyst must fulfil four conditions:

1. The active redox catalyst must transfer two electrons in one step or a hydride ion.
2. The electrochemical activation of the catalyst must be possible at potentials less negative than −0.9 V vs. SCE, since at more negative potentials the direct electrochemical reduction of $NAD(P)^+$ will lead to NAD dimer formation.

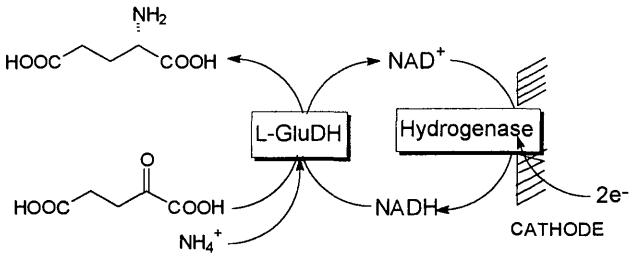


Figure 11. Hydrogenase-catalyzed NADH regeneration coupled to the reductive amination of α-ketoglutarate to L-glutmate catalyzed by L-glutamate dehydrogenase.

3. The active form of the catalyst must transfer the electrons or the hydride ion to $NAD(P)^+$, but not directly to the substrate. Otherwise, this nonenzymatic reduction will lead to low chemoselectivity and/or low enantioselectivity.
4. Only enzyme-active 1,4-NAD(P)H must be formed.

Steckhan et al. demonstrated convincingly that systems that fulfil these conditions are tris(2,2′-bipyridyl)rhodium complexes [57] and, more effectively, substituted or unsubstituted (2,2′-bipyridyl(pentamethylcyclopentadienyl)chloro or aquo rhodium complexes [58] (see Scheme 1). Electrochemical reduction of these complexes at potentials between −680 mV and −840 mV vs. SCE leads to the formation of hydrido rhodium complexes. Strong catalytic effects observed in cyclic voltammetry and preparative electrolysis indicate a very fast hydride transfer from the hydrido complex to $NAD(P)^+$ under formation of only 1,4-NAD(P)H and the starting complex as shown in the following reaction scheme [58]:

$$[Cp^*Rh(bpy)L]^{2+} + e^- \longrightarrow [Cp^*Rh(pby)L]^+$$

$$[Cp^*Rh(bpy)L]^+ \longrightarrow [Cp^*Rh(bpy)]^+ + L$$

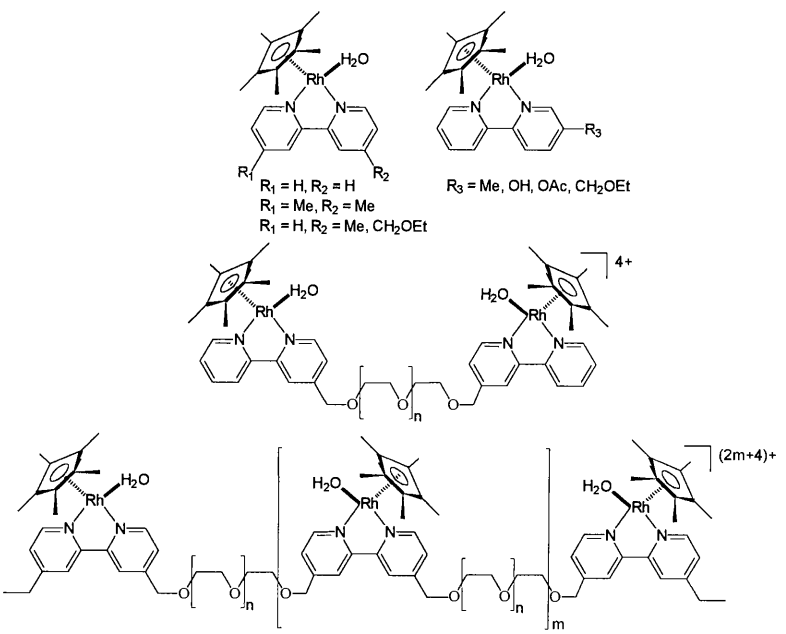
$$[Cp^*Rh(bpy)L]^+ + e^- \longrightarrow Cp^*Rh(bpy) + L$$

$$[Cp^*Rh(bpy)]^+ + e^- \longrightarrow Cp^*Rh(bpy)$$

$$[Cp^*Rh(bpy)L]^+ + [Cp^*Rh(bpy)]^+ \longrightarrow Cp^*Rh(bpy) + [Cp^*Rh(bpy)L]^{2+}$$

$$Cp^*Rh(bpy) + H^+ \longrightarrow [Cp^*RhH(bpy)]^+$$

$$[Cp^*RhH(bpy)]^+ + NAD(P)^+ + L \longrightarrow [Cp^*Rh(bpy)L]^{2+} + NAD(P)H$$



Scheme 1 Monomeric and polymeric PEG-bound $Cp^*Rh(bpy)(H_2O)^{2+}$ complexes that have been applied to redox catalysts for the NAD(P)H regeneration.

This system fulfills the already mentioned four conditions, as the active species is a rhodium hydride that acts as efficient hydride transfer agent toward NAD^+ and also $NADP^+$. The regioselectivity of the $NAD(P)^+$ reduction by these rhodium-hydride complexes to form exclusively the enzymatically active 1,4-isomer has been explained in the case of the $[Rh(III)H(terpy)_2]^{2+}$ system by a complex formation with the cofactor [59]. A recent detailed study of the $[Cp^*Rh(bpy)L]^{2+}$ system indicates that the coordination of the rhodium center to the carbonyl group of the NAD-amide function is responsible for the practically total regioselectivity of the hydride transfer [60]. The reduction potentials of the complexes mentioned here are less negative than −900 mV vs. SCE. The hydride transfer directly to the carbonyl compounds acting as substrates for the enzymes is always much slower as compared with the transfer to the oxidized cofactors. Therefore, by proper selection of the concentrations of the mediator, the cofactor, the substrate, and the enzyme, it is usually no problem to transfer the hydride to the cofactor selectively when the substrate is also present [61]. This is especially the case when the work is performed in the electrochemical enzyme membrane reactor (see Fig. 24). The hydrido rhodium complex seems to be the only chemical redox agent that is able to perform a totally selective and efficient NAD(P)H regeneration.

The successful synthetic application of this electroenzymatic system has been demonstrated for the in situ electroenzymatic reduction of pyruvate to D-lactate using the NADH-dependent D-lactate dehydrogenase. Electrolysis at −0.6 V vs. Ag/AgCl reference electrode of 50 ml of a 0.1 *M tris*-HCl buffer of pH 7.5 containing pentamethylcyclopentadienyl-2,2′-bipyridine-chloro-rhodium(III) (1×10^{-3} *M*), NAD^+ (2×10^{-3} *M*), pyruvate (2×10^{-2} *M*), and 1300 units D-lactate dehydrogenase (divided cell, carbon foil electrode) after 3 h resulted in the formation of D-lactate (1.4×10^{-2} *M*) with an enantiomeric excess of 93.5%. This means that the reaction occurred at a rate of 5 turnovers per hour with respect to the mediator with a 70% turnover of the starting material. The current efficiency was 67% [62] (Fig. 12).

The same system has been applied in a new reactor design by Délecouls and Bergel [63] by which the enzyme was retained close to the working electrode surface by a dialysis membrane. Thereby, only very small amounts of the enzyme are necessary. The reactor consists of two compartments separated by a Nafion membrane. The solution to be treated circulates in a loop involving the working electrode compartment and a 100-ml storage tank. In the working electrode compartment, a dialysis membrane covers the working electrode and defines a thin layer in which the enzyme is confined. The substrate and the product diffuse through the membrane. Using the already mentioned rhodium complex as mediator, cyclohexanone as a model system was reduced to cyclohexanol under

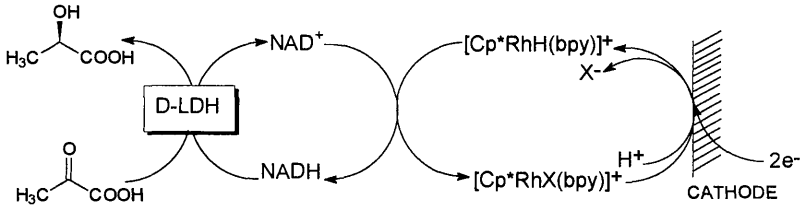


Figure 12. D-Lactate generation from pyruvate catalyzed by D-lactate dehydrogenase (D-LDH) with in situ indirect electrochemical NADH regeneration using a $[Cp^*Rh(bpy)X]^+$ complex as a selective mediator [62].

indirect electrochemical NADH regeneration in combination with horse liver alcohol dehydrogenase.

Steckhan et al. adopted the same redox catalytic system for the reduction of 4-phenyl-2-butanone to (*S*)-4-phenyl-2-butanol using the NADH-dependent horse-liver alcohol dehydrogenase (HLADH) and *S*-ADH from *Rhodococcus* sp. [64] with high enantioselectivity [26,29,30,65]. As mediator, first the low-molecular-weight pentamethylcyclopentadienyl-4-ethoxymethyl-2,2′-bipyridine-chloro-rhodium(III) was applied. Then, to test the possibility for a continuous application in the electrochemical enzyme membrane reactor (discussed later), water-soluble poly(ethylene glycol) (PEG)-bound rhodium complexes were used as mediators. Batch electrolyses of 10-m*M* solutions of 4-phenyl-2-butanone in 0.1 *M* *tris*-HCl buffer of pH 7.5 in the presence of HLADH (50 U, ethanol), the low-molecular-weight mediator (0.5 m*M*), and NAD^+ (2.5 mM) after 5 h resulted in the conversion of 70% of the starting material to the (*S*)-alcohol with 65% ee. After addition of diaphorase, the turnover increased to 82% with 75% ee. Using *S*-ADH (30 U with respect to 4-chloroacetophenone) and the unmodified Cp*-bipyridine rhodium complex (0.5 m*M*) under otherwise identical conditions resulted in the conversion of 76% of the starting material to the (*S*)-alcohol with 77% ee. Continuous application of the system during a period of 7 days in the electrochemical enzyme membrane reactor under application of a PEG-polymer bound mediator (0.5 m*M*), NAD^+ (2.5 mM), and *S*-ADH (100 U with respect to 4-chloroacetophenone) using a 10 m*M* concentration of the starting material in Tris-HCl buffer of pH 7.5 led to the formation of the (*S*)-alcohol with 90–95% ee with a continuous conversion between 15 and 30% of the starting material [26,29,30,65] (Fig. 13). Similar to other cases, it has been demonstrated that the continuous process in an electrochemical enzyme membrane reactor leads to higher selectivities. Optimization of the system to obtain a higher turnover of the substrate will be necessary.

Several approaches have been undertaken to construct redox-active polymermodified electrodes containing such rhodium complexes as mediators. Beley [66] and Cosnier [67] used the electropolymerization of pyrrole-linked rhodium complexes for their fixation at the electrode surface. An effective system for the formation of 1,4-NADH from NAD^+ applied a poly-Rh(terpy-py)$_2^{3+}$ (terpy = terpyridine; py = pyrrole) modified reticulated

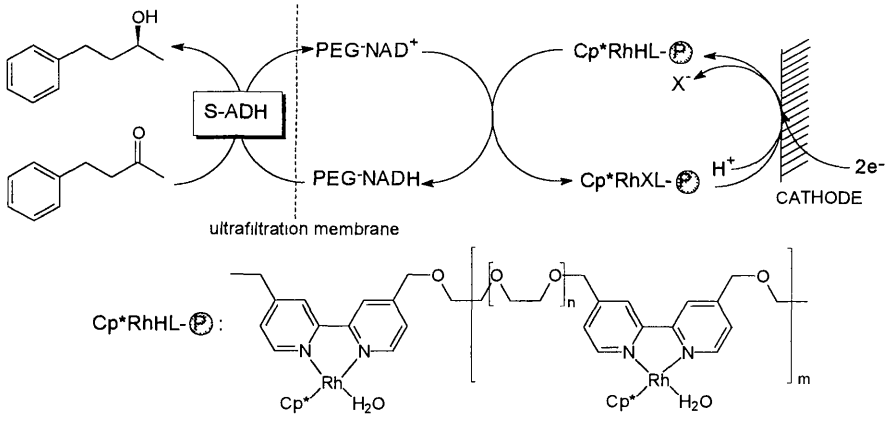


Figure 13. Continuous formation of (*S*)-4-phenyl-2-butanol from 4-phenyl-2-butanone using the electrochemical enzyme membrane reactor under indirect electrochemical NADH regeneration with a high-molecular-weight rhodium catalyst [26,29,30,65].

vitreous carbon electrode [66]. In the presence of liver alcohol dehydrogenase as the production enzyme, cyclohexanone was transformed to cyclohexanol with a turnover number of 113 in 31 h. However, the current efficiency was rather small. The films that are obtained by electropolymerization of the pyrrole-linked rhodium complexes do not swell. Therefore, the reaction between the substrate—for example, NAD^+—and the reduced redox catalyst mostly takes place at the film/solution interface. To obtain a water-swellable film, which allows the easy penetration of the substrate into the film and thus renders the reaction layer larger, Steckhan et al. used a different approach. Water-soluble copolymers of substituted vinyl-bipyridine rhodium complexes with *N*-vinylpyrrolidone were synthesized chemically and then fixed to the surface of a graphite electrode by γ-irradiation. The obtained polymer films swell very well in aqueous solutions. The penetration of substrates into the film is in some cases almost not hindered at all. It can be influenced by the amount of polymer fixed to the electrode surface and the irradiation dose used for the polymer immobilization. Cyclovoltammetric studies demonstrate the catalytic efficiency of these modified electrodes toward the mediated reduction of NAD^+ to form NADH [68]. In a different case, the $[Rh(bpy)_3]^{3+}$ mediator was immobilized onto an electrode coated with an anionic polysaccharide hydrogel. The selectivity of the reaction toward the NADH generation decreased with increasing charge consumption [69].

B. Indirect Electrochemical Activation of Reducing Enzymes Without Reduced Pyridine Nucleotides as Cofactors

There are also some interesting enzyme systems that are able to catalyze stereospecific reductions using electrogenerated viologen cation radicals directly as electron donors, even in the absence of reduced pyridine nucleotides. For example, enoate reductase [36,52] from *Clostridium tyrobutyricum* or from *Clostridium kluyveri* performs stereospecifically a *trans* hydrogen addition to the double bond of a large number of enoates in an electrochemical cell using methyl viologen as mediator. Instead of the isolated enzyme; resting cells of *C. tyrobutyricum* can also be used. Another viologen-accepting enzyme is 2-hydroxycarboxylate viologen oxidoreductase from *Proteus vulgaris*. It is very effective in the reduction of α-keto acids to form chiral (*R*)-α-hydroxy acids using methyl viologen (MV^{2+}) as the electron shuttle from the cathode to the enzyme system [36,52,70]. This reaction works especially well with resulting cells of *Proteus vulgaris* (Fig. 14). Such systems have been named "electromicrobial reductions." As mentioned before, the permeation of the mediator, the substrate and the product through the cell membrane of the microorganism might cause limitations.

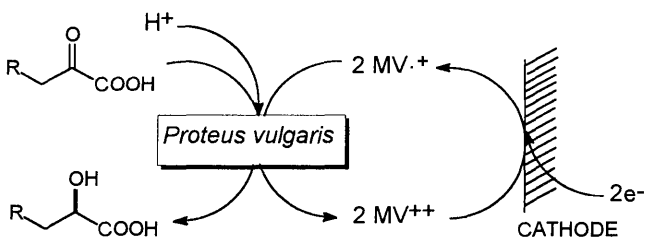
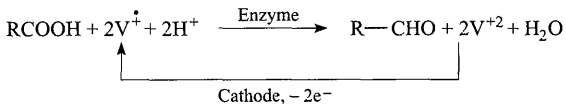


Figure 14. Electromicrobial reduction of α-keto acids with *Proteus vulgaris* in the presence of methyl viologen as a mediator.

The reduction of carboxylic acids to the aldehydes is catalyzed by reduced viologen-accepting tungsten-containing enzymes from *Clostridium thermoaceticum* and *Clostridium formicoaceticum*. This reaction is reversible [36,52,71]:



Similarly, the pyruvate (oxidase) dehydrogenase complex (PYOX) can be activated directly by electrogenerated methyl viologen radical cations (MV^{+}) as mediator. Thus, the naturally PYOX-catalyzed oxidative decarboxylation of pyruvic acid in the presence of coenzyme A (HSCoA) to give acetylcoenzyme A (acetyl-SCoA) (see section on oxidases) can be reversed. In this way, electroenzymatic reductive carboxylation of acetyl-SCoA is made possible (Fig. 15).

To render this system more effective, it must be coupled with the regeneration of acetyl-SCoA from HSCoA and acetyl phosphate under catalysis by phosphotransacetylase (PTA). A turnover number of 500 for PYOX was obtained after 50 h, at which point a saturation occurred and the reaction stopped. Under the reaction conditions, between 0.55 and 0.98 µmol of pyruvic acid was obtained [72].

The same authors proposed a complex system for the electrochemically driven enzymatic reduction of carbon dioxide to form methanol. In this case, methyl viologen or the cofactor PQQ was used as a mediator for the electroenzymatic reduction of carbon dioxide to formic acid, catalyzed by formate dehydrogenase, followed by the electrochemically driven enzymatic reduction of formate to methanol, catalyzed by a PQQ-dependent alcohol dehydrogenase. With methyl viologen as mediator, the reaction goes through the intermediate formation of formaldehyde, while with PQQ, methanol is formed directly [73].

Also, the carboxylation of oxoglutaric acid to form isocitric acid catalyzed by isocitric acid dehydrogenase (ICDH) can be driven electrochemically using methyl viologen as a mediator without reduced pyridine nucleotides as cofactors. Thus, electrolysis at −0.95 V vs. SCE of a 0.2 *M* Tris buffer solution of (pH 7.7) containing 0.2 *M* $NaHCO_3$, 1 unit of ICDH, 1.0×10^{-4} *M* methyl viologen, and 1×10^{-2} *M* oxoglutaric acid gave 7.33 µmol isocitric acid with a current efficiency of almost 100% [74]. Similarly, the ferredoxin system described earlier (In_2O_3 cathode in the presence of small amounts of poly-L-lysine) can be used as a mediator to drive this enzymatic reduction in a more efficient way, as indicated by much larger catalytic currents. [43]

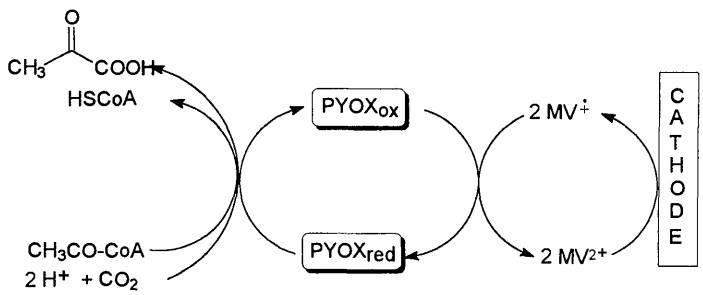


Figure 15. Electroenzymatic reductive carboxylation of acetyl-SCoA to give pyruvate.

IV. ELECTROENZYMATIC OXIDATIONS

The synthetic potential of oxidizing enzymes is extremely large, but has not yet found appropriate application [7,8]. Especially in the oxidation of alcoholic groups, a large number of applications have been developed or may be foreseen. The enantio- and diastereoselectivity together with the regioselectivity of the redox enzymes can also be used effectively for the synthesis of enantiomerically pure compounds in the oxidation of alcohols. This is the case for the enantiomer-differentiating oxidation of racemic alcohols and the group-selective oxidation of prochiral diols, *meso*-diols, or polyols mainly using the NAD^+-dependent horse-liver alcohol dehydrogenase [10,13,14,75]. On the other hand, the regioselectivity of the oxidation of a particular hydroxy function in a polyol by an enzymatic oxidation can be extremely valuable, thus avoiding a complicated protection–deprotection sequence. Interesting enzymes for this type of transformation are the NAD^+-dependent glycerol dehydrogenase [76], glycerol-3-phosphate dehydrogenase [77], sorbitol dehydrogenase [78], the hydroxy-steroid dehydrogenases [79], the $NADP^+$-dependent alcohol dehydrogenase from *Thermoanaerobium brockii* [80], the copper protein-dependent galactose oxidase [81,143], and the FAD-dependent enzymes glycerol-3-phosphate oxidase [82,137], cholesterol oxidase [83], and pyranose 2-oxidase [84]. Also, FAD-dependent alcohol oxidases [85] and PQQ-dependent dehydrogenases [86] may be interesting enzymes for the selective transformation of hydroxy groups into aldehyde functions, carboxylic acids, or ketones. The introduction of hydroxy groups into aliphatic and aromatic compounds can be just as interesting. Nuclear and side-chain oxidations of phenolic compounds by phenol oxidases [87] or by the flavocytochrome enzymes *p*-cresol methyl hydroxylase and 4-ethylphenol methylene hydroxylase [88], respectively, are useful for the synthesis of *ortho*-quinoid systems and chiral *p*-hydroxy benzylic alcohols. Another interesting class of oxidizing enzymes is the FAD-dependent amine and amino acid oxidases, as well as xanthine oxidase and the similar aldehyde oxidase. These flavoenzymes or copper proteins can be used for synthetically useful desaminations [89], the purification of amino acids from small amounts of the undesired enantiomer [90], or the oxygenation of *N*-heterocycles [91].

A very valuable class of oxidizing enzymes are the monooxygenases [7,8,92], which are able to introduce hydroxy functions into hydrocarbons, aromatic nuclei, or the side chains of alkylaromatics. They can also transfer oxygen to heteroatoms, catalyze Bayer–Villiger oxidations, or epoxidize alkenes. While oxidases are transferring the oxygen atom from water, the monooxygenases are transferring one oxygen atom from molecular oxygen while the second is reduced to give water. Therefore, monooxygenases need reducing equivalents, which are usually applied by NADH or NADPH, very often in the presence of a reductase as a second enzyme. The cofactors of monooxygenases are mostly cytochromes [93], flavins [94], or pteridins [95].

As mentioned before, the main problem for the application of such oxidizing enzymes in organic synthesis is the availability of an effective reactivation method for the prosthetic groups or the freely dissociated cofactors. Especially, the long-term stability of the whole system is the limiting factor [96]. The oxidases mentioned before can be reactivated by an aerobic autoregeneration sequence with oxygen as the final electron acceptor. Usually, hydrogen peroxide is produced via the intermediate superoxide. Hydrogen peroxide and the intermediates, however, are extremely reactive compounds, destroying the enzymes after a very short time. The combination of such enzyme systems with catalse to destroy the hydrogen peroxide gives acceptable results only in a very few cases [97,98]. Usually, the lifetime of the enzymatic system is not sufficient. In addition to the hydrogen peroxide problem, many enzymes are sensitive to oxygen due to the oxida-

tive degradation of thiol functions, and also the starting materials or the products of the enzymatic reaction may be negatively influenced by oxygen. Therefore, the most elegant solution to this problem would be anaerobic reactivation using the electrode (anode) as the final electron acceptor. However, because of the mostly very slow electron transfer rate between the redox-active protein and the anode, mediators have to be introduced to shuttle the electrons between the enzyme and the electrode effectively (indirect electrochemical procedure). As published in many papers, the direct electron transfer between the protein and an electrode can be accelerated by the application of promoters that are adsorbed at the electrode surface [20]. However, this type of electrode modification, which is quite useful for analytical studies of the enzymes or for sensor applciations, is in most cases not stable and effective enough for long-term synthetic application. Therefore, soluble redox mediators like ferrocene derivatives, quinoid compounds, or other transition-metal complexes are more appropriate for this purpose.

A. Oxidations with Dehydrogenases

In the case of the enzymatic oxidation with NAD^+-dependent alcohol dehydrogenases, direct electrochemical oxidation of NADH would be the most simple way for the regeneration of the cofactor. The electrochemical oxidation of NAD(P)H has been studied intensively already very early and is reviewed by Bartlett et al. [99]. In contrast to the direct electrochemical reduction of $NAD(P)^+$, which is synthetically not applicable because of the formation of NAD dimers via intermediate NAD radicals, the direct electrochemical oxidation of NAD(P)H to give $NAD(P)^+$ can be performed successfully [100–102,104]. However, direct electrochemical oxidation at unmodified electrode surfaces requires relatively high overpotentials ($< +0.5$ V) and generally results in electrode passivation [104] and a mixture of oxidation products. By using high-surface-area carbon electrodes like reticulated vitreous carbon or especially carbon felt, the otherwise slow NADH oxidation can be performed effectively to yield 99.5% NAD^+ at 250 cycles per hour [101]. As a model system, the production of D-gluconic acid from β-D-glucose, catalyzed by glucose dehydrogense, or the formation of pyruvate from lactic acid, catalyzed by lactate dehydogenase, was performed using the direct electrochemical regeneration of the cofactor NAD^+ at a flow-through graphite felt anode [102].

The deracemization of lactate in principle is also interesting. In this process, pyruvate is reduced at the cathode to racemic lactate which is reoxidized to pyruvate by the cheap L-lactate dehydrogenase combined with the anodic regeneration of the oxidized cofactor NAD^+. As D-lactate is not accepted by the enzyme, it is accumulated during the process (Fig. 16) [103].

The application of the same principle to the formation of D-alanine is possible but lacks applicability due to its slowness. In this case, in the presence of ammonia, pyruvate is in equilibrium with its imine. This is reduced at the cathode under formation of racemic alanine. The L-alanine of the racemic mixture is reoxidized by L-alanine dehydrogenase under anodic regeneration of the necessary cofactor NAD^+ to give pyruvate and ammonia, while the D-alanine is not accepted by the enzyme and accumulates in the reaction mixture. The drawback of this reaction is the kinetic control by imine formation, which is very slow, so that a complete inversion of a 10 m*M* solution of L-alanine would require 140 h [105].

An immobilized-enzyme continuous-flow reactor incorporating continuous direct electrochemical regeneration of NAD^+ has been proposed. To retain the low-molecular-

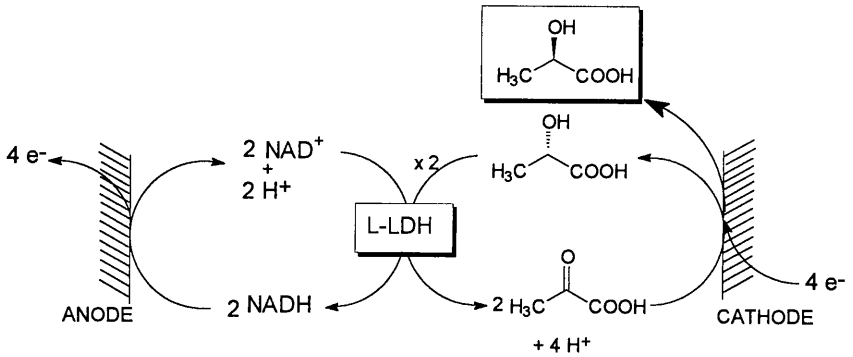
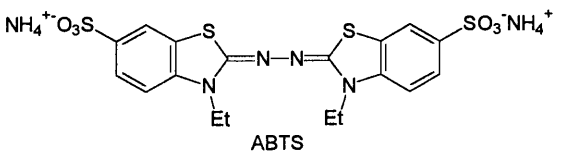


Figure 16. Coupled electrochemical process for the formation of D-lactate from pyruvate (L-LDH = L-lactate dehydrogenase) [103].

weight cofactor NADH/NAD^+ within the reaction system, special hollow fibers (Dow ultrafilter UFb/HFU-1) with a molecular weight cutoff of 200 have been used [104].

Because the direct electrochemical oxidation of NAD(P)H has to take place at an anode potential of +900 mV vs. NHE or more, only rather oxidation-stable substrates can be transformed without loss of selectivity, thus limiting the applicability of this method. The electron transfer between NADH and the anode may be accelerated by the use of a mediator. At the same time, electrode fouling, which is often observed in the anodic oxidation of NADH, can be prevented. Synthetic applications have been described for the oxidation of 2-hexene-1-ol and 2-butanol to 2-hexenal and 2-butanone catalyzed by yeast alcohol dehydrogenase (YADH) and the alcohol dehydrogenase from *Thermoanaerobium brockii* (TBADH), respectively, with indirect electrochemical regeneration of NAD^+ and $NADP^+$, respectively, using the tris(3,4,7,8-tetramethyl-1,10-phenanthroline) iron(II/III) complex as redox catalyst at an anode potential of 850 mV vs. NHE [106]. Under batch electrolysis conditions using a carbon felt anode, the turnover number per hour was 40. The current efficiency reached between 90 and 95%.

Mediators acting as one-electron transfer agents toward NADH must possess relatively positive potentials [107]. This is the case for the iron complexes mentioned earlier with potentials between 800 and 930 mV vs. NHE. The compound 2,2′-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid)-diammonium salt, ABTS (shown here), which is mainly used as a redox-dye indicator for the activity determination of certain enzymes, can act as one-electron redox catalyst for the NAD^+ regeneration at somewhat lower potentials of 430 mV vs. Ag/AgCl [108].



ABTS

The indirect electrochemical process for the regeneration of NAD^+ from NADH is very fast, which is indicated by a strong catalytic current in the presence of glycerol dehydrogenase, the oxidized cofactor, and *meso*-1,2-cyclohexanediol as substrate [109].

It was also demonstrated that the polyoxometalate redox pair $\alpha_2P_2W_{17}VO_{62}^{7-/8-}$ can act as an efficient one-electron redox catalyst for the NADH oxidation at around

+400 mV vs. SCE at pH 7. Because dehydrogenase-catalyzed oxidation is favored at higher pH values, the base lability of the oxometalates might become a problem [110].

Another possibility is the use of one-electron transfer agents such as ferrocene derivatives in combination with a thermostable diaphorase (lipoamide dehydrogenase), which transforms the one-electron transfer agents into two-electron oxidants, thus accelerating the reaction [111]. A combination of ferrocene derivatives and diaphorase, both immobilized at the anode surface, has been used for the NAD^+ formation from NADH in the presence of HLADH as a production enzyme [22,112]. This system has already been discussed (Fig. 4). The modified electrode was prepared by dip-coating the graphite felt material with poly(acrylic acid) (PAA) of a molecular weight of 1,400,000 in methanol solution followed by a treatment with either aminoferrocene or 2-aminoethylferrocene in DMF in the presence of DCC. After cross-linking the electrodes with hexamethylenediamine, the material contained about 11 μmol/cm^3 of ferrocene derivative and 21–22% free carboxylic acid functions. The oxidation potential of the ferrocene units was +0.24 and +0.23 V vs. SCE, respectively. This material was then treated with diaphorase in the presence of a water-soluble carbodiimide. Thus about 8% of the carboxylic functions were modified by diaphorase. This electrode was capable of oxidixing NADH to NAD^+ completely. It is reported to be very stable over several runs. After binding the diaphorase to the PAA network, it was possible to bind HLADH to the remaining free carboxylic acid functions. Thus, 3% of the carboxylic functions could be modified by the production enzyme. In the presence of a 1-m*M* buffer solution of NADH, this ferrocene/diaphorase/HLADH-PAA modified electrode could be applied successfully to the oxidation of cyclohexanol (50 m*M*) to cyclohexanone or of *meso*-diols to optically active lactones. Recently, this system has been further developed in such a way that also the cofactor NADH is immobilized by the polyacrylic acid, presumably via bond formation with the 6-amino group of NADH. Thus, 41% of the carboxylic functions of polyacrylic acid were modified with ferrocene, 11% were cross-linked, 11.5% were modified with NADH, 0.14% were bound to diaphorase, and 0.39% were reacted with alcohol dehydrogenase. In this way, 55 μmol of a *meso*-diol was converted to 18 μmol of enatiomerically pure lactone in 10 ml of phosphate buffer in 8 h. Thus, this system is rather slow and not sufficiently effective [22,112]. Other mediators that have been used in combination with diaphorase for the regeneration of NAD^+ are riboflavin and vitamin K_3, which is 2,3-dimethyl-1,4-naphthoquinone. However, especially riboflavin is not stable enough for synthetic applications [113].

To avoid the limitation of one-electron redox catalysts due to the necessity to use compounds with relatively high oxidation potentials, other types of mediator systems with very low oxidation potentials would be interesting to obtain high chemoselectivities. However, mediators with much lower oxidation potentials cannot react via electron transfer but must act as hydride ion abstracting agents. Mediators of his type are *ortho*- and *para*-quinones, or *ortho*- and *para*-diamines [107]. The reactivity of such systems has been rationalized as shown in Fig. 17.

To reach high reaction rates, the hydride ion abstraction must be fast and very effective. The chemical regeneration agent frequency used for NAD^+ is FMN, a quinoid system. It is most applied as a stoichiometric oxidant. It can also be introduced in the presence of oxygen, thus producing hydrogen peroxide, which has to be destroyed by catalase [10,13,14,114]. In this case, in principle, less than stoichiometric amounts of FMN should be sufficient. However, due to the low reactivity, even in this case more than stoichiometric amounts of the catalyst are applied. Thus, with FMN, the problem is a

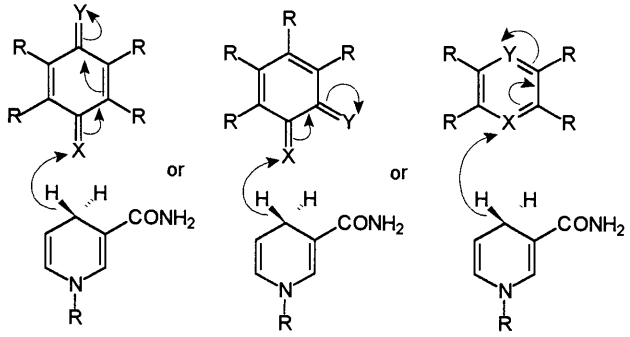


Figure 17. Proposed mechanism for the NADH oxidation by hydride transfer. Adapted from A Kitani, LL Miller [107]. X is a group capable of accepting a hydride, and Y is an electron-withdrawing group.

very slow regeneration rate for NAD^+. Therefore, the costly FMN is usually present in very high concentrations and the total turnover number for NAD^+ does not exceed 25 [15,96]. Typical concentrations are 14 mmol of the substrate, 1 mmol of NADH, and 20 mmol of FMN. Only turnover frequencies between 0.025 and 0.06 cycles/h with regard to FMN are obtained. Lee and Whitesides compared the efficiencies of NAD^+ regeneration systems [15]. Many quinoid systems are principally quite effective for the NAD^+ regeneration via hydride ion abstraction, thus lowering the necessary oxidation potential (Fig. 18).

A large number of these systems, often indamine, phenazine, and phenoxazine phenothiazine dyes (for examples see Fig. 19), have been studied mostly in the context of the development of an amperometric biosensor for glucose using the NAD^+-dependent glucose dehydrogenase. The literature up to 1994 has been reviewed [8,115].

Modified electrodes for this analytical purpose have mostly been formed by electrode adsorption of the mediator systems on the electrode surface or by electropolymerization [24,116]. Recently, for example, NAD(P)H oxidations have been performed on platinum or gold electrodes modified with a monolayer of pyrroloquinoline quinone (PQQ) [117] or on poly(methylene blue)-modified electrodes with different dehydrogenases entrapped in a Nafion film for the amperometric detection of glucose, lactate, malate, or ethanol [118]. In another approach, carbon paste electrodes doped with methylene green or meldola blue together with diaphorase were used for the NADH oxidation [119]. A poly(3-methylthiophene) conducting polymer electrode was efficient for the oxidation of NADH [120]. By electropolymerization of poly(aniline) in the presence of poly(vinylsulfonate) counterions,

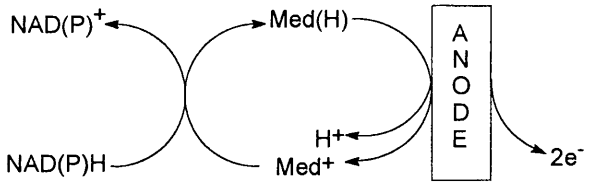


Figure 18. Indirect electrochemical $NAD(P)^+$ regeneration using mediators acting as hydride ion-abstracting agents.

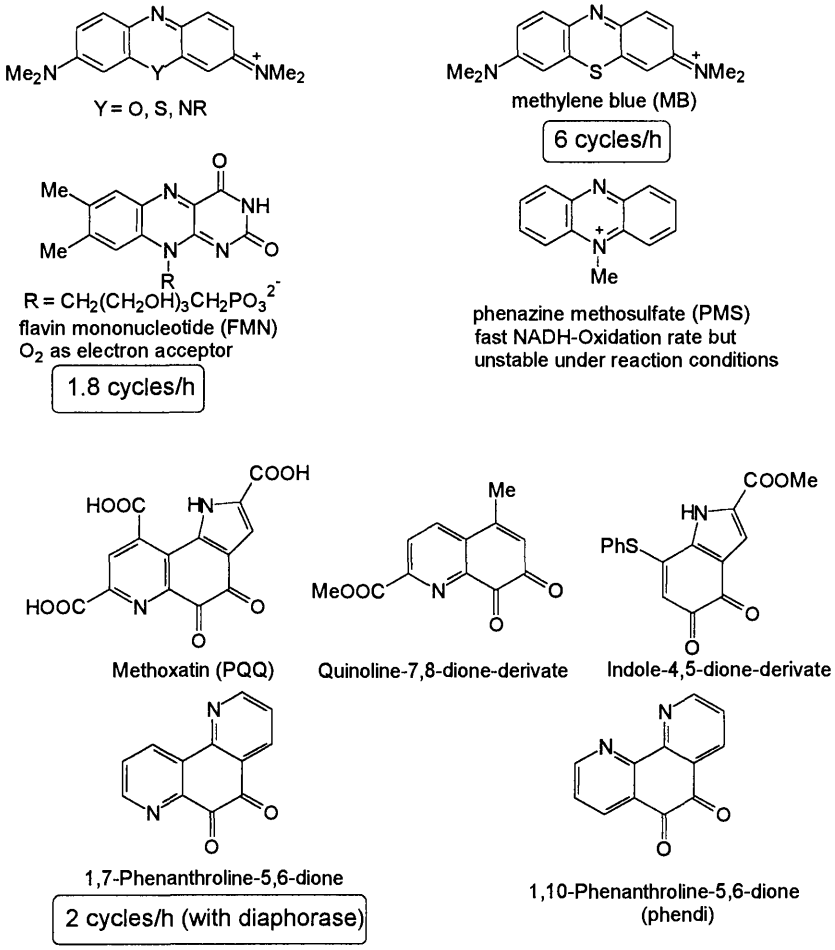
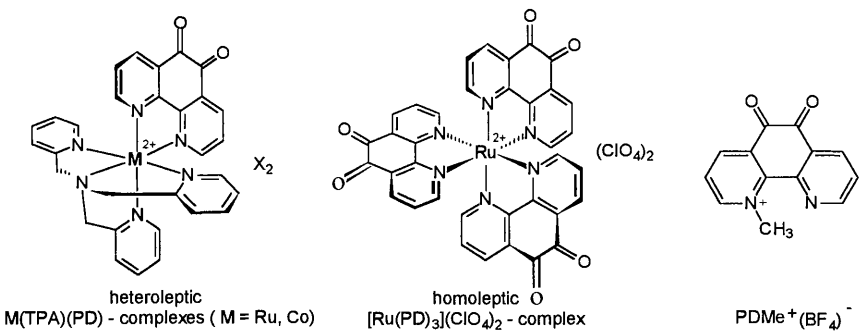


Figure 19. Some quinoid dyes and *ortho*-quinones acting as hydride ion-abstracting mediators, with some values of their turnover frequencies.

stable and electroactive films at pH 7 for the oxidation of NAD(P)H on glassy carbon electrodes at a potential of +0.1 V vs. SCE have been prepared [121]. Preparative applications were limited until now due to the limited stability of most of the modified electrodes or the degradation of the quinoid systems under conditions of pH 9 and higher, which is the optimum pH value for many dehydrogenases in their oxidative mode. However, some of the systems like the benzophenoxazines or phenoxazines show promising stability at pH 9 and could be interesting for synthetic purposes in the $NAD(P)^+$ regeneration under homogeneous conditions. Better stability is exhibited by phenanthrolindiones as mediators. Using 1,7-phenanthroline-5,6-dione in combination with diaphorase, Ohshiro [122] demonstrated the indirect electrochemical oxidation of cyclohexanol to cyclohexanone using the NAD^+-dependent HLADH with a turnover frequency of 2/h. However, for an effective enzymatic synthesis, this turnover frequency would be too small. To solve the already mentioned problems for the efficient chemical and electrochemical regeneration of $NAD(P)^+$, the 1,10-phenanthroline-5,6-dione system is a good starting point.

However, the electron density within the *o*-quinoid structure should be diminished to accelerate the hydride transfer from NAD(P)H and to lower the oxidation potential for the electrochemical regeneration to about 0 V vs. Ag/AgCl to exclude side reactions of the substrates at the electrode surface. At the same time, the solubility should be enhanced by the use of charged species, and the formation of insoluble precipitates by oligomerization of the reduced forms via hydrogen bonds should be avoided by blocking the nitrogen atoms. It was the strategy of Steckhan et al. to solve these problems by complexation of 1,10-phenanthroline-5,6-dione (PD) with a transition metal ion or by methylation of one of the nitrogens ($PDMe^+$). It had been shown before that homoleptic complexes of Co(II), Ni(II), and Cu(II), with 1,10-phenanthroline-5,6-dione were indeed undergoing fast hydride transfers from NADH. However, the reduced forms of the complexes were still slowly precipitating via oligomerization. Precipitation could be avoided in some cases by the modification of glassy carbon electrodes with transition metal complexes of PD, especially $[Fe(PD)_3]^{2+}$ [123]. In the case of Co(II), the precipitation in homogeneous solution could be avoided by using heteroleptic complexes in which four of the coordination sites are blocked by one *N,N,N*-tris(aminoethyl)amine (tren) or *N,N,N*-tris(pyridylmethyl)amine (TPA) ligand. In addition, the homoleptic tris-PD complex of Ru(II) showed an extremely high stability even in the reduced form. Since these complexes are promising mediators for the $NAD(P)^+$ regeneration, Steckhan et al. investigated their role in the cofactor regeneration systems, identified the active species that are involved in the process, and determined the number of active PD ligands in the already mentioned transition-metal PD complexes. The following systems have been found to be efficient mediators (Scheme 2): (1) 1-methyl-1,10-phenanthrolinium-5,6-dione tetrafluoroborate ($PDMe^+$) ($E_{p,ox} = -0.005$ V vs. Ag/Ag/Cl at pH 7.0), an alkylated charged derivative of PD as an alternative to the transition metal complexes; (2) the homoleptic complex Ru(II) $(PD)_3$ ($e_{p,ox} = -0.06$ V vs. Ag/AgCl at pH 7.0); and (3) the heteroleptic complexes Co(II) TPA) (PD) ($E_{p,ox} = -0.15$ V vs. Ag/AgCl at pH 7.0) and Ru(II) (TPA) (PD) ($E_{p,ox} = -0.11$ V vs. Ag/AgCl at pH 7.0). In all cases, cyclic voltammograms showed strong catalytic oxidation peak current enhancements, especially at higher pH values, which are favorable for the enzymatic oxidations [124].



Scheme 2 Structures of 1,10-phenanthrolin-5,6-dione (PD) complexes and derivatives, which are especially effective for $NAD(P)^+$ regeneration [124].

The newly developed redox catalysts can be applied in two types of processes: (1) indirect aerobic regeneration of the oxidized cofactor using oxygen as the final electron acceptor, thereby producing hydrogen peroxide; and (2) indirect electrochemical regenera-

Table 1 Turnover Frequencies (TN/h) for the Electrochemical Generation of NAD^+ from NADH with PD-Based Catalysts [124,125]

	Turnover frequency (h^{-1})		
Mediator	ph = 6.0	pH = 7.0	pH = 7.9
$[Ru(PD)_3]$	30	35	39
[Ru(TPA)(PD)]	23	21	21
PDMe	34	36	35
[Co(TPA)(PD)]	24	20	26

tion of the oxidized cofactor using the anode as the final electron acceptor. The turnover frequencies for the indirect cofactor regeneration are strongly dependent on the pH of the solution, reaching 900 TN/h at pH 8.0 for Ru(II) (PD_3, while those for the indirect electrochemical regeneration are practically pH independent (Table 1). The lower turnover frequencies and the independence of the pH indicate that in the case of the indirect electrochemical process, the diffusion of the reduced mediator to the electrode surface seems to be the limiting factor.

Using the intensive electroanalytical studies, the following regeneration mechanism could be deduced (Fig. 20). The regeneration system $[Ru(PD)_3](ClO_4)_2$ was coupled to the horse liver alcohol dehydrogenase (HLADH)-catalyzed oxidation of cyclohexanol to cyclohexanone as a model system. For the indirect electrochemical regeneration system, a turnover frequency of 28 turnovers/h was obtained. This is a factor of 14 larger than that reported for the indirect electrochemical oxidation using only the free ligand as mediator [122]. However, because of product inhibition only about 70% conversion could be reached. The product inhibition is avoided if *meso*-diols are employed as substrates. Using HLADH as a production enzyme, they are oxidized to form enantiomerically pure γ-lactones in a two-step oxidation process. These products are valuable enantiopure starting materials for complex syntheses of natural products or bioactive chemicals. Figure 21 shows the principle of the HLADH catalyzed oxidation of *meso*-diols using the indirect electrochemical regeneration of the cofactor.

Batch experiments under aerobic and anaerobic indirect electrochemical conditions were performed and compared with the published results by Jones [13] using the same substrate and FMN as redox catalyst under aerobic conditions. The newly developed

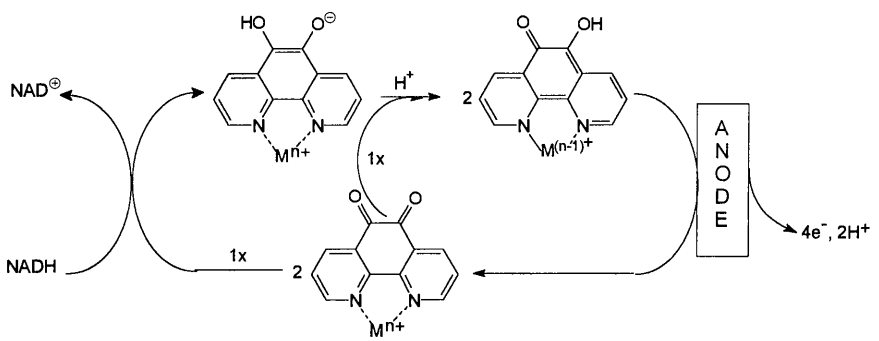


Figure 20. Electrocatalytic generation of NAD^+ from NADH under basic conditions employing 1,10-phenanthrolin-5,6-dione-based mediators.

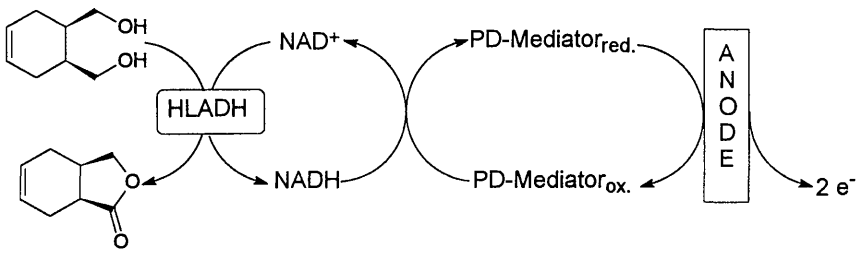


Figure 21. Electroenzymatic oxidation of *meso*-diols to give enantiomerically pure lactones with horse liver alcohol dehydrogenase (HLADH) and $PDMe^+$ as redox catalysts at pH 7.8 and ~150 mV vs. Ag/AgCl reference [125].

systems were more than three orders of magnitude faster than the FMN/O_2 system (Table 2).

The following data for the production of chiral γ-lactones from *meso*-diols using the indirect electrochemical NAD^+ regeneration procedure can be given: In a volume of 100 mL using 3.2 mg (1×10^{-5} mol) of PDMe, 70 mg (1×10^{-4} mol) of NAD, and 12.5 mg (16 U) of HLADH, after 20 h 99.5% of the *meso*-diol (0.5 to 1.0 g = 3.5 to 7.0 mmol) were converted to the enentiomerically pure lactone. Thus, the space–time yield can be calculated to be 6 to 12 g/L^{-1}-day^{-1}. The productivity is limited by the small amount of the enzyme.

The same system was applied to the HLADH catalyzed oxidation of a number of other *meso*-diols with similar results. Using the alcohol dehydrogenase from *thermoanaerobium brockii*, it was possible to oxidize 2,4-pentanediol to give (*S*)-4-hydroxy-2-pentanone under indirect electrochemical regeneration of $NADP^+$.

The NAD^+-dependent gylcerol dehydrogenase (GDH) [76] catalyzes the oxidation of secondary hydroxy groups in polyols to the keto function. Thus, chiral enantiomerically pure acyloins are accessible, or via enzymatic resolution chiral, enantiomerically pure

Table 2 Comparison of Different Cofactor Regeneration Systems, FMN/O_2, $Ru(PD)_3/O_2$, and $PDME^+$/Anode, for the Enzymatic Oxidation of *meso*-3,4-Dihydroxymethlcyclohexene Catalyzed by HLADH [125]

Conditions	1. FMN/O_2 (pH 9)	2. $Ru(PD)_3/O_2$/ catalase 9pH 7.8)	3. $PDME^+$/Anode (pH 7.8)
Catalyst	9.72 g (20.3 mmol)	7.26 mg (0.8×10^{-5} mol)	3.2 mg (1×10^{-5} mol)
NAD	720 mg (1.1 mmol)	52 mg (7.8×10^{-5} mol	70 mg (1×10^{-4} mol)
Substrate	2 g (13.9 mmol)	1 g (7 mmol)	0.5 g (3.5 mmol)
HLADH	40 mg (50 U)	15 mg (19 U)	12.5 mg (16 U)
Catalase		30 ml (7800 U)	10 ml (2600 U)
Time	48 h	28.5 h	20 h
Conversion	83%	99.4%	99.5%
Turnover frequency over the total reaction time	**0.025 TN/h**	**62 TN/h**	**35 TN/h**[a]
Ratio substrate:NAD: catalyst	0.64:0.05:1	900:10:1	350:10:1

[a]After 4.5 h a turnover of 27% was reached, corresponding to a turnover frequency of 82 TN/h.

polyols can be generated. Stating from *meso*-1,2-cyclohexandiol, the enantiomerically pure (*S*)-adipoine can be generated. The application of PDMe or ABTS as redox catalysts allows the efficient indirect electrochemical cofactor regeneration. Using only 0.054 units/ml of the enzyme, and the substrate, the cofactor, and the mediator in concentrations of 20 m*M*, 2 m*M*, and 0.2 m*M*, respectively, the maximum turnover frequency of 16 TN/h could be reached, which is limited by the enzyme concentration (Fig. 22) [126].

The indirect electrochemical NAD^+ regeneration was also applied to the oxidation of a hydroxysteroid using a hydroxysteroid dehydrogenase [79]. As a model system, the oxidation of testosterone to androstene-3,17-dione using a 17-β-hydroxysteroid dehydrogenase (testosterone-17-β dehydrogenase from *Cylindrocyrpon radiciola*) was studied. In batch electrolyses using a Sigraflex graphite foil anode, a platinum counter electrode, and a ratio of substrate:NAD:mediator ratio of 1000:5:1, a turnover of 60 to 80% of the substrate could be obtained after 6.5 h. As mediators, $PDMe^+BF_4^-$ or $Ru(PD)_3(CLO_4)_2$ was applied at an anode potential of 150 mV vs. Ag/AgCl, while ABTS was applied as a mediator at +650 mV vs. Ag/AgCl. As a result, 0.75 U of the enzyme was present in a pH 7.4 phosphate buffer. The turnover frequencies for the mediators reached between 180 and 220 TN/h after 0.5 h and between 92 and 122 after 6.5 h. Thus, a very efficient system could be developed. For ABTS, the highest stability was observed. After 6.5 h, practically no loss of activity was observed, while $PDMe^+BF_4$ lost about 30% of its activity. The total turnover number for ABTS or $PDMe^+BF_4$ reached 800 and the mediator was still active. The same process could also be performed continuously using a plugged-flow reactor containing an ultrafiltration membrane to retain the enzyme. A steady-state turnover of 80% was reached at a substrate:NAD:mediator ratio of 100:10:5. Because of the very low solubility of the substrate and the product, a two-phase system using 1-decanol as organic phase will be applied in the future [127].

In a very special system, the photoelectrochemical regeneration of $NAD(P)^+$ has been performed and applied to the oxidation of the model system cyclohexanol using the enzymes HLADH and TBADH. In this case, tris(2,2′-bipyridyl)ruthenium(II) is photochemically excited by visible light [25,128]. The excited Ru(II)* complex acts as electron donor for *N*, *N*′-dimethyl-4,4′-bipyridinium sulfate (MV^{2+}) forming tris(2,2′-bipyridyl)ruthenium(III) and the MV-cation radical. The Ru(III) complex oxidizes NAD(P)H effectively, thus regenerating the cofactor for the oxidizing enzyme. The MV-cation radical is reoxidized at an anode at a potential around 0 V vs. Ag/AgCl. On the other hand, if the aerobic reoxidation of the MV-cation radical is applied, the system loses its activity at a very fast rate due to the formation of hydrogen peroxide.

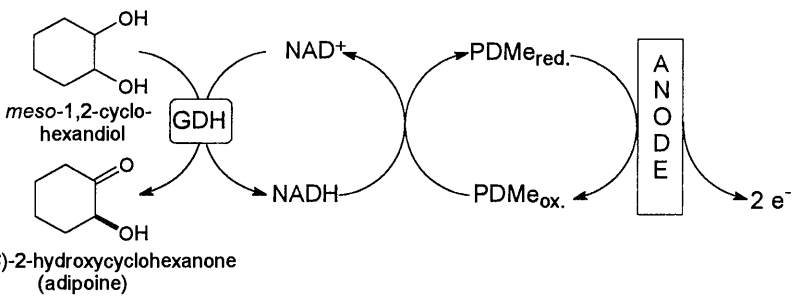
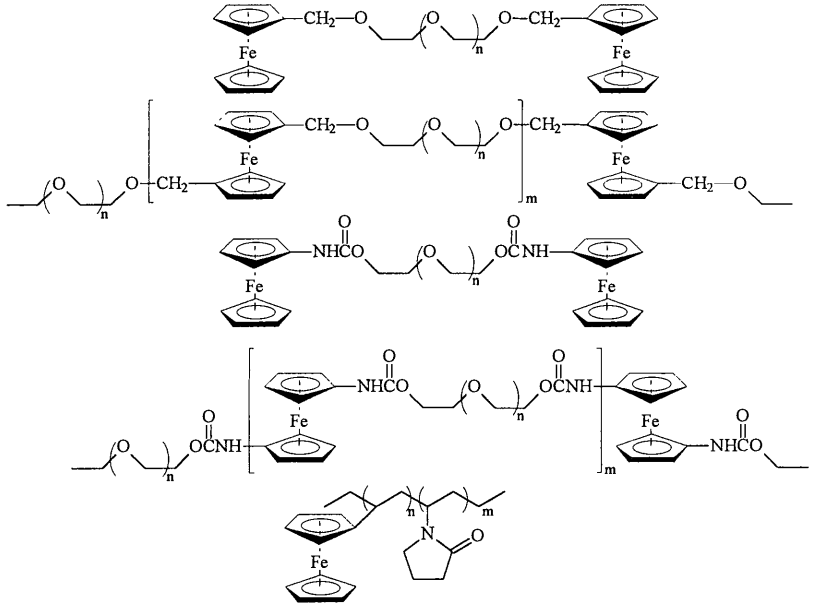


Figure 22. Glycerine dehydrogenase (GDH) catalyzed oxidation of *meso*-1,2-cyclohexandiol to give (*S*)-2-hydroxycyclohexanone with indirect electrochemical NAD^+ regeneration using PDMe as a redox catalyst.

A number of dehydrogenases, like some alcohol, aldehyde, glucose, and fructose dehydrogenases, are quinoproteins containing the quinoid cofactor pyrroloquinoline quinone as a prosthetic group (see Fig. 1) [129]. These enzymes can be of interest for electroenzymatic synthesis because in contrast to oxidases they are not using oxygen as electron acceptor. Thus, the formation of hydrogen peroxide which might inhibit or destruct the enzymes does not occur. Until now, these enzymes have mainly been used in amperometric biosensors using different mediator systems [130].

B. Oxidations with Oxidases

In the field of enzymatic oxidations using oxidases (oxygen acting as final electron acceptor), the class of flavoenzymes with bound FAD as cofactor is especially interesting for synthetic applications. The regeneration of the oxidized FAD within the enzyme can be performed by oxygen. However, as mentioned earlier, hydrogen peroxide is then formed, which drastically diminishes the enzyme stability and activity, rendering it unsuitable for synthesis. Even the presence of large amounts of catalase to destroy the hydrogen peroxide very often does not lead to a system that is stable enough for the application in synthesis. Therefore, an anaerobic reactivation of flavoenzymes and similar oxidizing enzymes is necessary. The most simple anaerobic oxidation would be the electrochemical procedure. However, as pointed out earlier, the large biomolecules do not undergo fast enough electron exchange with the electrode. For analytical purposes, this limitation can be solved by the application of "promoter" molecules that are adsorbed at the electrode surface [98]. For preparative applications, the most effective way is the indirect electrochemical procedure. As mediators, ferrocenes are most effective with flavoenzymes [131]. A number of water-soluble polymer-bound systems are shown in Scheme 3.



Scheme 3 Some water-soluble polymer-bound ferrocene derivatives used as mediators for the anaerobic reactivation of FAD enzymes.

The most often studied FAD-dependent oxidase is glucose oxidase oxidizing D-glucose to D-δ-gluconolactone. The indirect electrochemical mediation using mostly ferrocene derivatives as redox catalysts has mainly been applied to the development of glucose sensors [132]. The sensor applications will not be further discussed in this chapter. In a different application, glucose oxidase immobilized at the electrode surface is used for the formation of gluconic acid using oxygen. The electrode then oxidizes the enzymatically formed hydrogen peroxide back to oxygen, thus avoiding the inhibition of the enzyme by hydrogen peroxide [133].

A synthetically interesting synthetic application of flavo enzymes using ferroceneboronic acid as mediator [134] has been described for the transformation of *p*-hydroxytoluene (*p*-cresol) to *p*-hydroxybenzaldehyde, which is catalyzed by the enzyme *p*-cresolmethyl hydroxylase (PCMH) from *Pseudomonas putida*. This enzyme is a flavocytochrome containing two FAD and two cytochrome *c* prosthetic groups. To develop a continuous process using ultrafiltration membranes to retain the enzyme and the mediator, water-soluble polymer-bound ferrocenes [26–31,135] (Scheme 3) have been applied as redox catalysts for the application in batch electrolyses or in combination with an electrochemical enzyme membrane reactor (see Fig. 24) [26–31,135] with excellent results.

According to Fig. 23, a long-time batch electrolysis of *p*-cresol under catalysis by PCMH (PCMH: 16 U = 5.6 nmol) using 1,ω-bisferrocenyl-PEG-20,000 (0.51 mmol = 9.45 µmol ferrocen) as redox catalyst and a starting concentration of *p*-cresol of 41.25 m*M* (0.66 mmol) with further additions of substrate after 4140 min (0.0925 mmol), 5590 min (0.0784 mmol), 6630 min (0.184 mmol), and 112563 min (0.371 mmol) in 10 ml Tris/HCl-buffer of pH 7.6 under application of a divided cell (Sigraflex anode 26 cm^2) resulted in practically total turnover of the substrate to *p*-hydroxybenzaldehyde via the intermediate *p*-hydroxybenzylalcohol. The benzylalcohol is immediately further oxidized under catalysis of the enzyme to the aldehyde. The TTN of the enzyme was 210.000 and that of the redox catalyst 516 due to the higher concentration of the mediator. The system was still active at this point.

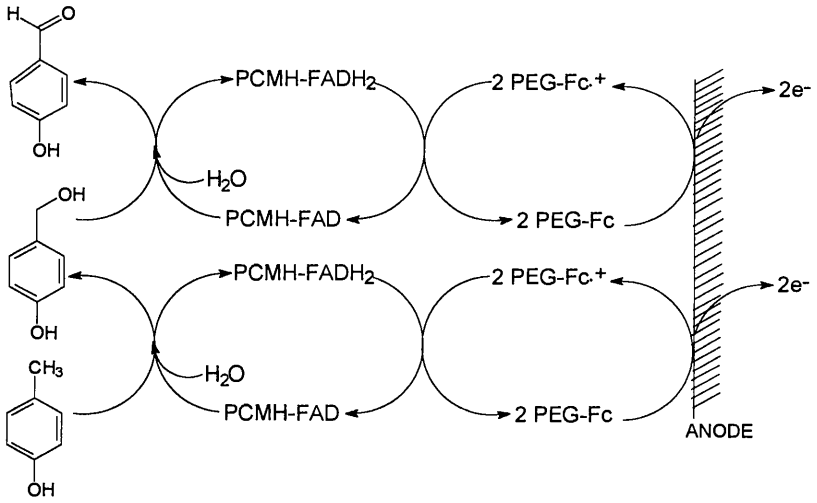


Figure 23. PCMH-catalyzed oxidation of *p*-cresol to *p*-hydroxybenzaldehyde via the intermediate benzylic alcohol with in situ electrochemical enzyme reactivation.

In an electrochemical enzyme membrane reactor (Fig. 24), an electrochemical flow-through cell using a carbon felt anode is combined with an enzyme membrane reactor. The residence time is adjusted by the flow of the added substrate solution. The off-flow of the enzyme membrane reactor only contains the products *p*-hydroxybenzaldehyde and *p*-hydroxybenzylalcohol. By proper adjustment of the residence time and the potential, total turnover of the *p*-hydroxytoluene, which is introduced into the reactor in 13 m*M* concentration, can be obtained. In a 10-day run, the enzyme underwent 400,000 cycles and the polymer-bound mediator, which was present in a higher concentration than the enzyme, underwent more than 500 cycles. At the end, the system was still active. By proper selection of the residence time, one can either obtain more than 90% of the *p*-hydroxybenzaldehyde at a turnover of more than 95% of the starting material or, at lower residence times and lower turnover of the substrate, the intermediate product *p*-hydroxybenzylic alcohol can be generated as major product [26–31,135,136].

The enzyme *p*-ethylphenol methylene hydroxylase (EPMH), which is very similar to PCMH, can also be obtained from a special *Pseudomonas putida* strain. This enzyme catalyzes the oxidation of *p*-alkyphenols with alkyl chains from C_2 to C_8 to the optically active *p*-hydroxybenzylic alcohols. This enzyme was used in the same way as PCMH for continuous electroenzymatic oxidation of *p*-ethylphenol in the electrochemical enzyme membrane reactor with 1,ω-bisferrocenyl-PEG 20,000 (MW 20,000) as high-molecular-weight water-soluble mediator according to Fig. 25. During a 5-day experiment using a 16-m*M* concentration of *p*-ethylphenol, we obtained a turnover of the starting material of more than 90% to yield the (*R*)-1-(4′-hydroxyphenyl)ethanol with 93% optical purity and 99% enantiomeric excess (glc at a β-CD-phase) at a residence time of 3 h. The (*S*)-enantiomer was obtained by electroenzymatic oxidation using PCMH as production enzyme.

Within the electrochemical enzyme membrane reactor, the formation of *p*-hydroxybenzaldehyde from *p*-cresol reached a space–time yield of 4.44 $mmol/L^{-1}\,h^{-1} = 11.8\,g/g \cdot L^{-1} \cdot d^{-1}$ using 60 U of the enzyme PCMH. At a residence time of 3 h, the turnover of *p*-cresol was 90 to 95%. For the formation of (*R*)-1-(4-hydroxyphenyl)ethanol from *p*-ethylphenol using the electrochemical enzyme membrane reactor, the space–time yield was

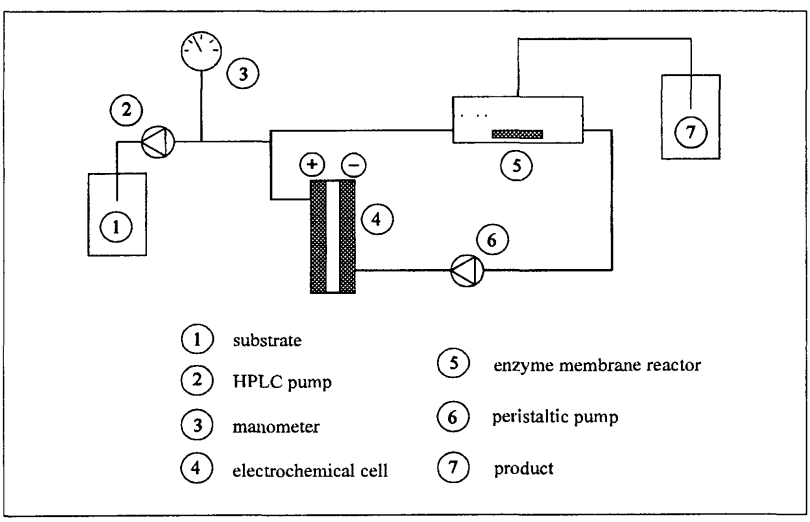


Figure 24. Electrochemical enzyme membrane reactor (EEMR).

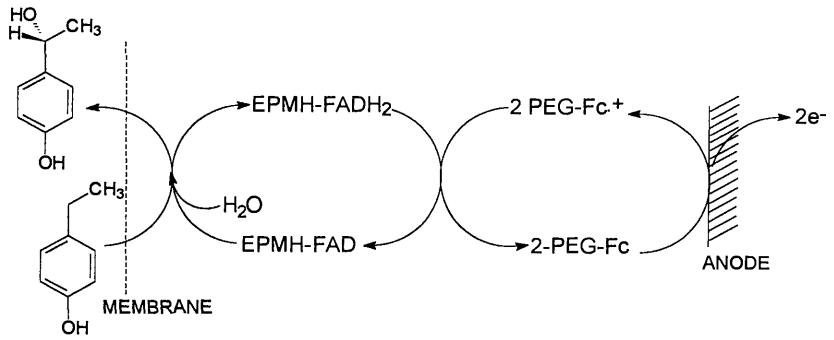


Figure 25. Principle of the electroenzymatic oxidation of *p*-ethylphenol catalyzed by EPMH to give (*R*)-1-(4′-hydroxyphenyl)ethanol in an electrochemical enzyme membrane reactor.

$5\,mmol/L^{-1}\,h^{-1} = 15\,g \cdot L^{-1} \cdot day^{-1}$ using only 16 U of the enzyme EPMH. At a residence time of 3 h, the turnover of *p*-ethylphenol reached 88%.

In the described experiments, the space–time yields are limited by the rather low enzyme concentration used. Higher concentrations of the enzyme would increase the space–time yields accordingly. Thus, it could be shown that flavoenzymes and comparable systems can be used for synthetic applications in a continuous process under anaerobic reactivation of the prosthetic group in the electrochemical enzyme membrane reactor [26–31,135,136].

It was also possible to electrochemically activate the flavo enzyme L-glycerine 3-phosphate oxidase (GPO) using monomeric water-soluble and polymer-bound ferrocenes as mediators. Strong catalytic peak current enhancements during cyclovoltammetric measurements could thus be observed with glycerine 3-phosphate in the presence of GPO [135]. GPO is of high synethetic interest because it catalyzes the oxidation of L-glycerine 3-phosphate to dihydroxyacetone phosphate (DHAP), which is the methylene component for the enzymatic C–C coupling reactions catalyzed by a large number of aldolases [82,137]. In contrast to other mostly complex or costly methods for the formation of DHAP, this anaerobic, indirect, electroenzymatic method is a one-step procedure starting from cheap glycerine 3-phosphate. In a batch electrolysis in a phosphate buffer of pH 7 (18 ml) using a polymer-bound ferrocene (1 m*M* in ferrocene) as redox mediator, a Sigraflex carbon foil anode, a working potential of 500 mV vs. Ag/AgCl, and 180 U GPO (*Pediococcus* sp., Merck) D,L-glycerine 3-phosphate (390 m*M*) was effectively transformed to DHAP (90 m*M*) within 1000 min. DHAP was determined by an enzymatic assay. Finally, the DHAP formed could be used in situ for C–C coupling with propanal in the presence of fructose-1,6-diphosphate aldolase [135].

Because of the long-term instability of GPO, this enzyme was stabilized by immobilization on Eupergit C 250 L. Under proper selection of the immobilization conditions, an activity yield of 84% was obtained with 51 units of activity per gram of supporting material [138,139].

According to the reaction scheme given in Fig. 26, the anaerobic oxidation of L-glycerol 3-phosphate was performed under the conditions of an indirect electrochemical process using a water-soluble ferrocene derivative as mediator in the presence of D-fructose-1,6-diphosphate aldolase from rabbit muscle for the in situ generation of the carbohydrate product. With a mediator concentration fo 1.5 m*M* using about 80 U of immobilized enzyme, after 25 h a 75% turnover of the substrate L-glycerol phosphate

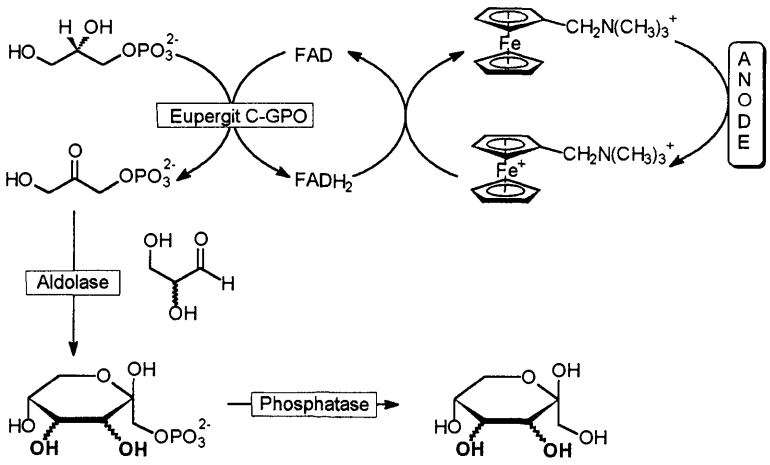


Figure 26. Indirect electrochemical anaerobic reactivation of the enzyme GPO for the synthesis of dihydroxyacetone phosphate and its follow-up in situ coupling to the aldolase catalyzed formation of carbohydrates.

was obtained. After 71 h, 85% turnover was reached. At this time, 50% of the enzyme activity was retained, demonstrating the good stability of the immobilized enzyme [139,140]. Thus, continuous aldolase-catalyzed reactions in combination with the electroenzymatic generation of DHAP catalyzed by GPO within an electrochemical enzyme membrane reactor can be foreseen.

It was also possible to bind the redox active ferrocene mediator directly to the lysine amino groups of the enzyme GPO via an oligo(ethylene glycol) anchor (Fig. 27). The catalytic activity was demonstrated convincingly by cyclic voltammetry (Fig. 28) [140,141].

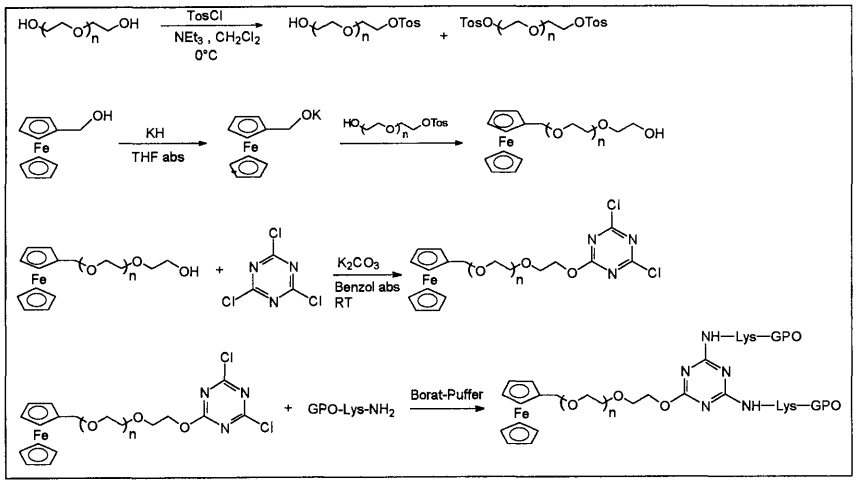


Figure 27. Synthesis of a ferrocene-modified glycerol-3-phosphate oxidase via a PEG spacer and a cyanuric chloride anchor group ($n = 5$–19) (activity of modified GPO 37% of the unmodified enzyme).

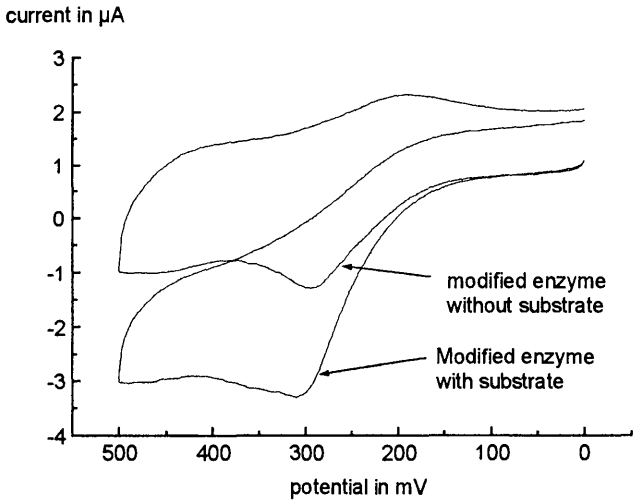


Figure 28. Cyclovoltammetric study of ferrocene-modified GPO in the absence and the presence of L-glycerol phosphate (scan rate 10 mV/s; reference Ag/AgCl, phosphate buffer, pH 6.8).

Pyruvate oxidase (Pyox) is a FAD- and thiamine diphosphate (ThDP)-dependent enzyme that catalyzes the reaction of pyruvate to give acetyl phosphate or vice versa (see Fig. 15). If used in the oxidative way, it can be activated and reactivated under nonaerobic conditions using ferrocene mediators. Kinetic parameters of the indirect electrochemical process using the enzyme incorporated into a biomimetic supported bilayer at a gold electrode have been reported [142]. Similarly, FAD-dependent amino oxidases may also be applied.

Galactose oxidase (GOase) (E.C. 1.1.3.9) from the fungus *Fusarium NRRL 2903*, formerly known as *Dactylium dendroides* [143], is a very interesting enzyme because of its special oxidation mechanism and also because of its value for synthesis. In the active center, the enzyme contains a copper coordinated to a thiotyrosyl group, and both are acting as cofactors. The enzyme has three redox states. The fully oxidized state of the enzyme contains copper(II) and the thiotyrosyl radical; in the semi form, copper(II) is coordinated to the neutral thiotyrosine, while in the reduced state, copper(II) is reduced to copper(I). The fully reduced form reacts with oxygen to hydrogen peroxide and the fully oxidized form, which oxidizes the substrate. The semi and oxidized forms are in equilibrium, which is reached after 3 h in aqueous solution. Because of this equilibrium, only 5% of the total enzyme is in the active oxidized form. The 95% in the semi form is not directly accessible for the normal aerobic regeneration [144]. The synthetic value of the enzyme lies in the fact that it oxidizes a wide range of primary alcohol substrates to the corresponding aldehydes. In the title reaction, the product of the GOase reaction with D-galactose is *meso*-galactodialdose and not D-galactohexodialdose, which is a common error in the literature. The synthetic application of GOase is of interest due to its broad substrate tolerance, its chemoselective oxidation of primary hydroxy functions in polyols, and its stereoselectivity. Thus, sugar alcohols may be transformed into the interesting nonnatural L-configured and other rare carbohydrates. Only in one case was the GOase recovered by ultrafiltration [145]. However, in the aerobic process, hydrogen peroxide is formed as the coproduct and has to be destroyed by the addition of large amounts of catalase. It is therefore of interest to replace the oxygen and couple the enzyme to the

anode via an appropriate mediator, thus avoiding the hydrogen peroxide generation. This has been done in several cases in the application of the enzyme in amperometric biosensors, mostly using hexacyanoferrates, ferrocene derivatives, tetracyano iron 1,10-phenanthroline complexes, TTF/TCNQ conducting salts, or osmium bipyridine complexes as mediators, at usually rather high pH values [146]. Yokoyama et al. applied PEG-modified GOase in organic and aqueous solvents in the presence of a variety of ferrocene mediators [147]. The cyclovoltammetric experiments showed that the charge of the mediator has a greater effect on the catalytic current than the redox potential. Mediators that are neutral in their reduced form showed the highest catalytic currents. The synthetic application under unaerobic indirect electrochemical conditions to avoid hydrogen peroxide formation has recently been studied intensively [148]. The already mentioned polymer-bound water-soluble ferrocenes of high moelcular weight (Scheme 3) are active mediators for the indirect electrochemical reactivation of galactose oxidase under analytical conditions [135]. Strong catalytic effects could be observed with galactose, D,L-threitol, and xylitol in the presence of galactose oxidase. Thus, with the polyethylene glycol-modified ferrocene mediator α, ω-bis-methylferrocenepolyethylene glycol (20,000), it was possible to continuously regenerate GOase by mediated anodic oxidation. By application of cyclovoltammetric measurements under anaerobic conditions, the pH optimum for the electrochemical regeneration in TRIS/HCl buffer was found to be 9.7, while for the aerobic regeneration the literature reports a pH optimum of 6.5 or 7.0–7.3. In the presence of oxygen, one important step in the catalytic cycle is the transfer of a proton from Tyr-495 to the intermediately formed superoxide radical anion, which is a strong base [149]. Because of the absence of oxygen in the electrochemical process, a higher pH value seems to be necessary to induce this deprotonation. It should also be mentioned at this point that under strongly basic conditions the aerobic process does not work. Therefore, in the indirect electrochemical processes at high pH values, it is not necessary to prevent the presence of oxygen. Intensive study of buffer systems showed that the enzyme GOase is quite instable in Tris-HCl buffer and other buffers containing amino groups like glycine/NaOH, especially at higher pH values. This seems to be due to complexation of the copper ion in the active site of the enzyme by amino groups in the buffer. In contrast to this, almost no activity loss could be detected after 10 days of storage in 50 m*M* carbonate buffer of pH 10 to pH 11 or in borate buffer at pH 9–11. The pH optimum for the electrochemical reactivation of GOase shifted from pH 9.7 to Tris-HCl buffer to 10.8 in carbonate buffer. Therefore, the carbonate buffer of pH 10.8 was applied in the electrochemical studies. The very high instability of GOase could be overcome by immobilizing the enzyme on the aminopropylated polysiloxane Deloxan [150] by the glutaric dialdehyde procedure. The best reproducible activity yield we achieved was 37%, with a specific activity of 2.4 U per g Deloxan TAP III. The enzyme stability under electrolysis conditions could be improved to 50% activity loss within 40 days, compared to 100% within 1 day. Galactose oxidase immobilized at Deloxan was applied in the indirect electrochemical oxidation of xylitol to give L-xylose applying polyethylene glycol-modified ferrocene as a redox catalyst in carbonate buffer of pH 10.8. Figure 29 shows the reaction progress. When the current is interrupted, the oxidation process stops. The irregularity at times longer than 30 days is due to nonsterility, leading to the growth of microorganisms on the electrolyte, thus making a reproducible analysis impossible.

Compared to the aerobic regeneration without catalase, the electrochemical regeneration is more effective by a factor of 3. The activity–time yield of the electrochemical regeneration compared to the aerobic regeneration with native GOase and catalase is approximately 50%, referred to the immobilized GOase activity. The total turnover num-

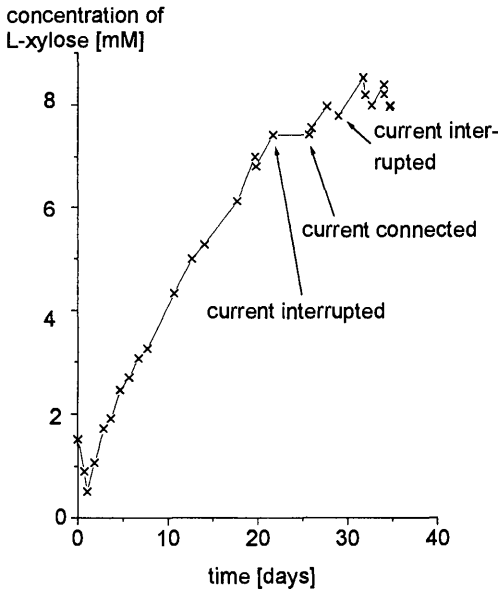


Figure 29. Time/turnover plot for the indirect electrochemical GOase-catalyzed oxidation of xylitol to give L-xylose in 50 ml of 50 m*M* carbonate buffer (pH = 10, 8); potential = 500–540 mV vs. Ag/AgCl; Sigraflex anode; Pt wire counter electrode.

ber (TTN) of the enzyme with about 210,000 cycles reaches practically the same value as the one observed under aerobic conditions. This shows that the electron chemical regeneration of immobilized GOase is approximately half as fast as the aerobic regeneration of native GOase. After the electrolysis, 50% of the original enzyme activity could be recovered, which demonstrates the increase of the enzyme stability due to its immobilization. [148]

C. Oxidations with Monooxygenases

Monooxygenases [7,8,92–95] use molecular oxygen as a source for regio- and stereospecificity introducing an oxygen function into an organic molecule. The other oxygen is cleaved reductively to generate water. Thus, reducing equvialents have to be present mostly in the form of NADH or NADPH. To transfer the reducing equivalents to the monooxygenase, usually a reductase and sometimes also an electron transfer protein must be present. The synthetic value of such enzymes stems from the fact that they are able to hydroxyze unactivated carbon–hydrogen bonds. There are three major types of monooxygenases. The first class of enzymes are flavoproteins [94] like the Baeyer–Villiger monooxygenases, which can oxidize cyclic ketones to enantiomerically pure lactones. In these cases, NADH is acting as reducing equivalent without an additional reductase. A second class are the so-called phenylalanine, tyrosine, and tryptophane hydroxylases [95]. These monooxygenases use pterin cofactors together with NAD(P)H as reducing equivalents in combination with a reductase. The third class are the cytochrome monooxygenases [93], especially the cytochrome P-450 enzymes. Thus, monooxygenases are often found in the form of multienzyme systems. The natural catalytic cycle for a particular member, the cytochrome CYP101 ($P\text{-}450_{cam}$; EC 1.14.15.1) from *Pseudomonas putida* (PpG786 is repre-

sented in Fig. 30. It catalyzes the hydroxylation of camphor at the 5-*exo* position and requires NADH together with two protein cofactors. The two electrons necessary for the reaction are supplied by reduced putidaredoxin, Pdx^{red}, a 2Fe–2S protein, which mediates the transfer of these electrons from NADH and the FAD-containing putidaredoxin reductase, Pdx reductase, to the heme active center of CYP101. For synthetic applications it would be advantageous to avoid the additional proteins, especially the Pdx reductase and the NADH, by using the cathode or a cathodically generated mediator as reducing agents.

Vilker et al. were able to transfer the reducing equivalents to purified cytochrome CYP101 through its natural redox partner putidaredoxin using an antimony-doped tin oxide working electrode, thus avoiding the reductase and NADH. The required oxygen was supplied at a platinum counter electrode by water electrolysis as shown in Fig. 31. A continuous catalytic cycle was sustained for more than 5 h, and 2600 enzyme turnovers were obtained at a maximum production rate of 36 nmol 5-*exo*-hydroxycamphor/nmol CYP101/min [151].

In a different approach, Estabrook and coworkers were able to mediate the electron transfer between a platinum gauze working electrode and a rat recombinant liver P-450 fusion protein containing the heme domain linked to the flavoprotein domain of NADPH-P-450 reductase, thus avoiding the NADPH cofactor. As mediator, cobalt sepulchrate^{3+}, (*S*)-(1,3,6,8,10,13,16,19-octazabicyclo-[6.6.6]eicosane)cobalt(III)$^{3+}$, was used. A turnover rate of more than 100 nmol product/min/nmol of P-450 (CYP102-BM3) was obtained for the (ω-1)-hydroxylation of lauric acid [152]. Kazlauskaite et al. [153] have shown that direct electron transfer from glassy carbon working electrodes to the CYP^{ox}-S, the first of the two electron-transfer steps of the catalytic cycle, is possible. It was also reported that cytochrome P-450 can be directly reduced at nickel cathodes at −1.0 V vs. SCE under anaerobic conditions without the formation of hydroxylated products. The addition of methyl viologen accelerates the electron transfer [154]. Rusling et al. [155] were able to perform direct electron transfer from lipid-modified pyrolytic graphic electrodes to CYP101.

D. Oxidations with Peroxidases and Similar Systems

Peroxidases are synthetically important enzymes that can catalyze the enantioselective oxygenation of sulfides to sulfoxides, alkenes to epoxides, alkyl benzenes to benzylic

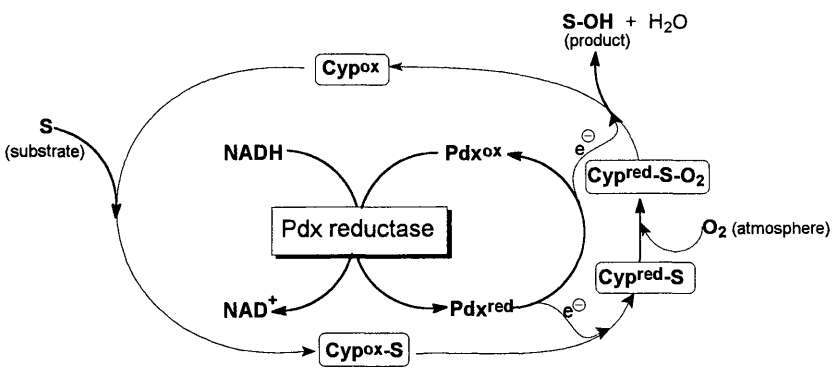


Figure 30. Natural catalytic cycle for the hydroxylation of organic compounds catalyzed by the Cytochrome (Cyt) $P\text{-}450_{cam}$ monooxygenase system (Cyp = Cyt. P-450 hemeprotein; Pdx = putidaredoxin).

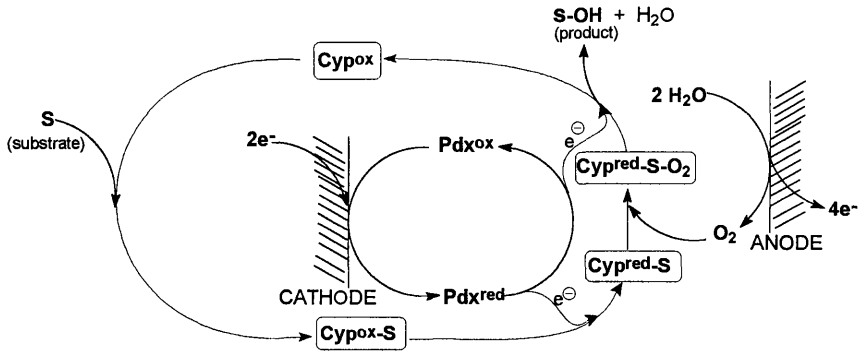
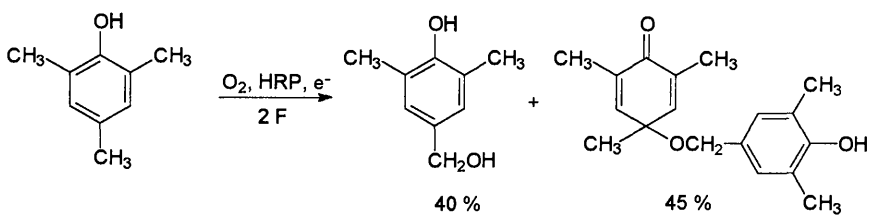


Figure 31. Electrochemically driven catalytic cycle for the hydroxylation of organic compounds catalyzed by the cytochrome (Cyt) P-450$_{cam}$ monooxygenase system (Cyp = Cyt P-450 hemeprotein; Pdx = putidaredoxin).

alcohols or aldehydes, or anilines to hydroxylamines or nitrosobenzenes [8,156]. These applications can be coupled to the in situ electrogeneration of hydrogen peroxide at the cathode. This coupling is favorable because the otherwise critical control of the hydrogen peroxide addition can thus be adjusted directly by proper selection of the current density. This approach makes the system more robust and applicable under continuous conditions. The peroxidase most often used in electrochemical applications is the quite stable horseradish peroxidase (HRP). In a leading application, Bartlett and Pletcher electrolyzed 2,4,6-trimethylphenol in a small, divided batch cell with a catholyte volume of 15 ml. The cathode was a reticulated vitreous carbon cylinder with a volume of 0.8 ml, rotated at 500 rpm. As catholyte, a 100-mM aqueous phosphate buffer, pH 7, saturated with oxygen containing 2,4,6-trimethylphenol (4.4 mM) and HRP (10 U/ml) was used. The electrolysis was carried out at −500 mV vs SCE. After consumption of 2 F · mol^{-1}, 3,5-dimethyl-4-hydroxybenzyl alcohol (chemical yield 40%) and 4-(4-hydroxy-3,5-dimethyl-benzyloxy)-2,4,6-trimethylcyclohex-2,5-dienone (chemical yield 45%) were obtained (Scheme 4). The second product is not formed in the nonelectrochemical process with HRP and added hydrogen peroxide [157].



Scheme 4 HRP-catalyzed oxidation of 2,4,6-trimethyl phenol with in situ electrogeneration of hydrogen peroxide [157].

In similar applications of HRP with in situ electrogenerated hydrogen peroxide, aniline derivatives have been oxidized using graphite felt immobilized HRP in a flow-through reactor [158]. Also, the polymerization of phenol has been studied under similar

conditions [159]. Chloroperoxidase has been used to catalyze the chlorination of barbituric acid to 5-chlorobarbituric acid under in situ electrogeneration of hydrogen peroxide [160]. The electrochemical and peroxidase-catalyzed oxidation of 9-β-D-ribofuranosyluric acid 5′-monophosphate generates a diimine intermediate, which subsequently decomposes [161].

In a different approach, HRP-modified electrodes were used for the enzyme-catalyzed cathodic reduction of hydrogen peroxide. Very stable and active systems could be obtained for hydrogen peroxide sensing [162].

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28
Amalgam and Related Reductions

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I. INTRODUCTION

Amalgrams are alloys between mercury and a metal; however, compounds that are not proper amalgams but function in a way similar to amalgams are also treated in this chapter. Thus, "alloys" between tetraalkylammonium and mercury or some other metals and also some interstitial compounds, for example, with graphite, are included in this review, even if these compounds have only a limited lifetime and are formed only as intermediates during direct electrolysis.

Amalgams function as electron donors in the same manner as a mercury electrode, and in many cases a similar product distribution is obtained by direct electrolysis at a mercury electrode and by an amalgam reduction. However, simultaneously with the electron transfer through the double layer a transfer of cations takes place, and this may influence the reaction, for example, by ion-pair formation.

Compared with direct electrolysis, reduction via an electrolytically produced amalgam may have some advantages. The preparation of an amalgam is more easily coupled with a useful anodic process, such as production of chlorine, than is direct electrolysis. Often a higher current density can be employed. If the production of and reduction by amalgam are performed separately, a higher degree of freedom is possible with respect to choice of solvent, temperature, and pressure in the second step. Amalgam reductions may

be run as either batch operations or continuous processes. Theories, both phenomenological [1] and quantum-chemical [2], for the electrochemical amalgam formation have been presented.

It is, however, more difficult to change the reducing power of an amalgam than to change the potential of an electrode, but by working with different metals and different concentrations of metal and by varying the rate of stirring (which influences the size of the amalgam droplets and thus the effective surface of the amalgam) it is possible to control within certain limits the degree of reduction by an amalgam.

The oxidation potential of an amalgam is related to its reducing power [3–6]; the oxidation potentials in *N*-methylpyrrolidone (NMP) of the metal amalgams become more negative in the sequence Ca > Sr > Br > K ~ Na > Li [5], and in agreement with this, Ca(Hg) is the weakest and Li(Hg) the strongest reducing agent among the amalgams mentioned. Lithium amalgam is thus the only one able to reduce in NMP 8-hydroxyquinoline to its dianion [5].

Sodium amalgam is the most widely employed amalgam, but sometimes other amalgams may be used to advantage. Aluminum amalgam is thus useful for reduction of alkali-sensitive compounds, but it cannot be prepared in situ by electrolysis of aqueous solutions of alumnum salts. Calcium amalgam has been employed when a weakly reducing agent is desired. When using amalgams the poisonous effect of mercury should be taken into account.

"Ammonium amalgam" (NH_4Hg_n) [7] is at room temperature a rather unstable compound, which decomposes to ammonia, hydrogen, and mercury, but at temperatures (−40°C) below the melting point of mercury the "ammonium mercury" may be stable for several minutes; the ammonium mercury has properties akin to the quaternary ammonium mercury compounds ($R_4N^+(Hg_5)^-$).

At very negative potentials neither the tetraalkylammonium ions nor the metallic electrode are inert; they combine to form reduced TAA-metals [7]. Tetraalkylammonium (TAA) metals are composed of quaternary ammonium ions, electrons, and a post-transistion metal such as Hg, Pb, Sn, Sb, Bi [5–18] or Pt [19]; most of them have the composition $R_4N^+Me_5^-$ [13] or $R_4N^+Me_4^-$ [20] and have been described as Zintl ion salts or Zintl phases [21,22]. They have been shown to be useful intermediates in the electrochemical reduction of certain substrates that are reducible with difficulty. On reduction of the quaternary ammonium salt, the initial layer of the metal compound is controlled by a two-dimensional nucleation, whereas the bulk phase is initiated by a three-dimensional nucleation and a growth controlled by the diffusion of R_4N^+ from the solution. In some cases (*N*-methylquinuclidinium (MQ^+) mercury) the catalytic efficiency of the initial layer is greater than that of the bulk phase [18], whereas in other cases (*N*, *N*-dimethylpyrrolidinium (DMP^+) lead) the opposite is found [16].

DMP(Hg) is formed in a reversible one-electron process on reduction of $DMP^+BF_4^-$ in DMF or diglyme at a mercury electrode; the cyclic votammogram of DMP is analogous to that of a metal forming an amalgam. DMP(Hg) is insoluble in DMF but reacts with DMF with a half-life of about 6 h at 5°C. DMP(Hg) is especially useful in promoting one-electron reductions; its reducing ability can be shown by the enhancement of the peak current in CV and limiting current in polarography on addition of certain difficultly reducible substrates. In some cases the electrochemical reduction of a substrate results in different products when tetrabutylammonium (TBA^+) is used as supporting electrolyte and when TBA^+ plus a low concentration of DMP^+ are employed [15].

In very dry DMF containing Bu_4BF_4 platinum electrodes are attacked at very negative potentials forming compounds of the type [Pt_4^-, Bu_4N^+. Bu_4NBF_4]. In the presence of Bu_4NI an exchange of BF_4^- with I^- occurs and a further reduction takes place. On oxidation in air for a few minutes the electrode modified this way displays remarkably low residual current to about −3 V (SCE) comparable to or better than a mercury electrode [19].

TAA ions may make interstitial compounds with graphite [23,24] that have reducing properties similar to those of the tetraalkylammonium metals.

II. OLEFINIC AND AROMATIC COMPOUNDS

Reduction of C=C double bonds may result either in saturation of the double bond or in hydrodimerization; the latter reaction is most common in compounds that can act as Michael acceptors.

Reduction of an unpolarized C=C double bond is exemplified in the conversion of biphenylenediphenylethylene to the corresponding ethane [25]. The reduction was performed in boiling amyl alcohol that is poorly suited for a direct electrolysis but adequate for dissolving the substrate.

The reduction of cinnamylidene fluorene by aluminum amalgam in moist ether to 1-fluorenyl-3-phenyl-1-propene (**I**), a 1,4-addition, exemplifies the use of Al(Hg) rather than Na(Hg) for the reduction of alkali-sensitive compounds; in the presence of Na(Hg), **I** might be tautomerized to 3-phenyl-1-propylidene fluorene [26]. Another example is the reduction of a cumulene, 1,1,6,6-tetraphenyl-1,2,3,4,5-hexapentaene, to 1,1,6,6-tetraphenyl-1,2,4,5-hexatetraene by Al(Hg) [27].

Of more interest than the saturation of double bonds is the hydrodimerization reaction (Chapter 21); sodium amalgam hydrodimerizations of α, β-unsaturated ketones were reported early [28], and the product distribution resembled that obtained from direct electrolytic reduction (Chap. 10).

The first sodium amalgam-induced dimerization of acrylonitrile to adiponitrile [29] was performed in aqueous solution, and the yield was discouragingly low (5%). Mainly, a base-induced addition of water resulting in β, β'-bis(cyanoethyl) ether occurred together with a reduction to propionitrile (PN).

Higher yields (30–60%) of a hydrodimerization with alkali metal amalgams were later reported [30,31] in the reduction of α, β-unsaturated esters and nitriles. The different alkali metal amalgams often gave different yields of hydrodimerized products; the hydrodimerization of acrylonitrile using potassium amalgam thus yielded 62% adiponitrile, whereas sodium amalgam under similar conditions gave only 37%.

After the development of the electrolytic reductive coupling of acrylonitrile to adiponitrile (Chapter 21), many investigations have been directed toward developing an alternative, indirect electrolytic process. The electrolytic hydrodimerization reaction in neutral solution [32,33] is critically dependent on the proton activity at the electrode. If the proton activity is too high, the product is predominantly propionitrile, whereas oligo- or polymerization occurs at too low a proton activity. The establishment of a reaction layer with a suitable proton activity in which conditions are favorable for a hydrodimerization of acrylonitrile to adiponitrile is, thus, of paramount importance. This can be accomplished in different ways.

One possibility is to add quaternary ammonium salts to an aqueous reaction mixture; the positive ions accumulate in the double layer [34–37] around the amalgam and

establish here a layer of low water content. The protonation may thus be slowed down sufficiently so the dimerization can compete successfully with it.

The unavoidable presence of sodium ions in the double layer during a Na(Hg) reduction introduces differences compared to the electrolytic hydrodimerization with respect to hydration and ion pairing.

The effect of the quaternary ammonium salt depends also on the substrate and on the electrode material [38]. Addition of tetraethylammonium salts thus sharply increases the yield of dimer product from acrylonitrile, has little effect upon the hydrodimerization of methyl acrylate, and does not affect the hydrodimerization of mesityl oxide.

It has been suggested [38] that quaternary ammonium amalgams are intermediates in the hydrodimerization of AN in an acetonitrile–water–CO_2 medium; other explanations [36,37,40], however, have also been considered. A layer of quaternary ammonium (Q^+) salts could first be produced by anodic dissolution of a sufficient amount of Q^+ from the amalgam.

Another way of producing a low proton activity at the amalgam surface is to add a suitable polar, aprotic compound to the medium. Suitable compounds include urea and its derivatives, amides, lactams, sulfoxides, and sulfones, such as 1,3-dimethylurea, ethyleneurea, biuret, formamide, *N*-methyl formamide, acetamide, δ-butyrolactam, dimethyl sulfoxide, di-*n*-butyl sulfoxide, and dimethyl sulfone [41,42]. Dimethylformamide (DMF) or acetonitrile, besides some of the compounds just mentioned, may be used as solvents [43,44]. One function of the added compound is to establish an aprotic reaction layer at the amalgam surface by selective adsorption of the compound on the amalgam; another is to solvate the ion pair (consisting of the radical ion and the cation) in a suitable way.

Hydrodimerization of AN by Na(Hg) may also take place in liquid ammonia [45] in the presence of a suitable proton donor; the dimerization is faster than the amination. If water is used as proton donor, ADN is formed in 80% yield, but when NH_4Cl is used, the yield is raised to nearly 100%. The ratio of PN to ADN depends on the ratio between NH_4Cl and AN; when the ratio is smaller than unity, some polymer is formed because there is not enough proton donor to terminate the anionic polymerization.

In the hydrodimerization of methacrylonitrile (MeAN) by Na(Hg) in liquid NH_3, NH_4Cl is too strong a proton donor; a mixture of isobuyronitrile (IBM) and dimethyladiponitrile (diMeADN) is formed. Phenol is a suitable weak proton donor in this case, and when the ratio of phenol to monomer is unity, only hydrodimerization is observed.

The ratio of the apparent rate constants of the formation of ADN and diMeADN from the monomers is about 2 in NH_3, whereas it is about 100 in diglyme [46] or diglyme–DMSO; this means that on cross-coupling of AN and MeAN in NH_3, all the possible combinations are obtained, whereas in diglyme–DMSO no diMeADN is found. An explanation for this difference may be that the monomer in phenol-NH_3 exists in a protonated form.

Many patents have been issued to groups working at ICI, UCB, and the Weizmann Institute on the amalgam hydrodimerization of AN and related compounds [47].

Reaction between Na(Hg) and acrylic acid (AA) in water, dioxane, or diglyme produces propionic acid (PA); however, when DMSO (containing about 10% water) is used as solvent, adipic acid (ADA) is the main product [48].

To achieve a high conversion it is necessary to add hydrochloric acid during the reaction. Under such conditions it is possible to obtain 70% ADA and 20–25% PA. Addition of HCl increases the rate of the reaction but not the ratio of PA to ADA; this

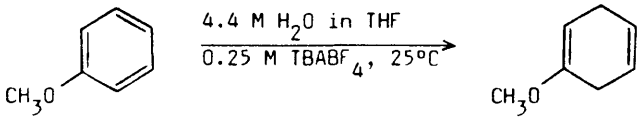
is because it is the free acid, not the acrylate ion, that is reduced. This is in accordance with the less negative reduction potential of the free acid compared with that of the acrylate ion.

The hydrodimerization of acrylic acid to adipic acid is a tail-to-tail addition; hydrodimerization of methacrylic acid and crotonic acid produces mainly the head-to-head and head-to-tail dimers [48].

Another example of this type of reaction is the hydrodimerization of dialkylfulvenes to dicyclopentadienyl alkanes by alkali metal amalgams in an aqueous-alcoholic medium [49,50].

Polycyclic aromatic hydrocarbons, such as anthracene and phenanthrene, can be reduced at elevated temperatures (80°C) at constant current to different hydroderivatives in an aqueous medium containing $(TBA^+)OH^-$ (2.1 *M*). The following products were obtained in yields depending on the number of $F\,mol^{-1}$ and the cell construction: 9,10-dihydroanthracene, hexahydro-, octahydro-, and decahydroanthracenes. Phenanthrene can be reduced under similar conditions; no isomerization step is necessary to obtain octahydro- and decahydrophenanthrene [43,51].

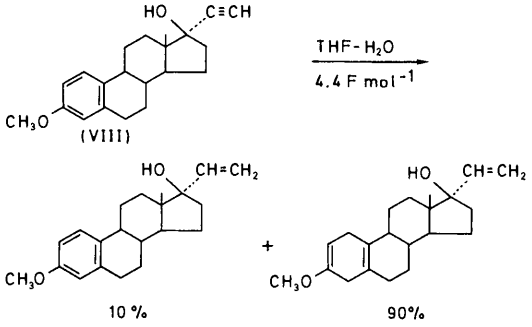
Benzene [52], anisole, 1,2,3,4-tetrahydro-6-methoxynaphthalene [53], and estradiol-3-methyl ether [54] have been reduced in a similar cathodic Birch reduction in water [52], aqueous diglyme, and aqueous tetrahydrofuran with TBA^+ as electrolyte at room temperature; TBA(Hg) has been proposed [53,54] to be a mediator in the reduction shown in Eq. (1):



(1)

The reduction of aromatic hydrocarbons in DMF to their radical anions has been used to show the reductive properties of a number of TBA metals [16,17,19] and interstitial compounds of graphite [23,24].

Alkynes may be reduced electrochemically to alkenes using aqueous THF-$TBABF_4$; thus 1-hexyne gave 93% 1-hexene using $2.8\,F\,mol^{-1}$. However, attempts to reduce 17-α-ethynylestradiol-3-methyl ether (**I**) to the alkene without reducing the aromatic ring failed, but in contrast to the classic Birch reduction the ethynyl group was not lost [54]:

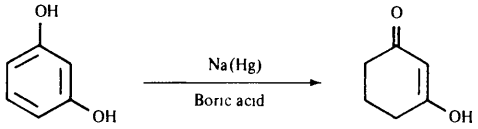


(2)

Reductions in aqueous THF-$TBABF_4$ of benzo[b]thiophene [55], benzofurans, and 1-methylindole [56] have been shown to yield the 2,3-dihydro compounds; this is probably a direct electrochemical reduction, whereas the further reduction involving ring opening of the hetero ring seems to be mediated by TBA(Hg).

The nucleus of certain phenolic compounds can be reduced by Na(Hg) in slightly acid solution containing boric acid. The latter probably acts as a complexing agent, besides maintaining a suitable pH.

Resorcinol can be reduced in the nucleus by Na(Hg) [57] in slightly acid solution at elevated temperature (90°C); the acidity can be maintained by bubbling CO_2 through the solution:



(3)

The process has not been reported by direct electrolysis, but it may be possible to do it by applying a suitable potential somewhat more negative than the decomposition potential of the medium at that pH in the absence of the substrate.

III. HALOGEN COMPOUNDS

An amalgam reduction of a halogen compound may result in cleavage of the carbon–halogen bond, a coupling reaction, a reductive elimination, or formation of an organic mercury compound.

Many halogen compounds are reduced to hydrocarbons by Na(Hg). This may be used to obtain reduction of isolated double bonds that are unreactive toward Na(Hg) by addition of hydrogen bromide to the double bond followed by amalgam reduction of the halogen compound to a hydrocarbon; the transformation of 4-pentenoic acid via bromovaleric acid to valeric acid is an example [58].

A reductive coupling of a halogen compound may be exemplified by the reaction of β-chloropropionitrile with Na(Hg) in the presence of some acrylonitrile and a small amount of water to adiponitrile; yields up to 90% have been obtained [59–61].

Treatment of vicinal halogen compounds with sodium amalgam results in many cases in a reduction–elimination reaction; 4,5-dibromovaleric acid thus forms 4-pentenoic acid on treatment with Na(Hg) [58]. 1,1,2-Trichloro-1,2,2-trifluoroethane and 1,2-dichloro-1,1,2,2-tetrafluoroethane react with Na(Hg) similarly, with formation of 1-chloro-1,2,2-trifluoroethylene and tetrafluoroethylene, respectively [62,63].

A special reaction of this type is the formation of benzyne. *o*-Fluorobromobenzene reacts with lithium amalgam in ether or furan with an intermediate formation of benzyne. In the former medium, diphenylene and small amounts of triphenylene and 9,10-dimercura-9,10-dihydroanthracene were formed, whereas the major product (76%) in furan was 1,4-dihydronaphthalene-1,4-endoxide [64].

1,3-Difluorobenzene can be reduced to fluorobenzene, which in turn can be reduced further to benzene using constant current in diglyme with TAA salts as electrolyte [65]. The best conditions for a selective reduction to C_6H_5F was a relative low current density (1.25 mA cm^{-2}), low concentration of $(DMP)BF_4$ (0.01 $M + 0.1\,M$ $TBABF_4$), and low water concentration (0.5%).

The monolayer of $DMP(Pb_5)$ catalyzes the reduction of alkyl halides, but does not mediate the electron transfer (ET) to ketones, alkylbenzenes, and difluorobenzene; the bulk $DMP(Pb_5)$ mediates ET also to these compounds [16].

An attack on a C–F bond may operate in the corrosion of poly(tetrafluoroethylene) (PTFE); the reaction of PTFE with amalgams of Li, Na, and K has been suggested [66] to proceed by an electrochemical mechanism in the solid phase, with the alkali metal

acting as an anode and the polymer as a cathodic-active material typical of a galvanic corrosion.

Polymerization of *p*-dichlorobenzene in xylene and of α,α'-dichloro-*p*-xylene in dioxane takes place on reduction with sodium or potassium amalgam; yields of 60–70% polymerized products are obtained [67].

Reduction of benzyl halides by Na(Hg) in propylene carbonate in the presence of CO_2 gave the Na salt of the corresponding phenylacetic acid [68].

IV. ORGANOMERCURIALS

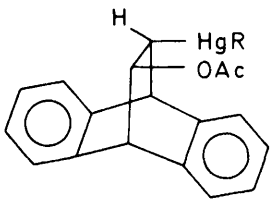
A good yield of dialkylmercury compounds [69] may be obtained from alkyl halides and Na(Hg); too high an Na content in Na(Hg) lowers the yield of dialkylmercury due to increased formation of the Wurtz coupling product. The reaction may be formulated as follows:

$$RX + Hg \longrightarrow RHgX \xrightarrow{Na} \tfrac{1}{2}R_2Hg + \tfrac{1}{2}Hg \qquad (4)$$

The ratio of the dialkylmercury to the Wurtz coupling product is dependent on the halogen; thus *n*-butyl iodide yields 80–81% dibutylmercury and 10% octane, whereas *n*-butyl chloride gave 11–17% Bu_2Hg and 65–70% octane.

Treatment of 1,2-dibromobenzene or its derivatives with Na(Hg) gave trimeric phenylenemercury derivatives [70].

Sodium amalgam reduction of organomercurials in alkaline deuterium oxide gives products with stereospecific retention during the replacement of mercury by deuterium [71]. This was shown in the reduction of *cis*-8-acetoxymercuri- (**IIa**) and *cis*-8-chloromercuridibenzobicylo[2.2.2]octadien-7-ol acetates (**IIb**), *trans*-8-chloromercuridibenzobicyclo[2.2.2]octadien-7-ol, and some norbornyl derivatives. Reduction of these compounds with sodium borodeuteride gave products without stereospecific deuterium incorporation [71].



IIa R = OAc
IIb R = Cl

Hex-5-enyl-1-mercuric bromide (**III**) is reduced to 1-hexene (**IV**) by sodium amalgam, whereas sodium borohydride, lithium aluminum hydride, and tri-*n*-butyltin hydride gave a mixture of **IV** and methylcyclopentane. This is taken as evidence that sodium amalgam reduction of alkylmercury salts does not proceed via a free radical pathway [72].

Reduction of **III** with sodium amalgam in a mixture of tetrahydrofuran and deuterium oxide gave >96% incorporation of deuterium [72]. Sodium amalgam is thus preferable as reducing agent for organomercurials for stereospecific deuterium labeling and for synthesis in systems that are prone to free-radical rearrangements.

Substituted 2-aminoethylmercuric chlorides, prepared by addition of $HgCl_2$ to an alkene in the presence of an amine, have been reported [73] to give the substituted 2-aminoethane in moderate yield, whereas direct reduction either in DMF or in 50% ethanol did not produce detectable amounts of the amine [74].

V. NITRO COMPOUNDS AND DERIVATIVES

Nitro compounds are reduced by amalgams in a manner similar to that found at a mercury electrode. Aliphatic nitro compounds [75] are thus reduced to alkylhydroxylamines by $NH_4(Hg)$, whereas aromatic nitro compounds may form amines, hydrazo, azo, or azoxy compounds and even nitroso compounds [75,76]. Aliphatic, tertiary vicinal dinitro compounds may be reduced to alkenes by elimination of the nitro groups as nitrite [77].

Reduction of nitrobenzene with Al(Hg) in ether at controlled temperature yields phenylhydroxylamine [78].

Azobenzene has been manufactured by reduction of a suspension of nitrobenzene by Na(Hg). Further reduction to hydrazobenzene is possible if higher temperatures and concentrations of alkali are employed [79]. The corresponding arsenic compounds may be prepared from a phenylarsenoxide by amalgam reduction; thus *p*-aminophenylarsenoxide yields 80% $H_2NC_6H_4As{=}AsC_6H_4NH_2$ on treatment with 4% Na(Hg) in methanol [80].

It is interesting that treatment of some aromatic nitro compounds with ammonium amalgam yields among other products nitrosobenzenes [76]. 2-Nitrobenzoic acid thus gives about 45% 2-nitrosobenzoic acid together with anthranilic acid (10%), and 2-nitrotoluene (5 g) yields 0.6 azoxytoluene, 2 g 2-nitrosotoluene, and 1.5 g *o*-toluidine on treatment with $NH_4(Hg)$.

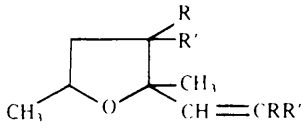
N-nitroso and *N*-nitro compounds may both be reduced to hydrazines. In this case care must be taken to avoid a reductive cleavage of the nitrogen–nitrogen bond [79,81]. Several other reductions by Na(Hg) has been described by Funke in his review [79].

VI. CARBONYL COMPOUNDS AND DERIVATIVES

On reaction with Na(Hg), saturated aldehydes or ketones may form either alcohols or pinacols [82–84]; the reaction is similar to the electrolytic reduction (Chapter 10).

The use of Al(Hg) in ether for the reduction of alkali-sensitive compounds may give higher yield than Na(Hg); thus, diethyl oxaloacetate is reduced to diethyl malate by Al(Hg) in 70–80% yield, whereas Na(Hg) gives about 50% yield [78].

α,β-Unsaturated ketones of the structure $RR'C{=}CHCOCH_3$ yield on treatment with sodium amalgam a mixture of products, including tetrahydrofurans (**V**) and dihydrofuran derivatives (**VI**), glycols (VII), ε-diketones (**VIII**), and ketols (**XI**) [85–87]. The ratio between the products depends on R and R′; bulky groups as found in steroids favor formation of glycols rather than of ε-diketones [88]. The reactions leading to these products are similar to those discussed in Chapter 10.



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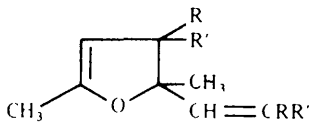
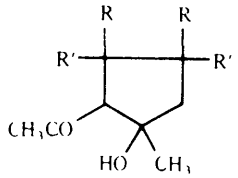
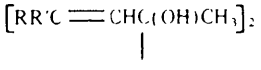


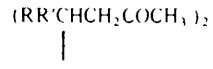
(VI)



(IX)



(VII)



(VIII)

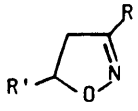
Reduction with Na(Hg) in toluene has been used to prepare *p*-hydroxy di- and triphenylmethyl radicals from the corresponding galvinols [89].

Although the reduction of cyclohexanone (**X**) in DMF–0.1 *M* $TBABF_4$ gives cyclohexanol in good yield, addition of $(DMP)BF_4$ (0.01 *M*) changes the product to the pinacol (95%). The cyclic voltammetric peak of $(DMP)BF_4$ in DMF–$TBABF_4$ is enhanced on additon of **X**, which suggests a reduction of X by DMP(Hg) and regeneration of DMP^+ [90]. That TBA^+ does not function in the same manner as DMP^+ could suggest that the reduction potential of TBA^+ is so negative that a direct reduction of **X** occurs.

Similarly, reduction of 6-heptene-2-one (**XI**) at Hg in DMF–0.1 *M* TBA^+ yields the alcohol, whereas reduction in the presence of catalytic amounts of DMP^+ yields *cis*-1,2-dimethylcyclopentanol (95%) [90]. The cyclization is suggested to occur at the stage of the radical anion of **XI**, since in diglyme–0.5% H_2O DMP^+ promoted the formation of the pinacol of **XI**. The cyclization is similar to that described by Shono et al. [91], who reduced **XI** in MeOH–dioxane at a carbon cathode with 2 *M* TEA^+ as electrolyte; see Chapter 10.

The reduction of carbonyl derivatives as oximes and hydrazones is similar to the electrolytic reaction. Oximes are reduced to amines [59], whereas hydrazones in alkaline solution may form hydrazines; benzalhydrazine can thus be reduced to benzylhydrazine [92], benzalazine to benzaldehyde benzylhydrazone, or further to dibenzylhydrazine [93,94], and benzaldehyde semicarbazone to benzylsemicarbazide [95].

Isoxazolines may be regarded as cyclic oximes; the reduction of 3,5-diphenylisoxazoline (**XIIa**) with $LiAlH_4$ gave 95:5 *erythro*: *threo* 1,3-diphenyl-3-aminopropanol (**XIIIa**) [96], whereas reduction with Na(Hg) [96,97] in methanol yielded the ratio 2:3 of *erythro*: *threo* **XIIIa**, as in Eq. (5). Similar results were obtained with 3-phenyl-5-methylisoxazoline (**XIIb**), whereas 5-phenyl-3-methylisoxazoline (**XIIc**) was not reducible.



XII

$\xrightarrow[MeOH]{Na(Hg)}$ $R'CHOH\text{-}CH_2CH(NH_2)R$

XIII

(5)

a $R = R' = C_6H_5$ *erythro threo* 2:3

b $R = C_6H_5$ $R' = CH_3$

c $R = CH_3$ $R' = C_6H_5$

5-(Bromomethyl)isoxazolines, prepared from a nitrile oxide and an allyl bromide, may be reductively ring opened to β,γ-enoximes **XIV**); **XIV** may be reduced in aqueous THF with Al(Hg) to the homoallylamine (**XV**), as in Eq. (6) [98]:

$$\underset{\textbf{XIV}}{CH_2=CR-CH_2-C(=NOH)R'} \longrightarrow \underset{\textbf{XV}}{CH_2=CR-CH_2-CH(NH_2)R'} \qquad (6)$$

VII. ACIDS AND DERIVATIVES

Esters of fatty acids are only to some extent reduced to the alcohols by sodium amalgam. Aldonolactones and their esters, however, are reduced to aldoses by Na(Hg) [99]. Optimal conditions are found at pH 3–3.5 and temperatures below 15°C; 2.5–3 atoms of Na [as 2.5% Na(Hg)] are used per mole of lactone. Yields of different aldoses range from 50 to 84% [100,101].

The reduction of aromatic carboxylic acids by Na(Hg) may take place in the nucleus or in the carboxyl group. Phthalic acid is reduced to *trans*-3,5-cyclohexadiene-1,2-dicarboxylic acid [102] or 2,5-cyclohexadiene-1,2-dicarboxylic acid [103], whereas certain phenolic carboxylic acids may be reduced to aldehydes.

Salicyclic acid and some other acids were reduced by Na(Hg) to the aldehyde [104–107] (40–60%) in a slightly acid medium containing *p*-toluidine and boric acid; the reaction mixture was kept slightly acid by addition of boric acid. A similar electrolytic reduction was not successful unless the mercury cathode was allowed to take up some sodium, thus making the reaction an indirect reaction [108].

The reduction by Na(Hg) of several *o*-hydroxynaphthalenecarboxylic acids in slightly acid solution containing boric acid has been investigated. 1-Hydroxynaphthalene-2-carboxylic acid [109] is, like salicyclic acid, reduced to the aldehyde (62% yield), isolated as the Schiff base, whereas 2-hydroxynaphthalene-3-carboxylic acid [110] under similar conditions yields mainly 2-hydroxy-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid (75–80%) and 5% of the aldehyde. When hydrochloric acid rather than CO_2 was used to neutralize the base formed during the reduction, the 2-oxo-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid [111] was isolated (60%). On heating, the compound, a β-keto acid, decarboxylated.

A loss of phenolic hydroxyl group occurs during the reduction of 1-hydroxynaphthalene-4-carboxylic acid with Na(Hg) in the boric acid medium from which 1,4-dihydronaphthoic acid is isolated [112]. The primary reduction probably yields 1,4-dihydro-1-hydroxy-4-naphthoic acid, which loses water to 1-naphthoic acid; this compound is under these conditions reduced mainly to the 1,4-dihydro derivative, whereas 2-naphthoic acid predominantly gives the 1,2-dihydro compound.

Reduction of an aromatic acid chloride by Li(Hg) or another alkali metal amalgam in diethyl ether or THF yields the enediol diester (**XVI**) [113]; further reduction by Li(Hg) yields diarylacetylene (**XVII**) [114]:

$$\begin{aligned} &4\ ArCOCl + 4e\ (Li(Hg)) \longrightarrow \underset{\textbf{(XVI)}}{ArC(OCOAr)=C(OCOAr)Ar\ (Z+E)} \\ &XVI + 2e\ (Li(Hg)) \longrightarrow \underset{\textbf{(XVII)}}{ArC{\equiv}\ uCAr} + 2\ ArCOO^- \end{aligned} \qquad (7)$$

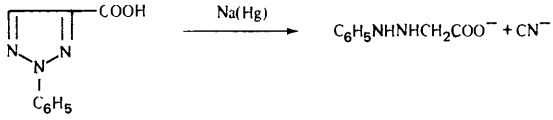
Carbon dioxide may be reduced by alkali metal amalgams in alcohol to alkali metal formate [115] in a yield of 85–90%; the rate increases with the CO_2 pressure and is dependent on the alkali metal, Na(Hg) < Li(Hg) < K(Hg).

An attempt has been made [116] to hydrodimerize CO_2 to oxalic acid, but only in hexane and with Na(Hg) was sodium oxalate obtained in a reasonable yield (40%).

In other cases a wide variety of products, ranging from simple organic acids such as formic and oxalic acid to totally reduced CO_2 in the form of carbon black, have been obtained by reduction of CO_2 by an appropriate alkali metal amalgam [117].

VIII. CLEAVAGE REACTIONS (OTHER THAN CARBON–HALOGEN)

A reaction that involves both a carbon–carbon and a nitrogen–nitrogen cleavage is found in the reduction of 2-phenyl-4-carboxytriazole by Na(Hg) in slightly alkaline solution [118]. The reaction probably starts with a reductive cleavage of the ring, followed by loss of CN^- and further reduction of the phenylhydrazone thus obtained to the hydrazine:



(8)

Treatment of benzopinacol with Na(Hg) in a mixture of anhydrous ether and benzene gives a dark blue solution that fades. Benzhydrol can be isolated in a quantitative yield. It has been suggested that the disodium salt of benzopinacol disproportionates with C–C cleavage into benzhydrol and benzophenone; the latter is reduced by Na(Hg) to benzopinacol, which then decomposes [119]. In that connection the cleavage of benzophenone pinacol to two benzophenone radical anions under the influence of electrogenerated bases [120] is germane.

A cleavage of carbon–oxygen bonds caused by amalgam reduction is found, for example, in the reduction of dihydroxyacetoxime to isopropylamine [121] and 2-hydroxy-4-phenyl-3-butenoic acid to 4-phenyl-3-butenoic acid [122]. These reactions are analogous to those discussed in Chapter 23.

Although sodium amalgam is unreactive toward phenyltrimethylammonium chloride, benzyltrimethylammonium chloride is cleaved to toluene and trimethylamine. A similar reaction is responsible for the reductive ring opening of *N*, *N*-dimethyltetrahydroquinolinium chloride to 2-propyl-*N*, *N*-dimethylaniline [123].

The reductive cleavage of achiral and optically active quaternary phosphonium and arsonium salts with alkali metal amalgams to form tertiary phosphines and arsines succeeds in high yield with retention of configuration [124]. The reduction with the amalgams was found to give better yields than the conventional cathodic cleavage.

Sodium amalgam has been used to cleave sulfur–sulfur bonds. Solutions or suspensions of organic di- or polysulfides can be reduced with Na(Hg) in the presence of an alkali sulfide to the mercaptide [125].

Certain sulfonic acids may be cleaved by Na(Hg); thus 1-aminonaphthalene-3,8-disulfonic acid can be reductively cleaved to 1-aminonapththalene-3-sulfonic acid. The sulfonic group in the 8-position is more easily removed reductively than sulfonic groups in the 2-, 4-, or 6-positions [79].

β-Ketosulfoxides react rapidly and cleanly with aluminum amalgam in a mixture of 90% tetrahydrofuran and 10% water to yield the ketones [126]:

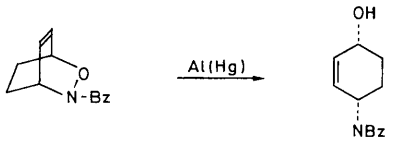
$$RCOCH_2SOCH_3 \xrightarrow[(H_2O)]{Al(Hg)} RCOCH_3 + CH_3SH \quad (9)$$

For preparation on a larger scale the direct electrolytic cleavage of β-ketosulfoxides or β-ketosulfones [127] has been found preferable.

Alkyl arylsufonates and diaryl sulfones are cleaved by alkali metal amalgams to the corresponding sulfinate salts. Some sterically hindered arylsulfonates, however, undergo cleavage at the ring–S bond [128].

Selective demesylation of 2-*O*-(methylsulfonyl)-D-mannopyranoside derivatives has been made with Na(Hg) in 98.6% yield in diethyl ether containing 2-propanol [129].

The N–O bond of Diels–Alder adducts of hydroxamic acids with 1,3-dienes may be cleaved by Al(Hg) or Na(Hg). Thus (**XVIII**) was reduced to (**XIX**) by Al(Hg) in quantitative yield [130]:

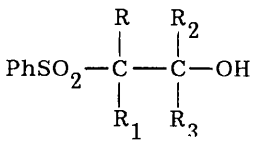


(10)

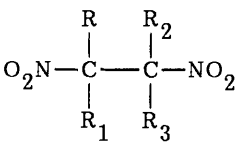
XVIII XIX

Symmetrical alkynes and symmetrical and unsymmetrical olefins may be prepared by reductive elimination of suitable groups by amalgams; the preparation of diaryalkynes from aromatic acid chlorides with Li(Hg) was described earlier [113,114].

One method of preparing alkenes is a reductive elimination using sodium amalgam of a substituted 2-phenylsulfonylethanol (**XX**) obtained by addition of phenylalkylsulfone to a ketone using a basic organometallic catalyst [131].



XX



XXI

Another one is to prepare vicinal, tertiary nitro compounds (**XXI**) by oxidative dimerization of the mononitro anion, followed by treatment of **XXI** with calcium amalgam in hexamethylphosphoramide [77] at room temperature.

IX. POLYMERIZATION REACTIONS

Finally, it might be mentioned that Na(Hg) can act as a catalyst in a polymerization of acetaldehyde to a polyvinyl alcohol-type polymer [132,133]. The polymerization may be performed in a cooled vessel at high pressure under nitrogen with vigorous stirring. The product was suggested to be a linear polymer of the type $CH_3(CHOHCH_2)_nCHO$, but later investigations suggested a branched structure [134].

An oligomerization of ethylene in the presence of cyclopentadienyltitanium dichloride, $C_5H_5TiCl_2$, is possible using Na(Hg). When the ratio of ethylene to $C_5H_5TiCl_2$ was 12, a mixture of 80% *n*-butane and 20% *n*-hexane was obtained [135].

Isobutylene polymers and copolymers can be prepared by polymerization in the presence of vanadium tetrachloride or titanium tetrachloride and sodium amalgam [136].

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29
Electrogenerated Reagents

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I. INTRODUCTION

Most electrochemical reactions essentially take place at the electrode interface by a heterogeneous, primary electron ransfer. Other electron transfer reactions in solution, such as disproportionation, are not excluded. However, the heterogeneous electron exchange process is often complicated and consequently slowed by the intrinsic nature of the interface. Therefore, the scope of electrochemistry can be widened by the use of organic or inorganic mediators (electron carriers between the conducting interface and the solution) that thereby act as reducing or oxidizing reagents. Ideal mediators may then be regarded as an ionic (such as the electrolyte itself) or molecular electrode of a well-defined potential where inhibiting processes are effectively excluded. However, other kinds of electrogenerated species possessing either redox and/or nucleophilic or electrophilic properties may react with oganic substrates by mechanisms in which electron transfer does not seem to play the major role.

Electrogenerated intermediates in general react in liquid electrolytes. More sophisticated indirect electrochemical and catalytic processes have been recently developed principally by using electrodes specifically coated with conducting organic polymers. Additionally, the electron itself (possibly transferred by indirect means for higher selectivity) may contribute to initiate organic reactions according to so-called electrocatalytic processes. Lastly, let us mention that homogeneous redox reactions of electrogenerated nucleophiles and electrophiles in solution toward solvent or electrolyte are not discussed in this chapter, as they are developed in detail in other parts of this book.

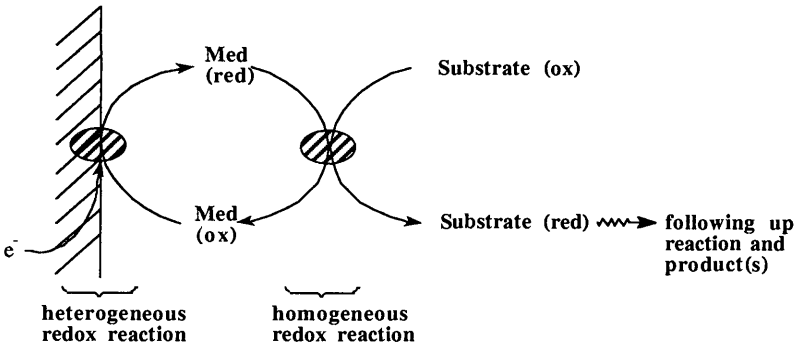
II. HOMOGENEOUS REDOX CATALYSIS: THEORY AND APPLICATIONS

A. General Aspects of Indirect Electron Exchanges

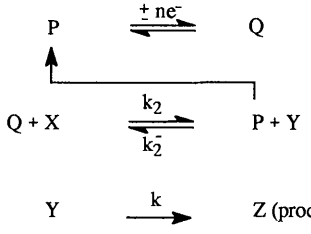
The electrochemical method allows, by means of electron transfer at a given electrode, the formation of a species (named also electron carrier) able to exchange homogeneously electron(s) with a less electroactive organic derivative (Scheme 1). The homogeneous redox process is assumed to occur in high yield, and then the indirect electron exchange can happen either in solution or very close to the interface.

Polarographic "catalytic currents" are well known, especially in inorganic electrochemistry, with classic examples, such as the reoxidation of ferrous ions—formed cathodically from ferric ions—by hydrogen peroxide or hydroxylamine. However, it appears obvious that the term *catalysis* is used too often quite ambiguously. Therefore it use in organic electrochemistry needs to be clarified; a distinction should be made between the two main kinds of catalysis. This differentiation has been emphasized by Andrieux and Savéant [1,2].

The term *redox catalysis* is used when the redox couple P/Q (implying an electron carrier as mediator) merely plays the role of an electron carrier to substrate (X) mainly in homogeneous phase (without any formation of an adduct between the organic species and the catalyst). The electron exchange between the two soluble entities Q and X occurs only by means of a so-called outer sphere process (see Chapter 2). It is for example, the case for indirect reduction of aromatic halides by radical anions electrogenerated from a properly chosen mediator (for instance, an aromatic hydrocarbon or a ketone).



Scheme 1



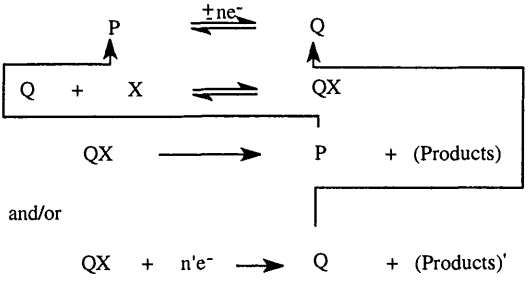
(1)

(2)

(3)

Scheme 2

The concept of *chemical catalysis* is applied when an electrochemical regeneration process is involved and proceeds through the formation of an adduct that decomposes before or after an additional electron transfer. The electron may be transferred either directly from the electrode or by indirect means in solution from a reducing (or oxidizing) species to regenerate one member of the catalyst couple P/Q. The indirect reduction of acidic protons in the presence of nitrogen aromatic heterocycles may provide a good example.



(1)

(4)

(5)

(6)

Scheme 3

Catalysis of the reaction brings in both cases the possibility of a decrease in the overvoltage for a given current density. Furthermore, for the redox-catyalyzed process, the change in the product distribution can be expected to be small, whereas in the case of chemical catalysis, the different possibilities for the formation and decomposition of the adduct (depending on the nature of the catalyst) may lead to a change in selectivity.

In this chapter, attention will be focused mainly on pure redox catalysis (Q is regenerated in high yields during the electrolysis) of organic compounds named X according to the process given in reactions (2) and (3) in Scheme 2. What are the conditions that make the observation of such catalytic currents possible? The only thermodynamic requirement is that the standard potential E°_{PQ} is lower (in case of a reduction) than the standard potential corresponding to E°_{XZ} taking into account the overall reaction $X \rightarrow Z$. Andrieux [1,2] have emphasized that the catalytic efficiency does not always depend on the difference $E^\circ_{PQ} - E^{1/2}_X$, since the half-wave potential of X is influenced by different factors, such as the rate of the heterogeneous electron transfer to X ($X \rightarrow Y$ at a given electrode) and/or the rate of the subsequent chemcial reactions ($Y \rightarrow Z$). Consequently, it has been proposed that a catalysis occurs (for a reduction) when one of the following sequencies is fulfilled:

$$E^\circ_{XZ} > E^\circ_{XY} > E^\circ_{PQ} > E^{1/2}_X \tag{7}$$

$$E^\circ_{XZ} > E^\circ_{PQ} > E^{1/2}_X > E^\circ_{XY} \tag{8}$$

With respect to redox catalyst, it appears that the situation is more favorable, from a kinetic point of view, in case (7) rather than in case (8). Case (7) favors indeed a displacement of equilibrium (2) to the right-hand side; the sequence corresponds to an indirect reduction of small molecules or ions in which the electron transfer involves a large change in solvation or structure. This is also the case of very bulky biological molecules in which the electroactive group for steric reasons is hindered from undergoing electron transfer at the electrode. On the other hand, large conjugated molecules, in which the change of solvation with the electron transfer is negligible, are more likely to be reduced according to case (8). Here equilibrium (2) remains displaced to the left-hand side when the solution electron transfer (SET) is not associated with a chemical reaction, which in certain cases is the rate-determining step. In other words, it may be expected, for a given difference $E^\circ_{PQ} - E^{1/2}_X$, that redox catalysis is more efficient in case (7). These considerations may explain why most of the observed cases of redox catalysis involve small inorganic molecules. Moreover, the use of redox catalysis theory allows one first to obtain thermodynamic values, such as the standard potential of very unstable transient (as for aromatic bromides, chlorides, and fluorides [3]), and second to determine the lifetimes of radical ions down to the nanosecond time range (Chapter 2) [4].

In practice, many macroelectrolyses reactions do not follow the general scheme [reactions (1), (2), and (3)] at a reasonable current density due to side reactions. At the working electrode, a modification of the surface may be observed that may change the nature and the overvoltage of the basic electrochemical reaction. This is, for example, the case when the mediator is an inorganic ion, leading during the electrolysis to either deposition or etching of the surface. Furthermore, the common use of mercury cathodes sometimes causes the unintentional formation of amalgams, which also may play the role of reducing reagents at the interface. Other kinds of electrogenerated reagents (not necessarily electron carriers) may be formed, and the careful interpretation of the product distribution after workup may be difficult.

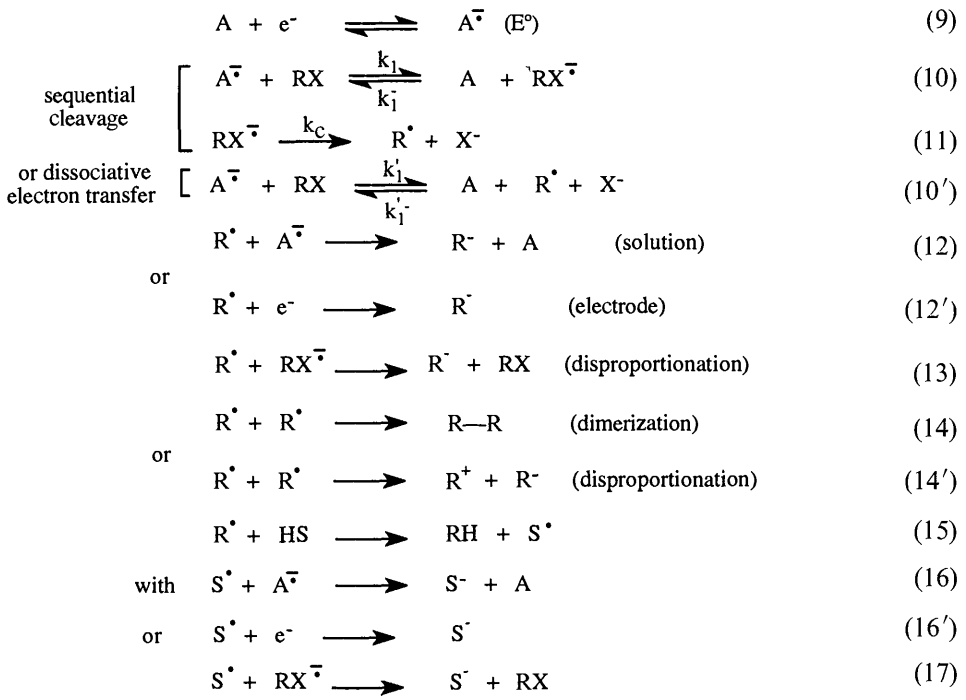
However, in some cases, heterogeneous electron transfers are very much slowed down (occurrence of a self-inhibition at the interface). Since $E^\circ_{Med} < E^\circ_{Substrate}$, the homogeneous electron transfer may take place rapidly, even with very small amounts of mediator (example: indirect reduction of disulfides [5]).

In the following, examples of indirect electrochemical reactions (mainly redox catalysis) with an organic mediator are given.

B. Pure Redox Catalysis: General Case

Due to regeneration of the organic depolarizer by means of an electron exchange with another species in solution, enhancement of polarographic currents has been investigated in detail only in the last three decades. One of the first examples of this type of organic catalysis was reported by Fry [6] and was concerned with the indirect reduction of *n*-butyl chloride by the electrogenerated radical anion of naphthalene in a nonaqueous solution. Since that time, a quite large number [7–24] of papers have given further information on the homogeneous electron transfer, with, in certain cases, a useful theoretical analysis of the problem [1,2] for EC and ECE catalytic processes.

The most classic case of redox catalysis undoubtly the indirect cleavage of carbon–halogen bond according to the process described in Eqs. (9) through (17) (Scheme 4, A, Taken as an acceptor, is the organic catalyst, RX is the species–with an appropriate Π* antibonding orbital level–able to cleave after a single electron transfer, and SH is the solvent):



Scheme 4

Reactions (9) through (12) of this mechanism, which present the main reaction pathway concerning RX, correspond to the global two-electron conversion of RX into R^-. The mediator A is assumed here not to be consumed (therefore no fast reaction of $A^{\cdot-}$ with some intermediates is considered in the shcme). The case of the perturbed redox catalysis (progressive consumption of the catalyst) will be presented later on. Consequently, the mediator A is totally regenerated (high turnover) during the electrolysis. For example, such a case appears to be [13] the indirect reduction of benzyl

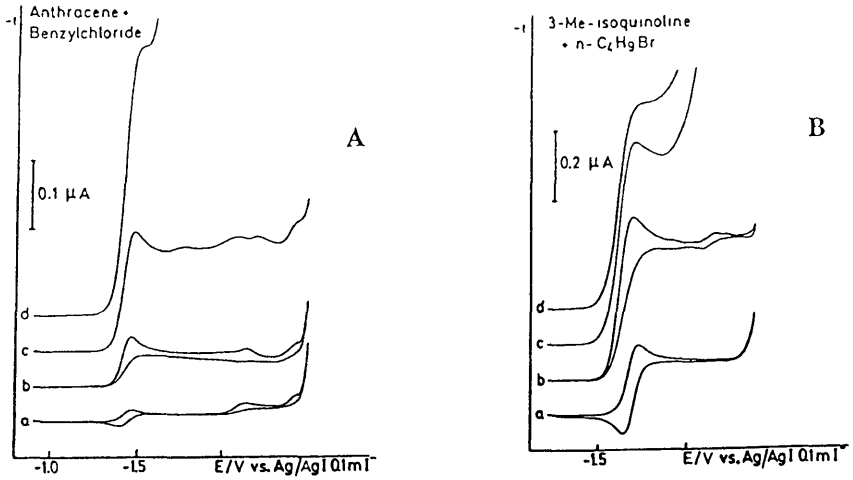


Figure 1. (A) Cyclic voltammograms of anthracene (3.4×10^{-4} M) in DMF 0.1 *M* TBAI in the presence of different concentrations of benzyl chloride. (a) 0 *M*; (b) 7.3×10^{-4} *M*; (c) $3.7z \times 10^{-3}$ *M*; (d) 1.85×10^{-2} *M* benzyl chloride. Sweep rate 10 mV s^{-1}. Note that benzyl chloride gives rise to a dissociative electron transfer [25]. (B) Cyclic voltammograms of 3-methyliso-quinoline (5.8×10^{-3} M) in DMF/0.1 M TBAI in the presence of different concentrations of butyl bromide. (a) 0 M; (b) 5×10^{-3} *M*; (c) 3.2×10^{-2} *M*; (d) 6.4×10^{-2} *M* butyl bromide. Sweep rate 10 mV s^{-1}. From Ref. [13].

chloride by antrhacene radical anion by means of a dissociative electron transfer (Fig. 1A). In this case, a continuous increase in the cathodic current is observed, at least for moderate ratios of [RX] to [A]

When the rate of the chemical reaction (11) following the solution electron transfer is high, it can be considered as the driving force of the overall process. The rate of the catalysis is therefore determined by the electron exchange reaction; k_1 depends on the potential difference ΔE° between the standard potentials of the two redox couples $A/A^{\cdot-}$ and $RX/RX^{\cdot-}$ (see Chapter 2). In the case where a homogeneous dissociative electron transfer occurs (reaction 10′), one should consider the redox couple $RX/R^{\cdot} + X^-$. However, the standard potentials relative to reactions (10) or (10′) are known to be very difficult to ascertain by conventional electrochemical methods, and it is easier to analyze the catalytic efficiency as a function of the half-wave potential (or half-peak potential for a given scan rate) difference ΔE. However it is worth noting that $E_{1/2(RX)}$ determined for an overall two-electron cleavage is in general somewhat less cathodic than the standard potential corresponding to the first charge transfer. Figure 2 shows the variation of $\log k_1$ with $\Delta E_{1/2}$ and ΔE° illustrating the indirect reduction of chlorobenzene, considered as RX type of species in which R is of low reactivity toward A and/or its reduced forms. The reducing species correspond to radical anions of several aromatic hydrocarbons and heterocycles. In Fig. 2A, k_1 was calculated [7] using polarographic limiting currents by the Koutecky method [26], and in Fig. 2B, k_1 is determined by a more careful and widely usable approach in voltammetry, taking into account the results of the Hush–Marcus theory of outer sphere homogeneous and heterogeneous electron transfers [1,2,20, and references cited therein].

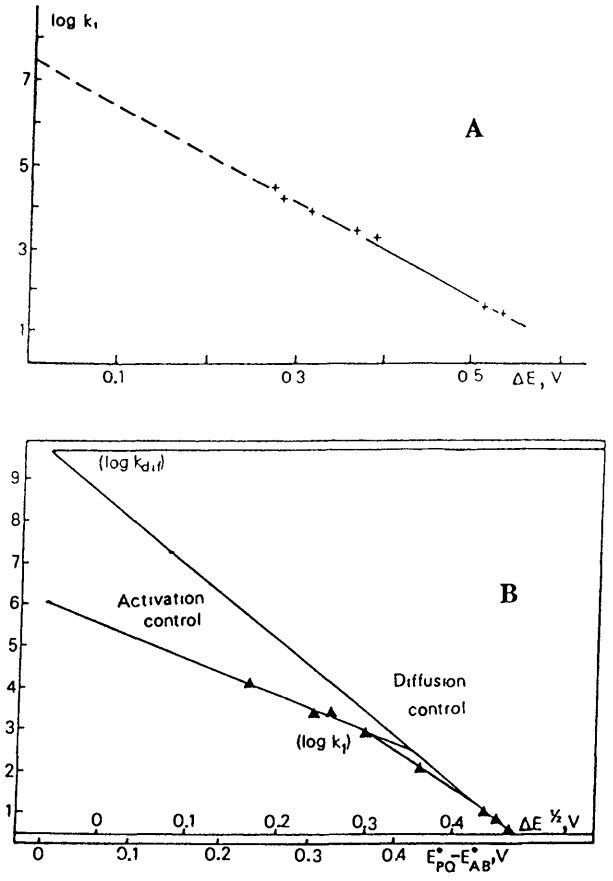


Figure 2. (A) Dependence on ΔE of the logarithm of the rate constants of reoxidation of the following radical anions (with increasing ΔE): biphenyl, 1-methylnaphthalene, naphthalene, 2-methylphenanthrene, phenanthrene, *p*-etrphenyl, and benzonitrile in the presence of chlorobenzene. From Ref. [7]. (B) Rate constants of the homogeneous electron exchange between chlorobenzene and redox catalysis as functions of the half-wave potential difference and of the standard potential difference (at room temperature k_{dif} in the considered solvent =). With increasing ΔE: biphenyl, naphthalene, dibenzothiophene, phenanthrene, *p*-toluonitrile, *m*-toluonitrile, *p*-terphenyl, and benzonitrile. From Refs 1 and 2.

From Fig. 2B, it appears experimentally that variation k_1–$\Delta E^{1/2}$ is more complex than expected. A nonlinear increase of k_1 with decreasing $\Delta E^{1/2}$ can be explained [27] by taking into account reactions (10) and (11) of Scheme 4.

$$\frac{d[A]}{dt} = -\frac{d[A^-]}{dt} = -\frac{d[RX]}{dt} = k_1 k_c \frac{[RX][A^-]}{k_1^-[A] + k_c}$$

The kinetic control by the forward homogeneous electron transfer (reaction 10)

$$\frac{d[A]}{dt} = -\frac{d[A^-]}{dt} = -\frac{d[RX]}{dt} = k_1[RX][A^-]$$

is achieved when $k_1^-[A]_0 \ll k_C$. On the contrary, if $k_1^-[A]_0 \gg k_C$, the chemical step (a cleavage in the case of chlorobenzene) becomes the rate-determining step:

$$\frac{d[A]}{dt} = -\frac{d[A^-]}{dt} = -\frac{d[RX]}{dt} = \frac{k_1 k_c[RX][A^-]}{k_1^-[A]}$$

Since k_1^- is often equal to the diffusion limit, calculations of k_1 and k_c may be obtained. Kinetic competition between the solution electron transfer and the following chemical step is possible in certain cases when acting—for example—on the relative ratios concentrations of [A] and [RX]. Convenient working curves [28] allow the calculation of k_1 (and that of k_c in some cases). In most of the examples showed in literature, the counterreaction (10) is diffusion controlled and the variation of k_1 upon ΔE° can be schematically represented by Fig. 3. The knowledge of k_D at a given temperature and in a given solvent (close to $10^{10}\, M^{-1}\, s^{-1}$) makes possible, by a careful extrapolation, the estimation of $E^\circ_{RX/RX^{\cdot-}}$. Thus, with chlorobenzene, the standard potential E° is shifted +66 mV compared with the polarographic half-wave potential. Other E° values for several compounds able to exhibit fast following up reaction after charge transfer can be determined by this method. Additionally, dissociative electron transfer may occur [reaction (10′)]. In such a case, the driving force of the reaction becomes [29]:

$$\Delta^\circ_G - E^\circ_A - E^\circ_{RX/R^{\cdot} + X^-}$$

Standard potentials of different alkyl halides and that of benzyl chloride were given. For example the standard potential of the latter was found [29] to be $E^\circ_{BzCl/Br^{\cdot} + Cl^-} = -0.87$ V vs SCE.

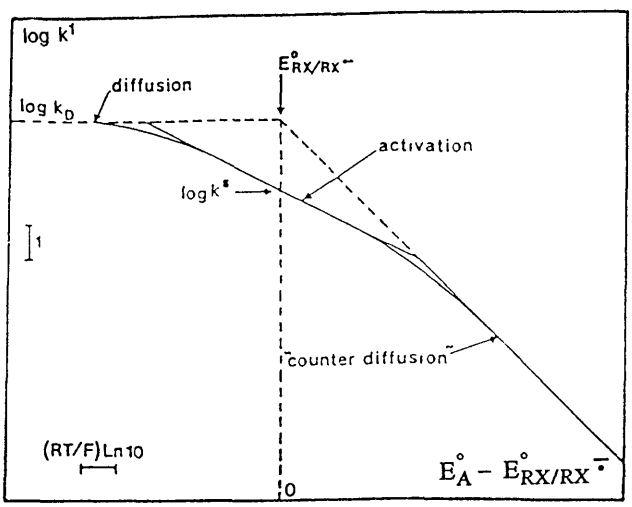


Figure 3. Schematic representation of the variation of k^1 upon ΔE° and potential applications in the determination of $E^\circ_{RX/RX^{\cdot-}}$ (k^s represents the standard rate for $\Delta E^\circ = 0$) [27]. Reproduced by permission of American Chemical Society.

III. USE OF INDIRECT ELECTROCHEMICAL REACTIONS IN SYNTHESIS

A. Reductions

1. Organic Electron Carriers

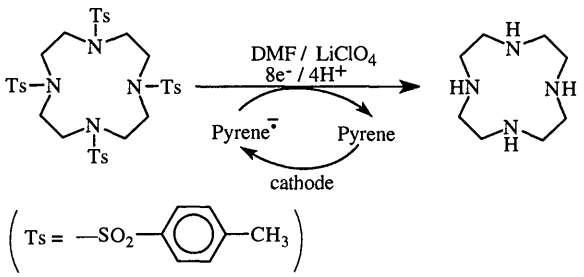
Indirect reductions have been performed with organic compounds for which the radical anion is able to cleave rapidly (aromatic halides, sulfones, ethers, sulfonamides, etc.) or for which a dissociative (here homogeneous) electron transfer may occur (like aliphatic halides, sulfonium and ammonium cations). The main interest of indirect electrolysis lies in a fine control of potential, since the reduced form of the mediator (often the radical anion) possesses a well-defined potential value (the radical anion can be also named the *molecular size electrode* for its very tiny volume). Additionally, an important use of such indirect electrolyses is that it allows reaction beyond the cathodic limit (avoiding reduction of the solvent, the electrolyte as well as the corrosion of the electrode material). Thus, it is possible to reduce substances whose reduction potential is more negative than that of the electrolyte. In this respect, indirect reduction of aromatic halides (of which standard potentials were given, like chlorobenzene $E^\circ_{CB} = -2.78$ V, bromobenzene $E^\circ_{BB} = -2.44$ V and 2-chloropyridine $E^\circ_{CP} = -2.40$ V) could be achieved in benzonitrile $E^\circ_{BN} = -2.44$ V) vs SCE) as a solvent [30]. The occurrence of the electron transfer could be then followed by the appearance of a prepeak to the solvent wall. The choice of the right mediator can be guided by the knowledge potentials E°_A as exhibited in Table 1.

If a mercury cathode is expected to be necessary, the aprotic solvent–alkali–metal salt system appears to be inconvenient since many compounds are cathodically cleaved, reduced, or/and deprotected at potentials beyond that of alkali-metal amalgam formation. nevertheless, in certain cases the use of lithium salts as an electrolyte possessing strong electrophilic properties appears necessary in order to avoid the possibility of a Hofmann degradation of the tetraalkylammonium ion by electrogenerated bases. Under such experimental conditions, the cathodic synthesis of some aza and aza-oxa ligands [31] has been successfully achieved from the corresponding and readily obtained poly-

Table 1 Examples of Mediators Currently Used in Redox Catalysis Experiments With Their Redox Potentials Established in DMF Containing 0.1 *M* $TBABF_4$, with Redox Potentials Referred to the Aqueous SCE

Mediator	E°_A (V)	Mediator	E°_A (V)
Acridine	−1.131	3-Methoxypyrene	−2.081
Chloroazobenzene	−1.183	Isoquinoline	−2.131
Azobenzene	−1.279	Phenyl benzoate	−2.140
2,4-Dimethoxyazobenzene	−1.416	Methyl benzoate	−2.183
Acenaphthylene	−1.590	Benzonitrile	−2.230
Perylene	−1.613	*o*-Tolunitrile	−2.277
Fluoranthene	−1.688	*p*-Tolunitrile	−2.337
Benzophenone	−1.707	Phenanthrene	−2.388
Antraquinone	−1.730	Naphthalene	−2.457
9,10-Diphenylanthracene	−1.794	Biphenyl	−2.519
Anthracene	−1.890	1-Methoxynaphthalene	−2.537
1,2-Benzanthracene	−1.922	1-Vinylnaphthalene	−2.72
Pyrene	−2.018	*N*-Phenylcarbazole	−2.77

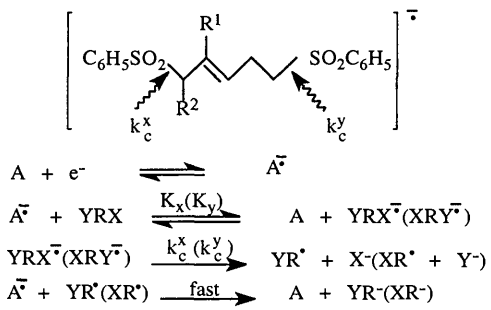
sulfonamides (Scheme 5). Thus pyrene, stilbene, and anthracene were shown to be convenient mediators. Kinetic parameters concerning such indirect cleavage of sulfonamides are also available [32].



Scheme 5

Arylsulfonyl groups, required to render the α-carbon atom more nucleophilic, can be easily removed by means of indirect reductions [33]. The increase in selectivity compared with that observed with a working electrode of large area and rather large current density can be obtained with well-chosen mediators. Thus, in Scheme 6 [21], reduction of dilsulfone denoted YRX (and X and Y are the two sulfonyl moieties differently activated) was investigated; with such structures, the difference in peak potentials corresponding to the electrochemical cleavage of C–X and C–Y bonds is rather small (around 0.15 V).

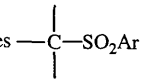
Therefore, under conventional electrochemical conditions, a very selective cleavage of the C–X bond (reduction of the sulfonyl allylic group) was difficult to achieve. On the contrary, when an *indirect* reduction was performed (A: antrhacene), the best selectivity was obtained when $K_x k_c^x$ has a reasonable magnitude whereas $K_y k_c^y$ should be nearly negligible. Thus, when the disulfone radical anion is formed via homogeneous transfer, the C–Y bond is cleaved first and then the fairly stable blue solution of $A^{\cdot-}$ appears at $2e^-$ per mole. Such an experiment demonstrates that the second cleavage reaction is much slower. This is in agreement with other experimental data taking into account saturated aromatic sulfones alone. However, it is worth pointing out that sulfones in strongly aprotic media may be sufficiently acidic to afford protonation of the radical anion of the mediator [34].



Scheme 6

Thus indirect reductions were successfully achieved when the chemical reaction that follows the charge transfer is fast and irreversible (Table 2). Redox catalysis was first

Table 2 Examples of Indirect Conversions by Means of Organic Mediators — Reductive Redox Catalysis

Type of Substrate	Mediator A used	Nature of the driving force of the catalysis (interest in synthesis)	References
Aromatic halides ArX and strongly activated RX	Benzonitrile or anthracene (depending on X)	Fast cleavage of the C-X bond (the indirect formation of $Ar^{\bullet}$ is useful in some $S_{RN}1$ reactions)	[3, 4, 13, 103]
Activated olefins	Anthracene	Fast coupling of radical anion or enone or unsaturated nitrile (indirect dimerizations)	[13]
Aromatic sulfones 	Anthracene, pyrene	Cleavage of C—S bond (hydrocarbon deprotection)	[21]
Aromatic sulfonamides	Pyrene	Cleavage of N—S bond (deprotection of amines: synthesis of polyamines as macro ligands)	[31]
$R^1R^2NSO_2Ar$ and $R^1N(SO_2Ar)_2$	Deposited polythiophenes	Chemical synthesis at solid interfaces with convenient and selective regeneration of amines	[36]
Bianthrone	Quinone	Fast rotation of the radical anion into the thermodynamically more stable form	[37, 38]
Small rings (epoxides, cyclopropanes)	Biphenyl	Fast opening of the anion radical	[39, 45]
onium cations of moderate acidity	Naphthalene	Fast cleavage of C—N and C—S bonds	[220]
Activated fluoromethylarenes $ArCH_2F$ and $ArCF_3$	Benzonitrile bipyridine	Easy breaking of C—F bonds	[40]
$\overset{+}{N}R_4X^-$ or $\overset{+}{S}R_3X^-$	Acenaphthylene	Convenient formation of $R^{\bullet}$ radicals in solution	[220]
α,α'-Dihalide derivatives	Aromatic hydrocarbons chosen as a function of more easily cleaved C—X bond	Cathodic elimination in solution	[16, 22]
Polyenes (dienes and trienes)	Naphthalene, anthracene	Fast protonation of basic radical anions by residual acidic impurities	[195]
Vic-dihalides and perfluoroalkyl halides	C_{60}	Fast cleavage of C—X bond(s)	[41]

evidenced in the case of carbon–halogen bond scission, but many other cathodic cleavage reactions are also candidates to permit a redox catalytic process to be feasible. let us say that bond breaking may occur with aromatic sulfides, sulfones, activated ethers, and alcohols. Openings of strained rings like cyclopropenes and epoxides were shown to occur under electron transfer when the corresponding LUMO level was adequate. Fast couplings of activated olefin radical anions may favor indirect reduction of these species. In such cases, the redox catalysis process is based on a global consumption of one electron per molecule of substrate. Other cases of one-electron redox catalysis processes are available in the literature, like the indirect reduction of triorganohalogermanes as well as triorganohalosilanes conducted in strictly dried solvents (tetrahydrofuran or dimethoxyethane). The homogeneous reduction mechanism (Scheme 7) has been written on the basis of sequential cleavage process [35].

$$A^{\bullet} + e^{-} \rightleftharpoons A^{\bullet -}$$

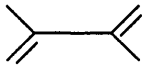
$$R_3GeX + A^{\bullet -} \underset{k_e^-}{\overset{k_e}{\rightleftharpoons}} R_3GeX^{\bullet -} + A$$

$$R_3GeX^{\bullet -} \xrightarrow{k_c} R_3Ge^{\bullet} + X^{-}$$

$$2R_3Ge^{\bullet} \xrightarrow{k_{dim}} R_3GeGeR_3$$

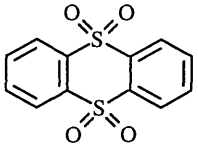
Scheme 7

Indirect reductions are also permitted because species (radical anions and/or dianions) formed after homogeneous electron transfer are so basic that they are rapidly protonated by solvent or any acidic impurities. Thus, dienes and trienes like allocimene and dimethyl 2,3-butadiene may afford a redox catalysis processes [42] in dimethylformamide (DMF) in the presence of naphthalene as a mediator.



Mostly, electron carriers used in reduction processes are ardical anions of commercially available acceptors like nitroaromatic compounds, polyaromatic rings, aromatic heterocycles, and ketones (dinitrobenzene, benzophenones, acridine, fluorenone, diphenyl anthracene, anthracene, phenanthrene, naphthalene, and so on). Table 1 exhibits some possible mediators within a large cathodic potential range.

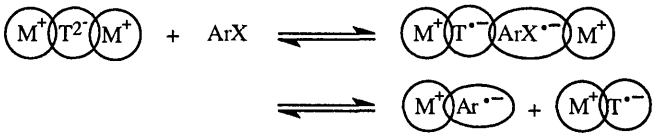
However, electron exchange is too slow from the radical anion, it can take place at the stage of the acceptor dianion, provided that the second step presents a character of quasi-reversibility. Thus, redox catalysis processes were found to occur at the level of the second step of anthraquinone (indirect reduction of alkylhalide) [14], 1,4-diacetylbenzene (indirect reduction of some aromatic



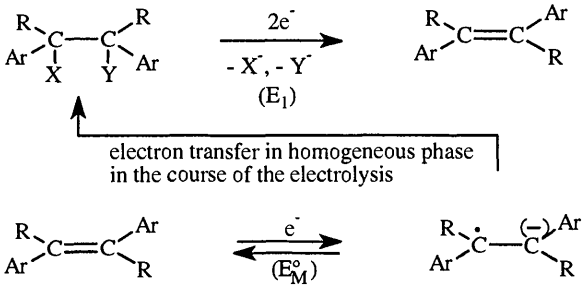
$E^{\circ}_1 =$ - 1.44 V

$E^{\circ}_2 =$ - 1.99 V (vs S.C.E.)

When in the presence of some heavy aryl chlorides. Especially in the latter case, the electron exchange between the disulfone dianion and ArX was found to be slower by at least one order of magnitude compared with data obtained with other acceptor radical anions. To explain the fundamental difference that arises when the nature of the reducing species is changed, the formation of strong and bulky ion pairs between the dianion T^{2-} and electrolyte cations MX was postulated. Such an ion pair should obviously present a much higher solvent reorganization in the course of the electron transfer and then retard the charge transfers [35] by increasing the energy of activation $\Delta G^{\neq}$ defined by the Marcus equation



Electrochemical reactions with other electrogenerated reducing reagents like radical dianions and anions were also investigated. In the latter case, the producted anion may reduce the starting halide (as in the reduction of strongly stabilized fluorenyl chlorides) and then trigger [43,44] some *snowball* process since the concentration of the electron carrier is continuously increased all along the duration of the electrolysis. Other types of "autocatalyzed" cathodic reactions have also been provided in which the first two-electron reaction (mainly a cleavage) is followed by a rapid elimination process leading to an unsaturated compound *more easily* reduced than the substrate itself. This was observed when α, α'-disbustituted 1,2-diarylethanes [22] or analogous epoxides [45] were reduced in nonaqueous media.



Scheme 8

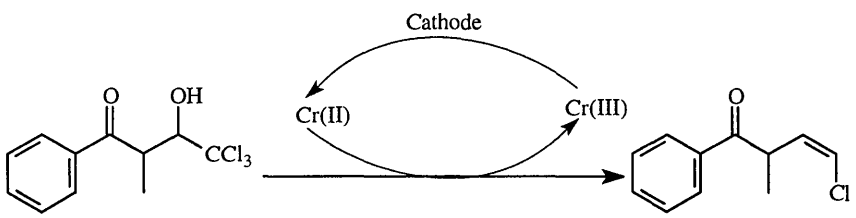
Such autocatalyzed redox reactions (effective when $E^{\circ}_{M} > E_1$) can, in the case of a rather fast SET, be followed by means of voltammetric techniques [abnormally large variation of $(d_p)/(d \log v)$; where v is the sweep rate] and chronopotentiometry ("unexpected" maximum in E–t curves)]. It thus appears that a careful stereochemical study of an elimination process (possibly influenced by the physical and/or chemical nature of the interface) must take into account a possible concomitant occurence of a homogeneous reaction. Knowledge of the redox potential of the produced olefin may provide valuable infomation on its implications in a possible homogeneous process.

2. Inorganic Salts as Mediators

On the other hand, inorganic redox mediators also appear to be useful for achieving indirect reductions of organic substrates (Table 3). Thus, electrogenerated, low-valence metal cations can be employed in both aqueous and aprotic dipolar solvents. In this latter category, great changes occur in the solvation of nascent low-valence (or even zero-valence) metal ions, which might give them a peculiar reactivity currently not found in organic chemistry. The use of environmentally undesirable transition metal ions in catalytic amounts with a continuous regeneration in situ is obviously of interest.

Thus, data concerning the use of salts produced directly at the cathode as reducing species are available. Many are well established; for example, the indirect reduction of nitrobenzene [59] in the presence of stannous ions appears to slow down the reduction of the intermediate hydroxylamine and therefore favor its rearrangement into *p*-aminophenol. There are also some advantages in conducting the Fenton reaction (hydroxylation of aromatic rings with reduced forms of oxygen) by indirect means in the presence of either copper salts [57,58] or iron salts [46]. The use of a double-mediator system [$Cu^{I}/Fe^{(III)}$] makes the reaction more effective. Similarly, the mixed reduction of hydroxylamine by $Ti^{(III)}$ can lead to a valuable source of aminyl radical, which can be trapped [47,48,61] in situ by alkenes and aromatic derivatives. For example, the mixed electrolyses of 1,3-butadiene and hydroxylamine in the presence of titanium salts afford diaminodimers, such as diaminooctadienes.

Electrogenerated $Cr^{(II)}$ exhibits special reducing properties. In situ electrogenerated $Cr^{(II)}$ ions [$Cr^{(III)}/Cr^{(II)}$ couple: $E^{\circ} = -0.41$ V vs. NHE] have been widely used for various kinds of reactions. Thus acetylene (totally electroinactive under usual conditions) may be reduced to ethylene in acidic media [63]. Similar reactions are found from nonactivated acetylenic derivatives using an ex-cell system [117]. Stekchan [68–71,99] has developed several indirect cleavage reactions, essentially of C–Cl and C–Br bonds, with simultaneous dimerization. For example, reported were the reductive coupling of allylic bromides into their corresponding dienes and also the interesting reductive rearrangements of trichloromethyl-substituted secondary alcohols or ethers leading to one step to vinyl chlorides of *Z* configuration (Scheme 9).



Scheme 9

In the case of geminal dibromocyclopropanes, the indirect reduction by cathodically generated $Cr^{(II)}$ in anhydrous DMF affords the corresponding allenes. Such a process was assumed to involve an inner sphere electron transfer mechanism [71].

Furthermore, the addition of chromium salts to electrolysis solutions may give unexpected results. Thus, as first demonstrated by Martinet [64], pinacolization reactions may be carried out successfully by reducing activated carbonyl compounds in DMF in the presence of $Cr^{(III)}$. Since this pioneer and intriguing work, several papers [65,72,73] have considerably enlarged the potential of that coupling methodology and clarified the specific

Table 3 Some Indirect Reduction or Oxidation Reactions of Organic Substrates via Electrogenerated Inorganic Mediators

Heterogeneous Electrochemical Reaction		Redox potential[a] (V)	Examples of indirect electrochemical reactions —> products (working electrode material)	References
$Ce^{4+} + e^-$ ⇌	Ce^{3+}	1.44	Oxidation of substituted methylbenzenes —> corresponding monoaldehyde and carboxylic acid[b]	[49, 104, 108]
			Electrochemical synthesis of saccharin from o-toluene sulfamide	[109]
$Mn^{3+} + e^-$ ⇌	Mn^{2+}	1.51	Oxidation of tetralin —> α-tetralone	
$Tl^{3+} + 2e^-$ ⇌	Tl^{+}	1.25	Mild oxidation of propylene —> acetone	[50, 51]
$Pd^{2+} + 2e^-$ ⇌	Pd^{0}	0.83	Oxidation of olefins[b] —> carbonyl compounds and degradation	[50, 52]
$OsO_4 + 8H^+ + 8e^-$ ⇌	$Os + 4H_2O$	0.85	Oxidation of acetylene —> oxalic acid Oxidation of olefins —> 1,2-glycols	[50, 52] [50, 53]
$2AgO + H_2O + 2e^-$ ⇌	$Ag_2O + 2OH^-$	0.60[c]	Oxidation of aliphatic amines —> nitriles	[50, 54]
$2Hg^{2+} + 2e^-$ ⇌	Hg_2^{2+}	0.90	Oxidation of propylene —> acrolein	[55]
$Cu^{2+} + e^-$ ⇌	Cu^{+}	0.16	Hydroxylation of aromatic rings in the presence of oxygen Oxidation of alkenyl stannates —> copper mediated homocoupling [56]	[57, 58]
$Sn^{4+} + 2e^-$ ⇌	Sn^{2+}	0.15	Reduction of nitrobenzene —> aminophenol	[59]
$Ti^{3+} + e^-$ ⇌	Ti^{2+}	- 2.0	Electrochemical formation of Ti2+ allowing the reduction of hydroxylamines, sulfoxides, nitroso [60]	[61, 62]
$Cr^{3+} + e^-$ ⇌	Cr^{2+}	- 0.41	Reduction of acetylene —> ethylene	[63]
			Reduction of aromatic and polyethylenic ketones —> pinacols	[64, 65]
			Cleavage of carbon-halogen bonds	[66]
[Fe^{3+}, TEA] complex ⇌	[Fe^{2+}, TEA]	- 1.05[b]	Reduction of indigo dyestriff to its alkaline soluble leuco-form	[67]

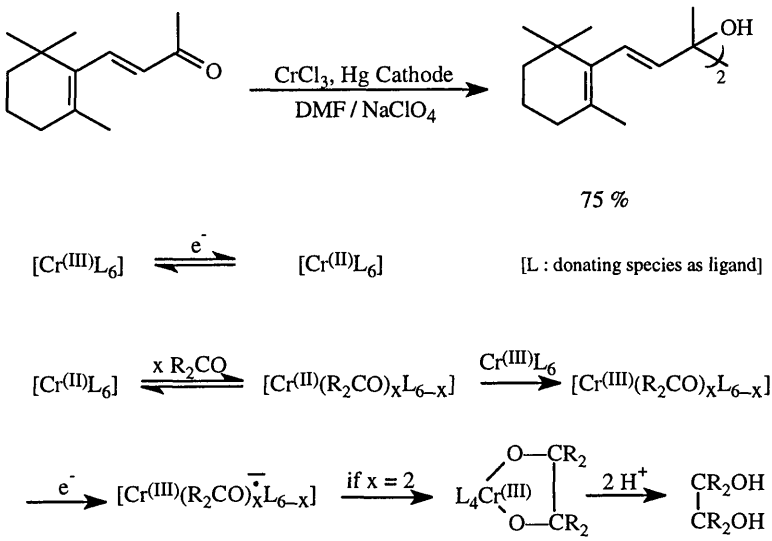
[a] Referred to NHE/[b] Referred to AG/AgCl, KCk 3M.

[b] Prefarably according to a two-stage process.

[c] In this case, the electron transfer takes place at the anode interface, probably through an electrocatalytic mechanism.

[d] Also using cobaltic, manganic ions, or insoluble oxides, such as lead or manganese dioxides.

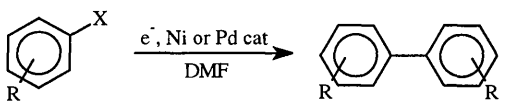
action of the redox couple $Cr^{(III)}/Cr^{(II)}$; the components may be solvated by a dipolar solvent, residual water, and of course by the carbonyl compound itself. A quite convincing explanation of the role of those metallic cations and their efficiency in the reduction–dimerization overall process has more recently been suggested by Utley [74]. Thus, chromium(II) would not act as a redox agent but would catalyze the formation of a chromium(III) complex in which the carbonyl compound is involved; $Cr^{(III)}$ may then be considered as an acidic species, making the reduction of the carbonyl group easier, which moreover favors the pinacol formation (Scheme 10).



Scheme 10

An important point is that the electrochemical method may also produce "zero" metals from transition metal cations: these metals can be used either as reducing species or as catalysts. Thus cathodically generated $Zn^{(0)}$, $Cu^{(0)}$, $Fe^{(0)}$, and $Sn^{(0)}$ are of particular interest [75,76] in indirect reductive dehalogenation or reduction of nitrogroups in two-phase system using high density current. The use of cathodically generated $Ni^{(0)}$ and $Pd^{(0)}$ in the presence of adequate ligands, mostly 2,2′-dipyridines (pby, see Chapter 21), in polar solvents is of great use in new coupling reactions involving aromatic rings (homocoupling of aryl moieties from the corresponding halide [77–79] or cross-couplings leading to differently substituted bisaryls [80]). The coupling reaction mechanism for ArX compounds was established in the presence of electrogenerated $Ni^{(0)}$ catalyst [81].

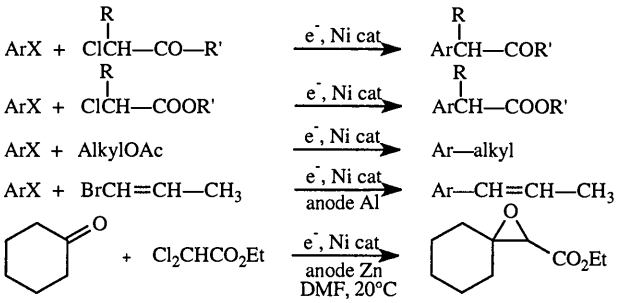
In an aromatic series, the interest of the use of $Ni^{(0)}$ and $Pd^{(0)}$ catalysts can be illustrated by the examples of homocoupling given next [82–84], but interesting cross-coupling reactions (in the presence of excess of electrophiles) were reported [85–87].



50 - 98 %

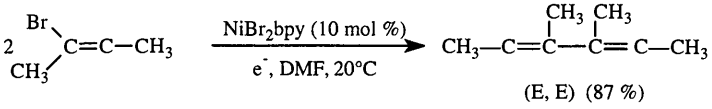
With X = I, Br, Cl, CF_3SO_2
R = alkyl, aryl, MeO, CN, CF_3, Cl, NMe_2, MeCO

Scheme 11



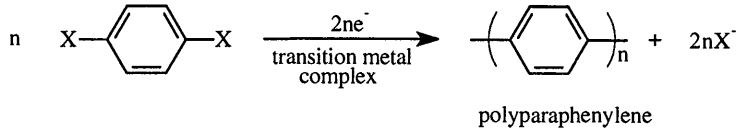
Scheme 12

The homocoupling of alkenylhalides was also reported, which demonstrated the interest of the $Ni^{(0)}$ catalyst method in the formation of substituted 1,3-butadienes from vinylic halides [88].



Scheme 13

The process of homocoupling of aromatic halides by means of $Ni^{(0)}$ and $Pd^{(0)}$ was used successfully in the oligomerization or/and polymerization of 1,4-dichlorobenzene [89], 4,4′-dibromobiphenyl [90], and many other dihalides derived from furanes or pyridines [91]. Similarly, 1,3-bis(chloromethyl) benzene led by this manner to poly-*p*-xylene [92] through a novel pathway.

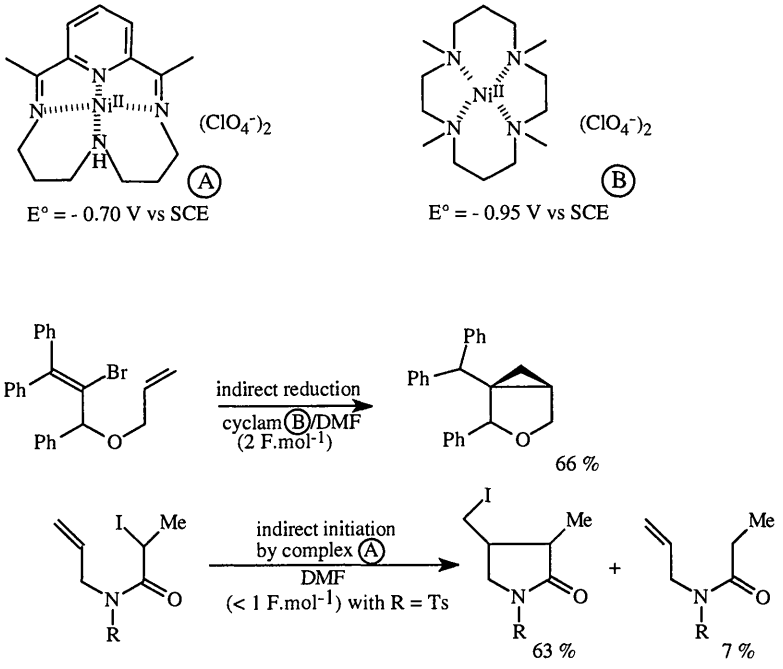


Scheme 14

For example, titanocene dichloride affords the two-electron reduction of activated ketones into alcohols [93].

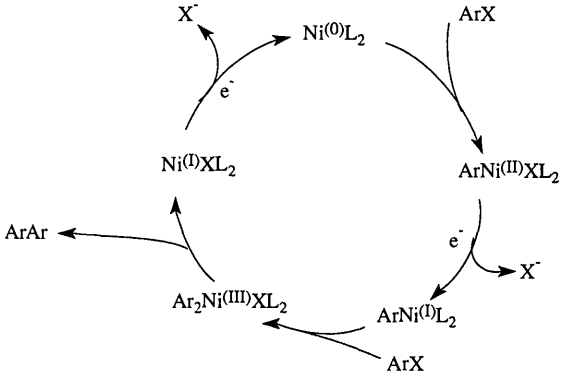
Several systems acting by inner sphere electron transfer may dramatically change the selectivity or/and the regioselectivity of the chemical reaction. They can be also a source of free radicals, which may trigger—or not—radical chains according to the experimental conditions (essentially the nature of the solvent). It is particularly the case for $Ni^{(II)}$ complexes, which allow [94,95] spectacular cyclization reactions implying vinyl, acetylenic, and aryl halides and where the redox potential necessary to trigger the cleavage of the C–X bond can be modulated as a function of the nature of polydendate ligands; there are two examples of complexes of this kind and their redox potentials, which exhibit cyclopropo-

nation by tandem radical [2 + 1]-cycloaddition on one hand and a radical chain cyclization on the other hand.



Scheme 15

On the other hand, an excess of another electrophile in solution may modify the chemical route, via the electrochemical activation of $ArNiXL_2$ complex. Thus, addition of carbon dioxide affords [96,97] the carboxylation of the aromatic nucleus. The similar preparation of pharmaceutically important 2-arylpropionic acids has been reported [98] to proceed in good yields from 1-arylethylhalides.

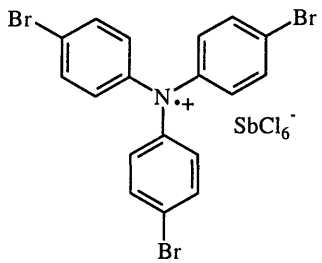


Scheme 16

B. Oxidations

Within oxidation range, a wide variety of mediators (organic and inorganic) can be proposed. Tables 3 and 4 particularly exhibit large possibilities for indirect oxidation of aromatic hydrocarbons by electrogenerated hypervalent cations (mainly by in-cell processes). However, when oxidation potentials of metallic cations are higher than that of organic substrates, it appears more convenient to consider ex-cell process. Note that a separation phase is always necessary to pull apart oxidation products from inorganic reagent, which can be recycled. Two-phase systems at this stage could be very useful.

1. Electrogenerated Oxidizing Organic Species



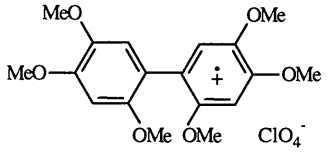
Tris(4-bromophenyl)ammoniumyl hexachloro antimonate is commercially available (e.g., Fluka product, 5 g cost: $70). It is commonly used as an oxidizing reagent by means of electron transfer and is elegantly applied to induce cycloadditions and cyclodimerization ([2 + 2] reactions) by Bauld [115]. However, aromatic amine radical cations as the oxidizing reagent can be easily obtained anodically [116] and their redox potentials (between +1 V and +2 V vs. NHE) modulated as a function of different substituents for utilization if *indirect* oxidation reactions are to be conducted. Therefore, such a redox catalysis process appears to be a cheap and elegant method to selectively achieved in situ oxidation, provided that polar solvents, electrolytes, and room temperatures are acceptable experimental conditions to perform a given reaction.

Thus, deprotection of benzylic ethers, oxidation of activated thioethers [117], and deprotection of gem-dithioacetals [117,118] could be completed by means of such electrogenerated triarylamine radical cations. Even a homogeneous Kolbe reaction (indirect oxidation of carboxylate ions) was shown to be feasible [19] (Table 5).

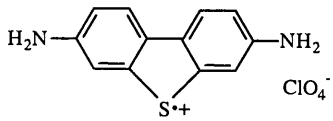
A few other organic oxidizing species directly formed at the anode interface could be good candidates for indirect oxidation (when considering that they are easy to obtain, as well as the stability of their radical cation). For example, paramagnetic salts [120] from polysubstituted diphenyl [120] or dibenzothiphenes [121] could be used for indirect oxidation (at the level of the first or the second reversible step):

Table 4 Some Examples of Indirect oxidative Conversions by Means of Electrogenerated Inorganic Mediators via In-Cell Processes

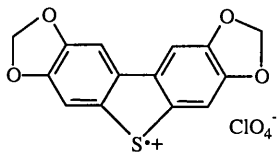
Type of organic substrate	Basic catalyst / electrolyte	Electrode material	Reaction	References
ArH	$Cr_2O_7^{2-}/H_2SO_4$	Pt	Anthracene —> Anthraquinone	[99-101]
	Mn^{3+}/H_2SO_4	PbO_2	Aniline —> Benzoquinone	[102]
$ArCH_3$	Mn^{3+}/H_2SO_4	PbO_2	Toluene —> Benzaldehyde	[103-105]
	$Ce^{4+}/HClO_4$	TiPt	Toluene —> Benzaldehyde	[106]
	$Pb°/Pb^{2+}$	Pb, Bi	"Barbier type" alkylation	[107]
	Ce^{4+}/CF_3COOH	Pt	Substituted Toluene —> Substituted Benzaldehyde	[104, 108]
	Chromic acid	PbO_2	Oxidation of p-nitrotoluene, Toluene, Xylenes —> ArCOOH	[109]
$ArCH_2R$	MnO_2/H_2SO_4	MnO_2	Tetralin —> α-Tetralone	[110]
$>NCH_3$	RuO_2/aq. NaCl + CCl_4 (double mediator system)	Pt or Ni (two phase process)	Amine —> Amide	[111, 112]
—C(—)—OH	Same	Same	Primary Alcohols —> Acids Secondary Alcohols —> Ketones	[111, 112]
H, H C EWG, EWG	Ce^{4+} salts $(NH_4)_2Ce(NO_3)_6$	Pt ganze	C—C formation in high yield	[113]
Phenyldiazomethanes	Cu^{2+}	Pt electrode	[$PhCHN_2$—> predominantly cis stilbene]	[114]



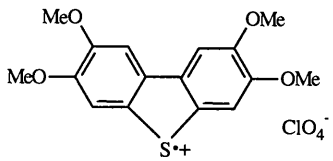
E_1° : + 0.56 V
E_2° : + 0.77 V rev



E_1° : + 0.18 V
E_2° : + 0.51 V rev

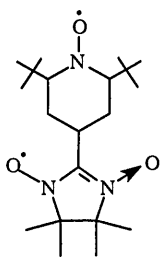


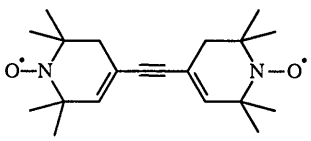
E_1° : + 0.92 V



E_1° : + 0.70 V

Lastly, nitroxides, which can be oxidized reversibly and also possess the property to couple with free radicals, can also be considered for redox catalyis within a wide oxidizing range. Here are examples of two mediators, both having two electroactive *N*-oxyl groups [122,123].





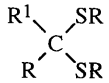
2. Metallic Cations as Redox Carriers

During the last four decades, techniques for indirect electrolyses using two-stage processes (also called "ex-cell" processes) have been developed. The inorganic reagent, acting in a separate chemical reactor either as oxidizing or reducing species, is generally regenerated in an electrochemical cell after its separation from organic products. Ideally, the system works when a continuous and constant stream of the electrogenerated redox reagent from the cell is fed to the reactor at the same rate as the soloution of the organic species [124].

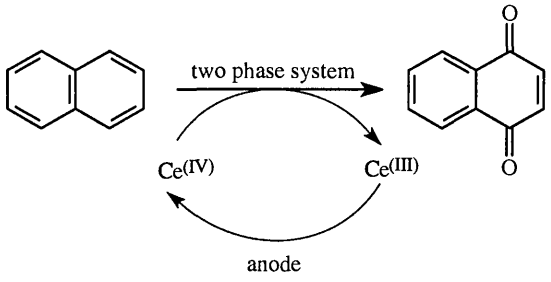
A wide variety of one-stage (in cell) or two stage (ex-cell) electrochemical conversions of aromatic systems using inorganic oxidizing mediators is listed in Table 3.

Among electron carriers used for indirect oxidation reactions, cerium salts [$Ce^{(IV)} + e^- \rightleftharpoons Ce^{(III)}$, $E^\circ = +1.44$ V vs. NHE] appear to be of particular interest when a mild oxidation has to be considered. Substituted toluenes and methylaryl compounds are easily functionalized to the corresponding aldehydes in high yields [125–129]. Acidic solutions are required (such as aqueous AcOH, aqueous methane sulfonic acid, or aqueous trifluorosulfonic acid). The conversion of aromatic compounds into quinones may also be conducted by means of electrogenerated ceric ions (see Table 3). Let us stress the example

Table 5 Examples of Indirect Conversions by Means of Organic Mediators — Oxidative Redox Catalysis

Type of Substrate	Mediator A used	Nature of the driving force of the catalysis (interest in synthesis)	References
Benzylic ethers	Tris (p-bromophenyl)amine	Fast deprotonation of radical cation in the presence of a soluble base	[117]
Activated thioethers	Triarylamines	Oxidative cleavage of the C—S bond	[117, 118]
Gem-dithioacetals 	9, 10-Diphenylanthracene and triarylamines	Rapid decomposition of radical cation by cleavage (R = aromatic) or nucleophilic attack (R = aliphalic); (oxidative deprotection of carbonyl compounds)	[117]
Carboxylate ions	Appropriate triarylamines	Possibility to achieve the Kolbe reaction in homogeneous phase	[19]
10-methylacridan (and aromatic amines)	Ferrocene/ferrocenium	Fast deprotonation of the radical cation by non-nucleophilic bases	[119]

of 1,4-naphthoquinone obtained from naphthalene using a two-phase oxidative system [130,131] (Scheme 17). In the latter example [130], the oxidizing mixture appears to be rather complex since the presence of electrogenerated Ag^{2+} is assumed to be essential. The formation of 3,2-dimethylgluatric acid (yield 90%) from cyclohexane-1,3-dione [132] and that of D-arabinose (yield 54%) from calcium D-gluconate [133], also using inorganic mediators, have been reported.

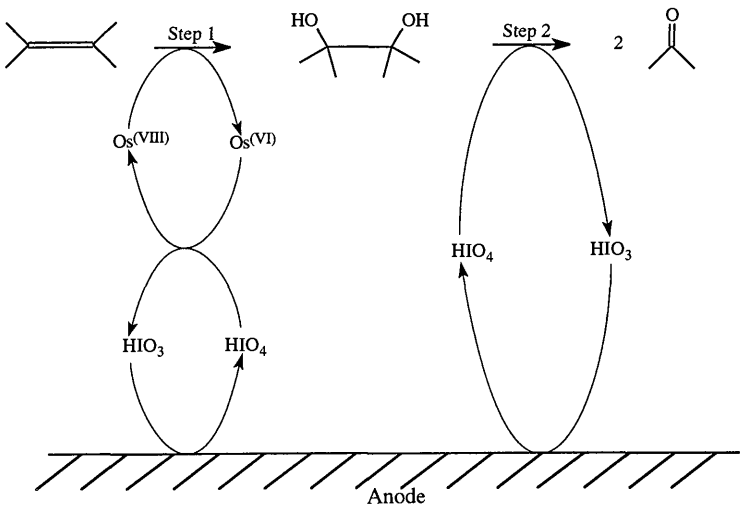


Scheme 17

The use of the Mn^{3+}/Mn^{2+} couple ($E^\circ = +1.51$ V vs. NHE) for indirect oxidations enables under mild conditions the conversion of methyl or methylene groups directly attached to a phenyl ring to the corresponding carbonyl function [103,104,108,110]. However, more drastic oxidations leading to carboxylic acids are generally performed by chromic acid, whose electrogeneration is catalyzed by chromium salts (also with concomitant Ag^{2+} generation at the anode). The interest of that type of oxidation is exemplified principally by the preparation of saccharin from *o*-toluene sulfonamde (see Table 3). Chromic acid formed by electrochemical means may be used in the conversion of anthracene into antraquinone.

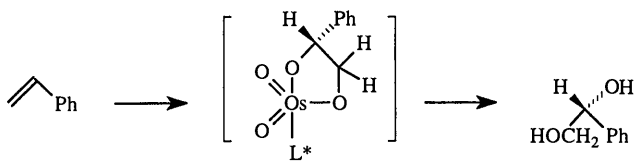
The indirect oxidation of olefins is usually performed in the presence of the couples Tl^{3+}/Tl^{+} ($E^\circ = +1.25$ V vs. NHE), Pd^{2+}/Pd^{0} ($E^\circ = +0.83$ V), or Os^{8+}/Os^{6+} ($E^\circ = +0.43$ V). Oxidations with Tl^{3+} [50,51] and Pd^{2+} [50–52] were reported to lead preferentially to carbonly compounds. Other examples concern the use of Tl^{3+} for diols obtention [134] or Os^{8+} for ethylenic bond cleavage [135].

Electro-oxidative reactions of carbon–carbon bonds by electrogenerated $Os^{(VIII)}$—potassium osmate—were recently reported. The presence of a second mediator (double-mediator system) like periodic acid allowed the olefins transformation into carbonyl compounds in one step [136] (Scheme 18).



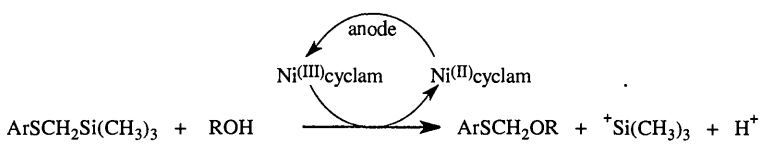
Scheme 18

Fruiful double-mediator systems in electrochemistry imply a constant and efficient regeneration of oxidizing reagents. Thus asymmetric dihydroxylation of various olefins could be achieved [137] in excellent yields by using complex mixtures such as I_2–K_2CO_3–$K_2OsO_2(OH)_4$ or I_2–K_2PO_4/K_2HPO_4–$K_2OsO_2(OH)_4$ systems in the presence of Sharpless's ligand L* [(dihydroquinodine or dihydroquinine 1,4-phthalazinediyl diether, $(DHQ)_2PHAL$)]. Thus, styrene could be oxidized [137] in diol in good yield (89%) with a remarkable ee (91.9%).



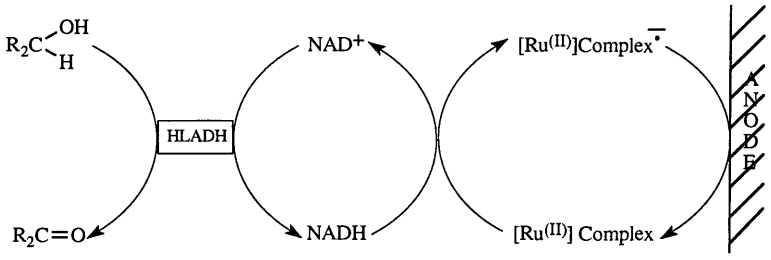
Scheme 19

Similar experimental conditions allowed the hydroxylation of 1,2-dihydronaphthalene in high yield with an ee >90% [137]. In the latter case, the addition of ferricyanide ion was used also to electrochemically maintain $Os^{(VIII)}$ concentration in the anolyte. Such reactions were achieved in two-phase systems. Metal complexes can be used for indirect oxidation such as the oxidation of phosphines by $Nb^{(V)}$ species [138] as well as $Ni^{(III)}$ salen used in the oxidation of silicon compounds [139] (Scheme 20).



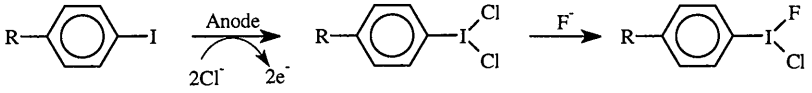
Scheme 20

Additionally, very complicated but efficient complexes implying $Ru^{(II)}$ were used to achieve the NAD^+ formation in solution in order to make feasible the oxidation of alcohols via HLADH (horse-liver alcohol dehydrogenase) [140] (Scheme 21):



Scheme 21

Another interesting electrogenerated species particularly important for indirect fluorination reaction is the formation [141] of hypervalent iodobenzene chlorofluoride derivatives. The reaction is performed in the presence of F^- and Cl^- ions in anhydrous methylene chloride (Scheme 22). With such reagents, the easy (ex-cell) fluorination of *gem*-dithioethers was achieved in good yield.



Scheme 22

3. Halides as Mediators for Oxidation

Br^-, Cl^-, F^-, and I^- ions can be useful to transform alcohols into ketones in very convenient and facile experimental conditions (see Table 6 and 7). Species suich as "Cl^+," "Br^+," or "I^+" were propose to be formed in the anode reaction layer. Probably, polarized halogen dipoles in the high electric field present at the electrode interface could also explain the specific reactivity of anodically generated oxidizing species from halides.

Oxidation carried out in the presence of iodide and bromide ions have been extensively developed during the last two decades. They may often be used with advantage within a potential range in which other kinds of catalyst are not numerous (e.g., organic mediators) or need to be used ex-cell. Moreover, oxidized species obtained from I^- and Br^- are of a very broad applicability and are very active, even in water, toward substrates that are more difficult to oxidize than the halides. In most cases it has been demonstrated that such electrooxidized species often play a specific role at the anode (or close to it), whereas the same halogens in bulk solution are much less efficient. Only reactions offering that advantage are reviewed here.

Oxidants obtained directly from easily oxidized halides often react chemically with organic substrates; the resulting adduct may then undergo a reaction that regenerates the halide ion. Indirect oxidations of this kind are essentially inner sphere processes, as previously defined.

Many examples of reactions that may involve electrogenerated chlorine and bromine can be found in the literature. Thus, alkenes may be converted into halohydrins [157–160]; ethylene chlorohydrin can be formed [157] in 90% yield at a graphite anode, but subse-

Table 6 Indirect Oxidation in the Presence of Halides ions

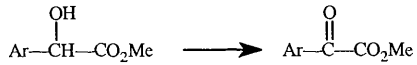
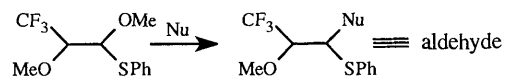
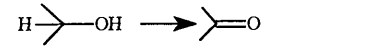
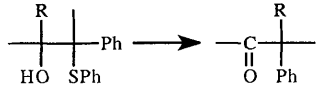
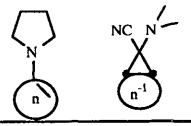
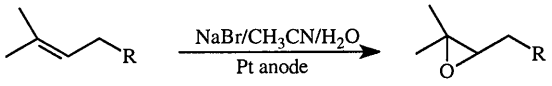
Mediator	Peculiar experimental conditions	Nature of the conversion	Réf.
Br^-	Selective anodic fluorination of dithioacetal ($Et_4NBr + Et_3N.3HF$ in CH_2Cl_2)		[142]
Br^-	Undivided cell-NaBr- Methylene chloride/water 1:1 Pt anode		[143]
Br^-	Double mediator system (Presence of $R_2N—O^\bullet$ as co-mediator) two phase solutions	Oxidation of alcohols to carbonyl compounds in high yields	[144]
Br^-/Cl^-	Anodic generation of polybromochloride ions. Ex-cell systems	Electro-oxidation of alcohols	[145]
Br^-	Presence of NaBr in neutral unbuffered solutions (Pt or Carbon anode)	Conversion of isorbide to monoketone 	[146]
Br^-	Example of paired synthesis in aqueous HBr solutions / divided cells	Synthesis of l-cysteic acid and l-cysteine from cystine RSSR —> RSO_3H	[147]
Br^-	Double mediatory system in the presence of $[Ru^{IV}O_2]^= —> [Ru^{VII}O_4]^-$ in acetonitrile (addition of Bu_4NOH and Bu_4NBr)	Oxidation of primary and secondary alcohols	[148]
Br^-	Undivided cell. Platinum electrodes	Indirect O-glycosylation of phenylthioglycosides	[149]

Table 7 Indirect Oxidation in the Presence of Halides ions

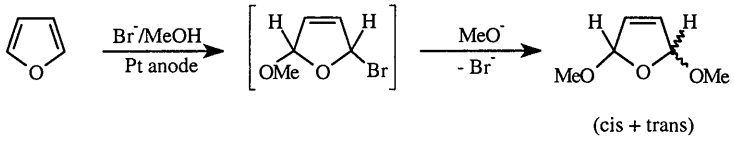
Mediator	Special experimental conditions	Nature of the conversion	Réf.
F^-	Oxidation in methanol containing $Et_3N.3HF$	Oxidation of 	[150]
Cl^-	Double mediator system. Presence of $RuO_2.2H_2O$	 Oxidation of di-isopropylidene -D-glucose to the ulose	[151]
Cl^-	Double mediator system	Oxidation of 1,3-dichloro-2-propanol to 1,3-dichloroketone	[152]
Cl^-	LiCl or R_4NCl in dichloromethane	Electrooxidative rearrangement of β hydroxy sulfides 	[153]
I^-	Catalytic amount of KI in ammoniacal methanol	One-step oxidation of ketimines (produced *in situ* from corresponding carbonyl compounds) conversion to 2H-imidazoles and parent α-diketones	[154]
I^-	Catalytic amounts of KI as mediator. Divided cells. Pt anode. Methanol containing NaCN.	Conversion of 2-alkyl and 2,2'-dialkylketone to the corresponding oxirane carbonitrile	[155]
I^-	KI / NaCN / MeOH		[156]

quent elimination to give ethylene oxide depends critically on pH [161]. A similar electrochemical conversion of propene into propylene oxide [162] has been reported; a porous titanium anode coated with Pt/Ir is required. More complex olefins have also been transformed into epoxides; in these cases aqueous organic solvents were used with dissolved sodium bromide [161,163] (Scheme 23).



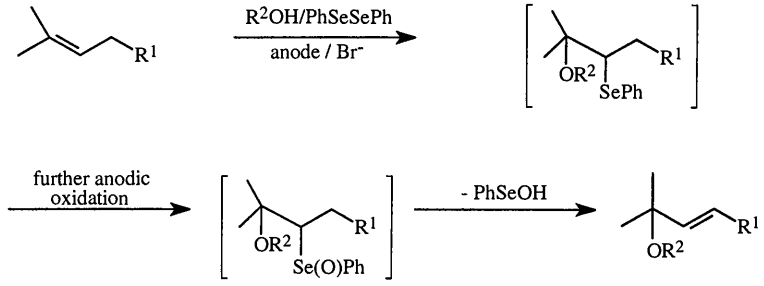
Scheme 23

The presence of halide ions in the anolyte may efficiently help the oxidative addition of the solvent to an unsaturated compound; the addition may be followed by a bond cleavage [164]. The conversion of furan into either 2,5-dimethoxy-2,5-dihydrofuran [165,166] or 2,5-diacetoxy-2,5-dhydrofuran [167] has been shown to be possible in methanol or an acetic acid-acetonitrile mixture, respectively (Scheme 24).



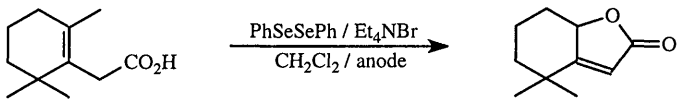
Scheme 24

The oxidative coupling of activated C–H bonds has been shown to be catalyzed by the addition of iodide [168]. The indirect oxidation of alcohols in the presence of Br^- or I^- may, depending on experimental conditions, lead to carbonyl or carboxylic compounds [169,170]. Therefore, glucose can be oxidized on industrial scale to gluconic acid by oxidation using aqueous $NaBr/CaCO_3$ solutions [171]. More complex oxidation processes can be carried out. Selenation and sulfuration reactions have been demonstrated using $PhSeSePh/Br^-$ or $RSSR/Br^-$ mixtures. In such reactions, anodically oxidized bromine species polarize Se–Se or S–S bonds positively, leading to additions or substitutions in "adequate" yields [164]. In most cases, simultaneous addition of nucleophilic solvents is observed. Adducts so formed may themselves be anodically oxidized to give valuable allyl ethers (Scheme 25).



Scheme 25

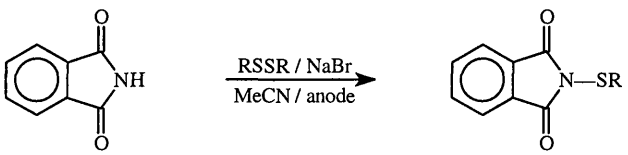
Such allyloxylation reactions allow, for example, the formation of (±)-rose oxide from citronellol [161]. The synthesis of butenolides can be efficiently performed starting from β-unsaturated acids [172]:



(73 %)

Scheme 26

The formation of nitrogen–sulfur bonds, as in the synthesis of sulfenimides and sulfenimines [173], and phosphorous–sulfur bonds [174] is achieved by electrolyses of activated N–H and P–H compounds in the presence of an RSSR/Br^- mixture:



(90-93%)

Scheme 27

IV. TRIGGERING OF RADICAL CHAIN VIA ELECTROGENERATED TRANSIENTS (ECE PROCESSES)

A. $S_{RN}1$ Reactions

Kornblum, Russel [175], and Bunnett [176] first demonstrated clearly that nucleophilic substitution reactions may occur in certain cases via a chain process initiated by a single electron transfer (Scheme 28). The initial step is a reaction between the "nucleophile" (here acting as a reducing reagent) and the "electrophile." Such reactions with organic anions as electron-donating species may be general. In addition to photochemical induction processes, dissolved metals, amalgams, and solvated electrons (as well as many adequate reducing species) are useful for achieving an external stimulation of such reactions. Reactions of this first may be conveniently initiated and studied by means of elctrochemistry [177]. The first example showing the role of the cathode in the triggering of aromatic nucleophilic substitutions ($S_{RN}1$) was provided by Pinson and Savéant [178] for aromatic halides compounds (ArX) reduced in the presence of a nonelectroactive nucleophile (Nu^-). Many other examples of substitution of ArX type compounds are now available in a recent literature. The electron transfer induction [179] can be checked easily by means of cyclic voltammetry. Thus, the efficiency of the substitution of 2-chloroquinoleine by benzenethiolate is exhibited in Fig. 4. The main step corresponding to the cleavage of C–X bond ($2e^-$) strongly disminishes (or disappears) in the presence of an excess of Nu^-, while the peak of ArNu merges at more negative

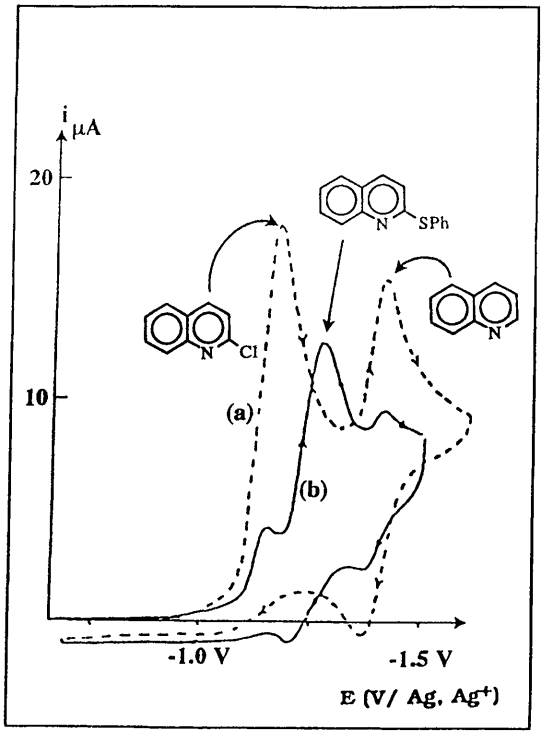
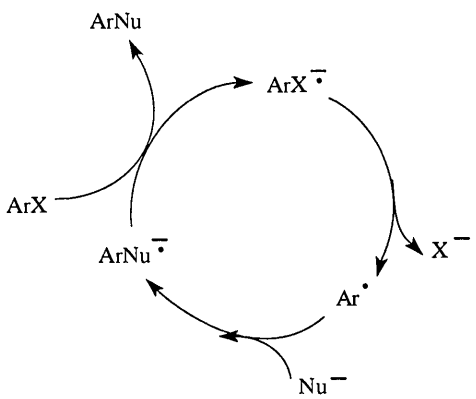
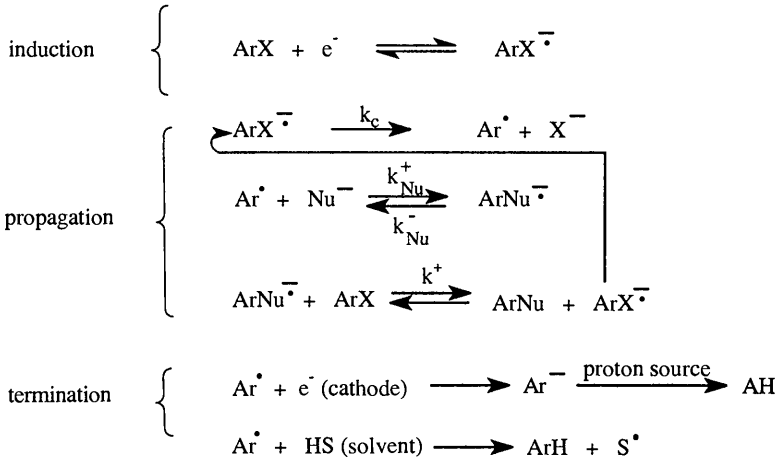


Figure 4. Cyclic voltammetry of 2-chloroquinoleine (2.5 m*M*) in liquid ammonia containing 0.1 *M* KBr as electrolyte (temperature −40°C) (a) in the absence and (b) in the presence of PhS (56 m*M*). Sweep rate: 0.2 V/s. From Ref. 180. Reproduced by permission of American Chemical Society.

potential values (case where $E^{\circ}_{ArX} > E^{\circ}_{ArNu}$ that allows the chain propagation). In both cases (presence or not of nucleophile), the step exhibiting the reversible one-electron reduction of ArH remains present.



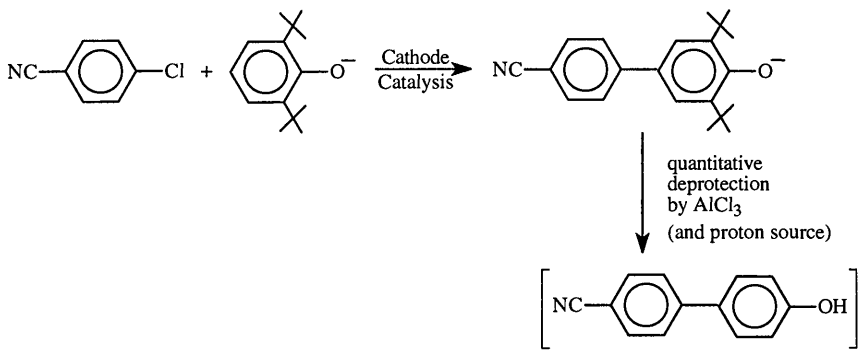
Scheme 28



Scheme 29

Generally speaking, the reduction or activation of ArX in the presence of a soft nucleophile Nu^- leads to ArNu formation. Once we have stated the thermodynamic requirement of $E^\circ_{ArX} > E^\circ_{ArNu} E^\circ_{ArX} > E^\circ_{ArNu}$, the yield of substitution is highly dependent on the ability of the medium to donate hydrogen atoms. Therefore, most analytical studies concerning $S_{RN}1$ reactions were carried out in liquid ammonia [181], which is a poor hydrogen-atom donor. The determination of absolute and realtive rate constants for sufficiently activated aryl radicals toward nucleophiles [such as PhS^- and $(EtO)_2PO^-$, and $CH_3COCH_2^-$] leads to the conclusion that the rates are often close to that of the diffusion control, especially when the ArX is substituted for by EWG (e.g., NO_2, CN, COOR, COR, SO_2R, CF_3 [182], etc.). The yield of substitution could be given upon the electrophilicity of the radical Ar· (constant k^+_{Nu}), the nucleophile concentration, and the atom donor ability (k_H) of a given solvent [183].

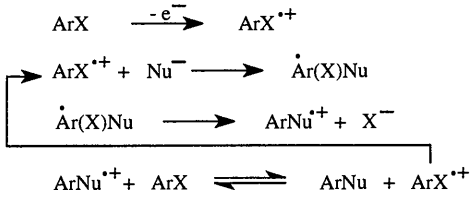
The direct reduction of an aryl radical Ar* formed in the electrode vicinity may be advantageously avoided using an electron carrier [184]. The advantage of such an indirect initiation process is apparent [185] in the synthesis of diphenyls substituted by both electron-donating and electron-withdrawing groups. However, one should take care that the ΔE between the ArX compound and the mediator does not exceed 0.5 V, or induction could become too slow, especially toward side reactions like termination reactions.



Scheme 30

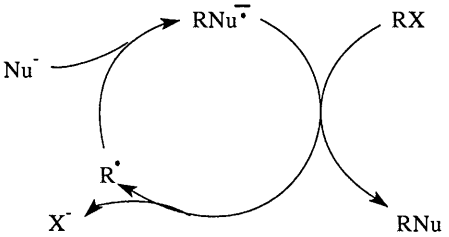
Additionally, the mediated electrochemical induction has also been used successfully with high yield in the synthesis of phneylselenobenzonitriles and phneyltellurobenzonitriles [186].

Similarly, another kind of nucleophilic substitution onto ArX compounds may be initiated by oxidative electron transfer (the S_{ON}^2 type of reaction corresponding to a nucleophilic substitution catalyzed by an oxidant with a crucial step namely of the attack of the nucleophilic onto the radical cation). The substitution of 4-fluoroanisole by acetoxy ion has been found to proceed through the following scheme [187,188].



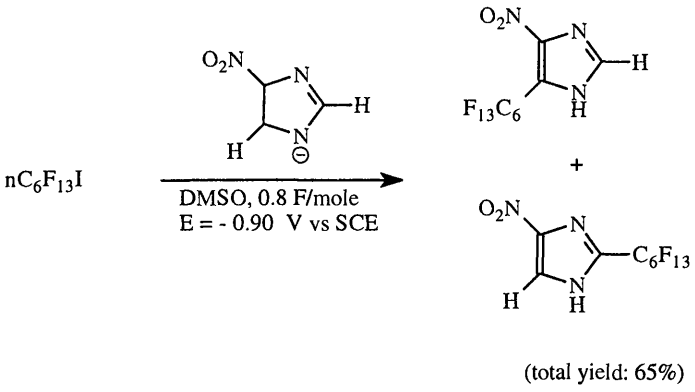
Scheme 31

The case of Kornblum reactions (substitution of X substituents borne by sp^3 carbons named RX) is sometimes more ambiguous, since an external stimulation of S_{RN}^1 reaction is not always necessary (thermal electron exchange from the nucleophile). Thus, by means of voltammetry, Savéant [189] has shown that a decrease in driving force was able to change the mechanism of homogeneous reductive cleavage reactions from stepwise to concerted in the precise case for substitution of 4-nitrocumyl chloride by 2-nitropropanate ion. In other words, the radical anion of the RX compound may not be formed along the initiation pathway, although it is an intermediate in the course of the propagation pathway given hereafter [189] (Scheme 32).



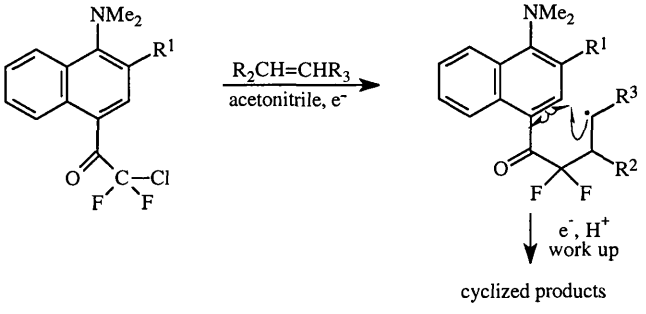
Scheme 32

Strongly electrophilic radicals from RX cleavage can specifically trigger S_{RN}^1 reaction. thus, R_f^* (perfluroalkyl radicals) generated by cathodic breaking of C–halogen bonds react in dimethyl sufloxide with various nucleophiles like imidazol, uracil, hypoxanthine and xanthine anions in a radical chain process [190–192] achieved. Reactions chains implying this kind of radical were often triggered by indirect means [182] (Scheme 33).



Scheme 33

Within a potential range where radicals (like $CF_3^{\bullet}$) are not readily reduced or/and using indirect formation in solution by means of electron carrier, a chemistry—rather similar to that already developed by the Kolbe method by oxidation of CF_3COO^- at a platninum anode—can be developed. Thus, Medebielle [193] showed that radical additional onto electron-rich olefins was possible and applied this for convenient synthesis of fluorinated heterocyclic compounds. Let us stress that the electrochemical process is in this case stoichiometric in electrons.

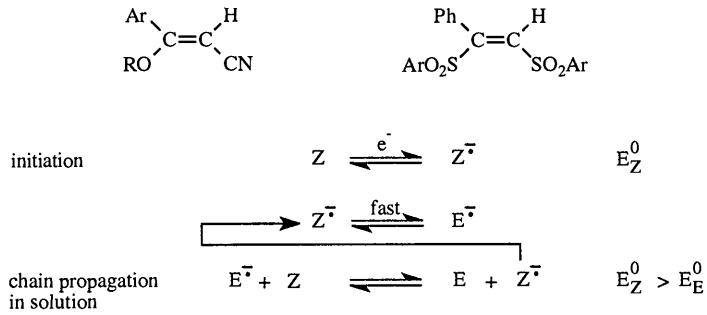


Scheme 34

In addition to initiate substitution reactions like $S_{RN}1$ processes, a cathode or anode may also be used for catalyzing organic reactions proceeding via electron transfer chains [194].

B. Other $\vec{E}C\vec{E}$ reactions

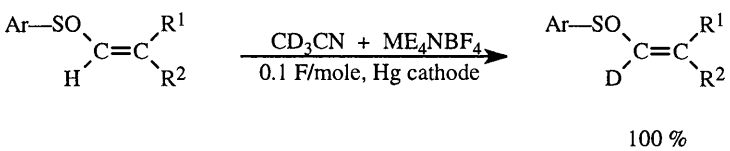
Efficient cathodic $\overrightarrow{E}C\overleftarrow{E}$ chain reactions are involved in *cis–trans* isomerism only if (1) two isomers are sufficiently different ($\Delta E^\circ > 0.1$ V), and (2) the less electroactive isomer is the more stable. Therefore, in the absence of fast cleavage or protonation reaction, kinetic factors of chemical conversion coupled with the cathodic electron transfer (as an activatikon step) may start a catalytic process. Examples of such processes are the isomerization of *Z*-enol ethers [195], as well as that of *Z*-1,2-diarylsulfonyl phenyl ethylenes [196].



Scheme 35

Other examples have been provided by the anodically initiated isomerization of several decarbene metal carbonyl couples [197]. Electrochemical induction of chemical reactions can also be successfully used for conversion of alcoolates into ketones with simultaneous reduction of aromatic halides [198], the tetramerization of aziridines [199], or ligand substitution [200] in organometallic compounds. A useful review on this subject was published [201].

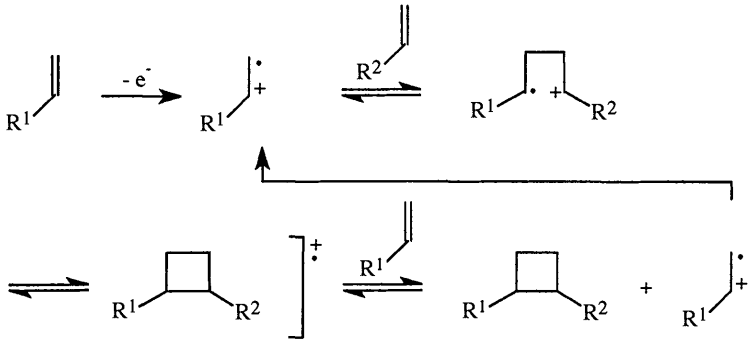
Exchanges of proton/deuterium in activated olefins like α-unsaturated arylsulfones and sulfoxides can be achieved either in deuterated solvent (acetonitrile d_3 or dimethyl sulfoxide d_6) or in aprotic solvents in the presence of deuterated water [202,203]. The substitution process was found to be catalytic in electrons, and the reaction (fully regio- and stereoselective) could be elegantly followed [203] by ^{1}H-NMR. In the following example (Scheme 36), the standard potential of the deutrated from is slightly more negative (40–50 mV) than the one of the starting sulfoxide, and radical anions could be involved in the chain process.



Scheme 36

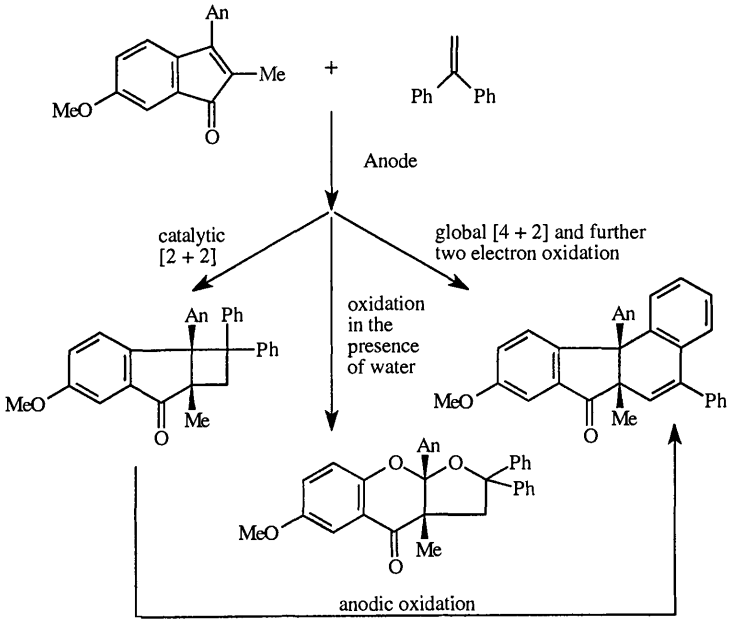
C. [2 + 2]-Type Reactions Activated by Electron Transfer from Charged Radicals

Cyclodimerizations and cycloadditions initiated by electron transfer oxidants were shown to occur with the generation of a radical cation included in the catalytic chain (see Bauld's work [204]). Thus, cyclodimerzation of an indene, radiationalized as a [2 + 2] addition, induced by oxidative electron transfer, was described by Eberson [205]. Several other kinds of global [2 + 2] and [4 + 2] additions were described during the last two decades [206–208]. However, pure [2 + 2] cycloadditions—in fact—formally [1 + 2] since the radical cation is stringly involved in the chain process—were pointed out for the first time between indenones and substituted styrene [206] together with [4 + 2] where the formed adduct is then electroactive (evidence for a global two-electron oxidation process) (Scheme 37).



Scheme 37

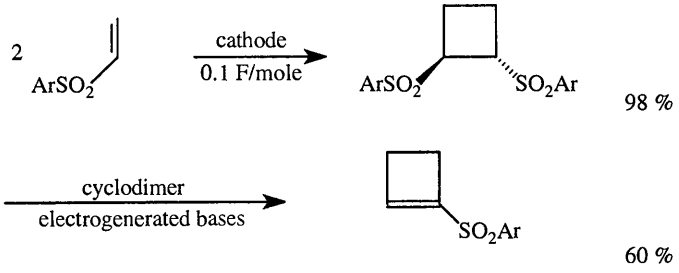
The reversibility of the cycloaddition or cyclodimerization via radical cation could be observed in certain cases. For example [209], with some indenones (Scheme 38), cyclodimerization into truxones may occur but the radical cation of the cyclodimer may lead to other kinds of cyclodimer. Note also that the open radical cation is strongly sensitive to the presence of residual water. Other induced [4 + 2]-cycloaddition reactions implying 2-vinylpyrroles and β-accept or substituted enamines were described [210].



Scheme 38

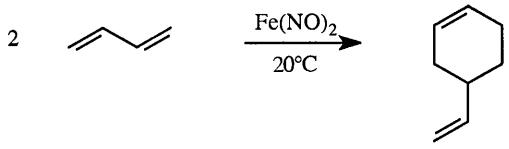
Within the cathodic range (catalysis by a radical anion), [2 + 2] cyclodimerizations (formally [3 + 2]) were also described. Thus, cyclodimerization of arylvinylsulfones in DMSO + $LiClO_4$ at a platinum wire cathode led to quantitative amounts of cyclodimers [211]. Such a family of cyclobutanes was before now unknown, and mimicking the cathodic reaction by a reducing reagent failed. Action of conventional electrogenerated bases

(such as superoxide or acridine radical anion) allowed [212] the obtaining of cyclobutenes usable as excellent dienophiles in Diels–Alder reactions (Scheme 39).



Scheme 39

Similar types of cyclodimerizations were also pointed out with vinyl pyridines and vinyl quinoleines [213]. Lastly, selective cyclodimerization reactions of 1,3-diolefins catalyzed by electrogenerated "$Fe(NO)_2$"—from athodic reduction of $FeCl_3$ in the presence of NO—allowed the conversion of butadienes into vinylcyclohexenes in good yields [214] (Scheme 40).



Scheme 40

V. PERTURBED REDOX CATALYSIS: MIXED ELECTROLYSES AND SYNTHETIC IMPORTANCE

A. General Aspects

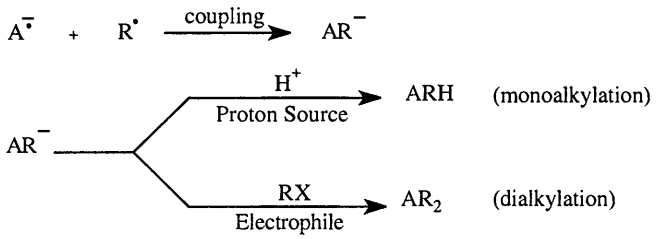
So far, only redox catalyses in which the mediator is regenerated in high yield after the solution electron transfer (SET) have been described in this chapter. However, quite frequently the redox catalysis process competes with side reactions that lead to a decay of the concentration of the mediator. In such cases, the SET rate varies with the concentration of the organic substrate and a limiting value of the catalytic current is observed. A typical example [12,13] is the indirect reduction of aliphatic organic halides RX with organic mediators (Fig. 2B and Table 3). For a given concentration of RX, it appears from mixtures of naphthalene and butyl chloride that the limiting current depends on the nature of the R group; the catalytic efficiency decreased in the order *n*-alkyl > *sec*-alkyl > *tert*-alkyl, and the largest effect was found experimentally for *t*-BuX compounds.

Electrolysis of an "A compound" in a mixture of two "RX compounds" may be interrupted after a certain quantity of electricity has been passed (e.g., 2 F/mol calculated

on the basis of the concentration fo A, here naphthalene, and product analysis demonstrated the reductive alkylation of the mediator. The best yields of alkylation were obtained with *t*-BuX (didhyro-*t*-*ter*butylanphthlene 70–80%), while *n*-BuX compounds are less efficient (10–20% of alkylation leading mostly to dihydrodibutyl naphthalenes).

A review by Lund [15] listed numerous alkylation reactions by means of electrolyses of different A type compounds in aprotic organic solvents, in the presence of organic halides. Other paper [9–13] described further possibilities for such mixed electrolyses and highlighted applications for alkyl halides or onium salts (given in Table 8).

Most of the reactions may be understood as a radical coupling (involved $R^{\bullet}$, see Scheme 41), which follows the solution electron transfer.



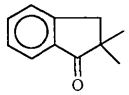
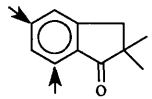
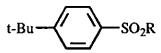
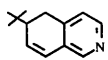
Scheme 41

The relative extent of dialkylation depends on the electrophilicity of RX (and the nucleophilicity of AR^-) when a realtively fast SET ($\Delta E_{1/2} < 0.5$ V) is the primary reaction. Other mechanisms may also satisfactorily explain the distribution of products. For instance, adduct formation between the alkyl radical and the mediator (acting as a radical trap) is possible and must be considered; in such a case, further reduction of $AR^{\bullet}$ may take place, either by electron transfer or by abstraction of a hydrogen atom from the solvent. However, let us keep in mind that radical anions or dianions may act as nucleophiles, since a partial inversion of configuration of some optically active secondary RX compounds has been found [222] after workup under experimental conditions similar or identical to those of the electrolyses. Table 8 exemplifies alkylation reactions following a SET. The reaction scheme may be complicated by the fact that reduced forms of the mediator may act as a "reducing nucleophile" toward RX. The SET may then be assumed as the rate-determining step in aliphatic nucleophilic substitutions [223], and/or R^- generated in solution may be added to an electrophilic mediator, such as an activated ketone [224].

B. Application for Estimating Standard Potentials of Unconjugated Radicals

In general, the thermodynamics of free radicals has been, up to now, almost unknown due to their extremely high reactivity and electroactivity. For clarification, several methods were proposed [225,226] from anodic half-wave potentials of carbanions and organolithium compounds. Redox catalysis may strongly help to estimate redox potential of a certain number of radicals generated electrochemically. Thus, as seen previously in Scheme 4 and in Scheme 6, in the absence of other side reactions, there are two main different ways

Table 8 Some Examples of Redox Catalytic Systems Implying Alkyl halides and Onium Salts Followed by Alkylation Reactions

Organic mediator	Reactive species (reduction in solution)	Nature of the alkylation	Compounds (yields, %)	Remarks	References
Fluorenone	MeCl (saturated)	Dialkylation	9-Methyl-9-methoxyfluorene	General reaction of activated ketones	[215]
Anthracene	$ClCH_2CH_2CH_2Br$	Cyclization	1,2-Cyclopenteno-1,2-di-hydroanthracene (41)	In DMF-n-Bu_4NI (0.1 M)	[15]
Pyrene	t-BuCl t-$BuSO_2Ar$	Specific monoalkylation	1-Tertiobutylpyrene (52)	Reoxidation of the dihydro form during the work-up; similar reaction with quinoline (35)	[216]
Anthraquinone α-diketone	MeCl (saturated)	O-dimethylation	Dimethoxyanthracene (80); cis- and trans-dimethoxyethylene (50)	For diketones, competition between C and O alkylation	[264]
Activated olefins	t-BuCl or t-BuBr	Monoalkylation	Different sites of alkylation along the chain	Alkylation in competition with the dimerization reaction	[216-218]
	t-BuBr	t-Butylation of aromatic ring		Possible poly-t-butylation	[219]
Naphthalene	t-$Bu\overset{+}{N}Me_3$ as electrolyte	Only monotertiobutylation	Mixture of tertiobutyltetrahydro-naphthalenes (80)	Similar reaction of butylation with Bu_4N^+ (but in low yields, < 1%)	[9, 220]
Aromatic hydrocarbons	R_3S^+	Different kinds of alkylation	Mono-t-butylation of acephtylene and benzo-phenone by t-BuS^+Me_2	Quite general reaction with R_3S^+; not aplicable to $^+PR_4$ because of its acidicty	[220]
Aromatic 1,4-disulfones	t-BuBr	ipso-substitution		Selective mono-t-butylation	[221]
Isoquinoline	t-BuBr	monoalkylation		attack C_6 unsual	[3]

for R• radical to react with the radical anion mediator $A^{\cdot-}$ (like direct reduction of the radical, fast disproportionation, H-donor effect of the solvent).

$$A^{\cdot-} + R^{\cdot} \xrightarrow{k_C} AR^{-} \qquad \text{(coupling)}$$

$$A^{\cdot-} + R^{\cdot} \xrightarrow{k_R} A + R^{-} \qquad \text{(reduction)}$$

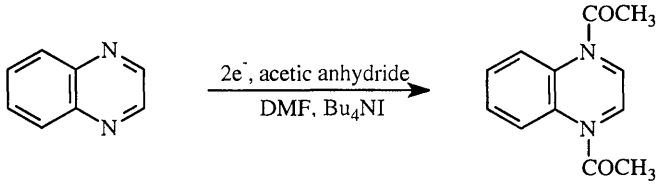
It has been indeed noticed in many preparative investigations that the overall reaction of aromatic radical anions with benzylic halides was a full catalytic reduction of RX, whereas unconjugated alkyl halides afford, to more or less extent, the alkylation of A. This behavior has been ascribed to the difference between the standard potentials of the alkyl radical and the mediator [227] giving rise to a competition between these two pathways according to the facility of R• to be reduced. Coupling reaction was assumed to be very fast (k_C was found close to $1 \times 10^9\ M^{-1}\ s^{-1}$ when using "radical clocks"). The competition between coupling reaction and homogeneous reduction of R• radical can be expressed by the dimensionless parameter q.

$$q = \frac{k_R}{k_C + k_R}$$

Thus q is obviously equal to 0 when the mediator is totally alkylated and equal to 1 when the overall reaction corresponds only to a two-electron reduction of RX. Experimentally, q values (with an accuracy of the order of ± 0.1) can be measured for each RX compound when associated to several A compounds, assuming (1) that steric effects are negligible and (2) the rate constant k_R can be calculated according to the Marcus theory from the reorganization energy in the course of the homogeneous electron transfer and the driving force (Fig. 5). This method allows us to propose—provided the self-exchange reorganization energies $\lambda_R^{\bullet}(0)$ is finely estimated—redox potential values of a large palette of R• electrogenerated from usual RX used in both pure and perturbed redox catalysis (Table 9).

C. Electrogenerated Nucleophiles

When radical anions and dianions leads to very slow SET, their nucleophilic properties have to be taken into account. Reactions of electrogenerated species toward CO_2, acetic anhydride, acetic chloride, and some classic RX compounds as electrophiles can be explained on the basis of nucleophilic substitutions, but extreme cares have to be taken on the intrinsic nature of the mechanism (S_{Ni}^2 vs. radical coupling). Thus reactions involving azo and diazo compounds in the presence of CO_2 could be explained by nucleophilic addition (formation of *N*-functionalized azine and diazines [13]). Several reactions [15,215,229] implying CO_2 and acetic anhydride [230] were described.



(92 %)

Scheme 42

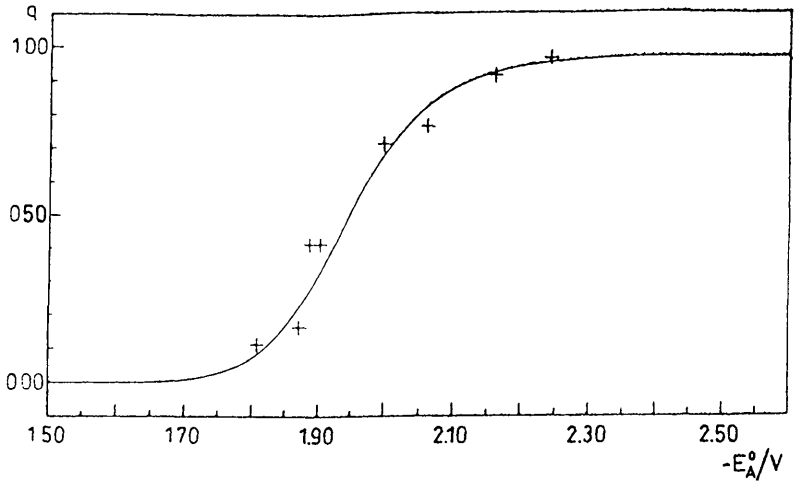


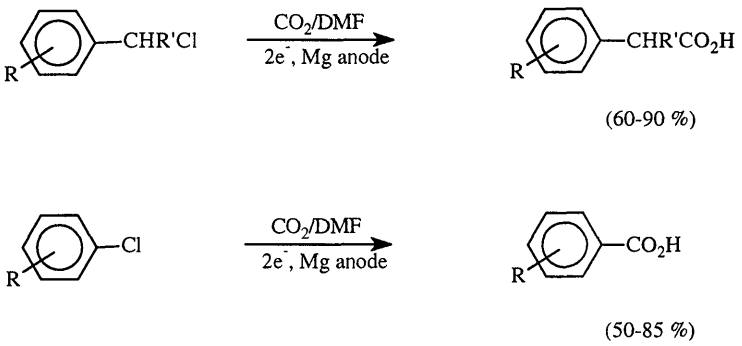
Figure 5. q-Values of phenylacetyl chloride vs. the redox potential $E°_A$ (vs. SCE) of some aromatic mediators. The curve is calculated using $E_q^{1/2} = -1.96$ V, $k_C/k_D = 0.a05$, and $\lambda = 20$ kcal mol^{-1} (k_D, diffusion-controlled rate; λ, reorganization energy. Mediators used: 9-phenylanthracene (−1.827 V), anthracene (−1.890 V), 9,10-dimethylanthracene (−1.906 V), 1,2-benzanthracene (−1.922 V), pyrene (−2.018 V), 3-methoxypyrene (−2.081 V), chrysene (−2.182 V), and *m*-tolunitrile (−2.264 V). From Ref. 228.

Here, special mention must focus on the carboxylation of organic halides to give the corresponding carboxylic acids, often in good yield. The proposed scheme should involve the formation of transient nucleophile by means of the two-electron scission of the carbon–halide bond. Best yields are obtained when using an undivided cell with a sacrificial anode (Mg, Zn, and Al) in DMF [231,232] (Scheme 43).

Table 9 Standard Potentials (Referred to SCE) and Reorganization Energies for Radicals Formed from Anion Radical of Mediators by Indirect Means

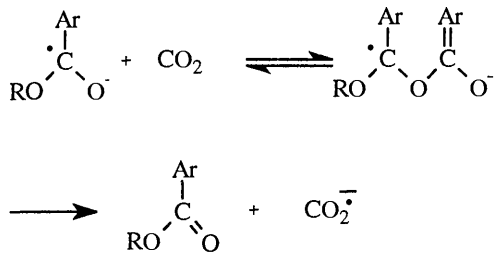
RX	$-E°_R$ (V)	$\lambda_{R(0)}$ (kcal mol^{-1})
Benzyl chloride	1.40	10
Benzhydryl chloride	1.07	10
Iodomethane	1.19	50
Bromomethane	1.64	50
Chlorocyclohexane	1.68	50
tert-Butyl chloride	1.77	30
2-Chloropropane	1.72	50
Bornyl chloride	1.67	50
3-Chloro-1-propane	1.39	20
3-Chloro-1-propyne	1.25	20
Acetyle chloride	1.70	30
Benzoic anhydride	1.13	30
1-Naphthyl chloride	1.07	30

Note. The uncertainty in the determination of $E°_{R\bullet}$ is ±150 mV and that of $\lambda_{R\bullet(0)}$ is ±10 kcal mol^{-1} [228].



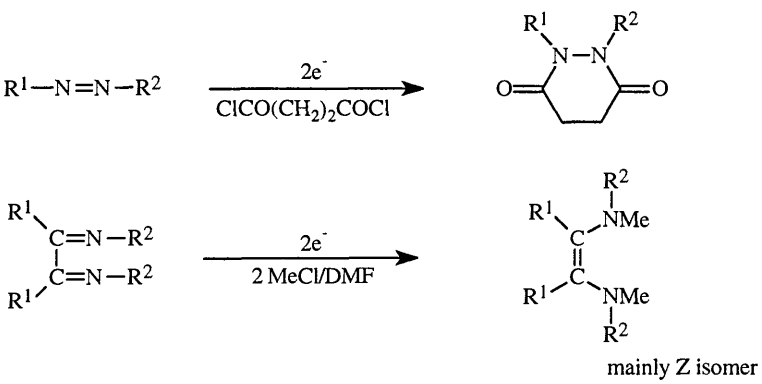
Scheme 43

Radical anions of aromatic esters and nitriles lead to catalytic reduction of CO_2, yielding exclusively oxalate. However [233], the generation of CO_2 radical anion was shown to proceed via a complex process via a S_N^2-type reaction, since the oxygen or nitrogen ends of the reduced form of the mediator bind to the carbon of CO_2 [233].



Scheme 44

In a general pattern, the reduction of the mediator (overall a two-electron process) may be represented as an electrochemical generation of nucleophiles. Two examples of reductive alkylation and acylation (here, the primary electron exchange in solution is not demonstrated or looks improbable) [234–236,264] are given:

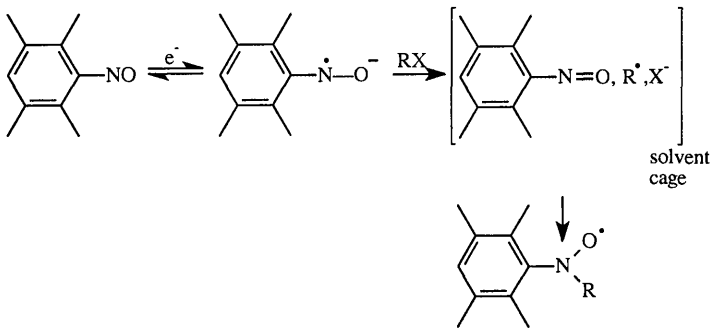


Scheme 45

Activated olefins were shown to be monoacylated when reduced in the presence of acetic anhydride [237–240] and therefore do not lead to a fast dimerization.

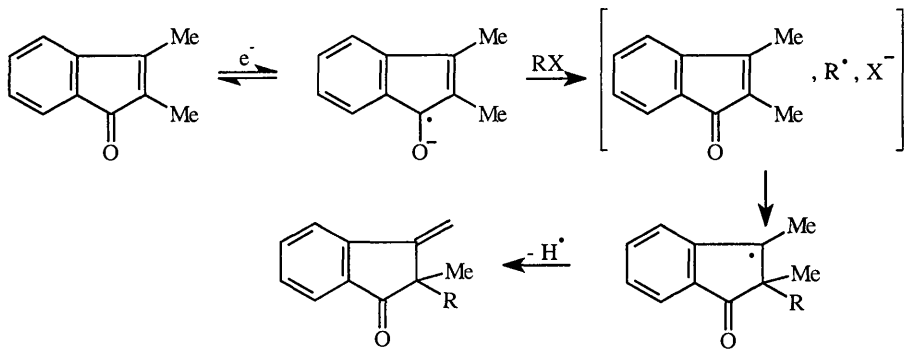
D. Addition of Electrogenerated Free Radicals on Unsaturated Systems

Free radicals are well known to add on activated olefins [241]. Thus, in electrochemistry, the indirect formation of a free radical in solution may happen concomitantly by reaction on the mediator inside a solvent cage. Two examples follow. First is the indirect reduction of RX types compounds by the radical anion of a spin marker [242] such as a nitroso derivative. In this case the reaction is monoelectronic, since the nitroxyde radical is totally electroinactive (note that a nucleophilic action of the radical anion cannot be totally excluded (Scheme 46).



Scheme 46

Second is the fast addition [243] of alkyl, allyl, or benzyl radical on indenones (Scheme 47).



Scheme 47

VI. ELECTROGENERATED SUPEROXIDE

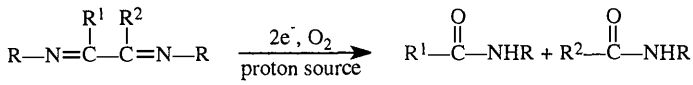
The advantage of the electrochemical method is often to produce intermediates that are not readily accessible by conventional means. The electrogeneration of transient nucleophiles and electrophiles is an example. The formation of superoxide ions by the cathodic reduction of oxygen in aprotic solvents (DMF, DMSO, and MeCN) is another case,

although KO_2 is commercially available (50 g: price about \$50). Thus, in the absence of an efficient protonating reagent, oxygen gives a quasi-reversible system at −0.85 V vs. SCE at commonly used cathodes (Hg, Au, Pt, graphite, or glassy carbon) in the presence of nonacidic cations, such as tetraalkylammonium salts [244–246]. The use of alkali metal salts as electrolytes cannot be recommended since the corresponding superoxide salts are often insoluble, especially LiO_2. Its precipitation at the electrode interface may be strongly inhibiting [245,247]. The relatively long half-life of superoxide (about 40 min at room temperature [248,249] allows reactions (even moderately slow ones) to occur in situ in the catholyte solution with continuous generation of the reagent; the rate of formation of $O_2^{\cdot-}$ is limited by the fairly low solubility of oxygen in the usual solvents (e.g., 10^{-3} mol l^{-1} in DMF and 0.5×10^{-3} mol l^{-1} in DMSO at room temperature [250]).

Tetraalkylammonium superoxide may act as a nucleophile, as an electron donor, and as a base. Global oxidizing reactions were also reported. Thus, the chemistry of peroxide is complicated by the fact that its protonated form $^{\cdot}O_2H$ is a powerful oxidant. Consequently, the behavior of superoxide appears to be highly dependent on the proton activity of the solution, but the organic substrate and its E° also have to be taken into account. Alternatively, the acidity of the electroactive organic substrate may be important, depending on whether it reacts rapidly with the superoxide ion at or near to the cathode. Some reviews [251–253] attempt to shed some light on the organic chemistry of $O_2^{\cdot-}$ and its alkali metal salts, for which both solubility and nucleophilicity may be increased by the use of well-chosen ligands, such as crown ethers [251,252,254]. Note that continuous cathodic reduction of oxygen may lead directly to tetraalkylammonium superoxide, which is more soluble and more reactive than the alkali metal salts of $O_2^{\cdot-}$, in which in any case must be prepared in situ in a polar solvent.

The nucleophilicity of superoxide toward different alkyl halides was estimated from kinetic measurements [255]. In particular substitution kinetics k_{sub} toward alkyl halides were compared to electron transfer rates k_{ET} with the same halides. Thus, the reactivity of aromatic radical anion $A^{\cdot-}$ (a donor having the some potential as $O_2^{\cdot-}$) was compared to that of superoxide. The influence of k_{sub}/k_{ET} on the difference in self-exchange reorganization energy $\lambda(0)$ between $O_2^{\cdot-}/O_2$ and $A^{\cdot-}/A$ was discussed.

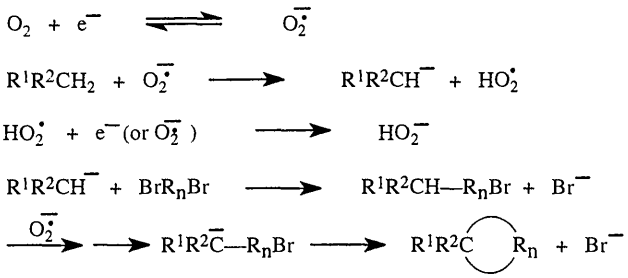
Electrogenerated superoxide reacts as a moderately strong nucleophile [124,248,256]; thus, the reaction with alkyl halides leading to dialkyl peroxides has been reported [248,257]. In situ reactions toward perfluoroalkyl iodides (formation of carboxylic acids [258]) and 5-halo-1,2,3-triazines (obtention of corresponding hydroxy compounds [259]) appear to proceed via SN displacements. Reactions toward Michael acceptors have also been described in the literature [248,254], such as the epoxidation of cyclohexen-3-one (yield 30%). However, such reactions are possible only for double bonds possessing a rather high activation; with less electron-rich double bonds, such as chalcones [254] and benzalacetones, oxidative cleavage of the unsatured bond can occur, leading to the corresponding acids. Similarly, aromatic α-diketones [260] may be cleaved into carboxylic acids, while α-diimines [261] afford amides.



Quite similarly, superoxide may react with some activated aromatic halides to give, through substitution, the corresponding phenols [262,263]. A consequence of the results and reactions described earlier is that for electrolyses conducted in aprotic solutions, adventitious oxygen may quite often cause large discrepancies, not only in coulometric

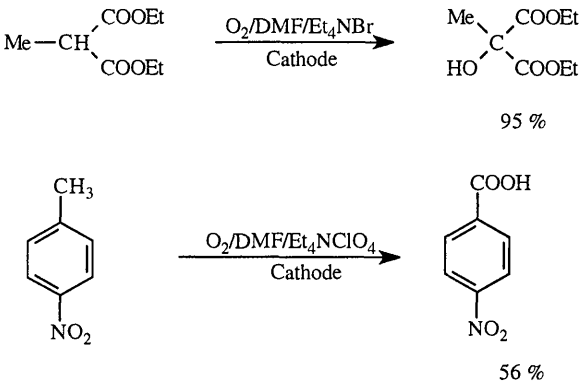
measurements but also in product distribution. Such interference has been shown [264] to be commonplace, especially for the reactions of activated ketones, carbon acids, and aromatic hydrocarbons.

Superoxide possesses a certain basicity [265–269]. Reactions of superoxide with activated C–H functions appear to be quite general and afford the formation of alchols, ketones, or acids. In such conversions, the primary chemical reaction step appears to be the protonation of the electrogenerated base (here the superoxide) by means of the organic substrate. A Perkin Markovnikov type reaction initiated by electrogenerated superoxide as a base was pointed out [270] with malonates $R^1R^2CH_2$ in the presence of α, ω-dibromoalkanes (see Scheme 48). However, the complexity of superoxide as reagent could be illustrated in the latter example, since ethers and epoxides were found as side products in the reaction mixture.



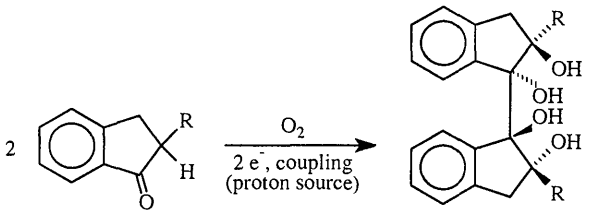
Scheme 48

Other reactions implying monoacidic malonates such as diethylmethylmalonate converted into diethylmethyltartronate in high yield [271] were reported. Anyway, the reactions that follow should be understood [271] on the basis that redox processes do occur, probably implying also $HO_2^{\bullet}$.



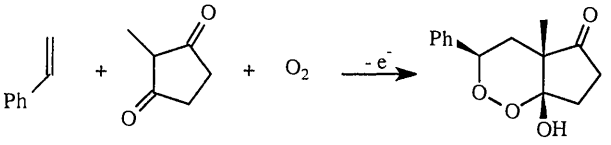
Scheme 49

The selectivity of CH hydroxylation by means of superoxide is well illustrated by the reduction of some acidic indanones in the presence of oxygen. Indeed, the CH hydroxylation and the reductive coupling of the carbonyl moiety can be achieved in one step (Scheme 50), concomitantly in high yield leading selectively to a tetrol [272].



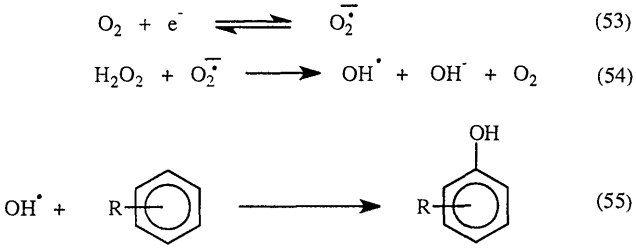
Scheme 50

Anodically initiated [2 + 2 + 3] cycloaddition reaction implying molecular oxygen; olefins and 1,3-diketone were also described [273] as yielding a peroxide found to be extremely stable.



Scheme 51

Finally, superoxide is able to catalyze [274] the decomposition of hydrogen peroxide according to the Haber–Weiss reaction [275]. This allows in the presence of hydrogen peroxide the simultaneous in situ reduction of oxygen and hydroxylation of aromatic rings by means of strongly oxidizing hydroxyl radicals. This reaction may be then regarded as an electrochemical Fenton's reaction. Hydrogen peroxide may be added to the solution or formed electrochemically from superoxide when the organic substrate possesses a sufficient acidity. Reactions of this kind can be also initiated by using an appropriate inorganic [$C^{(I)}/Cu^{(III)}$] redox pair [276] (Scheme 52). Addition of ferrous ions may also help to achieve such a reaction [277].

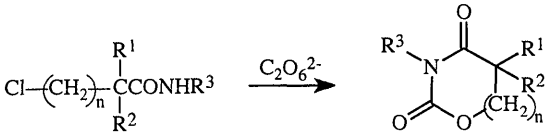


Scheme 52

The nucleophilic role of superoxide may be particularly well underlined when mixed O_2/CO_2 electrolyses are performed (solvent: DMF + tetraethylammonium perchlorate) to lead to strongly carboxylating species:

$$2\,CO_2 + 2\,O_2^{\cdot-} \longrightarrow C_2O_6^{2-} + O_2$$

The action of the transient reagent was tested on amides (ex-cell process) to point out the formation in high yields of oxazolidinediones [278].



Scheme 53

VII. ACTIVATION OF SULFUR BY MEANS OF SACRIFICIAL CARBON–SULFUR ELECTRODES

Sulfur S_8 is known to be electroactive. In reduction (in aprotic solvents like DMF), a first step (−0.55 V vs. ferrocene/ferrocenium) leading to S_8^{2-}, S_6^{2-}, and $S_3^{\cdot-}$ has been reported [279]. Surprisingly, the anodic activation of sulfur was only reported in molten salts ($AlCl_3$–NaCl at 150°C) and in fluorosulfuric acid. In molten electrolytes, the formation of species such as S_{16}^{2+}, S_8^{2+}, S_4^{2+}, and S^{2+} was proposed [280]. On the contrary, sulfur was shown [281] to dissolve in boiling $HFSO_3$ to give colored solutions with chemical formation of S^+ and S^{2+} as starting species in further oxidation processes. Thus, oxidized forms like S^{2+} and S^{4+} were reported to appear under electrolysis in aciditic melts as well as in basic melts.

However, sulfur is poorly soluble in common solvents at room temperature. Consequently, Berge [282] introduced sulfur in an electrode together with powdered graphite to assure sufficient electric conductivity (1 part carbon for 4 parts sulfur). Later on [283], improvement of the building of such a sacrificial electrode was proposed: A mixture of carbon + sulfur (1/2, w/w) was introduced in a test tube and heated at 130°C in an oven. After melting, a carbon rod or stainless-steel bar is introduced in the melt to assure electric contact. After return to room temperature, the test tube is broken to release the compact electrode. Similarly, by using this procedure, small-area electrodes could be built up by using Pasteur pipette for voltammetric analysis.

A. C/S Electrode as a Cathode

Ultraviolet–visible (UV-Vis) analysis was performed in the course of electrolyses in aprotic solvents to follow the formation of entities issued from the reduction of sulfur. At the beginning of electrolysis, the formation of $S_3^{\cdot-}$ and $S_8^{\cdot-}$ was clearly evidenced [284]. For larger amounts of electricity, S_4^{2-} was found to predominate in the cathodic bulk.

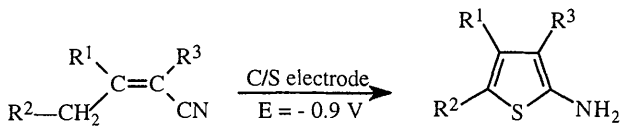
Most macroscale experiments run with C/S sacrificial cathode were conducted at a potential of −0.9 V (vs. SCE). Obviously, transients species coming from the fragmentation of sulfur (radical ions or anions) can act as reducing species and nucleophiles. Very often, it appeared difficult to discriminate between different chemical (and electrochemical) pathways. Preliminary experiments based on the nucleophilicity of reduced products of dissolved sulfur led with poor selectivity to dipropionitrile sulfide (Tomilov [285]) and to alkyl polysulfides (Paris [286]).

$$S_{dissolved} + 2\ CH_2{=}CH{-}CN \xrightarrow[\text{proton source}]{2e^-} S\,[CH_2{-}CH_2{-}CN]_2$$

$$S_{dissolved} \xrightarrow[\text{N, N-dimethylacetamide}]{2e^-,\ \text{alkyl halide (excess)}} R{-}S_x{-}R \quad (x = 3 - 8)$$

Scheme 54

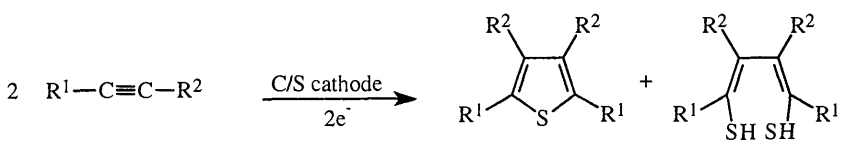
It appears that the sulfur–carbon electron can be a strong and efficient tool for creating, in situ, building blocks containing sulfur and disulfur bridges. Thus, reactions [287] with ylidenenitriles (R^1, R^2 are alkyl and R^3 is an electron-withdrawing group such as CN, $CO_2C_2H_5$, COC_6H_5), afforded the formation of 2-aminothiphenes in high yields (Scheme 55).



Starting ylidenenitrile			Isolated yields of 2-aminothiophene (%)
R^1	R^2	R^3	
	$-[CH_2]_4-$	CN	90
	$-[CH_2]_4-$	$CO_2C_2H_5$	61
	$-[CH_2]_4-$	COPh	65
	CH_3	CN	91
$PhCH_2$	CH_3	CN	72

Scheme 55

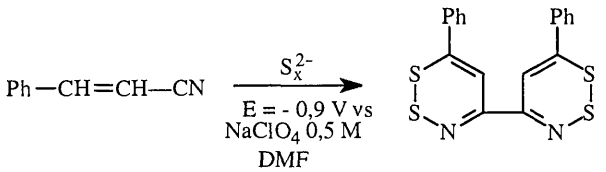
Another easy way to build up thiophene rings was to add sulfur anions on alkynes, often with a good regioselectivity. The possible transient specie as reported by Le Guillanton [288] could be $S_3^{\cdot-}$ (nucleophilic addition followed by a coupling).



Scheme 56

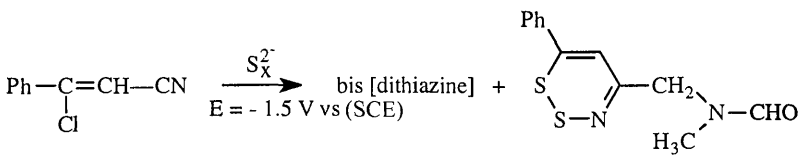
Alkyne			Isolated Yield (%)
R^1	R^2	Thiophene	Dithiol
H	Ph	no reaction	0
H	CO_2Et	10	0
Ph	CHO	82	0
Ph	CO_2Me	85	0
Ph	CN	80	0
CO_2Me	CO_2Me	32	53

Many reactions with alkenes (often activated) were investigated [289]. Many reactions implying these substrates are based on the nucleophilic addition of different S_x^{2-} formed during the cathodic corrosion of the C/S electrode. S–S bridge formation was frequently observed [283]. But the nature of the substrate (presence of a good leaving group) and that of the solvent (involvement of radicals stemed from the solvent) may also influence the final product distribution. Thus, cinnamonitrile gives a bicyclic product in high yield (75%) (Scheme 57).



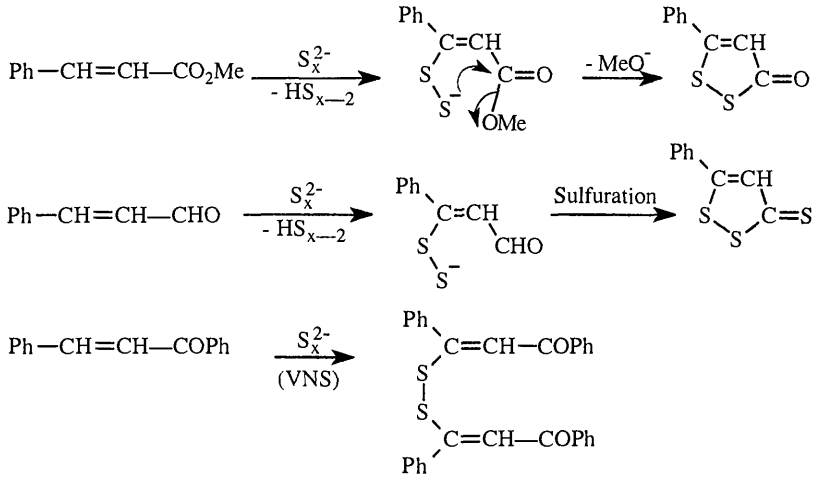
Scheme 57

On the contrary, 3-chloro-3 phenylpropenenitrile at a working potential of −1.5 V (thus allowing the concomitant cleavage of the C–Cl bond) led to the latter dimer, together with a dithiazine substituted by a DMF moiety as a side product (Scheme 58).



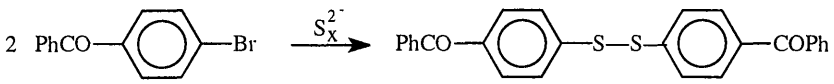
Scheme 58

In many cases, vicarious nucleophilic substitutions (VNS) were observed with activated olefins (Scheme 59).



Scheme 59

Substitutions of strongly activated aryl halides by S_x^{2-} were also reported [282]. Thus, 4-bromoacetophenone can afford a disulfide dimer (yield: 40%). Apparently the obtaining of such substituted compounds could be explained by a S_{RN}^1 process, but no experimental fact could presently support this.



Scheme 60

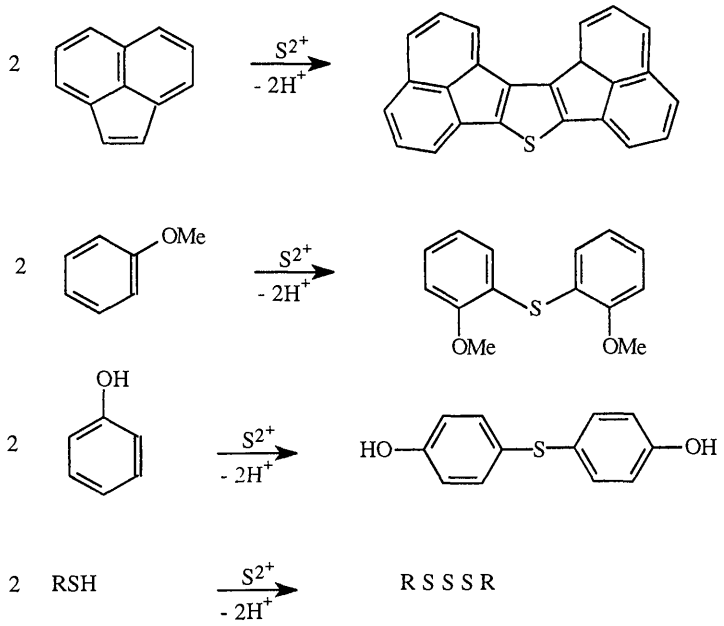
B. C/S Electrode as an Anode

When the C/S electrode is oxidized at high potentials (over +2.2 V vs. SCE), S^{2+} species can be easily generated. This electrophile appears to be stable in nonculeophilic solvents (such as methylene chloride) and is used after a desired concentration of S^{2+} is reached in the anolyte bulk. Additions and substitutions can then be achieved after addition of organic substrates and in the absence of current (two-stage process) (Scheme 61). Reactions with phenols, aromatic ethers, aromatic hydrocarbons, aromatic amines, and thiols were investigated and have demonstrated the convenience of use and the efficiency of this new and efficient electrochemically generated reagent [289–291].

$$S_8 \longrightarrow 8\,S^{2+} + 16e^-$$

CH_2Cl_2, +2.42 V vs. SCE

nBu$_4$NBF$_4$ 0.1 M

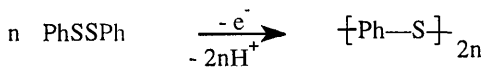


Scheme 61

The panel showing the many reacting possibilities of S^{2+} is briefly summarized in Fig. 6.

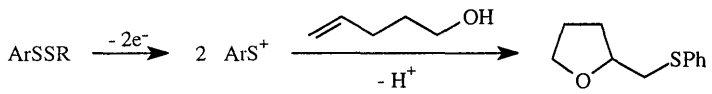
C. Other Electrophilic Species Containing Sulfur Produced Anodically

The electrochemical preparation of S^{2+} in organic media being reported, it is worth underlining the interest of disulfides bond under similar conditions. Thus, the anodic oxidation of diphenyl disulfide (in CH_2Cl_2 containing CF_3COOH) [293] may lead to an oligomer.



Scheme 62

However, the anodic reaction could be understood as a splitting of the S–S linkage, and the intermediate "PhS^+" (sulfonium cation) was postulated as the electrophilic transient species (to be added, for example, onto unsaturated bonds). Thus Steckhan [294] has proposed to cleave directly or indirectly (by means of Br– introduction in the anolyte as electrolyte) the central bond of diaryldisulfides and to add the produced electrophile onto ethylenic double bonds.



Scheme 63

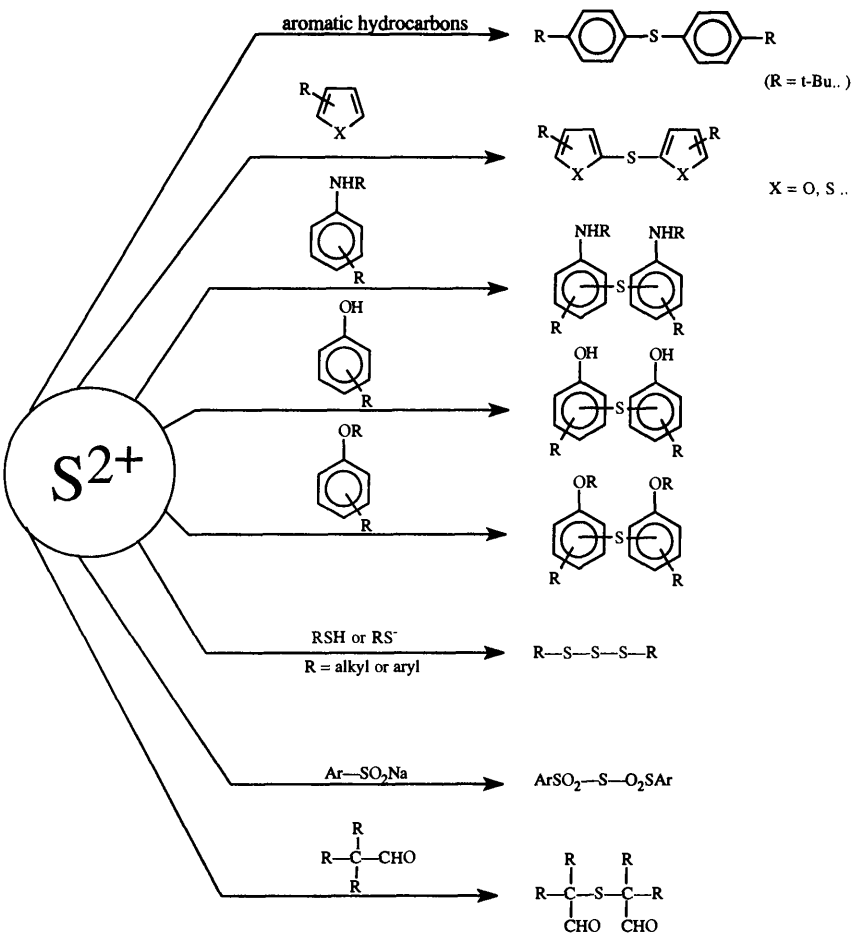
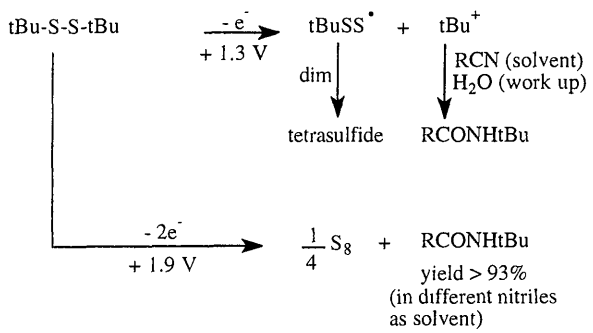


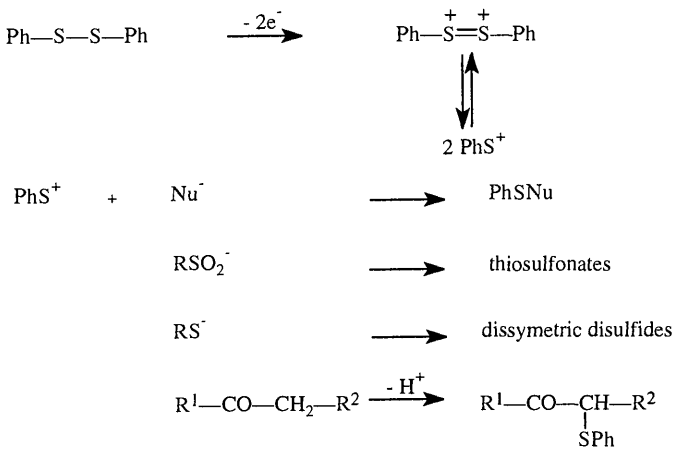
Figure 6. Some potentialities of S^{2+} reagent in acetonitrile or methylene chloride at room temperature, according to Le Guillanton [292].

More recently, the oxidation of aliphatic disulfides could be modulated (one-electron or two-electron process) according to the applied potential [295,296] and has afforded (Scheme 64) a convenient synthesis of amides.



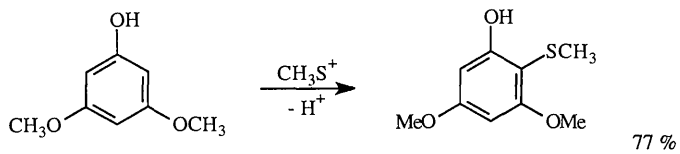
Scheme 64

The two-electron process allows the formation of "PhS^+" and "MeS^+" capable (Scheme 65) of reacting in situ with a large palette of nucleophiles [295,297].



Scheme 65

Similarly, electrogenerated "MeS^+" and "PhS^+" may afford [298] electrophilic substitution with phenols and ethers (Scheme 66). The addition of such electrophiles onto acetylenic bonds was also reported [297].



Scheme 66

VIII. INDIRECT REDUCTIONS BY MEANS OF SOLVATED ELECTRONS

At rather negative potentials, electrons may be released from the cathode in contact with the electrolyte, although an organic acceptor is present. The elctron may then end up in a potential energy "trap" possibly induced by its own polarization field. Such electrons possess strong reducing properties and are called solvated electron [299–302].

Reductions by means of electrochemically produced solvated electrons may be carried out under well-defined conditions [303,304]. The reduction then occurs by homogeneous electron transfer but without an organic or inorganic electron carrier present as defined previously. In this section are included only indirect reductions by solvated electrons in which their presence as intermediates has been demonstrated by means of physical methods, such as UV and electron paramagnetic resonance (EPR) spectroscopy.

The stability of solvated electrons in some polar solvents (liquid ammonia, HMPA, and amines) can be explained either by a solvent cavity in which the electron is trapped or by the presence of an "expanded orbital" occupied by the electron; this orbital could

involve the hydrogen atoms of the nearest solvent sphere around the metal cation (here used as electrolyte).

The electrochemical formation of solvated electrons (e_S) is usually very convenient since e_S solutions are known concentration can be prepared under coulometric control and consequently used in a strictly stoichiometric ratio. The generation of solvated electrons (usually understood as an electrochemical dissolution in a given polar solvent HS) can be represented generally as:

$$e^- \text{ cathode} + HS \rightleftharpoons e_{HS}$$

Such a reaction can be considered reversible. However, a slow reduction of the solvent may take place with hydrogen evolution. Therefore, indirect reductions by means of solvated electrons would be expected to occur only in solvents of quite low proton activity [305].

The cathode potential necessary for the production of solvated electrons is rather negative; the standard potential of the hydrated electron has been calculated to be −2.68 V versus NHE. Also, in other solvents compatible with its formation, very negative potentials must be used; for example, in liquid ammonia the generation of e_{HS} is achieved at −2.47 V versus $Ag/AgNO_3$ (0.1 *M*) [306], but the dissolution standard potential measured in HMPA was found to be −3.44 V versus $Ag/AgClO_4$ (0.1 *M*) [307]. Similarly, in methylamine ($t°$ − 50°C), a potential of −2.90 V versus $Ag/AgNO_3$ was reported [308].

Although solvated electrons were used to trigger chain reactions like $S_{RN}1$ reactions by primary scission of bonds [309], most reports in the literature mention the need for a proton donor. As a matter of fact, to render electron exchanges between e_{HS} and organic substrates irreversible, it appears necessary to add to the solvent some proton donor known to react very slowly with the solvated electron. Mixtures of HMPA–ethanol and HMPA–acetic acid have been used successfully [310] as proton rich solutions.

The most commonly used electrlyte in electrolysis mediated by solvated electrons is lithium chloride. The reasons are both its high solubility and the advantage of having in solution lithium ions known to form tight ion pairs. Tetrabuylammonium salts have also been employed successfully, however.

The electrode material may in certain cases affect the product distribution and the current yield, especially when reductions are run in amines. However, in other cases the material was shown not to be critical when such different materials as carbon, copper, platinum, lead, and aluminum were used as the cathode.

A. Use of Solvated Electrons in the Presence of a Proton Donor

The use of hexamethylphophoramide (HMPA) in the electrolytic reduction of substrates, such as benzene derivatives, aliphatic ketones, amides, and olefins, involves the intermediate formation of solvated electrons, since very negative potentials must be reached. The substrates are normally difficult to reduce. However, it is important not to add so much proton donor to the solvent that the rate of its reaction with the solvated electrons becomes too high. Generally, ethanol can be used as a cosolvent [311], and the best stability of the intermediate solvated electron combined with an optimum protonating efficiency was found to be the mxiture of HMPA–ethanol (33–66 mol mol^{-1}); the relatively high concentration of EtOH does not protonate e_{HS} because HMPA appears to be selectively adsorbed on the cathode interface and the reaction of e_{HS} with the substrated is fast. With such a ratio of ethanol, a maximum current efficiency was found [312].

The reduction of benzene itself may then be achieved either in LiBr + HMPA solution (water as proton donor) [313] or in ethanol–HMPA (66.6 mol% ethanol) at an aluminum catghode [311]; this gives a mixture of 22% cyclohexadiene, 10% cyclohexene, and 67% cyclohexane with an overall current efficiency of 95% [311]. The electrolysis must be carried out with a large excess of benzene. However, product distribution may depend on both the concentration of ethanol and the current density. As previously studied under chemical conditions (lithium metal added to ethanol in ammonia [314]), the product distribution would depend on the rates of reduction of benzene (k_b) and of cyclohexene (k_c) by the reducing species (here the solvated electron), the nature of the solvent, and efficiency of the proton donor in the considered solvent. In ethylenediamine, the ratio k_b/k_c was found to be equal to 200, and this value explains why reduction stops when an isolated double bond has been formed. In contrast, in HMPA–ethanol mixtures, the ratio k_b/k_c is only 1.4; this may explain the lack of selectivity and high yield of cyclohexane when a large excess of proton donor is used.

However, the product distribution may spectularly change to give selective formation of cyclohexadiene when lower current densities or a limited concentration of proton donor is used [311]. Under similar conditions, reduction of other aromatic compounds may be achieved. Phenol may be converted into cyclohexanol [312], and tetralin is reduced to decalin as the major product [315]. Other aromatic systems known to be quite easily reduced under conventional conditions in electrochemistry have also been tested using HMPA–ethanol–lithium salts as medium. The effective reduction of naphthalene and anthracene requires very negative potentials for the working cathode, suggesting that the potential–determining step is the release of electrons from the electrode to the solvent. Under such conditions, highly hydrogenated forms are isolated [310]. For example, anthracene is mainly reduced to 1,4,5,8,9,10-hexahydroanthracene and 1,4,9,10-tetrahydroanthracene.

Carbonyl derivatives and olefins are reduced by electrochemically produced solvated electrons. Camphor and 4-*t*-butylcyclohxanone thus form the corresponding alcohols in HMPA–ethanol; the proportion of epimeric alcohols would suggest that the reduction is thermodynamically controlled [316]. Surprisingly enough, sterically hindered alkenes are reduced at a rate only slightly lower than that of cyclohexene [311].

Acetamide may be converted into ethylamine and ethanol. In such reductions, the ratio of ethylamine to ethanol was found to be strongly dependent on the nature of the protonating reagent; better yields of amine were obtained when HCl was used as proton source [317].

B. Reduction in Amines

The Birch and Benkeser reactions of some unsaturated organic compounds [318 and references therein], which consist of a reduction by sodium or lithium in amines, can be mimicked electrochemically in the presence of an alkali salt electrolyte. The cathodic reaction is not the deposition of alkali metal on the solid electrode but the formation of solvated electrons. Most of the reactions described were performed in ethylenediamine [319] or methylamine [308,320]. A feature of these studies is variety introduced by the use of a divided or undivided cell. In a divided cell, the product distribution appears to be the same as that in the classic reduction by metal under similar conditions. In contrast, in an undivided cell the corresponding ammonium salt is formed at the anode; it plays the role of an in situ generated proton donor. Under such conditions, the proton concentration

during the electrolysis remains nearly unchanged, and this may affect the results of the electrolyses.

The reduction of aromatic hydrocarbons under these conditions has also been much studied. As expected, the reduction of benzene in methylamine containing lithium chloride is dramatically dependent on the design of the cell. Thus, reduction in an undivided cell affords 1,4-dihydrobenzene as a major product, but in a divided cell (the two compartments are separated by asbestos) cyclohexene is formed. Such fundamental differences have been ascribed to the fact that in the divided cell the isomerization of unconjugated dienes (and therefore a further reduction) should be favored by the increase in the basicity. Thus, the reduction of toluene under similar experimental conditions gives 2,5-dihydrotoluene in 95% yield in an undivided cell and a mixture of methylcyclohexenes in 83% yield [321] in a divided cell. The same mono-olefins were obtained chemically in a sodium–water–ammonia reduction of toluene at 0°C under pressure [322]. Other results concerning the electrolytic reduction of substituted benzenes dissolved in amines confirm that the influence of the separator is crucial [318]. It is of interest to compare the relative reactivity of solvated electrons toward an isolated double or triple bond and an aromatic ring. Thus, the electrolytic reduction of acetylenes in undivided cells (2-octyne, 3-octyne, and 5-octyne) gave mainly the corresponding *trans*-olefins, accompanied by only small amounts of the *cis* isomers [323]. Reductions of unconjugated arylalkynes (5-phenyl-2-pentyne) by solvated electrons gave the corresponding *trans*-olefin in good yield, although small amounts of products of further reduction were also obtained.

Although alkylbenzene is readily reduced, using $2\,F\,mol^{-1}$, to propylbenzene in methylamine in an undivided cell, the addition of a proton donor (such as ethanol) changes the product distribution; 2,5-dihydropropylbenzene is then the main product [324].

Amides of aliphatic acids are converted into alcohols in methylamine [325]. It appears that this is the only general reduction of all kinds of amides to alcohols.

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Electrogenerated Bases

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  A. Generation of EGBs
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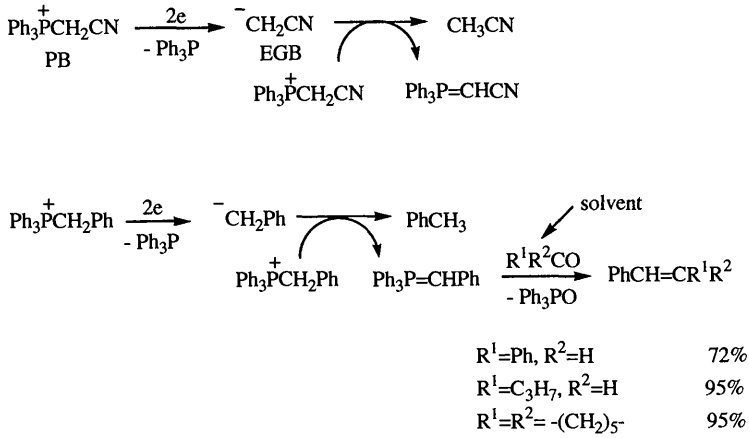
I. HISTORICAL

The environment of the cathode in electrolysis has long been known to be highly basic; indeed, the electrolysis of brine is the major route for the production of sodium hydroxide. However, it was not until 1966 that possibilities for the deliberate cathodic generation of bases, for a synthetic purpose, began to be explored.

Manuel Baizer was probably the first to recognize these possibilities, and he has recorded [1] that "you may now wish to place the phosphonium investigations in proper context and perspective. The 1966 paper by John Wagenknecht and myself in J. Org. Chem., **31**, 3885 had both synthetic and (rudimentary) mechanistic aspects. We concluded that: (1) The starting material $[Ph_3PCH_2CN]^+$ was sufficiently acidic to protonate anionic intermediates produced by electrolytic fission. (2) A result of the deprotonation of the above was the formation of the ylid; the latter was reduced at the second wave." Baizer went on to record that this paper [2] provided the impetus for subsequent work by Lund and Iversen [3] and by Shono et al. [4]. A slightly earlier paper [5] had demonstrated the analogous reductive cleavage of benzyltrimethylsulfonium salts, a theme echoed by Shono [6]. The chemistry referred to is summarized in Scheme 1, and the *electrogenerated base*

(EGB) is seen to be the carbanion derived from the *probase* (PB), which, in this case, is also the substrate to be deprotonated (the phosphonium ion).



Scheme 1

II. CLASSIFICATION AND PROPERTIES

EGBs are most commonly radical anions, anions, or dianions. A convenient classification of EGBs, used here, is according to the atom to which proton transfer takes place, typically nitrogen, oxygen, or carbon. Proton transfer to or from heteroatoms (N or O) is generally much faster than to or from carbon, when comparing reactions with similar driving forces. Often proton transfer to anions (or dianions) is faster than is proton transfer to radical anions (assuming equal thermodynamic basicity and the same type of atom). This is because radical anions that are viable as EGBs are unreactive in radical reactions and are generally extensively delocalized. Within different classes of EGBs there is therefore no simple relationship between thermodynamic and kinetic basicities.

Since all reactions discussed in this chapter are carried out in aprotic solvents, reference to known or estimated thermodynamic basicities relates to dimethyl sulfoxide (DMSO) unless otherwise noted. This is because DMSO is the polar aprotic solvent in which most thermodynamic acidities have been measured, especially by Bordwell and coworkers [7–10]. The term pK_a is used throughout, although in the literature terms such as pK_a, pK, and pK_{AH} are often used interchangeably for values determined in aprotic organic solvents. Values of pK_a determined in DMSO can usually be assumed to parallel values in dimethylformamide (DMF) [11], acetonitrile (MeCN), and other polar aprotic solvents, whereas pK_a values (and relative pK_a values) related to water and other hydroxylic solvents can be very different.

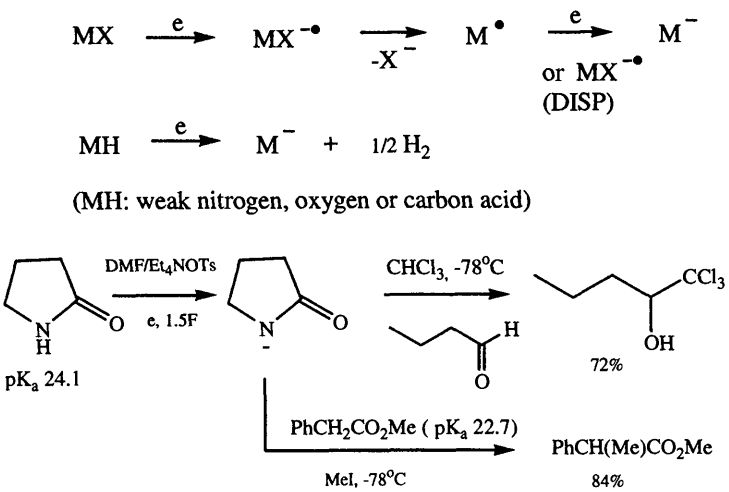
Basicity is not the only general property of radical anions, anions, and dianions. Each may act as a nucleophile, a single-electron transfer agent, and as a base—sometimes all three! As with conventionally generated bases, in what Baizer has dubbed "secular chemistry," sterically hindered EGBs are useful because proton abstraction becomes favored over nucleophilic substitutions and additions.

A. Generation of EGBs

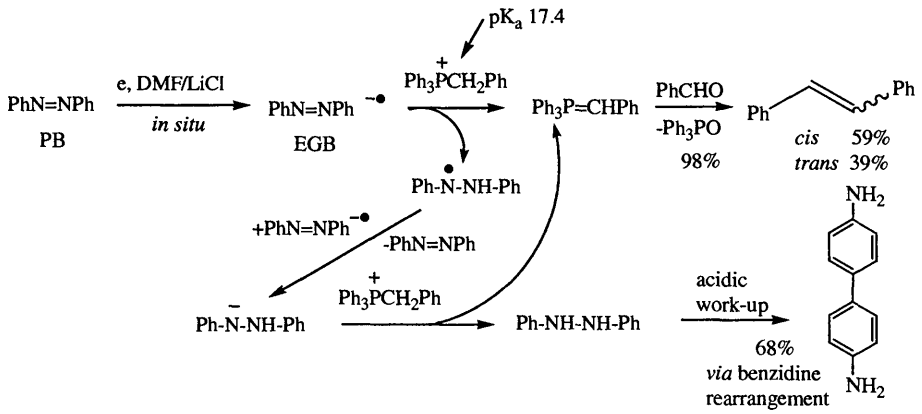
The EGBs may be formed by direct reduction of the substrate in an overall two-electron process, as is the case in Scheme 1. From neutral substrates EGBs are typically formed by reduction followed by cleavage and further reduction of a resulting neutral radical leading to an anion that acts as the EGB. This possibility is shown schematically in Scheme 2. In both cases the anion formed may then abstract a proton from the starting material (the probase), initiating another reaction of the substrate (e.g., formation of the ylide as in Scheme 1). A major disadvantage of this method is that only half of the substrate is undergoing the desired base induced reaction (except in cases that may be made catalytic; see Section III.C.2).

Probably of more significance for synthesis are examples where EGBs are generated from probases that are distinct from the acids acted upon. Formation of EGBs from such deliberately added probases (PBs) may be carried out in two ways. The first is ex situ where the EGB is generated by exhaustive reduction of the PB followed by subsequent addition of reactants. The use of an ex situ formed EGB is therefore similar to the use of an ordinary base. The advantage of this method is that even fairly easily reduced reactants can be used in combination with EGBs generated from PBs, which are very difficult to reduce. The formation of anions by direct reduction of weak nitrogen, oxygen, or carbon acids normally has to be carried out using this method, which is illustrated in Scheme 2 both generally and with reference to one of the more important examples. A disadvantage of the method is that the EGB has to be suitably long-lived in the solvent/electrolyte system.

The second is in situ, where generation of the EGB by reduction of the PB takes place in the presence of reactant(s). The advantage of this mode of operation is that the EGB can be short-lived, and the applied current can control the amount of base present at any time. The major disadvantage is that the PB must be more easily reduced than the reactant(s). This method is the one most commonly used. An early example of a radical anion EGB is shown in Scheme 3. The method has also frequently been used to generate carbanion EGBs from alkyl or aryl halides as illustrated schematically in Scheme 2.



Scheme 2



Scheme 3

B. The Efficiency of an EGB

For an EGB to work efficiently on a synthetic scale, the proton transfer reaction [Eq. (1)] has to be effectively irreversible. This may be achieved in several ways.

$$EGB + HS \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} EGBH^+ + S^- \quad (1)$$

1. In this case the equilibrium constant ($K_1 = k_1/k_{-1}$) for reaction (1) is large and the EGB is thermodynamically a much stronger base than the conjugate base of the substrate, S^-. Consequently, all of the substrate may be deprotonated by an EGB formed either in situ or ex situ and converted into product by addition of another reactant in a subsequent step. This situation is rarely met in reactions where EGBs have advantages over conventional, chemically formed, bases.
2. If either $EGBH^+$ or S^- (or both) is removed from the equilibrium in an irreversible follow-up reaction, the formation of products may, as with ordinary bases, be efficient when $K_1 \ll 1$. (a) In the common case of a radical anion ($B^{-\bullet}$) acting as an EGB, protonation gives a radical ($BH^\bullet$). This is quickly removed from the equilibrium, since neutral radicals formed by protonation of radical anions are normally more easily reduced than the PB, most commonly in a rapid disproportionation reaction with the EGB ($B^{-\bullet}$) [Eq. (3)].

$$B^{-\bullet} + HS \; (\rightleftharpoons) \; BH^\bullet + S^- \quad (2)$$

$$B^{-\bullet} + BH^\bullet \longrightarrow B + BH^- \quad (3)$$

$$BH^- + HS \longrightarrow BH_2 + S^- \quad (4)$$

The anion BH^-, formed in Eq. (3), is thermodynamically a stronger base than $B^{-\bullet}$ and will react with another molecule of substrate, as in Eq. (4). Each PB will therefore consume a total of two protons (and two electrons). An exception to the fast removal of $BH^\bullet$ by further reduction is sometimes found for radical anion oxygen bases derived from carbonyl compounds, as discussed in Sec. III.B.2. Radical anion EGBs are usually derived from aromatic systems such as aromatic hydrocarbons, *N*-heteroaromatic systems or azo-arenes. An example was given in Scheme 3 [3]. Radical anion EGBs are normally pro-

duced in situ, since slow dimerization or disproportionation to dianions excludes formation of stable solutions of the radical anions. The in situ generation, however, limits the usefulfness of most aromatic hydrocarbons, since their reduction takes place at potentials where many reactants are also undergoing reduction. One further disadvantage of aromatic hydrocarbons as PBs is that the proton transfer is to carbon in a delocalized system, and the rate constant for proton transfer is therefore small (discussed earlier) even for (strongly) exergonic reactions. (b) Irreversible follow-up reaction of the deprotonated substrate, S^-, is a common way in which the initial proton transfer equilibrium is driven toward products (see, e.g., Schemes 18 and 25). A disadvantage is that if the intended follow-up reaction is with an added electrophile, the EGB may itself react with the electrophile, or, if the EGB is a dianion, the monoprotonated form may react with the electrophile. Examples of these complications are given later.

Most studies involving the deliberate application of EGBs have been concerned with seeking synthetic advantage. Such advantages might include control of the concentration of a base through manipulation of current density (for EGBs formed in situ); control of the strength of a base by the ability to form it in various solvents and in the presence of a range of counterions; convenient electroinitiation of base-catalyzed processes; and "clean" technology through the avoidance of stoichiometric amounts of base. The last possibility requires another feature of a PB/EGB system: that is, the product of protonation of the EGB should be easily converted back into the PB, ideally in a "one-pot process."

III. SYNTHETIC UTILIZATION OF ELECTROGENERATED BASES

A. Electrogenerated Nitrogen Bases

1. Azo Compounds as Probases

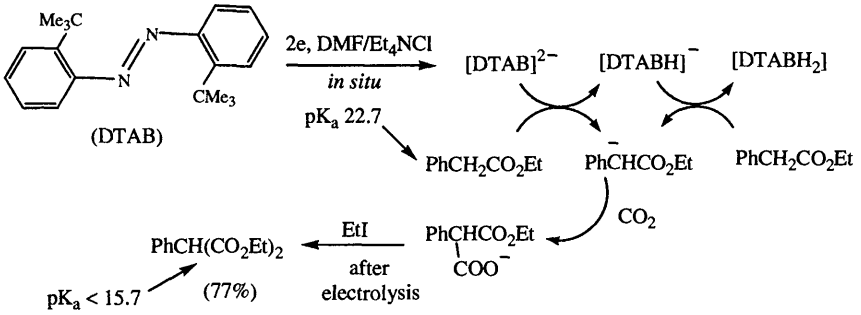
We consider here the detailed consequences of the reduction in aprotic solvents, two sequential steps, of azobenzene and analogous aromatic azo compounds [12–15]. The dianion is considerably more basic than the radical anion, and the dianion is only long-lived in very dry nonacidic solvents [14–16]. Both the dianion and the radical anion derived from azobenzene and substituted azobenzenes have been used as EGBs. The anion resulting from protonation of the dianion is less basic (by several pK_a units) than the dianion itself but more basic than the radical anion [15]. Using the dianion as EGB may therefore result in mono- or diprotonation, depending on the strength of the acid. The radical anion leads directly to hydrazobenzene due to the further reduction of the protonated radical anion (Scheme 3) and fast protonation of the more basic anion [pK_a(Ph-NH-NH-Ph) = 26.1, pK_a(Ph-NH-N^--Ph) $\approx$ 31, pK_a(Ph-NH-N$^{\cdot}$-Ph) < 20].

One peculiar feature of the monoprotonated dianion of azobenzene (Ph-NH-N^--Ph) is that it is oxidized at the potential of radical anion oxidation and not, as expected, in a separate step anodic of the radical anion reoxidation [15,17]. This behavior has been explained as catalyzed oxidation of the anion [15].

Azopyridines are in general more easily reduced to dianions than azobenzene, but the dianions are also less basic and of little preparative value [14,18]. Whether the dianion of azobenzene is able to deprotonate MeCN (pK_a = 31.3) has been discussed [12,14,16].

However, efficient generation of $^{-}CH_2CN$ takes place at the second reduction potential of azobenzene using MeCN as solvent, which has been used in preparative-scale reactions initiated by cyanomethylation of benzamide [19] carbonyl compounds and α, β-unsatured nitriles either present in situ [18,20] or added subsequently [21–23]. However, product mixtures are often complex, and although the products indicate the range of acid–base reactions possible, and the reacivity of the species generated, the electrochemical method offers little preparative advantage for these conversions.

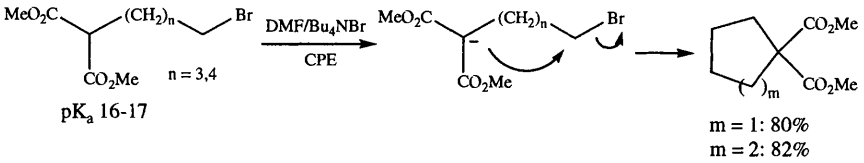
The dianion of azobenzene and the dianions of substituted azobenzenes have been used as EGBs for deprotonation of ethyl 2-phenylacetate ($pK_a = 22.7$), as in Scheme 4 [16]. Using azobenzene as PB resulted in carboxylation not only of the deprotonated substrate but also of the azobenzene. This side reaction could be avoided using the 2,2′-di-*t*-butylazobenzene as PB instead. Unsubstituted azobenzene was shown to undergo carboxylation already at the radical anion stage, whereas 2,2′-di-*t*-butylazobenzene does not show reactivity as a nucleophile toward CO_2 either at the radical anion or at the dianion stage on a voltammetric time scale [16]. Azobenzene, reduced in DMF at both the first and second reduction potential in the presence of methyl iodide, gives a mixture of mono- and *N*, *N*′-dimethylated hydrazobenzene [24]. Another disadvantage of unsubstituted azobenzene as a probase on a multigram scale is the conversion of hydrazobenzene into the potent carcinogen, benzidine, on acidic aqueous work-up (Scheme 3). This inconvenience is removed by 2- or 2,4-alkyl substitution that also enhances the basicity of the EGBs (radical anions or dianions) by inhibiting delocalization of charge by sterically preventing coplanarity of the aryl rings.



Scheme 4

Scheme 5 summarizes some recent examples of the unambiguous use of azobenzene radical anion [25–28]. The reactions in Scheme 6 are probably initiated by the dianions of either hexa-*i*-propylazobenzene or 2,2′-di-*t*-butylazobenzene on the basis of the weak acidity of the substrates involved. However, the reactions were actually run [29–31] at potentials controlled in the range of −1.8 to −2.7 V against the silver wire "pseudo reference electrode," which is notoriously variable. The last value almost certainly corresponds to reduction to the dianion, but for the electrolysis at −1.8 V (vs. Ag wire) the blue color of the radical anion was observed throughout. This implies that the radical anion is not rapidly protonated, and it may be that protonation actually occurs via disproportionation to the dianion.

EGB : $PhN{=}NPh^{-\bullet}$ generated *in situ*



pK_a 16-17

m = 1: 80%
m = 2: 82%

Alkene , yields 60-80% depending on R

1 : 1

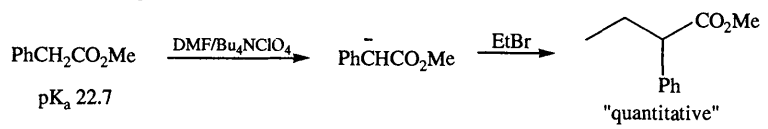
R	pK_a
CH_2CO_2Et	18.6
$CH(Me)CO_2Et$	18-19
CH_2CN	16.4
CH_2Ph	27.6
$CHCl_2$	?

NB: azobenzene dianion active base via disproportionation

Scheme 5

EGB : $ArN{=}NAr^{\bullet -}$ or $ArN{=}NAr^{2-}$ generated *in situ*, see text.

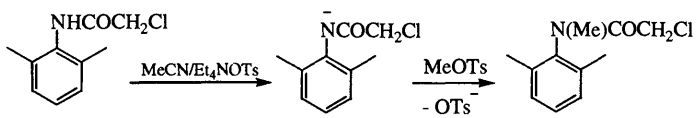
Ar = 2,4,6-tri-*i*-propylphenyl:



pK_a 22.7

"quantitative"

Ar = 2-*t*-butylphenyl:



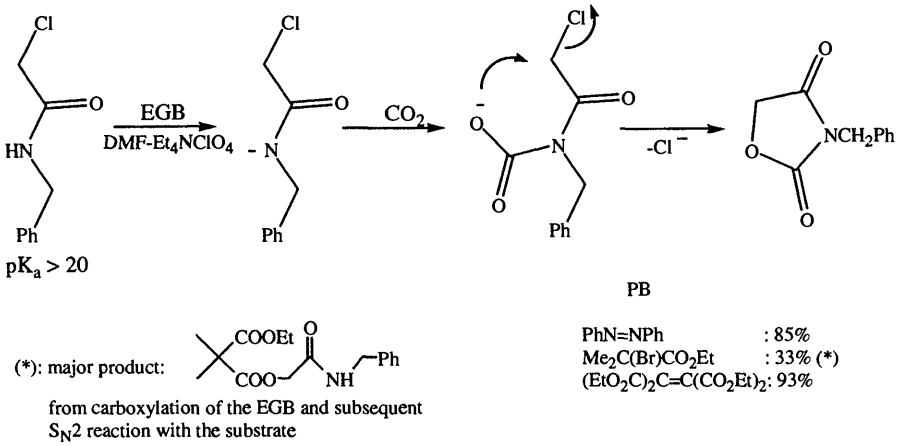
pK_a 21-22

"quantitative"

Scheme 6

The recent work [32] of Inesi et al. allows for a single-reaction comparison of the efficacy of several probases (Scheme 7). Azobenzene comes out well in this comparison, which includes the use of tetraethyl ethenetetracarboxylate and a carbanion derived by

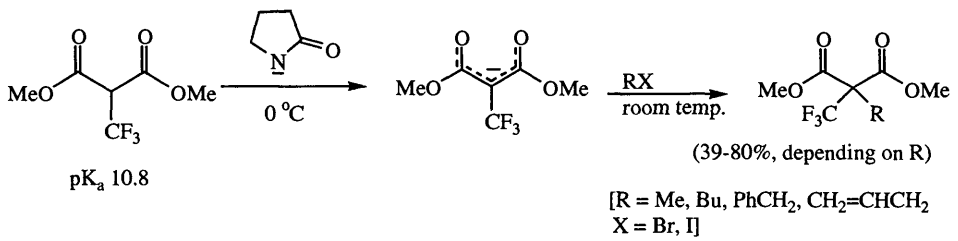
reductive cleavage (see Secs. III.C.1 and III.C.2 for discussion of the last two types of PBs).



Scheme 7

2. Amide Anions as Electrogenerated Bases

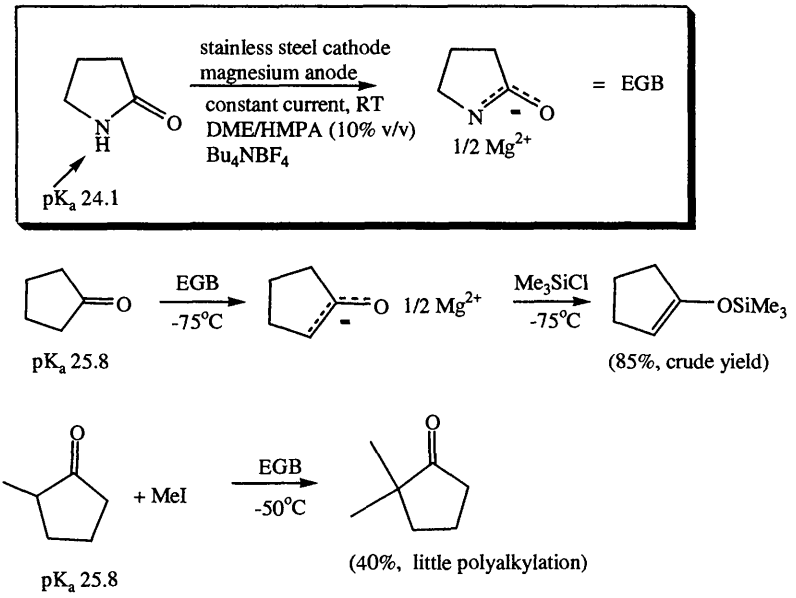
The production of the 2-pyrrolidone anion by direct cathodic electrolysis of 2-pyrrolidone has been referred to [33,34] and examples of its use as an ex situ reagent presented (Scheme 2). Despite the early promise of this conveniently prepared strong base [pK_a(2-pyrrolidone) = 24.1], it is only recently that its advantages have been exploited more widely. The 2-pyrrolidone anion is formed as an ex situ reagent by direct cathodic electrolysis at $E_p^{red} \approx -2.5$ V (VS.SCE) and a further example of its use is given in Scheme 8, in which reaction the tetraalkylammonium counterion was essential in preventing defluorination [35].



Scheme 8

More recently, the fashion for using sacrificial anodes has spread to this area and the magnesium cation-stabilized 2-pyrrolidone anion has been used [36] to good effect in the synthesis of a number of silyl enol ethers (Scheme 9). High yields and, where relevant, high stereoselectivity are claimed. The reaction conditions are simple (constant current, undivided cell, stainless-steel cathode, magnesium bar anode), but the electrolyte (dimethoxyethane-Bu_4NBF_4 with 10% v/v HMPA) raises problems. The HMPA is required to give acceptable conductivity in the preparation of the EGB but is also crucial in avoiding strong ion pairing between Mg^{2+} and the EGB (which decreases the reac-

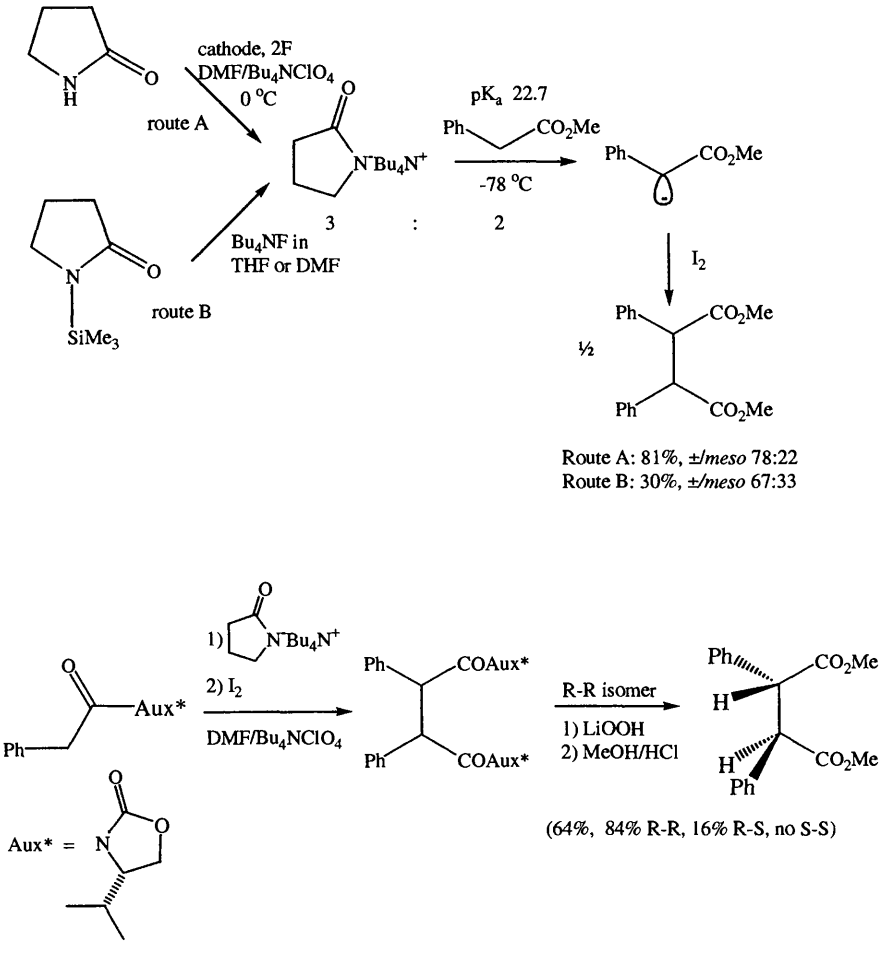
tivity of the EGB) and in equilibrating the enolate *Z*-form [36]. However, in many laboratories HMPA is a banned substance because of its high carcinogenicity. It is reported that it may be replaced with $Me_2N(CH_2)_2NMe_2$ (TMEDA). The solution of the magnesium-stabilized anion may be stored at room temperature for up to 10 h. Further examples have been reported [35,37] of the application of the 2-pyrrolidone anion to enolate formation with subsequent alkylation, and representative cases are included in Scheme 9.



Scheme 9

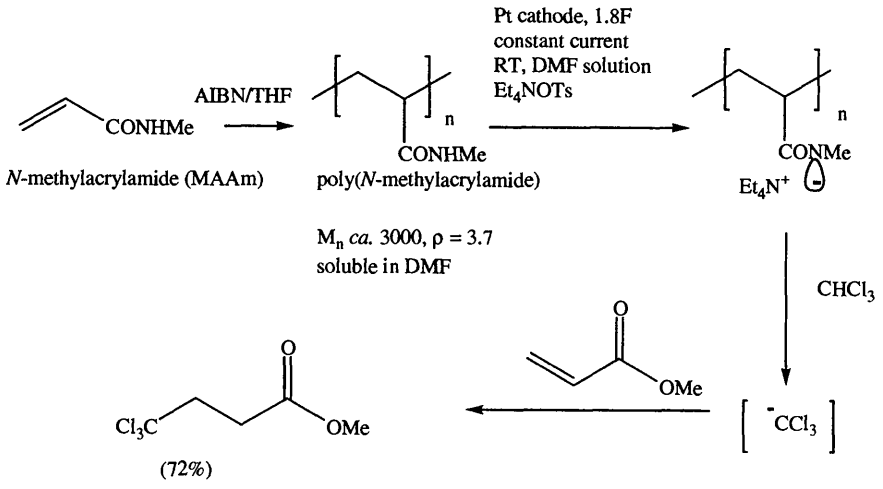
In the last example in Scheme 9, MeI was added to the EGB solution simultaneoulsy with the ketone to prevent isomerization of the enolate, although the competing alkylation of the EGB resulted in low conversion of the ketone.

Matsumura and his coworkers [38] have employed the 2-pyrrolidone anion, in DMF solution, to deprotonate arylacetic acid esters with subsequent oxidative dimerization of the corresponding carbanions. This study includes a useful comparison between the electrochemical and chemical generation of the 2-pyrrolidone anion (by fluoride anion displacement in *N*-trimethylsilyl-2-pyrrolidone). The advantage lies with the electrochemical route, which gave yields of final product of ~80%, compared with the ~30% obtained with the chemically generated base (Scheme 10). The overall process, formation of dimethyl 2,3-diphenylsuccinates, is not only efficient and convenient but also operates with high diastereoselectivity when under the control of an oxazolidinone chiral auxiliary (Scheme 10).



Scheme 10

Polymer-supported reagents are becoming widely used in organic synthesis. An ingenious and possibly very significant example of EGBs generated from functional polymers (polyacrylamides) has been reported [39], and their major features and applications are displayed in Scheme 11. The effective base is in all cases an amide anion of the 2-pyrrolidone anion type, and the system is very effective in a model conversion (addition of Cl_3C^- to methyl acrylate). Since ex situ formation of EGBs from amides is the result of direct reduction with hydrogen formation, the monomeric as well as the polymeric EGBs are reprotonated in use and recovered as the PB (parent amide). This ready recovery of PB was nicely illustrated for the polyacryloamides, which were repeatedly reused [39].

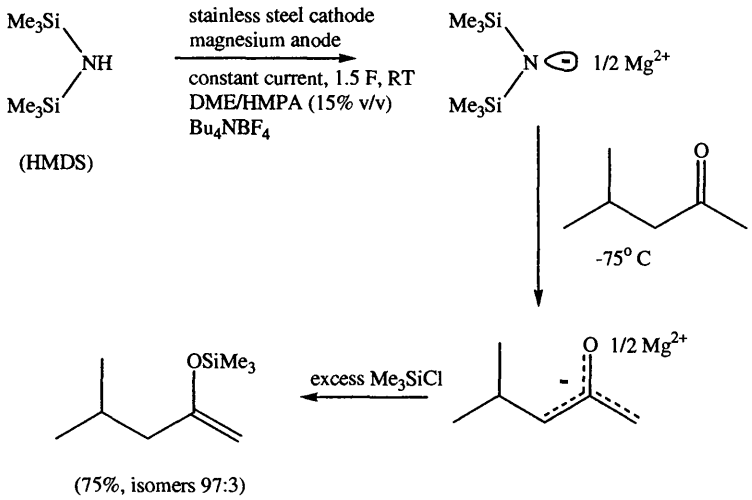


[77-94%, using copolymer of MAAm (57%) and styrene (M_n = 8700, ρ = 1.7)]

Scheme 11

3. Other Electrogenerated Nitrogen Bases

Lithium diisopropylamide (LDA) is probably the yardstick against which other strong bases are judged. The 2-pyrrolidone and the polyacrylamide bases are comparable. The amide anions initiate alkylation or silylation of enolates in two steps (deprotonation of the substrate followed by alkylation/silylation). To avoid alkylation/silylation of the EGB [40], the proton transfer equilibrium has to be pulled toward products by the thermodynamics of the proton transfer reaction, and consequently stronger bases are required for deprotonation of the least acidic ketones. A stronger base and notably weaker nucleophile is the anion of hexamethyldisilazane (HMDS), which is electrogenerated [40] as its magnesium salt in dimethoxyethane–HMPA (15% v/v). For this base a one-step procedure could actually be applied using Me_3SiCl as the silylation reagent without any silylation of the EGB. HMDS is commercially available and relatively cheap. It is unfortunate that the presence of carcinogenic HMPA effectively rules this system out for widespread use, because in other respects it behaves very much like LDA. There is a suggestion [40] that *N*-methyl-2-pyrrolidone (NMP) might substitute for HMPA, but more work is needed to optimize conditions with this alternative cosolvent. The HMDS anion promotes normally difficult alkylations with high regioselectivity (Scheme 12).



Scheme 12

Nitrogen heteroaromatics are expected to be useful probases. The cathodic reduction of phenazine resembles closely that of azobenzene [41,42], and studies of the kinetics of proton transfer indicate [43] that the kinetic basicity of phenazine radical anion is comparable to that of azobenzene radical anion. Phenazine as probase does not appear to have been used in electrosynthesis.

There is one report concerning the use of electrogenerated acridine radical anion as EGB, namely to induce the elimination reaction depicted later in Scheme 17 leading to the substituted cyclobutene [44]. The workup, however, was found to be easier using superoxide anion as EGB; see Sec. III.B.1.

B. Electrogenerated Oxygen Bases

1. Dioxygen as Probase

Dioxygen is conveniently reduced to superoxide anion ($O_2^{\cdot-}$) by reduction at about -1.0 V (vs. SCE) in acetonitrile or DMF; dioxygen is introduced by bubbling through the electrolyte solution and is therefore present in excess.

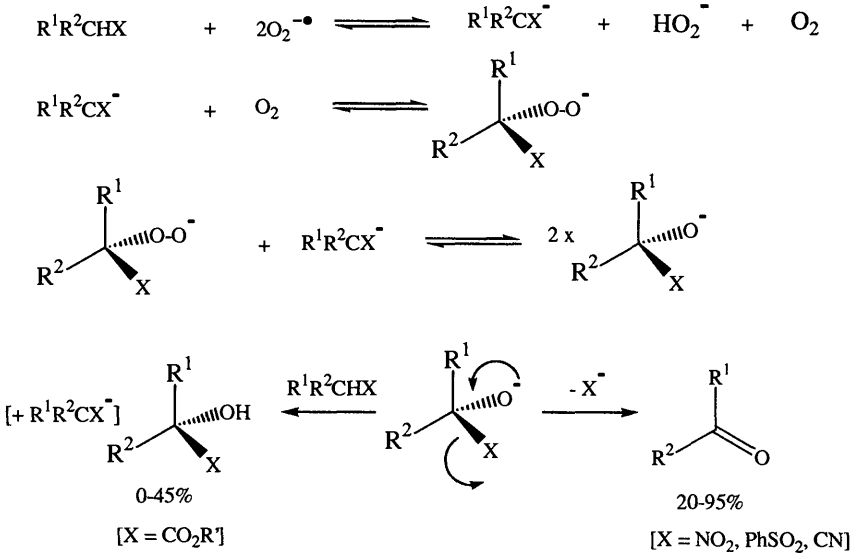
The properties of superoxide anion have been well reviewed [45,46]. In water it is a relatively weak nucleophile, whereas in aprotic solvents, such as those commonly used for electrolysis, it is a powerful nucleophile. Its basic properties stem from the driving force of the disproportionation [45,46] depicted as Eq. (5), similar to the disproportionation discussed for organic radical anions in Sec. II.B. Thus, although superoxide anion itself is a relatively weak Brønsted base—$pK_a(HO_2^{\cdot}) \approx 12$ in DMF [46]—the overall equilibrium constant for reaction (5) is of the order of 10^5 for simple alcohols and water ($pK_a \approx 30$) in DMF [46]. However, the rate-determining protonation of the superoxide anion is a slow reaction with a second-order rate constant around $10^{-3}\ M^{-1}\ s^{-1}$ [46].

$$2\,O_2^{\cdot-} + HA \rightleftharpoons O_2 + HO_2^- + A^- \tag{5}$$

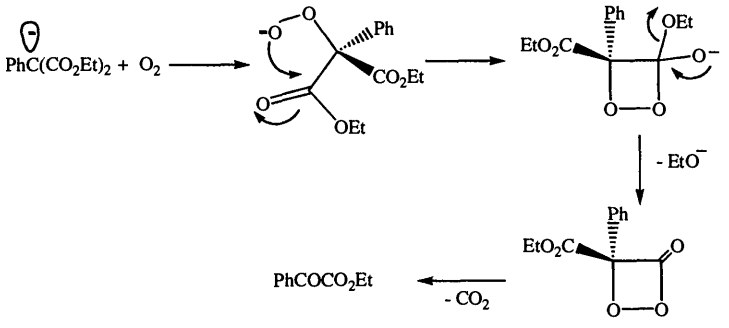
The commonly used method of generation of superoxide anion (bubbling of dioxygen into the catholyte) allows the maintenance of an excess of dioxygen so that carbanions formed by proton donation to superoxide anion may react further with O_2. Consequently, many synthetically interesting reactions involve not only deprotonation but also oxidative

follow-up reactions. In most cases charge consumption is recorded [47] as being in the range 0.23–1.0 F, which implies catalytic processes.

The most important types of reaction are with substituted malonate esters [47], monoesters [48], amides [48], nitriles [48,49], sulfones [48] and *sec*-nitrolkanes [50]; see Table 1. The oxidative follow-up reactions mean that useful conversion into aldehydes and ketones is possible. Examples are given in Scheme 13, which also repeats the mechanistic suggestions in the literature [47], which, without experimental support, postulate reaction between two anions as a key step. More pragmatically, it is observed that esters in which the electron-withdrawing group, X, is not a good leaving group form alcohols and the enones are converted into epoxides when, for example, Ph_2CHCN is used to form the active epoxidizing reactant. The conversion into carbonyl compounds depends on the electron-withdrawing groups also being good anionic leaving groups. In support of this, the expulsion of $PhSO_2^-$, from sulfones, and of NO_2^-, from nitroalkanes, was demonstrated, but there was no direct evidence for expulsion of cyanide anion. It would be prudent to assume that this is indeed a product. A representative selection of the conversions possible via Scheme 13 is given in Table 1. However, the second entry in Table 1 does not conform to the general scheme and is probably better explained by the route suggested in Scheme 14.



Scheme 13



Scheme 14

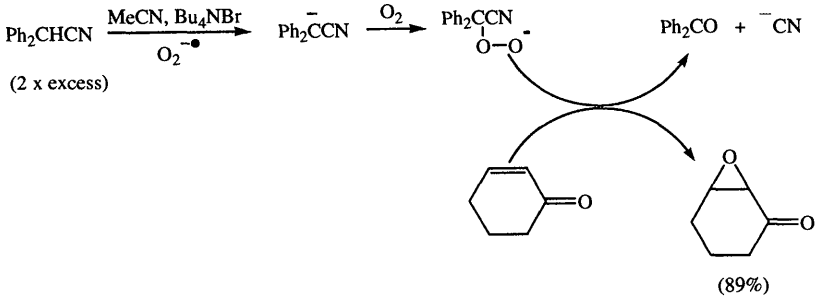
Table 1 Reaction Between Electrogenerated Superoxide Anion and Carbon Acids in the Presence of Oxygen in DMF

Carbon acid	Charge (F)	Product	Yield (%)	Ref.
$(EtO_2C)_2CHMe$	0.17	$(EtO_2C)_2C(OH)Me$	95	[47]
$(EtO_2C)_2CHPh$	0.23	$PhCOCO_2Et$	74	[47]
$MeCH_2CO_2Et$	1.0	$MeCH(OH)CO_2Et$	15	[48]
		$MeCH(OH)CO_2H$	35	
$Ph(Me)CHCONEt_2$	1.2	$Ph(Me)C(OH)CONEt_2$	53	[48]
Ph_2CHCN	0.8	Ph_2CO	95	[48,49]
EtO_2CCH_2CN[a]	1.3	EtO_2CCHO	72	[48,49]
1-Nitrocyclohexane[a]	1.0	Cyclohexanone	70	[50]
5-Nitrohexan-2-one	1.0	Hexan-2,5-dione	82–86	[50]
Ph_2CHSO_2Ph	2.0	Ph_2CO	90	[48]

[a]In MeCN.

The examples given in the schemes and in Table 1 are quite representative but many more may be found in the literature referred to and in an earlier review [51].

An especially elegant use of superoxide anion, in combination with dioxygen, is as both an EGB and as an epoxidation reagent [52]. In this way the RO_2^- species, formed from the carbanion R^-, reacts in situ with an enone, which is converted into the epoxide (Scheme 15). Specifically, the "carrier" ($PhCH_2CN$), which has been dubbed an "auxiliary carbon acid," is deprotonated by the superoxide anion, and the resulting anion reacts with O_2. The $Ph_2C(CN)O_2^-$ species thus formed reacts in situ with an enone, which is converted into the epoxide with elimination of cyanide anion from the "carrier" and concomitant formation of ketone (Scheme 15). Another possible auxiliary carbon acid is $MeCH(CO_2Et)_2$ and, apart from the example in Scheme 15, 4,4-dimethyl-2-cyclohexen-1-one, 4-methylpent-3-en-2-one, and *trans*-chalcone ($PhCH{=}CHCOPh$) may be converted [52] into the corresponding epoxides in >80% yield.

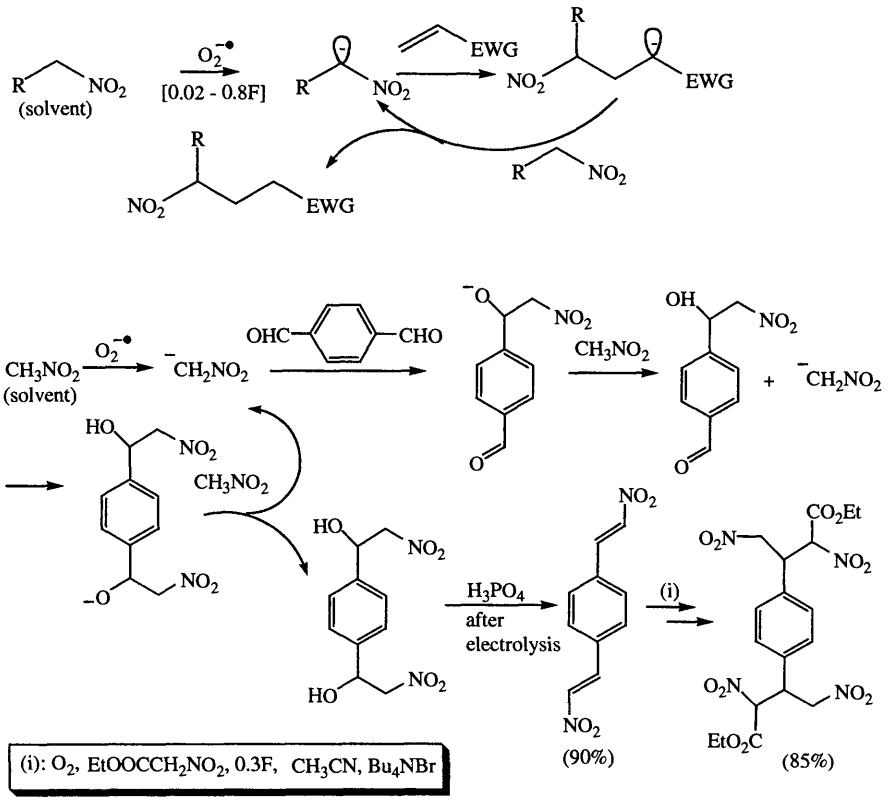


Scheme 15

Superoxide anion formed in situ in a solution exposed to air (i.e., with only a small concentration of O_2) has been used purely as an EGB to generate, by analogy with other well-tried chemical alternatives, nitroalkane anions that may add to activated alkenes (Michael addition) or to carbonyl compounds [53–55]. Selected examples are given in Scheme 16, but the reaction seems to be quite general, although the advantage over

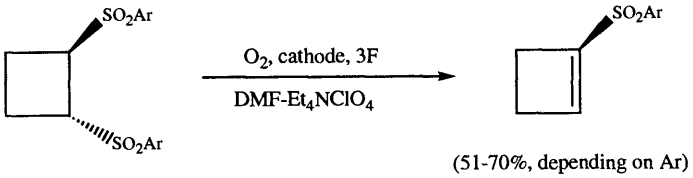
comparable conventional base-induced conversions is not clear. In particular, however, some examples are aimed at pursuing "solventless" conditions, that is, electrolysis of a stoichiometric mixture of the two liquid reactants.

In the first [55] of the examples given in Scheme 16, only a catalytic amount of superoxide anion is necessary since the addition product may act as a base toward the nitroalkane (in competition with addition to another molecule of activated alkene whereby a polymerization would be induced). Using the nitroalkene as solvent favors the proton-transfer pathway [55]. In some cases, however, better yields of the Michael addition product were obtained if the nitroalkane anion was formed ex situ and the activated alkene added in subsequently [55]. In the other example in Scheme 16 the nitroalkene anion formed by reaction of the nitroalkane (used as solvent) with superoxide anion is added to an aldehyde, and also in this case only initiation by the EGB is necessary. The nitroalchol or bis(nitroalcohol) formed could be dehydrated in almost quantitative yields in dilute H_3PO_4 in a subsequent step [54,55]. Starting with terephthalaldehyde, this process thus provides a convenient route to the highly electron-deficient 1,4-bis(nitroethene) derivative. This bis(activated alkene) could be used as the Michael acceptor in a superoxide anion-initiated reaction with a (strong) carbon acid in MeCN (Scheme 16). A strong carbon acid ($EtOOCCH_2NO_2$, $pK_a = 9.2$) is required for protonation of the addition product necessary in preventing polymerization.



Scheme 16

Displayed in Scheme 17 is another case of pure EGB behavior of superoxide anion. The base-catalyzed sulfone anion expulsion giving a previously unknown activated cyclobutene is not catalytic in EGB [44].

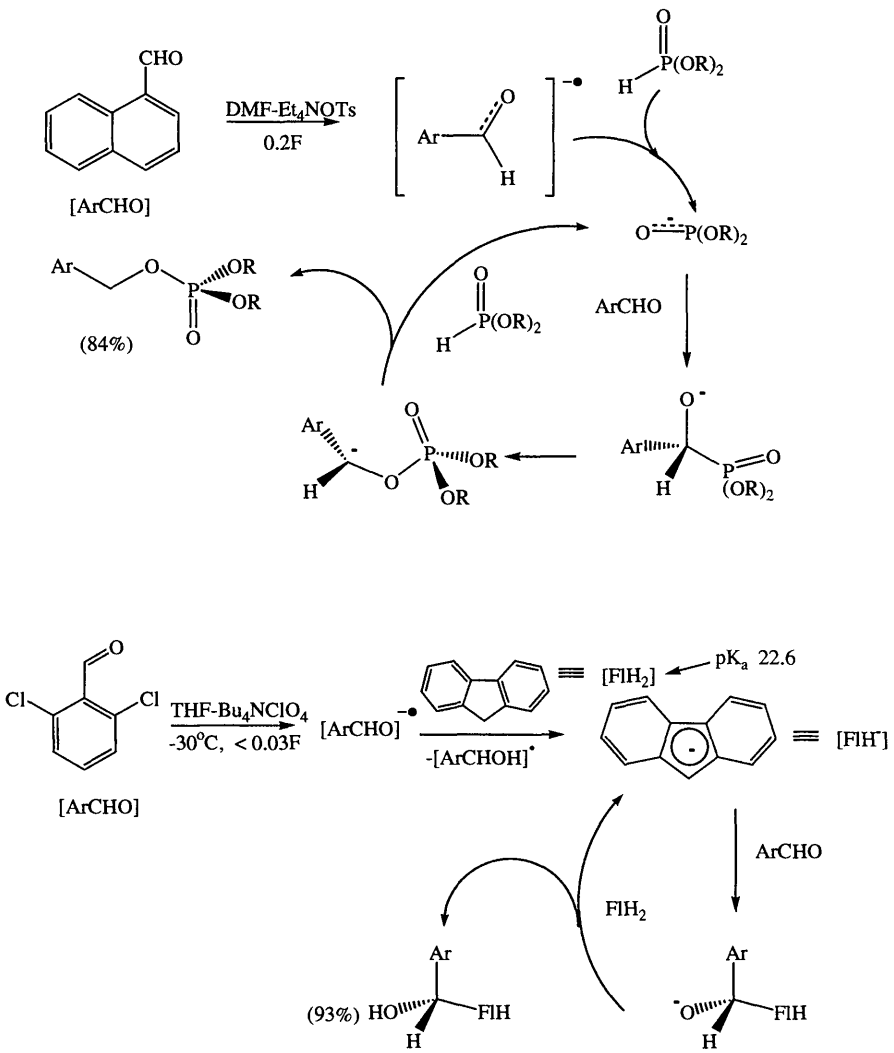


Scheme 17

2. Other Electrogenerated Oxygen Bases

Radical anions formed by cathodic reduction of ketones and aldehydes are potentially strong EGBs. In an early demonstration [4] of the effectiveness of EGBs, the coelectrolysis of carbonyl compounds (benzaldehyde, butyraldehyde, and cyclohexanone) and phosphonium salts (Ph_3PRX, X = I, Br, or Cl, R = Me, Et, $PhCH_2$, CH_2CO_2Me) gave mostly high yields of alkene by Wittig reaction (Scheme 1). The carbonyl compounds were used as solvent, but the electrolysis conditions are not sufficiently well described to determine whether the phosphonium cation or the carbonyl compound was undergoing reduction. In at least some of the examples the effective base must have been the carbonyl radical anion. In each case the yields were high when benzaldehyde (relatively easily reduced) was involved; for the aliphatic carbonyl derivatives, yields were good when R = benzyl in the phosphonium salt. In this case it is likely that the relevant ylide was formed by direct reduction.

The better defined participation of carbonyl radical anions is evident [56] in the electrocatalyzed reaction between aromatic carbonyl compounds (or other easily reduced carbonyl compounds) and dialkyl phosphonates (Scheme 18). In similar vein, and also in Scheme 18, radical anions generated from aromatic aldehydes may abstract a proton from an added acidic hydrocarbon such as fluorene (pK_a 22.6) or indene (pK_a 20.1), and the resulting carbanion adds to unreduced aldehyde. The chain reaction is propagated by protonation of the addition product by another molecule of hydrocarbon [57]. Reaction is by controlled potential coelectrolysis in THF, at the aldehyde reduction potential, and substantial yields are only obtained with 2,6-dichlorobenzaldehyde.

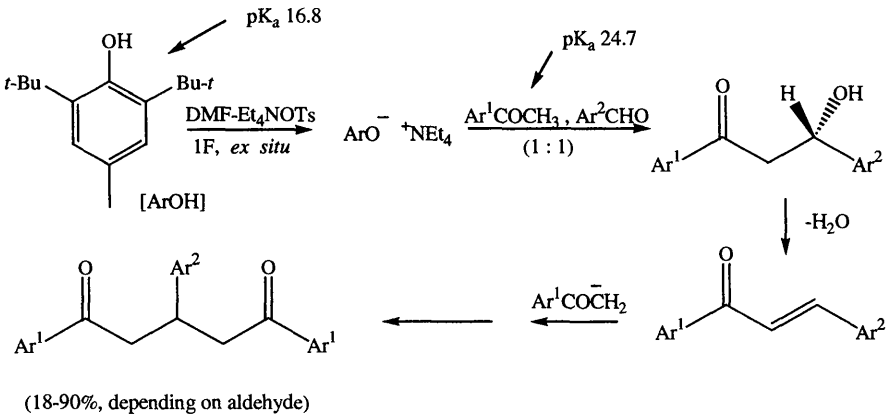


Scheme 18

Reduction of aromatic carbonyl compounds in dry MeCN may lead to significant amounts of cyanomethylation products rather than the expected pinacols [58]. This is explained by the deprotonation of MeCN (pK_a 31.3) by the dimer dianions formed by initial dimerization of the carbonyl radical anions and subsequent attack of $^-CH_2CN$ on unreacted substrate.

Hindered phenolates have low nucleophilicity and in aprotic solvent may act usefully as EGBs. 2,6-Di-*t*-butyl-*p*-cresol ($pK_a = 16.8$) was reduced directly with concomitant hydrogen evolution to give, ex situ, the corresponding tetraethylammonium phenolate [59,60], which was clearly capable of deprotonating aromatic ketones and in the presence of aromatic aldehydes promoted aldol reaction to α,β-unsaturated ketones which underwent Michael addition. The initial proton transfer from the aromatic ketone ($pK_a = 24.7$) is thermodynamically very unfavorable. Even so, aldol reaction took place within a matter of hours upon addition of an aromatic ketone together with an aromatic aldehyde leading to α,β-unsaturated ketones which subsequently underwent Michael addition with a sec-

ond equivalent of deprotonated ketone (Scheme 19). This illustrates once more the applicability of a relatively weak EGB being entirely dependent on the removal of a product, in this case the deprotonated ketone.



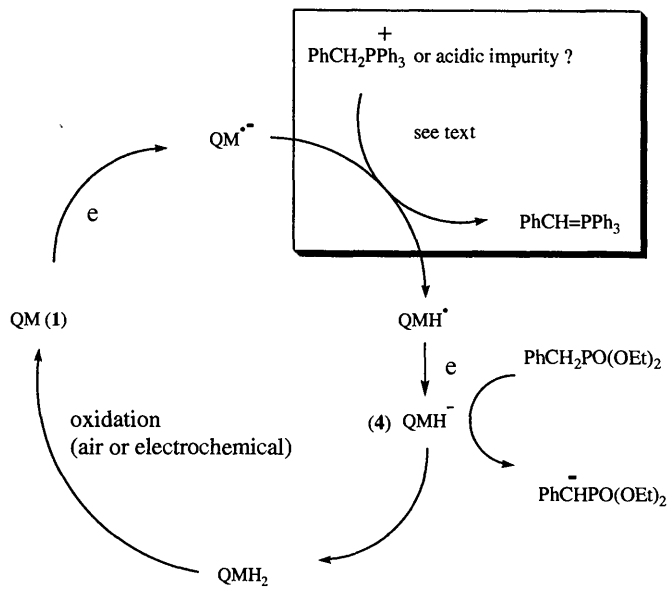
Scheme 19

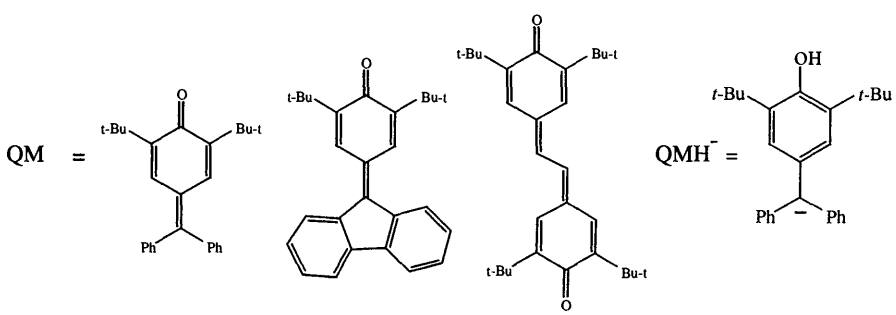
An alternative route to phenolate-like EGBs is cathodic reduction of quinonemethides [61,62], such as **1–3** in Scheme 20. The advantage of these probases is that they are reduced at modest potentials, which allows EGB formation to take place in situ, and they are ultimately converted into phenols that are easily reoxidized to the quinonemethides. The use of these probases is effective in converting both benzylphosphonium salts and benzylphosphonates into ylides or carbanions respectively (Scheme 20). Their properties as in situ EGBs have been tested [61] using as a model reaction Wittig formation of stilbene from benzaldehyde and either benzyltriphenylphosphonium bromide or diethyl benzylphosphonate. Reduction of fuchsone, **1**, at its first reduction peak potential is sufficient to deprotonate both of these weak acids and lead to subsequent near-quantitative reaction with benzaldehyde. The quinonemethides **2** and **3** need to be reduced at their second reduction potential to be effective toward the benzyltriphenylphosphonium cation, and in these cases it is the dianion that is the EGB; yields of stilbene are 48% from **2** and 84% from **3**. These processes are summarized in Scheme 20, and regeneration of the quinonedimethides can be achieved by air oxidation or by anodic oxidation.

However, the acidities of the benzyltriphenylphosphonium cation (pK_a = 17.4) and of diethyl benzylphosphonate (pK_a = 27.6) are sufficiently different to throw into question the likelihood of deprotonation of diethyl benzylphosphonate by the radical anion of **1**. On the basis of a detailed study of the processes associated with the reduction of **1** (discussed later), it is likely that the effective base may well be the much more basic triphenylmethyl-derived carbanion, **4** in Scheme 20 (pK_a of Ph_3CH = 30.6). This may possibly be produced by adventitious protonation of the fuchsone radical anion. Alternatively, the active EGB may be the dianion formed by disproportionation.

The electrochemical behavior of fuchsone (**1**) has been studied [62] in some detail. An unusual pathway is followed in the presence of acids (in this case phenols). The first-formed radical anion is protonated reversibly at oxygen and the triphenylmethyl radical so formed is not further reduced at the first reduction potential (Scheme 21). However,

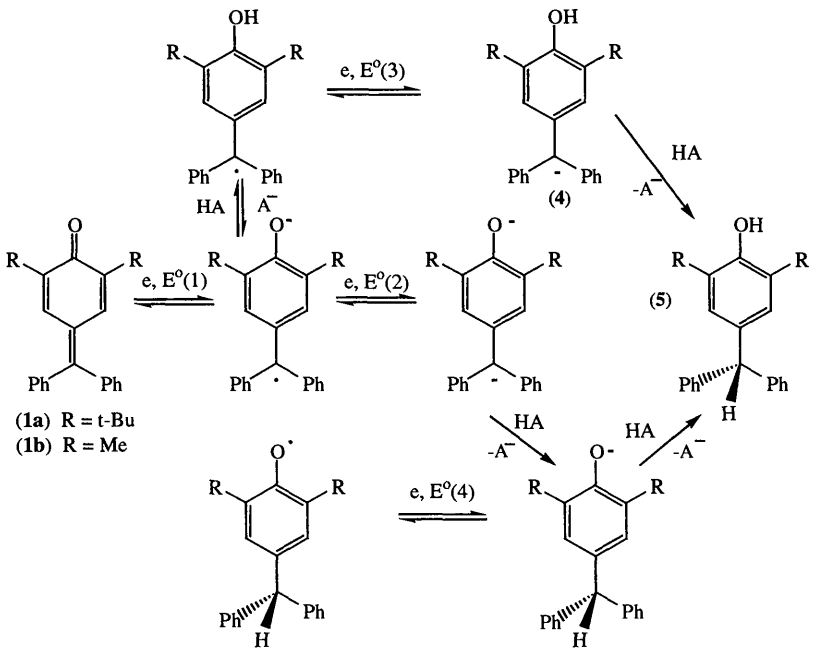
its reduction to the corresponding triphenylmethyl carbanion is clearly visible in voltammetry and is ~ 0.1 V cathodic relative to the potential required for formation of the radical anion. This is the basis for the view given earlier, that under the conditions of a preparative electrolysis, with the potential possibly beyond the potential of radical anion formation, any oxygen-protonated radical anion may be further reduced to the basic substituted triphenylmethyl anions (e.g., **4**) which act as very effective EGBs. The reaction may then be sustained by the protonation of a new radical anion by phenolic product (**5** in Scheme 21).





(1) (2) (3) (4)

Scheme 20



$E^{\circ}(4) > E^{\circ}(1) > E^{\circ}(3) > E^{\circ}(2)$

Scheme 21

C. Electrogenerated Carbon Bases

Two types of electrogenerated carbon bases are commonly used: dianions derived from activated alkenes, and carbanions formed by cleavage or direct reduction of weak carbon acids.

1. Activated Alkenes as Probases

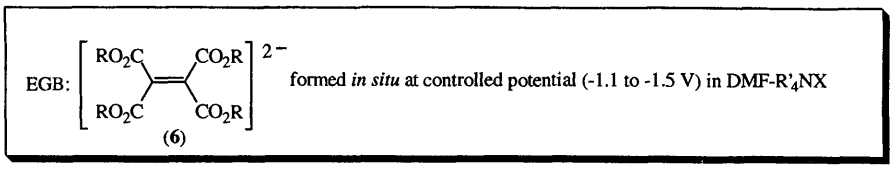
Esters of ethenetetracarboxylic acid (**6**) and disubstituted-(fluoren-9-ylidene)methane derivatives (**7**) are reduced sequentially to radical anions and dianions. It is the dianions that display useful basicity on a preparative scale (discussed later).

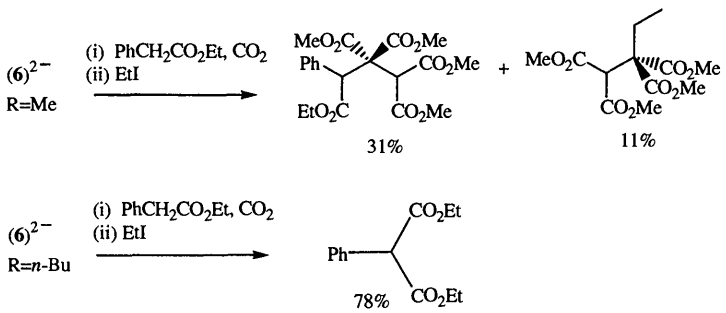
An attractive feature of these probases is that, in the absence of side reactions, they are converted into the hydrogenated product that is easily oxidized back to the probase, such as by bromine or by anodic oxidation [16,63].

For probases of type **6** the more hindered tetrabutyl ester is much to be preferred; the probase is less susceptible to Michael addition and the anion resulting from monoprotonation of the dianion EGB is less nucleophilic than the corresponding anion formed from the lower esters. For instance, although ethyl phenylacetate ($pK_a = 22.7$) is deprotonated in the presence of CO_2 by the dianion derived from tetramethyl ethenetetracarboxylate, the only isolated product (31%) is that of Michael addition of the anion to the PB with none of the carboxylated product [16]. The subsequent addition of ethyl iodide, intended to trap a carboxylated product, only resulted in a by-product (11%) arising from alkylation of the EGB (Scheme 22). Smaller amounts of such side products are obtained using the tetraethyl ester as PB, and using the tetrabutyl ester as PB affects [16] clean carbox-

ylation and alkylation of ethyl phenyl acetate (Scheme 22). In contrast to azobenzene, none of the EGBs derived from tetraalkyl esters were found [16] to react with CO_2. A further direct comparison (cf. Scheme 7) between the probases (**6**) and azobenzene has been made [27] for the base-induced Favorski rearrangement of 2-tosyloxycylohexanone; in this case the dianion of **6**, R = Et, is markedly less effective than the azobenzene radical anion.

In all of these cases it is safe to assume that the EGB is the dianion because for **6** the two reduction potentials are separated by only 0.2 V [16], and even for reduction at the first potential formation the dianion will be formed from the radical anion by disproportionation. Since the anion resulting from monoprotonation of the dianion will often be stable in solution (pK_a of the dihydro product expected to be around 16), the reaction is only driven toward products if the deprotonated substrate reacts in an irreversible follow-up reaction.

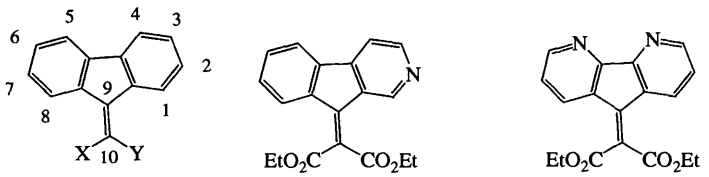




Scheme 22

Disubstituted (fluoren-9-ylidene)methane (**7**) derivatives are easily prepared by Knoevenagel-type condensation between fluorenone or substituted fluorenones and activated methylene compounds (CH_2XY, X = Y = CN or CO_2R, X = CN, Y = CO_2R). Like azobenzene and ethenetetracarboxylate esters, they undergo sequential one-electron reduction to the radical anion and the dianion [51,64,65]. The dianions are basic to the extent that they will efficiently deprotonate benzyl or polyenyl phosphonium salts ($pK_a \approx 18$), typically in DMF solution. Because the dianions are easily formed, the ylids formed by deprotonation are not further reduced and, indeed, can be thus generated for study by cyclic voltammetry [66,67]. When the ylids are generated in the presence of less easily reduced carbonyl compounds, usually aldehydes, they undergo efficient Wittig reaction to alkenes. The mild conditions for the formation of (fluoren-9-ylidene)methane dianions are useful for the synthesis [67] of *cis*-rich mixtures of alkenes that are often completely isomerized to the *trans* product in the presence of conventional and stronger bases. Furthermore, the base strength of the dianions may be modified in an understandable manner either by substitution [68] or by complexation [67,68] with alkali metal counterions. For the dianion of diethyl (4,5-diazafluoren-9-ylidene)malonate (**9**) it has

been demonstrated [69] by cyclic voltammetry in DMSO that a well-defined 1:2 complex is formed with Na^+ with a formation constant of $1.7 \times 10^8\ M^{-1}$. Scheme 23 presents examples of the use of (fluoren-9-ylidene)methane probases which, in conjunction with the data in Table 2, illustrate the points just discussed. It is evident from Table 2 that, for a given (fluoren-9-ylidene)methane probase the presence of Li^+ is beneficial both for yield of alkene and in promoting cis-rich mixtures. Certainly for the vitamin A acetate example [67], this effect is connected with a reduction in basicity and therefore less effective *cis–trans* isomerisation. It is known that the 11-*cis* vitamin A acetate is readily converted into the all-*trans* isomer in the presence of bases commonly used in this particular Wittig reaction ($KOBu^t$, BuLi).

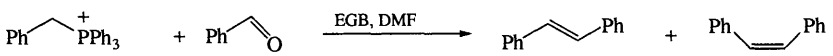


(7) a X=Y-CN
b X=Y=CO_2Et
c X=CN, Y=CO_2Et

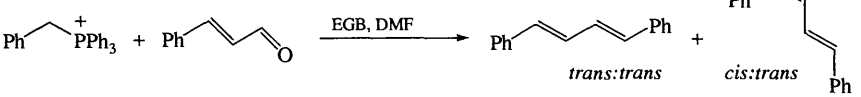
(8)

(9)

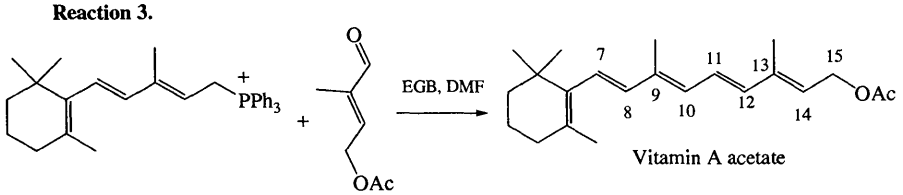
Reaction 1.



Reaction 2.



Reaction 3.



Scheme 23

Hydrogenation of the dianions is, according to ^{1}H-NMR spectroscopy [68], at positions 9 and 10 (Scheme 23 for numbering), but in reaction as an EGB the dianion is singly protonated, probably at the more basic position 9, because the monoanion is too weakly basic. In principle, the 9,10-hydrogenated probases can, by analogy with the ethenetetracarboxylates, be reoxidized to the probases.

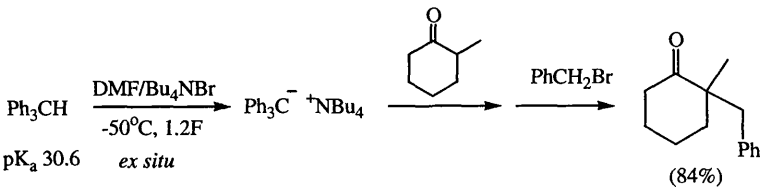
Table 2 Alkene Synthesis Via (Fluoren-9-ylidene)methane Probase-Promoted Wittig Reaction

Reaction	Probase	Cation	Stereoselectivity			Reference
			Alkene (%)	*Trans*	*Cis*	
1	**(7b)**	Bu_4N^+	80	9	1	[68]
	(8)	Bu_4N^+	91	1	1	
	(9)	Bu_4N^+	87	4	1	
	(7a)	Bu_4N^+	46	1.6	1	[67]
	(7a)	Li^+	74	1	1.4	
	(7c)	Bu_4N^+	68	1	1	
	(7c)	Li^+	94	1	1	
2				*Trans–trans*	*Cis–trans*	
	(7a)	Bu_4N^+	7	13	1	[67]
	(7a)	Li^+	54	1	1	
				All-*trans*	11-*cis*	
3	**(7c)**	Li^+	40	1	3.2	[67]
	(7a)	Bu_4N^+	Nil			

2. Carbanions as Electrogenerated Bases

The literature in this area is often ambiguous because although carbanions are common intermediates in electrosynthesis, especially as the result of cathodic cleavage, their follow-up reactions include involvement as nucleophiles or as bases. Also, as we shall see, electrogenerated carbanion bases may be used to generate nucleophiles from other acidic components of the reaction mixture. A comprehensive review [53] of this topic covers both types of behavior. Here an attempt is made to concentrate on those reactions where basic behavior of the electrogenerated carbanion is paramount.

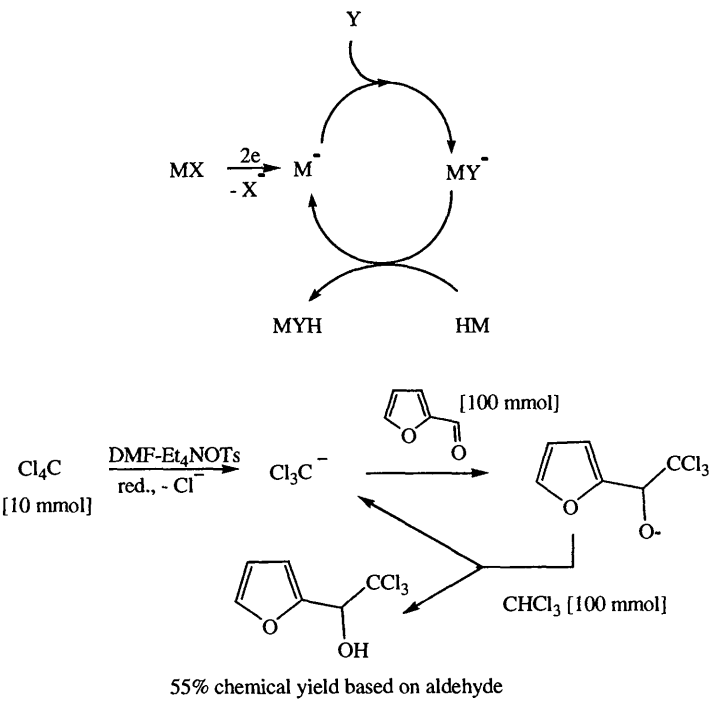
Direct reduction of weak carbon acids can lead to carbanions, but in practice ex situ operation is normally appropriate because, as for the formation of nitrogen and oxygen anionic EGBs by direct reduction of weak nitrogen or oxygen acids, most reactants would be reduced at the potentials required, Triphenylmethane, a very weak acid ($pK_a = 30.6$), is directly reducible and in dry conditions may be used in a batch reaction to give the corresponding strongly basic triphenylmethyl carbanion. The carbanion formed ex situ is only stable at low temperature, but due to its low nucleophilicity it is an effective EGB. As illustrated in Scheme 24, it may be used conveniently for monoalklylations of cyclohexanones, reactions that can be problematical with conventional bases [59,70]. It is noteworthy that the kinetically favored 2,5-dialkylcyclohexanone was formed when MeI was used as alkylating reagent rather than the thermodynamically favored 2,2′-dialkylcyclohexanone. This is in contrast to the formation of the 2,2′-dimethylcyclopentanone from 2-methylcyclopentanone using MeI and 2-pyrrolidone anion as EGB (see Scheme 9 in Sec. III.A.2). In most other cases, direct reduction of weak carbon acids has been used as an alternative pathway for the generation of nucleophiles, such as direct reduction of phosphonium cations, phosphonates, or malonic acid derivatives.



Scheme 24

Easily reduced halo-compounds such as diethyl bromomalonate have occasionally been used as probases. The EGBs are identical to those obtained by direct reduction of the conjugated acid, an advantage being that reduction and cleavage of the halo-compound is normally easier and therefore may allow in situ formation.

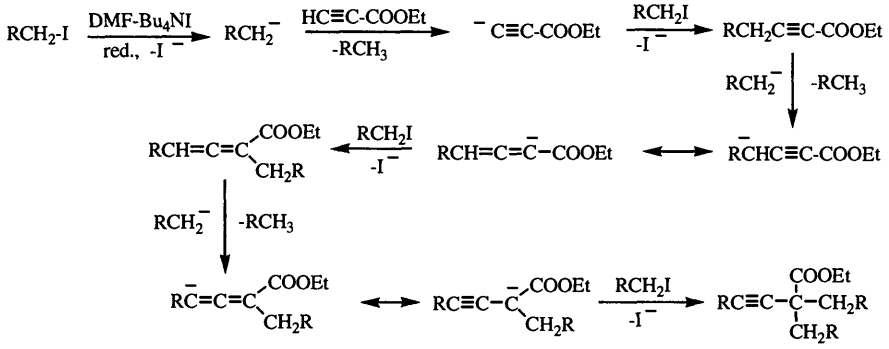
Shono and his coworkers cleverly exploited [71] the preparative possibilities of dual nucleophile/base behavior according to the relationships set out in Scheme 25. Essentially, they argued that the production of a nucleophile (M^- in Scheme 25) could be maintained by deprotonation of its conjugate acid, provided that the initial product of nucleophilic reaction was sufficiently basic. The way this works is illustrated in the reaction [71] in Scheme 25. Reaction is initiated by direct reduction (of CCl_4) but sustained through the deprotonation of $CHCl_3$ by the product of nucleophilic addition to furfural. Several other examples are reported [71], and the reaction type may be extended to other systems for which MX is easily reducible to M^- and where the acidity of MH is higher than that of the protonated addition product, MYH (Scheme 23).



Scheme 25

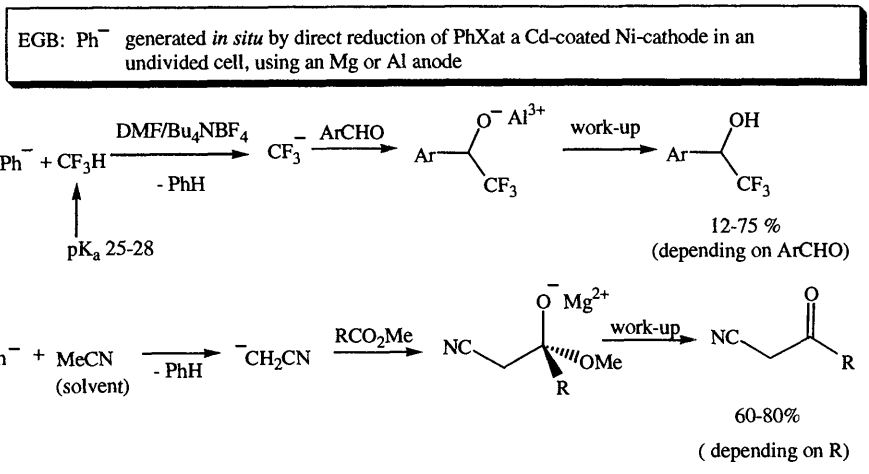
Dual electrophile/probase behavior of alkyl iodides has also been explored [72]. Two-electron reduction of, for example, methyl iodide generates a very basic carbanion

that may deprotonate activated alkynes and allenes. The anions so formed react as nucleophiles with excess alkyl iodide (the alkyl iodide typically used in 10-fold excess). This leads in a multistep reaction to alkylation of the carbanions produced rather than conjugate addition, as outlined in Scheme 26 [72]. The distribution of products on di- and trialkylated substrates depends on the amount of charge passed through the solution.



Scheme 26

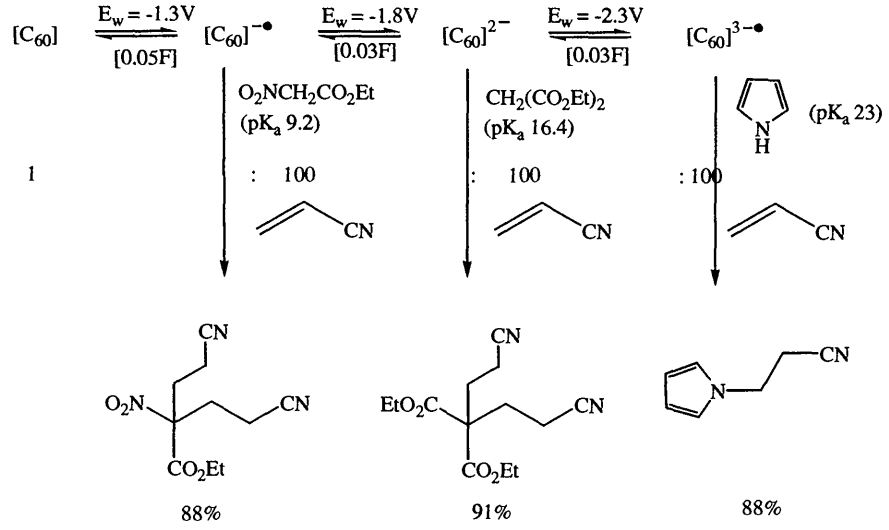
The phenyl σ-anion is strongly basic yet relatively easy to obtain by reductive cleavage of halobenzenes at a cadmium-coated nickel cathode; iodobenzene is reduced at -1.6 V vs. SCE and bromobenzene at -1.9 V. The examples given in Scheme 27 come from a series of papers by Troupel and his coworkers [73–76] and illustrate the use of in situ electrogenerated phenyl anion, in stoichiometric amount, to generate synthetically useful nucleophiles by deprotonation of their conjugate acids. Typically, the reactions use Al or Mg sacrificial anodes, Cd-coated Ni cathodes, DMF (or MeCN for cyanomethylation) solvent with Bu_4NBF_4 electrolyte with constant-current electrolysis, and undivided cells. For the carbonyl addition reactions described, the magnesium cation is useful in stabilizing the oxygen anion intermediate. It should be noted that CF_3H is a gas at room temperature and that the reaction involved [76] bubbling the substrate into the electrolyte throughout the electrolysis. Many other examples are described in the series of papers referred to.



Scheme 27

3. Other Generated Carbon Bases

Cathodic reduction of arenes gives π-radical anions that are possible EGBs. However, as discussed in Sec. II.B, their applicability is limited by the required reduction potentials and the slowness of proton transfer to carbon in a delocalized radical anion. Furthermore, the probases normally have low solubilities in polar aprotic solvents, and there are few cases of aromatic hydrocarbons being deliberately used as probases in electrosynthesis. One of the more interesting examples [77] (Scheme 28) involves reduction of the fullerene C_{60}. This compound can fairly easily be reduced sequentially to mono-, di-, and trianions, of increasing basicity. The principle of using the one probase for reactions demanding differing basicity has been well demonstrated for base-catalyzed reactions (Scheme 28). The fullerene is in principle recyclable but may also be reused in situ since the protonated forms may also work as PBs. However, C_{60} is poorly soluble in polar solvents and the reactions are performed in MeCN/$PhCH_3$, 2:3 v/v. Practical use of C_{60} as a PB is therefore limited to base-catalyzed reactions. The reactions in Scheme 28 are base catalyzed, since the addition products are less acidic than the carbon acids used, and the reactions can therefore be carried out using relatively small amounts of the C_{60} PB.



(Potentials *vs.* Fc/Fc^+)

Scheme 28

IV. ELECTROGENERATED BASES IN THE MEASUREMENT OF KINETIC ACIDITY AND BASICITY

In many preparative applications of EGBs the rate-determining step in product formation is the proton transfer. This is often the case when the deprotonated substrate is removed in a fast product-forming reaction (cf. Sec. II.B). For EGBs formed in situ, electrochemical methods such as cyclic voltammetry (CV), derivative cyclic voltammetry (DCV), linear sweep voltammetry (LSV), double-potential-step chronoamperometry (DPSC), and other electroanalytical methods can often be used to estimate the kinetics of proton transfer from the substrate to the EGB. When the EGBs are formed ex situ (because the acidic

substrate is more easily reduced than the PB), these methods are not applicable, but in principle (it has not been done) the decay of the EGB or substrate upon mixing may be followed by, for example, spectroscopic methods.

Those EGBs for which proton-transfer rates are easily measured are radical anions derived by one-electron electrochemical reduction from azobenzenes (Sec. III.A.1), aromatic (Sec. III.C.3), and heteroaromatic hydrocarbons (Sec. III.A.3), and dioxygen (Sec. III.B.1). In those cases the protonated EGB is removed in a fast disproportionation reaction (cf. Sec. II.B, Eq. 2–4), and the proton-transfer step therefore is made effectively irreversible. In CV experiments with addition of an acidic substrate, protonation of the already mentioned radical anions is observed as an increase in the cathodic peak current (change from a one-electron to a two-electron process) and a decrease in the anodic peak current. Where the proton transfer reaction is fast compared to the time scale of the CV experiment, the cathodic peak current is doubled and the anodic peak completely vanishes. If the CV at low scan rates is unchanged after addition of (an excess of) acidic substrate, the EGB is too weak a base to deprotonate the substrate at a reasonable rate.

Another class of EGBs for which proton transfer rates often can be determined is dianions formed by two (normally) sequential one-electron reductions, for example, of azobenzenes (Sec. III.A.1), activated alkenes such as **7** (Sec. III.C.1), and a number of other dianions that are, however, not often used as EGBs. For the very basic dianions of azobenzenes kinetic measurements can only be made under extremely dry conditions. In contrast to the group of radical anions discussed earlier, these protonated EGBs are not further reduced. Therefore protonation is only observed as a decrease or disappearance of the anodic peak current and not as a large increase in the cathodic peak current. Also, irreversibility of the proton-transfer reaction is not guaranteed unless the deprotonated substrate is removed in a fast product-forming reaction. However, for preparative purposes the basicity of the dianionic EGBs is normally chosen so that the proton-transfer reaction has a considerable driving force—that is, the back reaction will be slower than the desired proton transfer.

Quantitative determination of proton-transfer rates to radical anion EGBs derived from carbonyl compounds (Sec. III.B.2) is problematic using voltammetric methods, since the protonated EGB is not undergoing further reduction at the potential of radical anion formation (cf. Sec. III.B.2). this may lead to reversibility of the proton transfer.

Standard electroanalytical approaches are not suitable for investigation of the kinetics of proton transfer to EGBs formed in situ by cleavage, that is, carbanions formed from direct reduction of phosphonium cations (Sec. II.A) or from reduction of halides (Sec. III.C.2). In CV experiments the reduction of these PBs will, because of the cleavage reaction, be observed as two-electron reduction peaks with no corresponding oxidation peak even in the absence of acidic substrates. Oxidation of the carbanionic EGB may in some cases be observed at higher potentials, but the high basicity of, for instance, phenyl anions will in the absence of acidic substrates normally give rise to (slower) reactions with supporting electrolyte or solvent.

For determination of the second-order rate constants for proton transfer, the electroanalytical measurements are normally carried out using the PB in millimolar concentrations and the acid in a large excess (> 10 times) and at several different concentrations. This is done because pseudo-first-order conditions facilitate the data analysis necessary for rate constant determination. In these concentration ranges, second-order proton-transfer rate constants in a range from $\sim 10\,M^{-1}\,s^{-1}$ to $\sim 10^5\,M^{-1}\,s^{-1}$ (depending on the electrochemical equipment) may be determined by reversal techniques such as CV, DCV, or DPSC where unreacted EGB is detected on the reverse scan or step. For faster reactions,

LSV measurements, in which the reduction peak potential is determined relative to the E° of the PB/EGB couple, may be used to determine the rate constant.

As a consequence of the limitations just mentioned, attempts to characterize the kinetic basicity of preparatively used EGBs by determination of proton-transfer rates have mainly been done on the first-mentioned group of radical anions, particularly radical anions derived from azobenzenes, and the group of dianions derived from activated alkenes. At the same time, these type of measurements have been used to compare kinetic and thermodynamic acidities of weak organic acids.

Early experiments in this direction by Kinlen et al. [78] sought to establish the relationship between rates of protonation in DMF and the pK_a(DMSO) of the acid for reaction between the radical anions of 2,2′-di-*t*-butylazobenzene and of 2,2′,4,4′,6,6′-hexa-isopropylazobenzene and substituted phenylacetonitriles (pK_a 17.5–21.9) and benzylsulfones (pK_a 21.4–26.2). The protonation rate constants (in the order $1–10^4\ M^{-1}\ s^{-1}$) were measured by chronoamperometry using a large excess of the acids. The use of chronoamperometry (i.e., not a reversal technique) is possible in this case since the reduction of the PBs changes between a one-electron and a two-electron process upon addition of acid. The Kinlen kinetic measurements were made in DMF solution, but the relative pK_a values seem little affected by the change from DMSO, the solvent favored by Bordwell et al. for the compilation of pK_a data (see Sec. II).

Reasonably good linear Brønsted plots were found, and there was hope that the approach would have general use and even be a means to determining pK_a values for weak acids by comparison of rates of deprotonation with those of acids of known pK_a. It turned out that the weak acids chosen by Kinlen et al. [$Ar(R^1)CHCN$, and $ArCH_2SO_2R^2$] were appropriate because they are true carbon acids with deprotonation taking place unambiguously from the methylene group. Common "carbon acids" in which methylene protons are activated by adjacent carbonyl functions are often significantly enolized, which results in the possibility of competition between proton transfer from oxygen (relatively fast) and from carbon (relatively slow). Thus the kinetics of proton transfer may be profoundly affected and, as the extent of enolization varies from acid to acid, linear Brønsted plots are seldom obtained.

The nature and extent of this complication were revealed in a thorough investigation [79,80] of the kinetics of protonation, in aprotic solvent, of aromatic hydrocarbon radical anions in the presence of enolizable weak acids of the $R^1COCH_2COR^2$ type. Consistent with the proposal that protonation by enols is significant was the observation [79] that the rate of disappearance of the radical anion of 2-methoxynaphthalene (1 mM), in DMF in the presence of $EtCO_2CH_2CO_2Et$ (64 mM), was increased ~ 7-fold by the addition of $EtO_2CCH_2CO_2^-$ (40 mM). The strong implication is that enolization is catalyzed by the addition of the base; in kinetic studies, of course, the EGB can itself catalyze enolization.

The choice of techique for the measurement of rates of protonation must also be carefully considered. In CV, DCV, and LSV measurement, complications due to reduction of reactants other than the probase are relatively easily detected. In contrast, processes taking place just after the PB reduction may affect the results obtained by methods such as DPSC, which involves stepping beyond the probase reduction peak. An example comes from a study of the reaction between 9-fluorenylidene dianions and phosphonium salts. The product of the acid–base reaction is the ylid, which turns out to be reducible in the region to which the potential is stepped in DPSC experiments [81]. For reaction in DMSO between the dianion of 9-fluorenylidene derivative (**7b**, Scheme 23) and $[Ph_3PCH_2Ph]^+$ the rate constant determined [81] by DPSC appears to be $4.5 \times 10^3\ M^{-1}\ s^{-1}$. In contrast, DCV gives [43] a rate constant of only 12.31 $M^{-1}\ s^{-1}$. The DPSC method works well for

measuring proton transfer rates with β-dicarbonyl compounds [69], where no reducible product is formed.

Table 3 lists a selection of rate constants for proton transfer in DMSO solution, which indicate not only the range of rates involved in common EGB reactions but also that structural features operate in a qualitatively predictable manner. It is safe to conclude from these data that, kinetically, azobenzene radical anion is probably a stronger base than the phenazine radical anion and that the dianions of the 9-fluorenylidine derivatives are relatively weak bases.

Enolization plays a role for a number of the acids in Table 3—for example, $(MeCO)_2CH_2$ is more than 50% enolized in DMSO [80], and the rate-enhancing effect of enolization is also expected to play a role in the high rate constant in the final entry in Table 3. The other phosphonium salts listed may be regarded as true carbon acids, but $EtO_2CCH_2PPh_3^+$ is almost certainly readily enolized with a substantial contribution to the rate constant coming from proton transfer from oxygen.

Qualitative comparisons of kinetic acidity and basicity are therefore possible when differents are large and when complicating factors are absent or understood. Attempts at quantitative comparisons are, however, fraught with hazard. A comprehensive investigation [43] of the kinetics of proton transfer from phosphonium ions to electrogenerated bases illustrates the care needed in interpreting such information. In these cases no single Brønsted relationship holds for the series of phosphonium salts studied. Apart from the propensity of some of the phosphonium salts to enolize (discussed earlier), kinetic acidities are profoundly affected by steric factors and by whether the EGB is a carbon or nitrogen base. The pitfalls in drawing general conclusion from measurements of kinetic acidity or basicity are well illustrated in this study [43], to which the reader is referred for more detail.

Table 3 Rate Constants for Reaction in DMSO Between EGBs of Different Types and Common Weak Acids

EGB	Acid	(pK_a)	$k(M^{-1}\,s^{-1})$	Method	Reference
$(\mathbf{7a})^{2-}$	$(MeO_2C)_2CH_2$	(15.7)	9.58×10^1	DPSC[a]	[69]
$(\mathbf{7b})^{2-}$	$(MeO_2C)_2CH_2$	(15.7)	9.25	DPSC	[69]
$(\mathbf{8})^{2-}$	$(MeO_2C)_2CH_2$	(15.7)	4.00×10^2	DPSC	[69]
$(\mathbf{9})^{2-}$	$(MeO_2C)_2CH_2$	(15.7)	2.28×10^1	DPSC	[69]
$(\mathbf{7c})^{2-}$	$(MeO_2C)_2CH_2$	(15.7)	1.03×10^1	DPSC	[69]
$(\mathbf{7c})^{2-}$	$(EtSO_2)_2CH_2$	(14.4)	9.70×10^1	DPSC	[69]
$(\mathbf{7c})^{2-}$	$(MeCO)_2CH_2$	(13.3)	1.00×10^3	DPSC	[69]
Anthracene$^-$	$(MeCO)_2CH_2$	(13.3)	2.10×10^4	DCV[b]	[80]
$(\mathbf{7c})^{2-}$	$PhCH_2PPh_3^+$	(17.4)	1.23×10^1	DCV[c]	[43]
Azobenzene$^-$	$PhCH_2PPh_3^+$	(17.4)	2.40×10^3	DCV	[43]
Phenazine$^-$	$PhCH_2PPh_3^+$	(17.4)	1.90×10^2	DCV	[43]
Phenazine$^-$	$PhCH{:}CHCH_2PPh_3^+$		2.10×10^4	DCV	[43]
Phenazine$^-$	$EtO_2CCH_2PPh_3^+$	(8.5)	2.80×10^8	LSV	[43]

[a] Pt disk, DMSO—Bu_4NClO_4 (0.1 *M*), 25°C.
[b] Hg/Pt cathode, DMSO–Bu_4NBF_4 (0.1 *M*), 20°C.
[c] Hg/Pt cathode, DMSO–Bu_4NPF_6 (0.1 *M*), 20°C.

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Industrial Electroorganic Chemistry

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  References

I. INTRODUCTION

"Although the history of the electrochemical industry can be traced to the early 1800s, few processes for the electrolytic production of organic chemicals have been commercialised" [1]. The authors of this quote name four reasons for this phenomenon, namely, the slow development in the areas of:

1. Education of organic chemists
2. Availability of electrochemical equipment

3. Materials for cells
4. Engineering in electrochemistry

This may be true. But as the authors concede, things have changed. Nevertheless, the number of electrochemical organic processes has not risen significantly in the last two decades. On the contrary, the two most prominent electroorganic processes, the hydrodimerization of acrylonitrile and the production of tetraethyllead, have lost some of their importance. The ADN process is operating at several sites worldwide, but it is stagnating because other technical alternatives show better performance [3]. The NALCO tetraethyllead process was discontinued because the demand for leaded fuels is decreasing for ecological reasons.

There is a fifth reason for the slow development of organic electrochemistry in industry:

5. The cost structure of electrochemistry

It is significant that this point has been "forgotten" by the authors. Here probably lies the most important reason for the difficulties or organic electrochemistry in industry. Although the electron is one of the most versatile and one of the cheapest redox agents [2,4], chemists usually favor other alternatives.

So it makes no sense only to make electrons cheaper or to look for much better cells. The job for organic electrochemists in industry is to make the *whole* process the cheapest!

That is why the object of this review is not to show all electrosyntheses that have been commercialized or produced at least in a pilot plant, but to give the reader an idea of the structure of some prominent electrochemical processes. This should be helpful for the reader to estimate—together with one's engineers—the cost structure of electrochemical processes for a company on a specific site [5].

II. TYPICAL STRUCTURES OF ELECTROCHEMICAL PROCESSES

Every electrochemical production process, both organic and inorganic, is strongly dependent on "classical" chemical unit operations. Even the impressive cell room of a chloralkali electrolysis process [6] is only a small part of the whole plant. This can be seen not only in simple process schemes but also in areas or volumes of buildings and, last but not least, in investment and operating costs.

Typical other parts of the plant apart from the cell room are storage facilities for starting materials and end products, equipment for safety and environment protection, purification systems for products and by-products, facilities for recycling of solvents and electrolytes, energy supply, and process control.

A. The Cell Room

The heart of all electrochemical processes is the cell room; this contains the electrochemical cells, the piping connecting the cells to the electrolyte containers and their pumps, the rectifiers and power distribution, the process and safety control, and, last but not least, parts of a building.

The "cell room" does not necessarily have to be located in a closed building, but it must offer proper conditions for the operation of the cells and free access for their maintenance and repair. The area of cell room and its costs rise linearly with the electrode area.

That is why the cell construction has to take into account these requirements and not only electrochemical parameters.

A classical example of this strategy is the capillary gap cell (see Sec. IV.B), which has been run by BASF for more than a quarter of a century [7]. Several dozen electrodes are piled onto each other to give a stocky pillar. The electrodes consist of graphite rings. The diameter of the central hole is a tenth of the outer diameter of the electrodes. The hydrodynamics and the current and potential distribution are far from optimal.

But the electrode stack fits into a very compact cell. A vertical pile of electrodes saves cell room area in an optimum way, and the simple removal of the cells from the system makes maintenance an easy job.

This cell is very convenient for many electroorganic processes and is probably the most successful system in respect of the numbers of realized industrial processes.

Usually the costs of the cells and the cell room are of the same order of magnitude.

B. Workup Facilities

In electroorganic processes, the typical workup procedure is accomplished in three steps:

1. Recycling of solvent by distillation
2. Removal (and recycling) of electrolyte
3. Recovery of the crude product

A typical and very recent example is given in Ref. 8. The methoxylation of cyclohexanone is carried out in methanol with potassium iodide as electrolyte. One distillation step and one filtration follow the electrolysis.

A more complicated but also very instructive and versatile process was published by Hydro Quebec, namely, the indirect oxidation of aromatics, specifically naphthalene, by ceric salts [9]. The electrolysis is only a small part of the process: Cerous methanesulfonate is oxidized to ceric methanesulfonate. The organic part of the process takes place in a separate reactor: The aqueous ceric salt oxidizes the organic substrate in a heterogeneous two-phase reaction that requires good mixing. After the separation of the aqueous and organic phases, the aqueous phase is extracted with a solvent that is recycled continuously. In a follow-up step, organic impurities must be removed from the cerous solution before it is fed back to the electrolysis. The product (naphthoquinone) has to be dried.

The group of P. Pintauro has applied computer aided electrochemical process design to the electrocatalytic hydrogenation of soybean oil [10]. The process consists of 12 unit operations apart from the electrolysis. Only one of them is directly connected to the electrochemical step; two others are assigned to the "reaction loop." The flow sheet for the oil hydrogenation plant and the specification list for the unit operations impressively demonstrate the ratio between electrolysis and recovery of product and electrolyte.

There are no specific rules for the costs of the workup compared to the electrolysis step, but generally the expenditures are of the same order of magnitude.

C. Recovery of the Products and By-Products

Usually the product has to be purified by distillation, crystallization, or other techniques to meet the high specifications of the customer or to remove the by-products from the system. Sometimes electrochemical products are intermediates that undergo further reactions before they leave the process.

Electrochemical methoxylations usually lead to acetals or ketals; these must be distilled and/or hydrolzed [8] to give the target molecules. The resulting ketones or aldehydes are purified again. In the anthraquinone process of Hydro Quebec [9], some of the crudenaphthoquinone is purified further, but most of the crude products is reacted with butadiene to yield tetrahydroanthraquinone, which is dehydrogenated to anthraquinone.

Anodic and cathodic dimerizations often start with esters that are hydrolyzed to the carboxylic acids in a final step; the electrosynthesis of sebacic acid [74] and butanetetracarboxylic [11] acid illustrate this.

Other electrosyntheses produce salts of organic acids (e.g., NiOOH oxidations of alcohols to carboxylic acid salts) or—in the case of the electroreduction of aromatic nitro compounds—salts of anilines. To recover the pure organic products, the addition of acids or bases is needed and after separation of organic and salt phases further purification steps are necessary.

Usually only one electrode product is recovered as a product of commercial value; the product of the counterelectrode must be removed as waste or as a low-value by-product. During anodic oxidations, hydrogen gas is evolved and has to be freed of solvent and low-boiling by-products. In the case of cathodic reductions, the gas given off is oxygen, sometimes containing halogens and acids as impurities.

The purification steps are even more specific than the workup procedures, but their costs also have to ben taken into account at an early stage of the process development. They can exceed the costs for cells by far, if there are many product streams that have to be recycled.

D. Storage and Transportation

Although this aspect of the plant seems to have no specific relationship to the electrolysis, it can be decisive for the success (or failure) of electrochemistry.

The availability of hydrogen, for instance, at a chemical site makes it difficult for cathodic reductions to succeed [15]. In India, where there is (or was) no hydrogen infrastructure, cathodic reductions of nitro compounds were carried out in industrial electrolysis cells. These processes have no chance in more industrialized countries with cheap hydrogen. On the other hand, a strategy on the part of EDF for producing mucic acid brings the cells to the product source instead of the starting material to a central electrolysis plant: The "modified Grignard reactor" uses mother liquor from sugar purification [12]. The idea is that molasses should be electrooxidized directly in the sugar plant.

III. THE COSTS

In *Ullmann's Encyclopedia*, published in 1998, the costs for organic electrochemical processes are discussed in Chapter 5.7 of "electrochemistry" [13]. The author, F. Beck, concentrates on material costs and electricity costs (Table 24) but he also differentiates between investment costs for the electrochemical part and the "conventional parts," as he calls them. The ratio lies between 2% and 50%. These are definitely two extremes, but they show again the necessity of checking the cost situation right at the beginning of development. If the cell costs are negligible compared to the total investment, the project strategy will have different priorities than in cases where the cells require half of the money.

A. Electrolytic Investment Costs Versus Total Investment Costs

A very impressive illustration of the relative costs of the electrolysis step compared to workup and purification procedures is given in Ref. 14. The electrochemical hydrodimerization of acrylonitrile to adiponitrile is reported here. The electrolytic part makes up less than 20% of the whole process sheet, and the costs for the electrolytic part are less than 30%. The process is later discussed in more detail.

The same situation is true for the most popular electrochemcial process, namely, chloralkali electrolysis. The "heart" of the process, the cell room, is an even smaller component of the whole process [15].

B. Manufacturing Versus Electricity Costs

Not only the ratio of the relative investment costs but also the ratio of the costs for electric energy versus total manufacturing costs gives an interesting insight into electrochemical processes, which is quite different from the (organic) electrochemist's point of view. The importance of DC power costs is usually highly overestimated. C. R. Huntley, ICI, has demonstrated that for "small" organic products (capacity: 100–1000 metric tons/year), the ratio of conversion costs versus DC power costs ranges from 5 to 10. For medium-capacity products this ratio is around 3. Only for large-scale products, like chlorine and caustic, are the costs of similar size [16]. There is an important economy of scale, making organic specialities nearly independent of power costs but sensitive to manufacturing cost.

This means that the main objective for the successful development of a new product from organic electrochemistry will not be the optimum cell, but the best combination of *all* process steps.

To start with, it is advisable to do pilot-plant experiments in a standard (commercial) cell and use standard electrochemical equipment. Don't try to optimize the electrochemistry first, but try to minimize the outlay for the whole process.

C. Total Costs

But even this is only a part of the whole story. In Ref. 17 the BASF production site, Seal Sands, is discussed. All parts of the site are integrated in order to produce (HMD_1) hexamethylenediamine. The ADN (adipodinitrile) process is only one part of the site (Fig. 1).

As an illustration of the strong interdependence between all process steps: BASF has built a 75-MW combined heat and power plant on the site. Steam for the other processes makes electricity for ADN cheaper.

Consider another interrelationship: The costs of ACN (acrylonitrile) are a function of the price of propylene, the starting material, and the price of HCN and ammonium sulfate, the by-products.

This explains why the optimization of cell performance does not necessarily play a central role in cost-reduction programs.

IV. ENGINEERING FOR ORGANIC ELECTROCHEMISTRY

The fundamental concept for the task of electrochemical engineering [18] has been reviewed recently by D. Pletcher and F. D. Walsh in Refs 19 and 20, or by F.

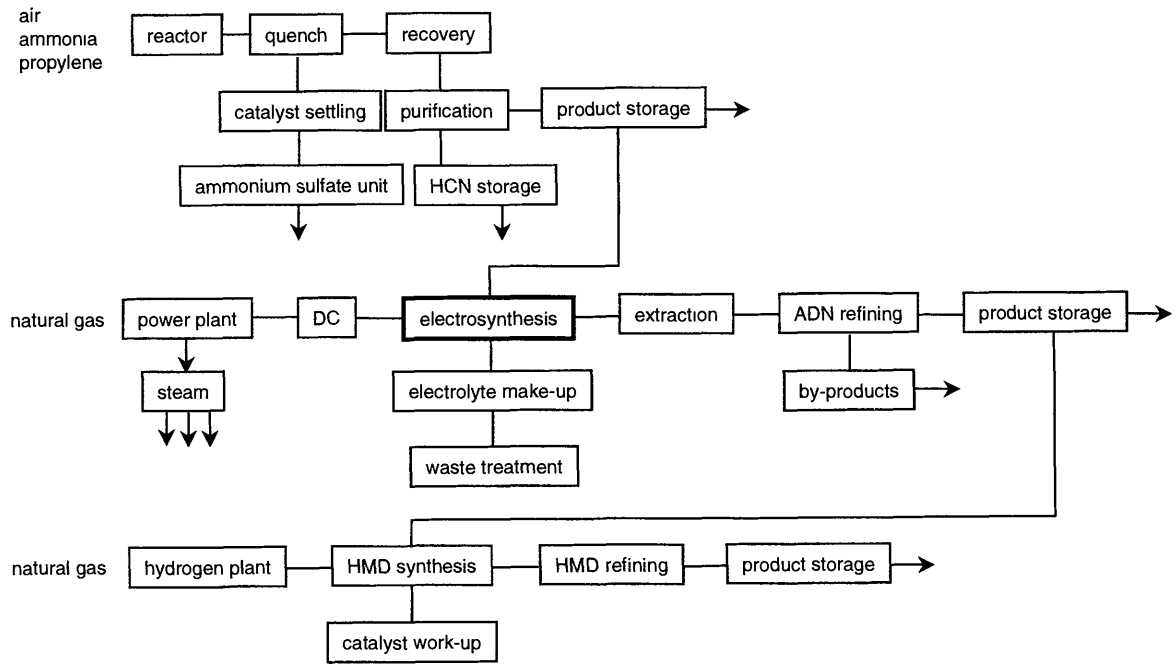


Figure 1. Manufacturing of hexamethylenediamine (HMD) at Seal Sands.

Goodridge and K. Scott [21]. These outlines are, in general, also valid for organic electrochemical processes as well. Organic electrochemical processes are usually not as straightforward as inorganic reactions, because secondary reactions and subsequent reactions reduce selectivity and mass yield.

That is why in industrial practice two points will differ significantly for organic electrochemistry:

1. Laboratory research will take more effort than fundamental electrochemistry.
2. Piloting takes more time than electrochemical technology.

If the product is an intermediate of high price and low tonnage, people will most likely invest in an established electrolysis system, using proven electrochemical equipment.

This is not so much the fault of project management (according to the electrochemical paradigm, "conventional" chemists are ignorant of electrochemistry), but more likely due to the reluctance of the supplier of the electrolytic systems to invest into the development of a relatively small number of units.

There is also a fundamental addition to make to the scheme of Pletcher and Walch: The scale-up of the nonelectrochemical parts of the new process, a job that has to be done in parallel with all laboratory and pilot-scale trials. This is shown in Fig. 2.

A. Electrochemical Fundamentals

In spite of the need to look at the entire process, it is advisable to take a look at some fundamentals. Some topics are:

Electrodes [22]
Electrolytes and solvents [23]

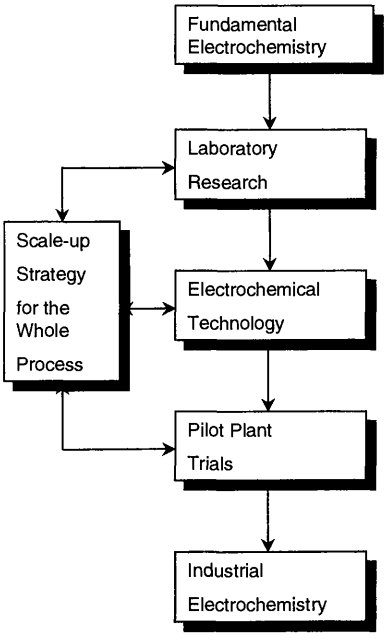


Figure 2. Development of an organic electrosynthesis.

Mass flow and current density
Cell voltage and cooling systems
Corrosion phenomena
Recycling of impurities
Continuous versus batch processing
Selectivity versus mass yield

Organic electrochemistry is based on heterogeneous reactions. The boundary layer between the electrode or its coating and the electrolyte plays a decisive role that is similar to phenomena in heterogeneous catalysis. Long-term effects, especially poisoning and corrosion of the electrodes, are critical. The formation or modification of layers on the electrode influences the long-term selectivity of a reaction and its chances of becoming a process. High current density can reduce investment costs but increase energy costs [24]. The concentrations of starting material and product determine electrochemical parameters like faradaic yield and current density.

Corrosion phenomena in remote parts of the system can adversely affect the electrode performance. This is a real threat to processes in which solvents, intermediates, or supporting electrolytes have to be returned to the electrolysis. This danger can influence the decision between batchwise processing with total conversion of starting materials or continuous alternatives in which the starting material has to be recycled.

The reactivity of electrolytes and solvents also has to be checked. In most electrochemical reactions, the solvent competes with the substrate as depolarizer at the electrodes.

Many electrochemical parameters can be calculated [25], but as A. T. Wragg points out, even the best model in electrochemical modeling is futile if it's not based on sound assumptions in the beginning [26].

Two general strategies have to be considered at the beginning of every development for an organic electrolysis:

1. Direct versus indirect electrooxidation
2. Type of cell

Direct electrolysis means oxidation or reduction of the substrate at the electrode via an electron transfer or the stoichiometric attack of an oxidized or reduced species. Indirect electrolyses use mediators, namely, redox systems transferring electrons between the substrate and the electrode. The indirect electrolysis can be accomplished in two ways:

In cell: substrate present in the electrolyte
Ex cell: substrate contacts the electrolyte outside the cell

An example for the choice between direct or indirect electrolysis is given in Sec. V.B.6: Substituted toluenes can be oxidized to the corresponding benzaldehydes via different routes.

The choice of electrolysis conditions determines the kind of cells; the available design alternatives are discussed in Sec. IV.B. To multiply the number of electrodes in industrial reactors, one can choose between bipolar and monopolar alternatives.

A bipolar electrode consists of an anode in electrical contact with a cathode—it is polarized in the electric field of the cell. Bipolar cells have two feeder electrodes and a number of bipolar electrodes between them. Ideally, the current supplied to the system can be multiplied by the number of anodes or cathodes to calculate the charge that is passed to the electrolyte. In reality, some current losses occur due to bypass or shunt currents, so-

called leakage currents. One advantage of bipolar systems is the fact that only two electrodes need to be electrically connected to the power supply system.

In monopolar systems every electrode has to be connected to the power supply. The overall current is the sum of the currents between all anodes and cathodes, and the cell votlage is applied between every electrode pair. Monopolar connection requires high current and low voltage supply; bipolar systems require the opposite (Fig. 3).

During the development of a process it is sometimes advisable to check the original assumptions for their validity and, if necessary, correct them. It is often very helpful to discuss the electrochemical assumptions with people not involved in electrochemistry. To give these people an insight into synthetic organic electrochemistry and electrochemical engineering, some recent books can be recommended [27–38].

B. Electrochemical Equipment

There is one important fact in favor of organic electrochemistry: During the last two decades a number of versatile electrochemical cells have been developed for the market. The state of the art until the end of the 1970s is reviewed in Ref. 39. The availability of stable electrodes [40] is increasing, and for many purposes it is possible to find membranes [41] with decent lifetimes, if needed. These materials meet the preconditions [42] for new electrochemical processes. Some companies active in this field are:

Cells and/or electrodes
Atraverda, Sheffield, UK
De Nora, Milan, Italy
De Nora Deutschland (former Heraeus Elektrochemie GmbH), Rodenbach, Germany
EA Technology Ltd., Chester, UK

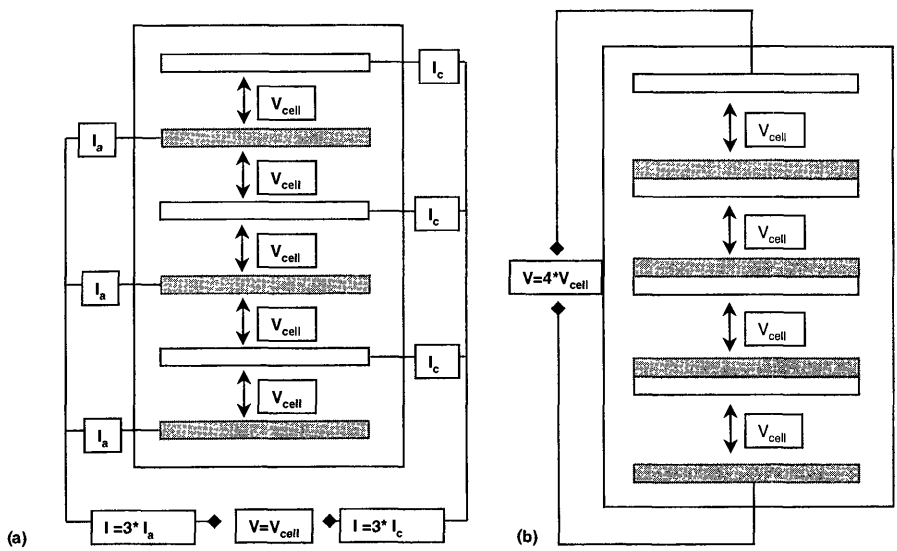


Figure 3. Electrical connections in multielectrode cells. (a) Monopolar. (b) Bipolar

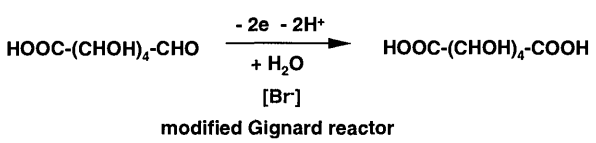
Electrosynthesis Company, East Amherst, NY, USA
ELTECH, Chardon, Ohio, USA
ElectroCell Systems AB, Täby, Sweden
Electrocatalytic, Union, NJ, USA
ICI Chemicals and Polymers Ltd., Runcorn, UK
Johnson Matthey, Royston, UK
SGL, Meitingen, Germany

Membranes
Ameridia, (formerly Aqualytics), Warren, New York
Asahi Glass, Tokyo, Japan
Asahi Chemicals, Kawasaki, Japan
DuPont, Wilmington, DE, USA
Eurodia, Wissous, France
FuMA-Tech, St. Ingbert, Germany
W. L. Gore, Elkton, MD, USA
Ionics, Watertown, NY, USA
Osmota, Stuttgart, Germany
Tokuyama Corp., Yamaguchi, Japan

An overview on the various types of electrochemical cells that are of importance for industrial processes is given in Ref. 43. Four major types of cells are used:

1. Tank cells
2. Plate-and-frame cells
3. Capillary-gap and thin-film cells
4. Cells with three-dimensional electrodes

The tank cell has found an interesting and elegant application in the sugar industry [44]. A modified Grignard reactor is used for the scale-up of the indirect oxidation of galacturonic acid [45] (Scheme 1). A vessel equipped with a mechanical stirrer and cylindrically shaped electrodes is used to produce mucic acid. The reaction conditions are given in detail in Ref. 46.



Scheme 1. Oxidation of galacturonic acid to mucic acid.

The plate-and-frame cell design is usually applied to divided cells. Anode and cathode chambers are separated by, for example, a cation-exchange membrane. Anolyte and catholyte have separate circulation systems with separate feeds and outlets and separate waste-gas purification (Fig. 4).

The advantage of separating the products is accompanied by higher costs and often problems with the life of the membrane and the electrodes. Typical divided cells are:

1. DEM cell (Electrocatalytic) [47,48]
2. FM 21 electrolyzer (ICI) [49]
3. ElectroProd cell (Electrocell AB) [50]

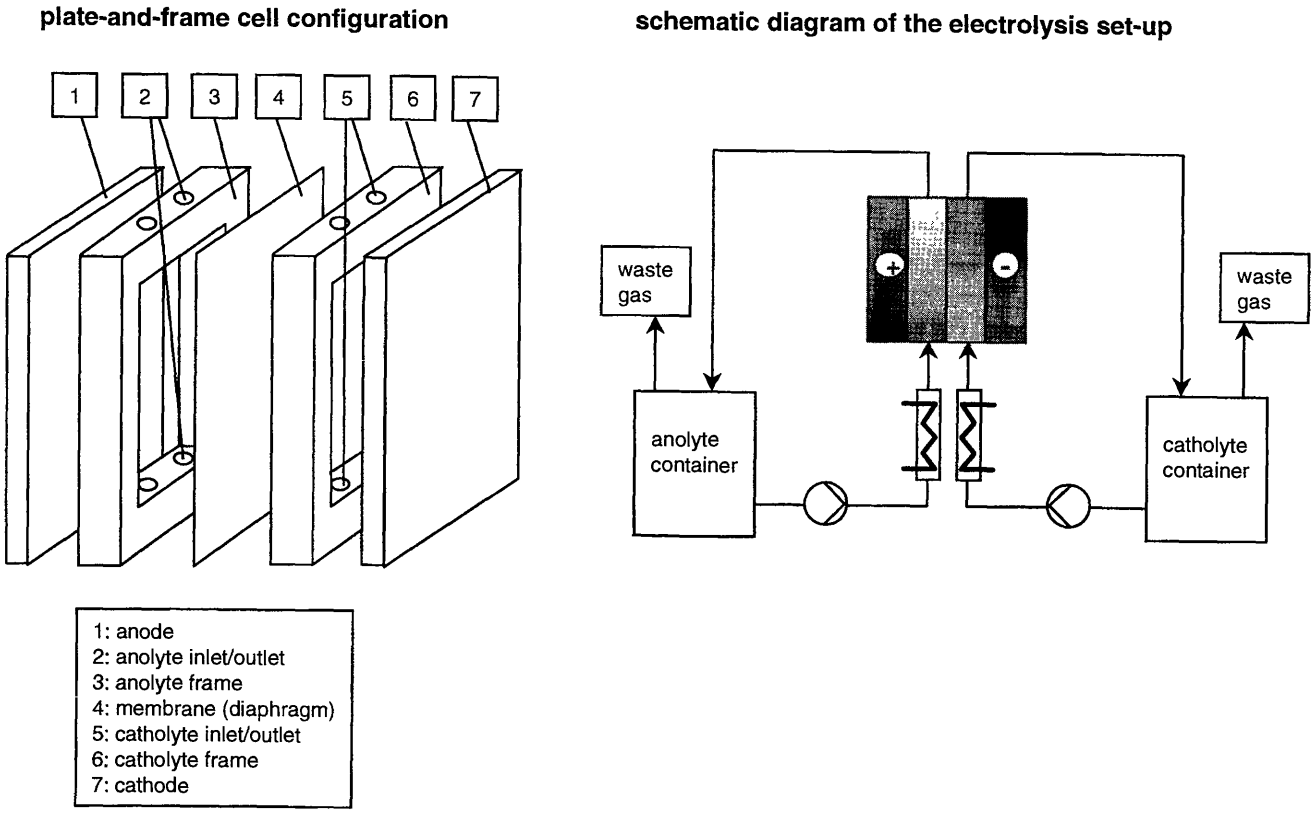


Figure 4. Divided cell.

Some filter-press type electrochemical reactors can be used both in a divided and undivided mode. This is illustrated in Ref. 51. The ICI filter-press cell system FM 21 is discussed in the context of several pilot-plant applications, most of them organic.

The undivided cell is used in cases where the electrode processes don't adversely affect one another negatively. The most common case is the anodic oxidation of an organic substrate combined with the cathodic production of hydrogen. If the evolution of oxygen as the anodic by-product can be excluded, this alternative is most convenient and—usually—the least costly. A typical "thin-film cell" is the trickle tower cell (Fig. 5b) [52]. The trickle tower cell has been applied to the production of propylene [53].

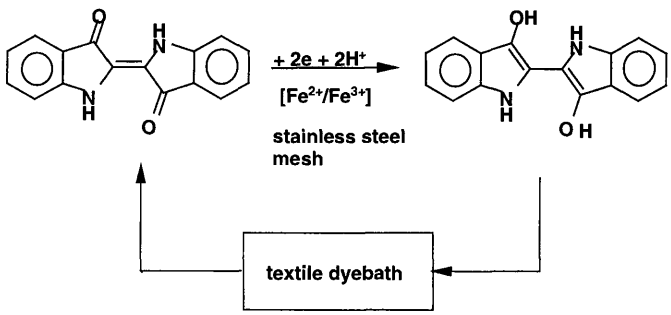
Typical undivided cells are:

1. Capillary gap cell [54] (BASF, Fig. 5a)
2. Cylindrical capillary gap cell (Eberson-cell [55])

Three-dimensional electrodes are employed in cases of low depolarizer concentrations, such as in indirect electrolyses, use of mediators, or electrolyses of gases. Typical cells with three-dimensional electrodes are:

1. Multicathode cell (Heräus/de Nora) [56]
2. Swiss-roll cell (Hoffman-La Roche) [57]
3. Carbon felt cell ("Porocell," EA Technology) [58]

In a recent industrial application, the multicathode cell of Heräus [59] is used for the indirect reduction of dispersed indigo during a dyeing process [60] (Scheme 2). An iron(II)–triethanolamine complex is the active reducing species. The cathodes consist of folded layers of stainless steel or copper. Graphite felt can also be used for this purpose [61]. The outline of this multicathode cell process is shown in Fig. 6.



(1)

Scheme 2. Reduction of indigo to leuco-indigo.

Besides these more generally applicable cells, there are several cells dedicated to specific organic processes [19,67,69], for example:

Divided cell for ADN (Monsanto, Asahi).
Undivided cell for ADN (Monsanto, BASF).
"Swiss-roll" cell for NiOOH oxidations (Hoffman-La Roche).
"Pencil Sharpener" cell for electrolyses with sacrificial anodes (SNPE).
Undivided cell for the production of *t*-butylbenzaldehyde (Givaudan).
Cell for tetraethyllead (Nalco).
Cell for hydrogenation of soybean oil [10].
Carbon particle bed cell (EnviroCell) [62].
Solid polymer elctrolyte cell (University of Dortmund) [63].

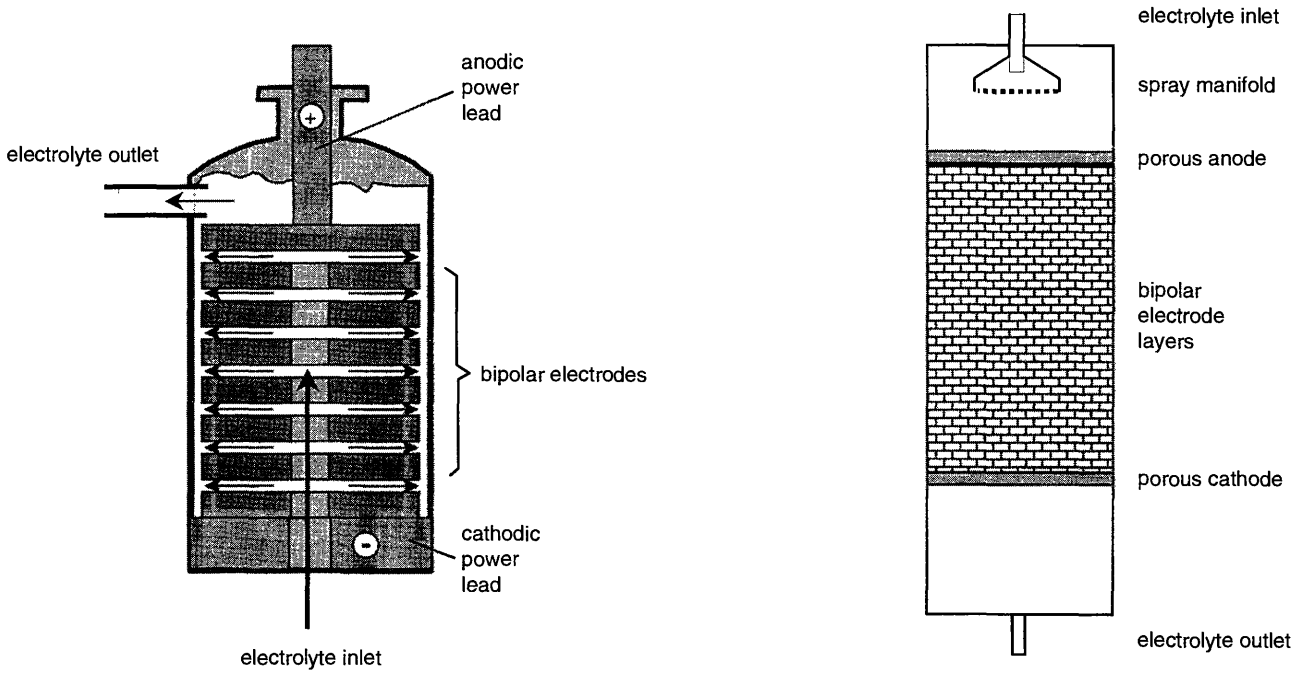


Figure 5. Thin-film cells. (a) Capillary-gap cell. (b) Bipolar trickle tower.

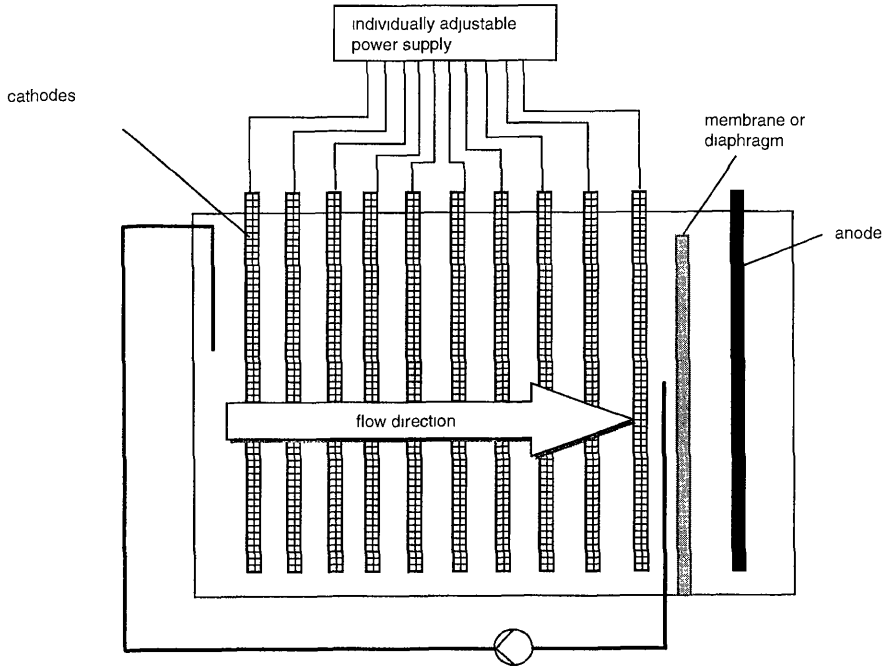


Figure 6. Heräus multicathode cell.

C. Electrochemical Know-How

Some prominent companies/institutes that are or have been (like Hoechst and Monsanto) active in the field of organic electrochemistry are:

Asahi Chemical, Japan (electrohydrodimerizations, Kolbe electrolyses)
Bayer, Germany (electrofluorinations)
BASF, Germany (electrochemical methoxylations)
Degussa, Germany (amino acids)
EDF, France (indirect oxidations)
Electrosynthesis Company, USA (electrochemical know-how center)
Givaudan, France (indirect oxidations using Mn(III))
Hoechst, Germany (chromic acid regeneration)
Hüls, Germany (alcoxides)
Hydro Quebec; Canada (ceric oxidations)
Hoffmann-La Roche (indirect electrolyses, vitamin C)
L. B. Holliday, UK (chromic acid oxidations)
E. Merck, Germany (indirect electrolyses, vitamin C)
3M Company, USA (electrofluorinations)
Monsanto, USA (ADN, organic electrochemistry in general)
Mitsui Toatsu, Japan (electroreductions)
Otsuka, Japan (methoxylations)
Osaka Organic Chemical Ind., Japan (indirect electrooxidations)

SNPE, France (electrolyses with sacrificial electrodes)
SynProTec, UK (indirect oxidations, contracting)
CERCI (Central Electrochemical Research Institute), India (nitro group reductions)
Capenhurst Electricity Council Research Centre, UK (cell systems)
Institute for Textile Chemistry and Textile Physics, Dornbirn, Austria (vat dyes recycling)

V. INDUSTRIAL PROCESSES

There are some recent reviews on the topic of organic electrochemical processes in industry [13,64–69]. Most of these reviews list several dozens of electrochemical reactions that are reputed to have reached commercial status, at least for a period of time. Many cases are not definitely confirmed; some have been operated commercially for some years but are believed to be obsolete today (see Table 1). D. Degner has compiled the relevant patent literature for industrially important reactions that have been studied between the early 1970s and the late 1080s [70]. Table 1 presents many of these examples, but its message often is only: These are electrochemical reactions that have or had the opportunity to achieve costs equal to those of alternatives.

A. Organic Electrochemistry and Industrial Alternatives

Nearly every chemical process has realistic alternative routes. Organic electrosyntheses compete with "conventional"—as electrochemists like to say—reactions, such as reductions, oxidations, and catalytic hydrogenations. Competition doesn't necessarily mean that the same starting material is converted into the same end product. The route to the target molecule can be totally different, starting from other precursors or following alternative reaction paths (Fig. 7).

An interesting example is ibuprofen and naxoprofen chemistry. The 20 years of naxoprofen technology have been reviewed recently [71], and the electrochemical route has also been described [72]. Ibuprofen electrochemistry has been described by SNPE [73].

Sometimes it is not the product but its effect that is the real aim. Dihydrophthalic acid was produced by BASF for many years as an intermediate for a first generation of fuel additives. Its success ended when new alternative products arrived on the market. Production was abandoned, although cathodic reduction is still the best way of producing dihydrophthalic acid.

B. Some Typical Processes

To given an impression of the broad spectrum of the technology, some typical processes have been taken as examples. These are not all in use today, but they had or will have the potential to become an industrial process, both technologically and commercially.

On the cathodic side, two processes in undivided cells have been chosen, namely the *ADN Process* and the *electrocarboxylation of chloroethyldiphenylether*, a process needing sacrificial anodes.

The reduction of phthalic acid to *dihydrophthalic acid* and the electrolytic hydrogenation of dichloroacetic acid to *monochloroacetic acid* are two examples of divided cells. These illustrate a nearly typical situation in organic electrochemistry: There is only one product needed, and the reaction at the counterelectrode is only of interest as a problem.

Table 1 Commercial Electroorganic Products [67,68]

Number	Product	Precursor	Company/Country	Status scale (t/a)
Commodity Chemicals (> 10,000 metric tons/year)				
1	adipodinitrile	acrylonitrile	Monsanto (inventor)	C; 300,000
2	bleached montan wax	raw montan wax	Hoechst	C; 11,000
3	tetraalkyllead	alkyl chloride	Nalco	D; > 10,000
Fine Chemicals Cathodic (100–10.000 metric tons/year)				
4	2-methyldihydroindole	2-methylindole	L. B. Holliday, BASF	D; 120
5	hexahydrocarbazole	tetrahydrocarbazole	L. B. Holliday, BASF	D
6	dihydrophthalic acid	phthalic acid	BASF	D; 600 [127]
7	piperidine	pyridine	Robinson Bros.	D; 100–500 (50 years comm. [127]
8	2,2-dichloro-1-(4-hydroxyphenyl (ethene	3,3,3-trichloro-1 hydroxy-1-(4-hydroxyphenyl) ethene)	Japan	C; 120
9	3-hydroxybenzyl alkohol	3-hydroxbenzoic acid	Mitsui Toatsu	C; 100
10	terafluoro-p-xylene	bis-quat. ammonium salt	Europe	C; 200
Fine Chemicals Anodic (100–10,000 metric tons/year)				
11	dimethyl sebacate	monomethyl adipate	Asahi, others	C
12	anisic aldehyde	4-methoxytoluene	BASF	C; 3500 [93]
13	4-*t*-butylbenzaldehyde	4-*t*-butyltoluene	BASF; Givaudan	C
14	tolualdehyde	*p*-xylene	BASF	C; 1000 [93]
15	substituted aromatic aldehydes (acetals)	substituted toluenes	Otsuka, BASF, Hydro Quebec	C; > 1000
16	anthraquinone	anthracene	L. B. Holliday, ECRC	C; 100 (> 1000 [127])
17	2,5-dimethyoxy-2,5-dihydrofurfuryl-1-ethanol (precursor for maltol)	furfuryl-1-ethanol	Otsuka	C; 150
18	2,5-dimethoxy-2,5-dihydrofuran	furan	BASF	C; 100
19	calcium gluconate	glucose	India, Europe, Sandoz (Novartis)	C; > 1000
20	calcium lactobionate	lactose	see above	
21	*fluorocarbons*: perfluorinated alkanoic acids, fluorinated alkanes, perfluorinated chloroalkanes, alkanoic acid fluorides	carboxylic acids, alkanoic acid chlorides, alkanes, chloroalkanes	3M, Bayer, Phillips Petroleum, DuPont, Hoechst	C; > 10_
22	diacetoneketo-gulonic acid	diacetone-L-sorbose	Hoffmann La-Roche, Merck	C

Table 1 Continued

Number	Product	Precursor	Company/Country	Status/scale (t/a)
Specialities Cathodic (1–100 metric tons/year)				
23	4-aminomethylpyridine	4-cyanopyridine	Reilly Tarr	D; 70
24	2-aminomethylpyridine	2-cyanopyridine	Reilly Tarr	D; 30
25	1,4-dihydronaphthalene	naphthalene	Hoechst	P
26	salicyclic aldehyde	(2-hydroxybenzoic acid)	India	C; 20
27	succinic acid	maleic acid	CERCI, India	C; 30
28	cysteine	cystine	several companies	C(?); 30
29	S-carboxymethylcysteine	cystine, chloroacetic acid	Spain	P
30	4-aminophenol	nitrobenzene	India	C(?)
31	4,4′-benzidine	nitrobenzene	India	C; 30
32	4-aminobenzoic acid	4-nitrobenzoic acid	India	C; 3
33	azoxybenzene [127]	nitrobenzene		C; 3 tons/day
34	sorbitol	glucose	India, USA	C(?), D
35	mannitol	mannose		C(?)
36	cephalosporin intermediate (3-exomethylenecephem derivative)	3-chloromethylcephem derivative	Japan	C(?)
37	polysilanes	dichlorosilanes	Osaka Gas	C(?)
Specialities Anodic (1–100 metric tons/year)				
38	dialdehyde starch	starch	USA, India, Europe	D; 100
39	mucic acid	galacturonic acid	EDF	C
40	acetoin	butanone	BASF	C
41	adipoin (as dimethyl ketal)	cyclohexanone	BASF	C
42	1-formyl-2-methoxy-piperidine	1-formylpiperidine	Europe	C(?); 25 [127]
43	picolinic acid	2-methylpyridin	Reilly Tarr	D; 10
44	isonicotinic acid	4-methylpyridin	Reilly Tarr	D
45	perfluoropropylene oxide	perfluoropropylene	Hoechst	D; 5
Developments Cathodic				
46	2-aminobenzyl alcohol	anthranilic acid	BASF	P
47	2-arylpropionic acids	alkyl aryl ketones	Searle, Solutia, SNPE, Monsano	P
48	phthalide	ammonium phthalamate, dimethyl phthalate	BASF	P
49	pinacol	acetone	USA, Japan, Europe	P
50	4-methyl-5-hydroxymethyl-imidazole	4-methylimidazole-5-carboxylic acid	Smith, Kline & French	P
51	glyoxylic acid	oxalic acid	Rhone, Poulenc, Steetley Chem.	P
52	aminobenzoic acids	nitrotoluenes (via 4-nitrobenzoic acid at the anode)	EDF, India	P; paired electro-synthesis

Table 1 Continued

Number	Product	Precursor	Company/Country	Status scale (t/a)
53	hydroxymethylbenzoic acid	dimethyl terephthalate	Hoechst	P
54	monochloroacetic acid	tri-, dichloroacetic acid	Hoechst	P
56	3,6-dichloropicolinic acid	3,4,5,6-tetrachloropicolinic acid	Dow	C(?)
Developments Anodic				
57	5-nitronaphthoquinone	1-nitronaphthalene	Hydro Quebec	P
58	propiolic acid	propargyl alcohol	BASF	P
59	acetylenedicarboxylic acid	2-butyne-1,4-diol	BASF	P
60	hexafluoropropylene oxide	hexafluoropropene	Hoechst	P
61	chiral 1,2-diols	prochiral olefins	Engelhard, Chi Rex	P
62	benzoquinone	benzene	Electricity Council	P
63	propylene oxide	propylene	USA, Europe, Japan	
64	Kolbe products	fatty acids (sodium salts)	Europe, Japan, India, Russia	P
65	sorbic acid	acetic acid/butadiene	Monsanto	P
66	1-acetoxynaphthalene	naphthalene	BASF	P
67	1/4-acetyl-2-methylnaphthalene	2-methylnaphthalene	BASF	P
68	naphthochinone/anthraquinone	naphthalene/butadiene	Hydro Quebec	

Note: t/a, Metric tons per annum.
C: Commercial; D: discontinued; P: pilot.

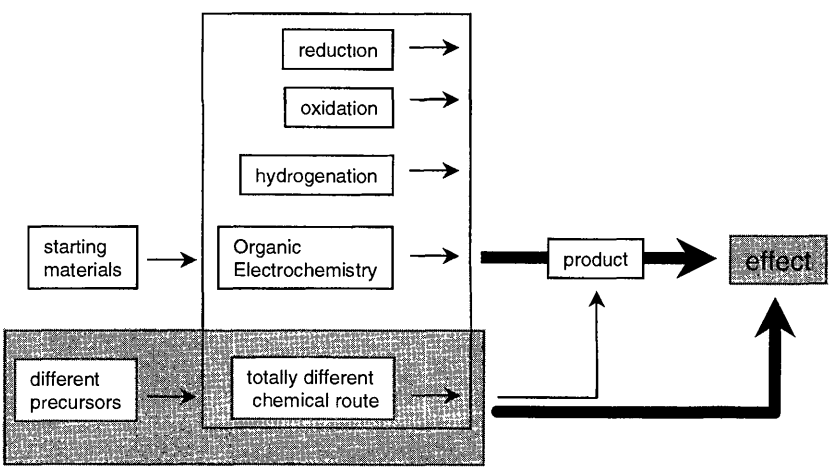


Figure 7. Organic electrochemistry in competition with other synthetic methods.

On the anodic side, four cases of undivided cells and two cases of divided cells have been chosen. Two processes are direct and four are indirect anodic oxidations. The *sebacic acid* process, as described by Asahi Chemical [74], is the industrial realization of the oldest and most thoroughly studied electrochemical reaction, the Kolbe reaction.

The oxidation of substituted toluenes leads to *aromatic aldehydes*.

An indirect route to aromatic aldehydes is also presented.

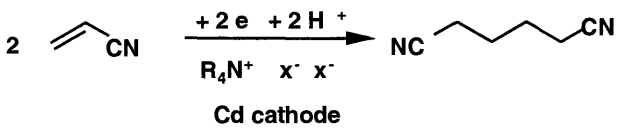
The indirect, ex-cell *chromic acid oxidation* is the oldest industrial organic electrochemical process.

The indirect ex-cell *oxidation with ceric ions* opens up new opportunities.

The halogen-mediated in-cell *oxidation of ketones* is a recently commercialized electrosynthesis.

1. ADN Process

The electrohydrodimerization of acrylonitrile was a milestone in the history of organic electrochemistry. The success of this process is associated with the name of Manuel M. Baizer. In 1960, he initiated the biggest success story of organic electrochemistry to date, namely, the "Monsanto" process for the hydrodimerization of ACN, acrylonitrile, to ADN, adipodinitrile (Scheme 3).



Scheme 3. Hydrodimerization of acrylonitrile.

Although the electrochemical coupling to form ADN had been known since the 1940s, the breakthrough came only when Baizer found out that the use of quaternary ammonium salts such as tetraethylammonium *p*-toluenesulfonate as supporting electrolytes led to mass yields of 90% of ADN [75]. Following Baizer's discovery, an intensive process development effort was undertaken at Monsanto's Technical Centre in Pensacola, Florida [76].

In the first stage of the development, a divided cell was employed for this process. The catholyte consisted of an aqeous solution of ACN and ADN in 40% tetraethylammonium ethyl sulfate, and the anolyte was a dilute solution of sulfuric acid. Lead electrodes were used (the anode contained 1% silver). Anolyte and catholyte were separated by an ion exchange membrane, Ionics CR 61. One cell press consisted of 24 bipolar cell units. The total voltage was 300 V, and the current density was 4.5 kA/m^2.

This concept had some severe shortcomings, like high costs for repair and maintenance as well as high energy costs. Soon after the first industrial plant had been started up, efforts were made to change over to an undivided cell. This concept has been proven to be superior to the first one, although it is complicated with regard to safety. Oxygen and (the cathodic by-product) hydrogen as well as other volatile organics are present together in a single gas phase.

Here is a comparison of Monsanto's EDH processes [77]:

	Divided	Undivided
Cathode	Pb	Cd
Anode	Pb (1% Ag)	steel
Membrane	Ionics CR61	none
Temperature	50°C	55°C
Current density	4.5 kA/m^2	2.0 kA/m^2
Electrode gap	7 mm	3 mm
Cell voltage	11.65 V	3.83 V
Power consumption	6.61 kWh/kg	2.43 kWh/kg
Quaternary ammonium salt		
Cation	tetraethylammonium	BisQat[a]
Anion	ethyl sulphate	phosphate
Concentration	40%	0.4%

[a]Hexamethylenebis(ethyltributyl)ammonium.

The process scheme [79] is shown in Fig. 8. The details of the process are reviewed in Refs. 78 and 79.

The production capacities [77,80] are:

Solutia (Dekatur, AL, USA)	181,000
BASF (Seal Sands, Teeside, UK)	91,000
Asahi Chemical (Nobeoka, Japan)	37,000
Rhodia (Camaciri, Brazil) (only mentioned in Ref. 77)	30,000

The undivided cell process is shown in Fig. 9; the electrodes are kept at a 2-mm distance by plastic spacers. The electrode assembly is installed in a pressure vessel. The life of the electrodes is only 2 or 3 months at best, so the cells have to be removed and opened regularly. For this purpose, there is a dedicated workshop for cell maintenance in the vicinity of the electrolysis facility.

The electrolyte is pumped continuously through the cells and the electrolyte cooler; the velocity in the cell gap is roughly 1 m/s. A side stream is withdrawn from the electrolyte circuit, cooled, and extracted in a multistage extraction column. The organic phase is extracted in a second column to recycle the quaternary ammonium salt. After this extraction, the crude ADN is passed to a multicolumn distillation system, where pure ADN and by-products are recovered and ACN is returned to the electrolysis.

The purity of ADN must be >90% for it to be suitable for conversion into hexamethylenediamine by hydrogenation.

The aqueous phase is freed of metal salts and organic impurities. For this purpose, a side stream is first extracted with ACN, then evaporated and subjected to crystallization for the recovery of the quaternary salt. The mother liquor is treated with sodium sulfide to precipitate iron and cadmium ions as sulfides.

2. Fenoprofen

One of the most intriguing developments in the field of industrial electrochemistry is electrochemical couplings with sacrificial anodes. In the 1980s, the French company SNPE developed the prototype of a specific cell for this purpose, the so-called pencil-sharpener cell [81].

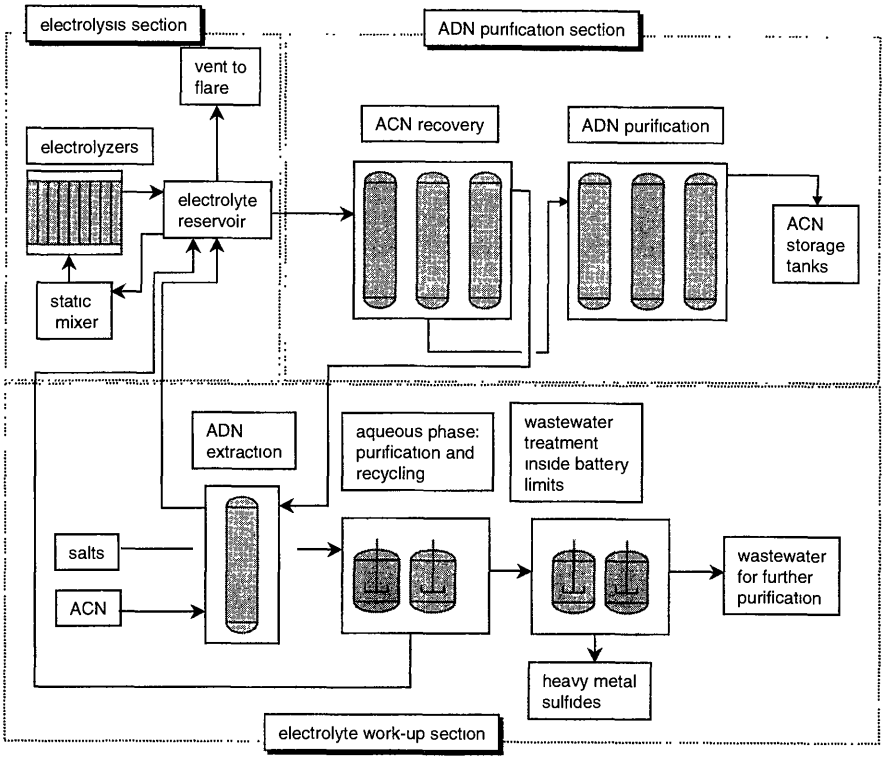


Figure 8. Electrohydrodimerization of acrylonitrile.

The pilot-plant production of some analgesics like fenoprofen (Scheme 4) and ibuprofen was accomplished in this type of cell [82]. The process has been reviewed [83] by one of the inventors, J. Chaussard. Some electrolysis parameters [81,83] are:

Anode	Mg
Cathode	Stainless steel (electroplated with lead)
Solvent	DMF, saturated with CO_2
CO_2 pressure	5 bar
Supporting electrolyte	1% Tetrabutylammonium bromide
Temperature	30°C
Current density	5 A/dm^2
Mass yield	80%
Faradaic yield	66%
Electrical energy	6.6 kWh/kg (electrolysis only)

The pilot cell was run discontinuously, starting with 340 kg of a solution of 60 kg chloroethylphenyl phenyl ether and 3 kg tetrabutylammonium bromide. The current was maintained at 600 A. The batch time was 28 h, and the magnesium loss was 9 kg per batch.

According to the authors, an economic evaluation showed that the electrochemical step was reasonably cheap. Unfortunately, this is not the whole truth. In a recent publication [84], authors from Searle and (formerly) Monsanto describe the workup procedure. The removal of colloidal metal, the handling of the oxide and salt mixture, the

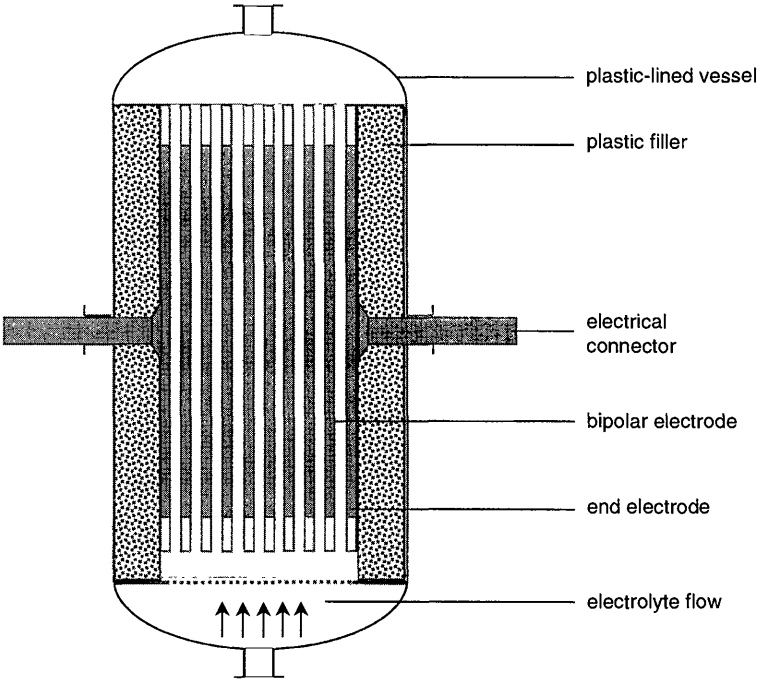


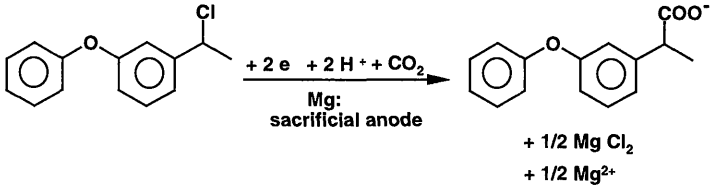
Figure 9. Undivided ADN cell.

purification of the crude product, and the recycling of dry and pure DMF must also be taken into account.

The electrolysis is described in Fig. 10, together with a rough outline of the possible workup.

3. Dihydrophthalic Acid

Dihydrophthalic acid (DHPA) was produced by BASF for several years (Scheme 4). It was required as an intermediate for gasoline additives and plasticizers. Production was not abandoned because of technical problems or commercial difficulties, but was stopped when new families of chemicals for the same applications became available. DHPA was not only a pioneer product of organic electrochemistry but also a door opener for new applications.



Scheme 4. Electrocarboxylation of chloroethylphenyl ether.

The development of the process is reviewed in Ref. 85. The technical development was initiated by H. Nohe [86]. However, the first electrochemical synthesis had already been published at the turn of the century [87]. The electroreduction on an industrial scale

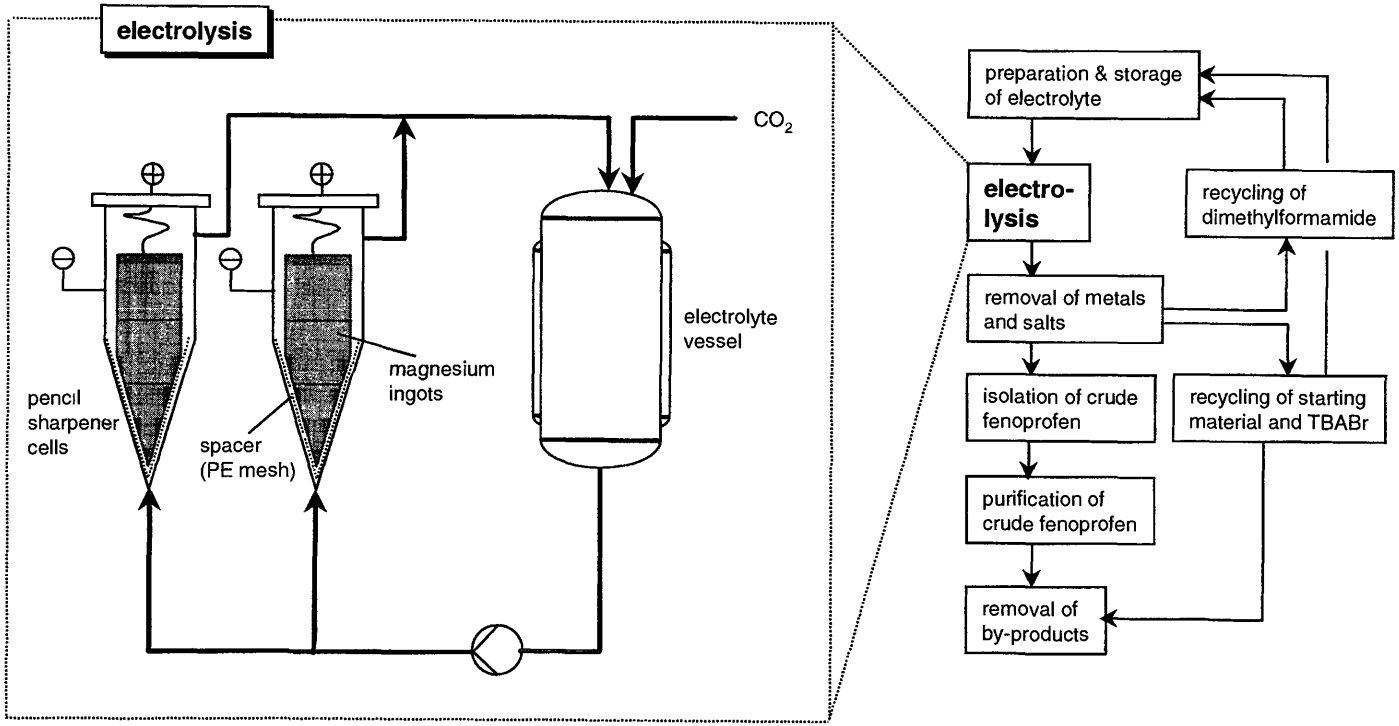


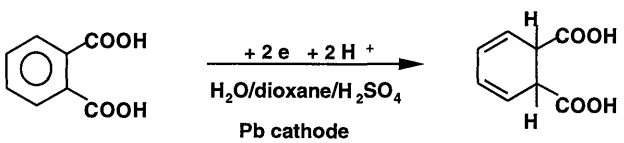
Figure 10. Electrocarboxylation of chloroethylphenyl ether.

only could take place when suitable divided cells became possible. The development took advantage of the first generation of ion exchange membranes [88].

The process parameters [7] are:

Cathode	Pb
Anode	Pb/PbO_2
Catholyte	15% Phthalic acid, 55% dioxane, 25% H_2O, 5% H_2SO_4
Anolyte	5% Aqueous sulfuric acid
Temperature	30–40°C
Current efficiency	70%
Current density	1 kA/m^2
Mass yield	94%
Energy consumption	4.3 kWh/kg

The process is shown in Fig. 11. The performance of the divided cell, the membranes and the electrodes, as well as the work-up are described in Ref. 88. Specially constructed lead-plated electrodes with internal cooling are used. The electrolysis is run batchwise in order to achieve high conversions, and the workup is carried out continuously. Waste gases are removed separately. Hydrogen, the cathodic by-product, and oxygen, the main anodic product, are cooled and scrubbed to remove acid impurities before venting. Hydrogen is fed to a flare to incinerate traces of organics.



Scheme 5. Reduction of dichloroacetic acid to monochloroacetic acid.

The cathodic batches are collected in the DHPA tank and fed to a two-stage crystallization. In the first vessel dioxane is distilled off; in the second, the product suspension is cooled and forms homogeneous crystals. These are collected and washed in a centrifuge to remove traces of sulfuric acid. The pure product is dried in a continuous dryer and stored.

The performance of the cell depends greatly on the life of the ion exchange membranes. Cation-exchange membranes from Ionics and Tokuyama Soda (e.g., Ionics 61 AZG, Tokuyama CLE-E) were most stable, having lives of more than half a year.

The membranes on the market today are more stable than those available in the 1970s, but they would probably not be suitable. One critical problem occurring in all electrolyses in divided cells using organic solvent arises from solvent migration. Even low concentrations of organics in the anolyte can lead to severe problems with regard to anode corrosion.

This can sometimes be circumvented by using DSA electrodes, but care must be taken to avoid poisoning of the cathode as a result of traces of metals migrating from the anode to the cathode. Some of these problems are discussed in more detail in Ref. 88.

4. Monochloroacetic Acid

This process was operated by Hoechst AG in a pilot plant at Frankfurt [89] in the late 1980s and was improved in the early 1990s [90]. It has not been commercialized. The problem with the production of monochloroacetic acid (MCA) is a certain amount of

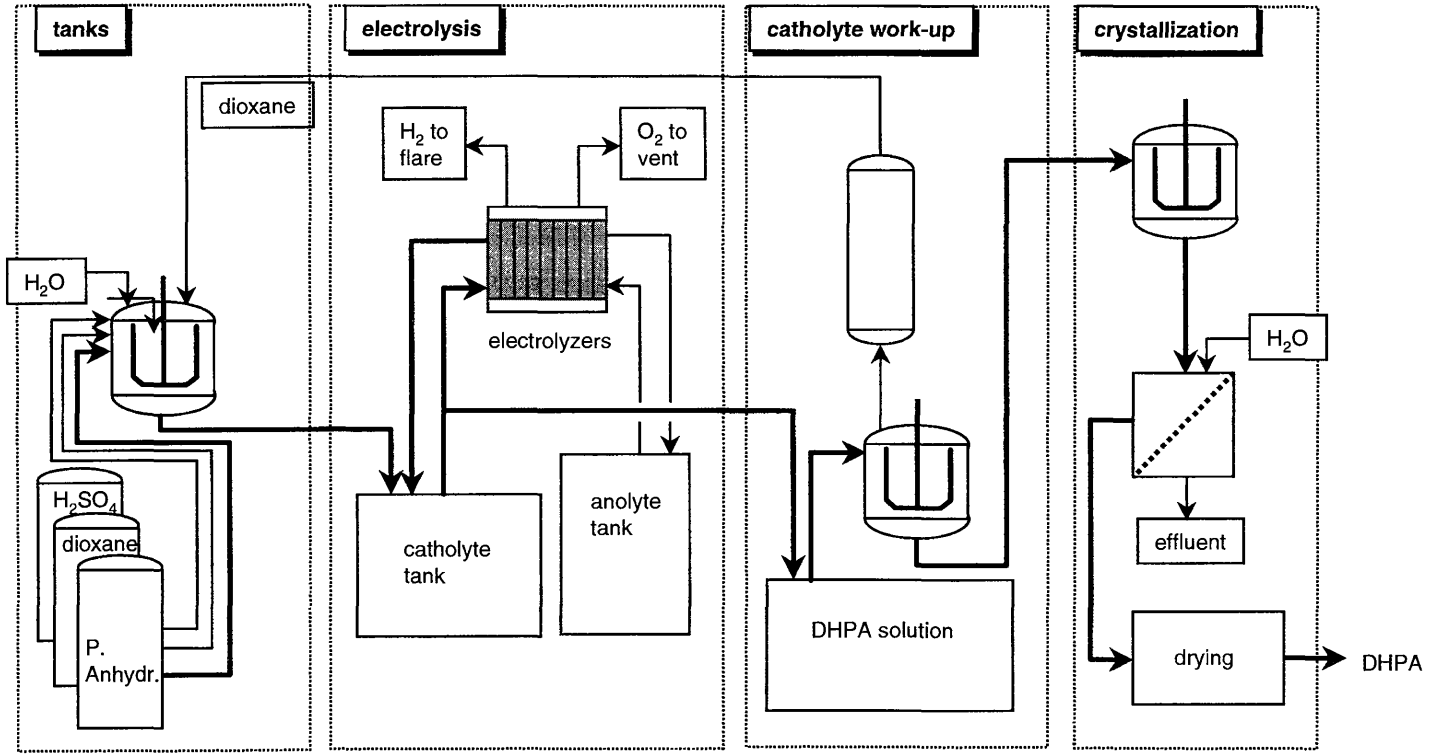
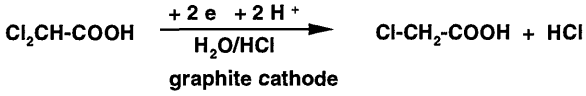


Figure 11. Reduction of phthalic acid to dihydrophthalic acid.

overchlorination. The removal of dichloroacetic acid (DCA) and, to a lesser extent, trichloroacetic acid is usually accomplished by melt crystallization.

The melt crystallization yields a mother liquor that is usually rejected; the alternative is reductive dehalogenation by electrochemistry (Scheme 6). The electrochemical step is shown in Fig. 12.



Scheme 6. Reduction of dichloroacetic acid to monochloroacetic acid.

The mother liquor from the melt crystallization first is fed to a distillation column to remove residual acetic acid. The electrochemical reduction is carried out in a divided cell; the technical prototype had an electrode area of $0.8\,m^2$.

Some process parameters [89] are:

Cathode and anodes	Plates of impregnated graphite
Membrane	Nafion 324
Current density	4000–5000 A/m^2
Cell voltage	4–5 V
Temperature	80°C
Flow rate	0.4 m/s
Current efficiency	90%
Conversion	>99%
Selectivity	>97%
Final catholyte	MCA/H_2O/HCl: 56/33/11
Catalyst	Lead acetate (10–1000 ppm)

Lead is not deposited on the cathodes (or anodes) but is removed from the crude MCA. It can be recycled to the catholyte tank.

Hydrochloric acid is fed into the anolyte. The authors emphasize that all loops are closed, so acetic acid and chlorine must be returned to the chlorination unit if the plant is totally integrated into the whole process.

It is difficult to say why this elegant process didn't succeed. One possible difficulty is the links to the chlorination process that influence the electrochemical step. This could mean that the process needs buffer tanks for the raw material and for crude MCA from the electrolysis. Depending on the requirements of the chlorination, these tanks will be relatively expensive.

Another problem could be the life of the electrodes. In Ref. 90, the authors claim the use of ammonium salts, an indication that the effect of lead acetate doesn't yield the desired long-term stability.

5. Sebacic Acid

Asahi Chemical is said to have been using the Kolbe synthesis for the production of sebacic acid for 20 years now. The electrolysis itself is one of three chemical steps (Scheme 7). In the first step, the monoester of adipic acid is produced. This is anodically dimerized to dimethyl sebacate. This ester is hydrolyzed to give crude sebacic acid.

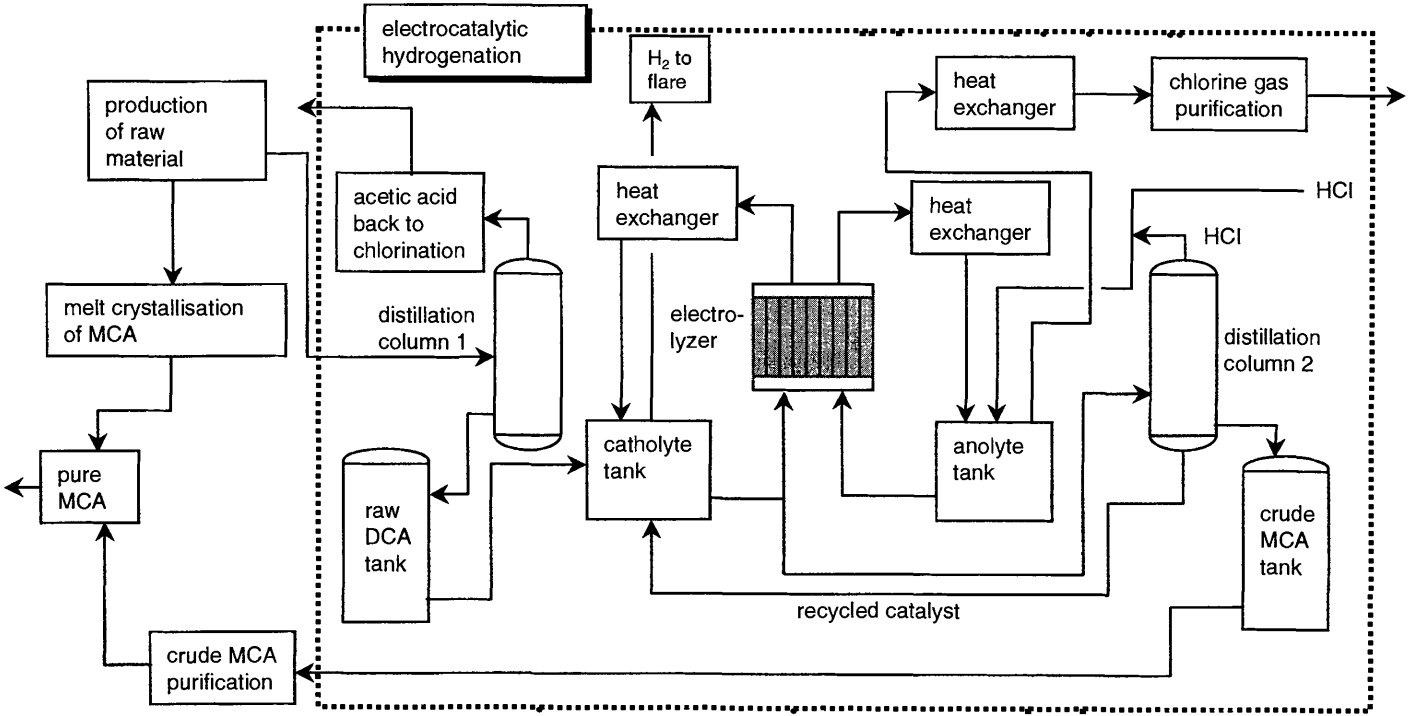
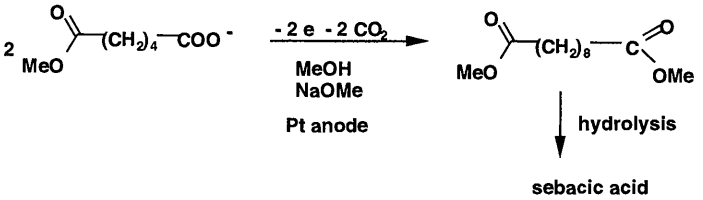


Figure 12. Electrocatalytic dehalogenation of dichloroacetic acid.



Scheme 7. Kolbe electrosynthesis of sebacic acid.

The process flow diagram is shown in Fig. 13 [74]. The first step comprises the esterification of adipic acid, which is a readily available feedstock from Asahi's own production processes, with methanol to form the monoester. A cation-exchange resin is employed as catalyst. Since the esterification is an equilibrium reaction, a multistep distillation is necessary to drive it to completion.

Monomethyl adipate is fed into the electrolysis loop. This specific variation of the Kolbe reaction is known as the Brown–Walker reaction. The electrodes are bipolar (the anode is platinum-plated titanium).

The main characteristics [74] are:

Current density	10–30 A/dm^2
Cell voltage	5–12 V per gap
Temperature	50–60°C
Supporting electrolyte	Potassium monomethyl adipate
Solvent	Methanol containing water (0.15–3 wt%)

The workup consists of several steps in order to recycle solvent and starting material and to recover the crude dimethyl sebacate. The raw material is purified by distillation before going to the hydrolysis.

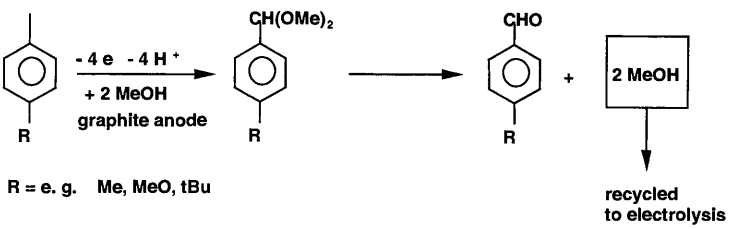
The hydrolysis is achieved without catalyst under slight pressure. The removal of methanol, water, and impurities again involves several process steps.

As can be seen easily in Fig. 13, electrolysis plays only a minor role in the capital costs of the whole process.

6. Aromatic Aldehydes

Some 4-substituted aromatic aldehydes, such as anisic aldehyde, toluic aldehyde, or *t*-butylbenzaldehyde, are produced commercially. The electrosynthesis can be accomplished by several different methods and is a good example of the versatility of selective electrochemical oxidations [91].

a. Anodic Methoxylation BASF has announced that the electrochemical production of aromatic aldehydes is a core technology for the company [92,93]. The electrosynthesis is an anodic methoxylation of substituted toluenes (Scheme 8).



Scheme 8. Methoxylation of substituted toluenes.

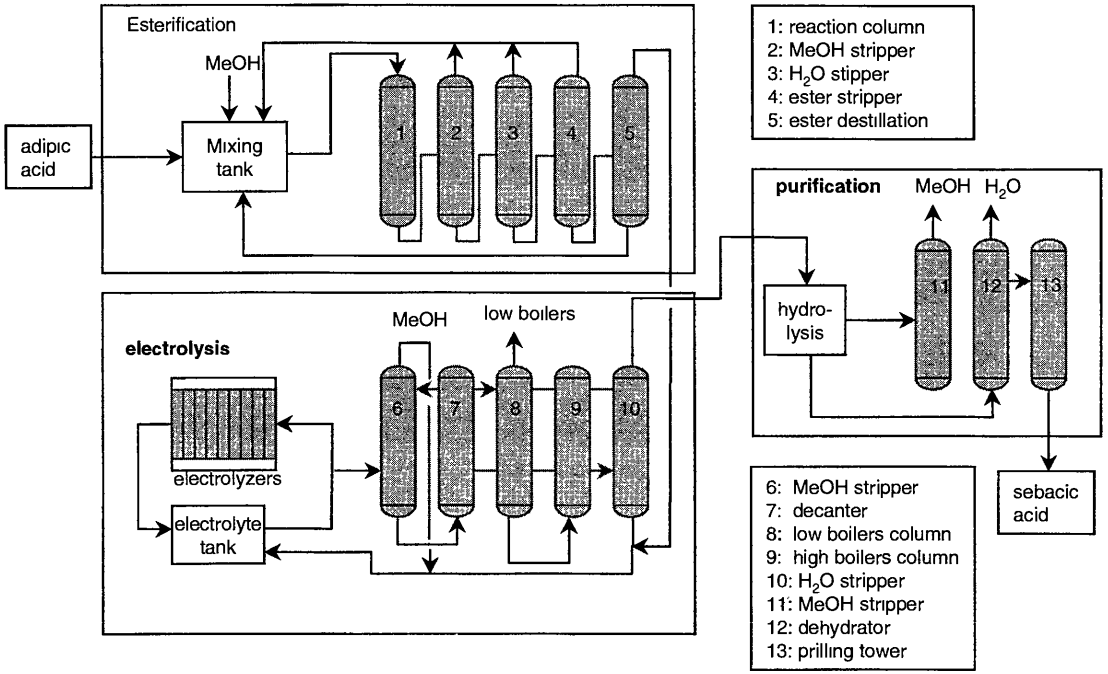


Figure 13. Manufacture of sebacic acid for adipic acid.

The process is based on BASF's unique capillary-gap cell (Fig. 5a). One of the big assets of the process is that it can use methanol both as solvent and as reagent. Since methanol can be recycled conveniently, the process closes most loops, a decisive ecological advantage of this technology over "classical" alternatives such as chlorination. The chlorination of toluenes yields substituted benzal chlorides and HCl in the first reaction step. The hydrolysis is accompanied by chlorinated by-product and gives rise to effluents containing hydrochloric acid [94]. The reagent chlorine has to be discarded as diluted contaminated hydrochloric acid, whereas the reagent methanol can be reused.

The commercial benefits are also based on the high selectivity and the low energy demand of the total process.

Some typical parameters [70,95,96] of the electrolysis step are:

Electrodes	Bipolar graphite rings
Interelectrode gap	1 mm
Substituted toluene	10–25%
Supporting electrolyte	0.3–3%
Methanol	90–75%
Current density	3–5 A/dm^2
Temperature	40–50°C
Voltage per gap	4–6 V
Yield	> 80%
Conversion	90–99%
Selectivity	85%

The electrolysis cells are continuously fed with the methanolic electrolyte from the electrolyte tank. A part of the solution is constantly fed into the first distillation column to recycle the solvent methanol. Hydrogen gas is cooled down to recover methanol and is then discharged from the process circuit and flared off.

The crude dimethyl acetal is filtered to recover the supporting electrolyte, for example, a commercial salt such as potassium fluoride or sodium sulfonate, which is returned to the electrolyte tank.

In a second distillation, unreacted starting material, intermediates or low-boiling by-products are separated from the acetal. Hydrolysis of the acetal with water is accomplished under mild conditions to give a nearly quantitative yield of the aldehyde. The by-product of the hydrolysis, methanol, is rectified and fed back to the electrolyte tank.

The aldehyde is recovered in high purity in a final distillation.

Both the acetal and the aldehyde can be used as intermediates for crop protection agents, fragrances, plating additives, ultraviolet (UV) absorbers, optical brighteneres, and other applications.

As can be seen from the process scheme (Fig. 14), the success of this electrochemical process is not entirely based on an elegant cell design or optimized electrolysis conditions but depends greatly on "general" chemical engineering know-how, which has integrated all unit operations into an effective overall system.

b. Indirect Oxidation of t-Butyltoluene Another commercial route to substituted aromatic aldehydes was developed by Givaudan, namely the electrosynthesis of *p*-(*tert*-butyl)benzaldehyde starting from *t*-butyltoluene [97] (Scheme 9). This indirect electrolysis uses a slurry of Mn(II)/Mn(III) sulfate in 55% H_2SO_4. Traces of silver are added to the electrolyte slurry to improve the anodic current efficiency and the current density, and traces of ceric salts are added to improve the selectivity and the rate of oxidation of *t*-butyltoluene [98]. A specific electrochemical reactor was developed for this process

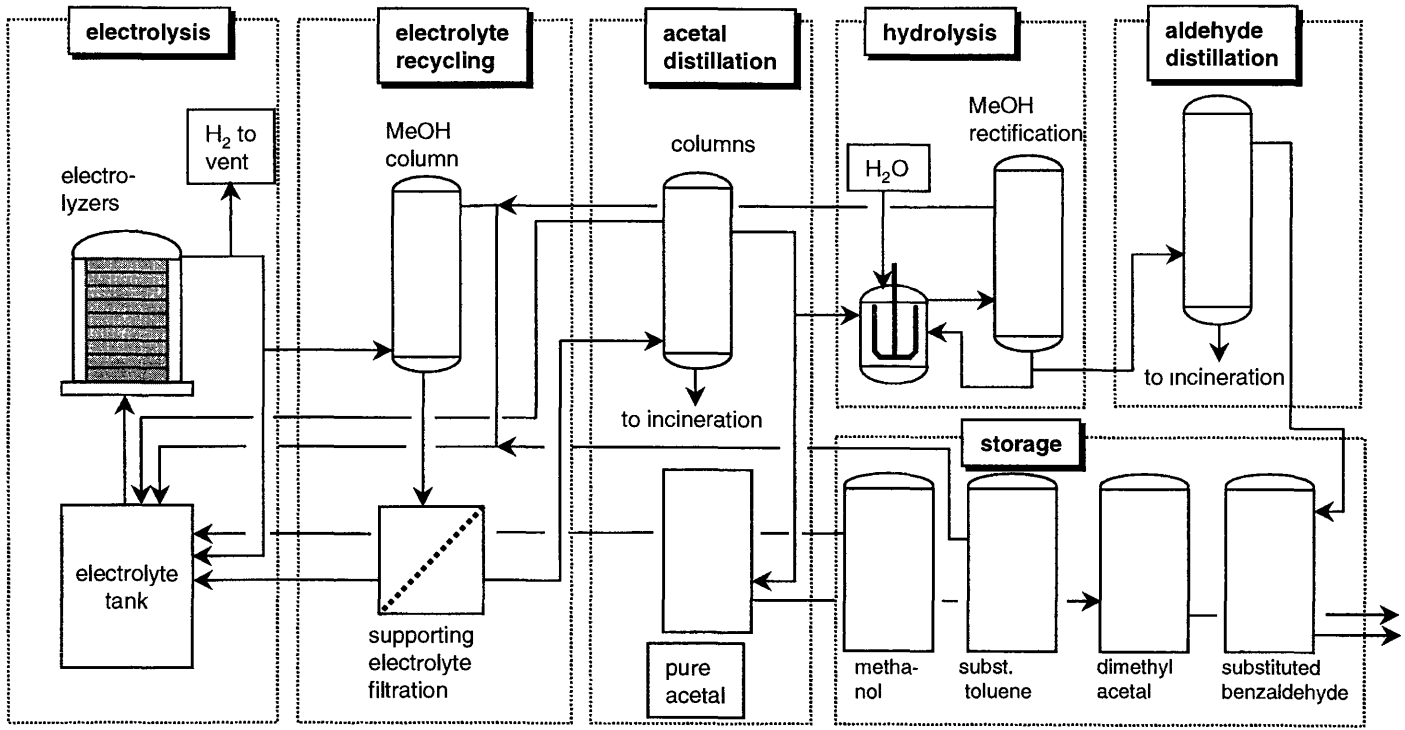
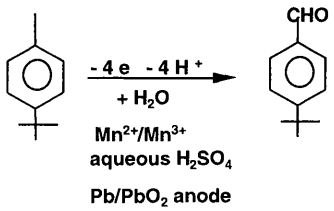


Figure 14. Electrochemical production of aromatic aldehydes.

[99]. The reactor is an undivided reactor with flat parallel bipolar lead electrodes [100] (Fig. 15).



Scheme 9. Oxidation of *p*-(*tert*)-butyltoluene to *p*-*tert*-butylbenzaldehyde.

The loss of current efficiency due to the reduction of Mn^{3+} at the cathode is less than 10% [98].

Some characteristics of the electrolysis are:

Anode	Stabilized lead
Anode area	1.11 m^2 (per element)
Number of elements	18
Total area	20 m^2
Current density	3.6 kA/m^2
Voltage/element	4.1 V
Temperature	85°C
Mn_2SO_4	3 mol/l
Ag^+	0.01 mol/l
Ce^{3+}	0.01 mol/l

The process was started up in 1992. The capacity is around 1000/year.

Hydro Quebec did some pilot-plant oxidations of substituted toluenes with ceric methanesulfonate. These activites were based on studies by a research group at W. R.

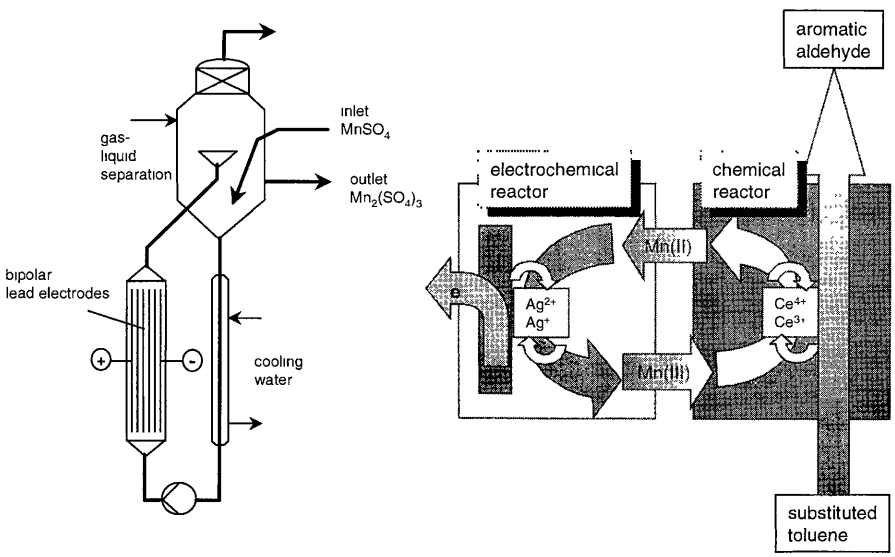


Figure 15. Regeneration of Mn(III) in a bipolar undivided cell (Givaudan).

Grace and Co. [101]. This reaction is a possible third way to aromatic aldehydes in high yields.

7. Chromic Acid Regeneration

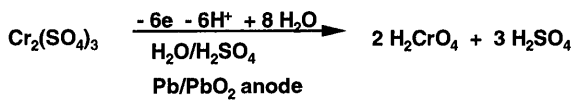
The oldest process of organic electrochemistry is the indirect oxidation of hydrocarbons with chromic acid. It has been employed industrially for more than 90 years by Hoechst—now Clariant—in Gersthofen, Germany [102]. Other sites are or were located in Great Britain. The oxdiations of naphthalene, anthracene, and camphene are examples. Companies like Emery Industries, L. B. Holliday, and Boots have also used chromic acid regeneration commercially [103]. It has been employed for the bleaching of montan waxes for more than 70 years.

In terms of tonnage, current demand, and product versatility, the chromic acid oxidation of montan waxes is one of the most important organic electrochemical processes.

Clariant is producing 11,000 metric tons per annum of bleached montan waxes in Gersthofen [104]. The starting material is deresinified crude montan wax, extracted from lignite. It consists of esters of long-chain alcohols and carboxylic acids. Montan wax acids and their derivatives are widely used, for example, as soaps, polishes, and lubricants.

Under acidic reaction conditions, the esters are hydrolyzed. The alcohol is oxidized by chromic acid in a four-electron step to give the corresponding carboxylic acid. The regeneration of Cr(VI) looks simple and straightforward (Scheme 10), but the faradaic demand is significantly higher than 3 F/mol since low-molecular-weight organic impurities are oxidized to carbon dioxide.

The bleached wax is purified in a subsequent step to remove residual chromium salts. The classical cell systems used ceramic diaphragm plates or PVC-based tissues. These materials and the massive lead anodes, coated with lead dioxide, defined the cell construction for nearly a century. Today technology is changing over to modern cell constructions, using cation-exchange membranes and dimensionally stable titanium anodes with PbO_2 coatings. This technology has been tested in pilot plants and will improve the existing processes in many respects. A flow sheet of the "classical" process is shown in Fig. 16.



Scheme 10. Chromic acid regeneration.

Several cells are combined to form a cascade. Both anolyte and catholyte sides are fed with the same starting solution. This consists of the depleted solution from the oxidation, condensates, and washing streams from the catholyte scrubbing towers.

In the anolyte the concentration of chromic acid increases from cell to cell; in the catholyte hydrogen is evolved and Cr(III) is partly reduced to Cr(II).

The combined anode and cathode gases are mixed with air to avoid explosions and are scrubbed with water in a scrubbing tower to remove traces of acids. The catholyte is oxidized with air to bring down the Cr(II) concentrations. The catholyte is then recycled to the electrolyte tank. The anolyte is collected and used as feed for the oxidation process as shown in Fig. 16.

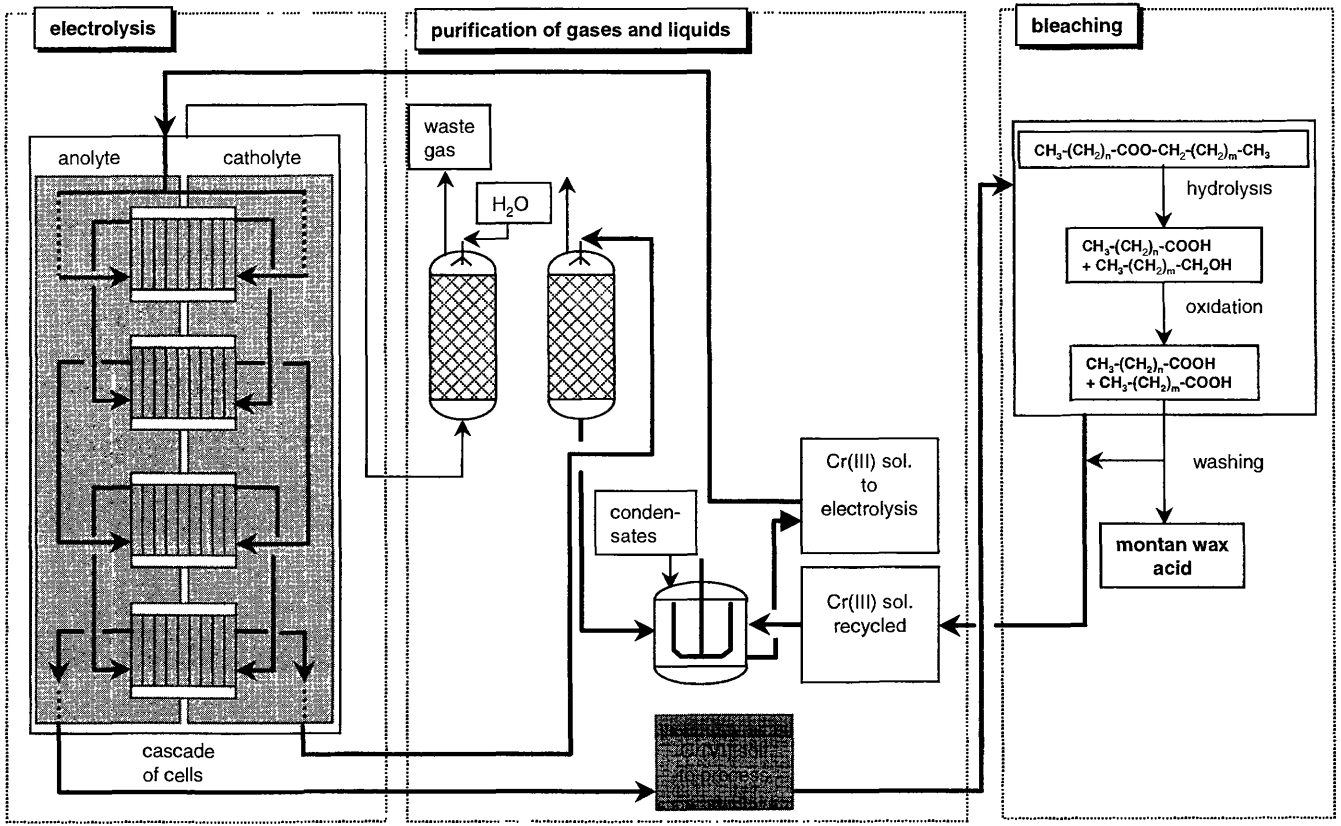


Figure 16. Chromic acid regeneration—montan wax bleaching.

8. Anthraquinone from Ceric Oxidation

The anthraquinone process was developed by Hydro Quebec [105]. The licensing of plants for several thousand tons per year is negotiated with potential customers. The pilot-plant performance has been published [106].

The process is composed of six process steps (Fig. 17), each consisting of several unit operations:

Electrolysis of Ce(III).
Oxidation of naphthalene.
Solvent separation and purification.
Cerous solution purification.
Diels–Alder reaction.
Dehydrogenation and purification.

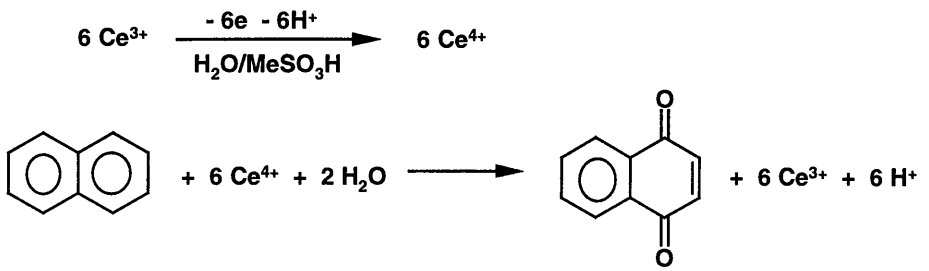
The scheme does not show the preparation of the cerous salt solution. (Cerous carbonate is dissolved in aqueous methanesulfonic acid.)

The electrolysis takes place in divided cells; the anodes are platinum on titanium. The cell construction is similar to a chloralkali cell. One possible configuration is the ICI FM21 cell. The cathodic product, hydrogen, is discharged after removal of acid mist.

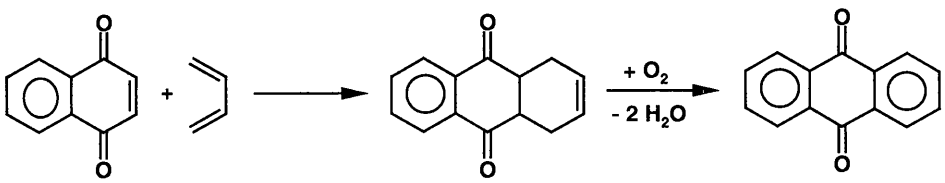
The electrolysis conditions are:

Current density: up to 4000 A/m^2.
Cell voltage: < 40 V.
Temperature: 60°C.
Current efficiency: > 90%.

The aqueous ceric solution reacts with naphthalene in a stirred vessel (Scheme 11a). The solvent is not disclosed; dichloroethane is mentioned.



Scheme 11. (a) Indirect oxidation of naphthalene.



Scheme 11. (b) Production of anthraquinone.

In a third process step, the organic phase is removed and the aqueous phase is purified by extraction.

In a solvent recycling area, crude naphthoquinone is recovered. The chemical yields exceed 95%.

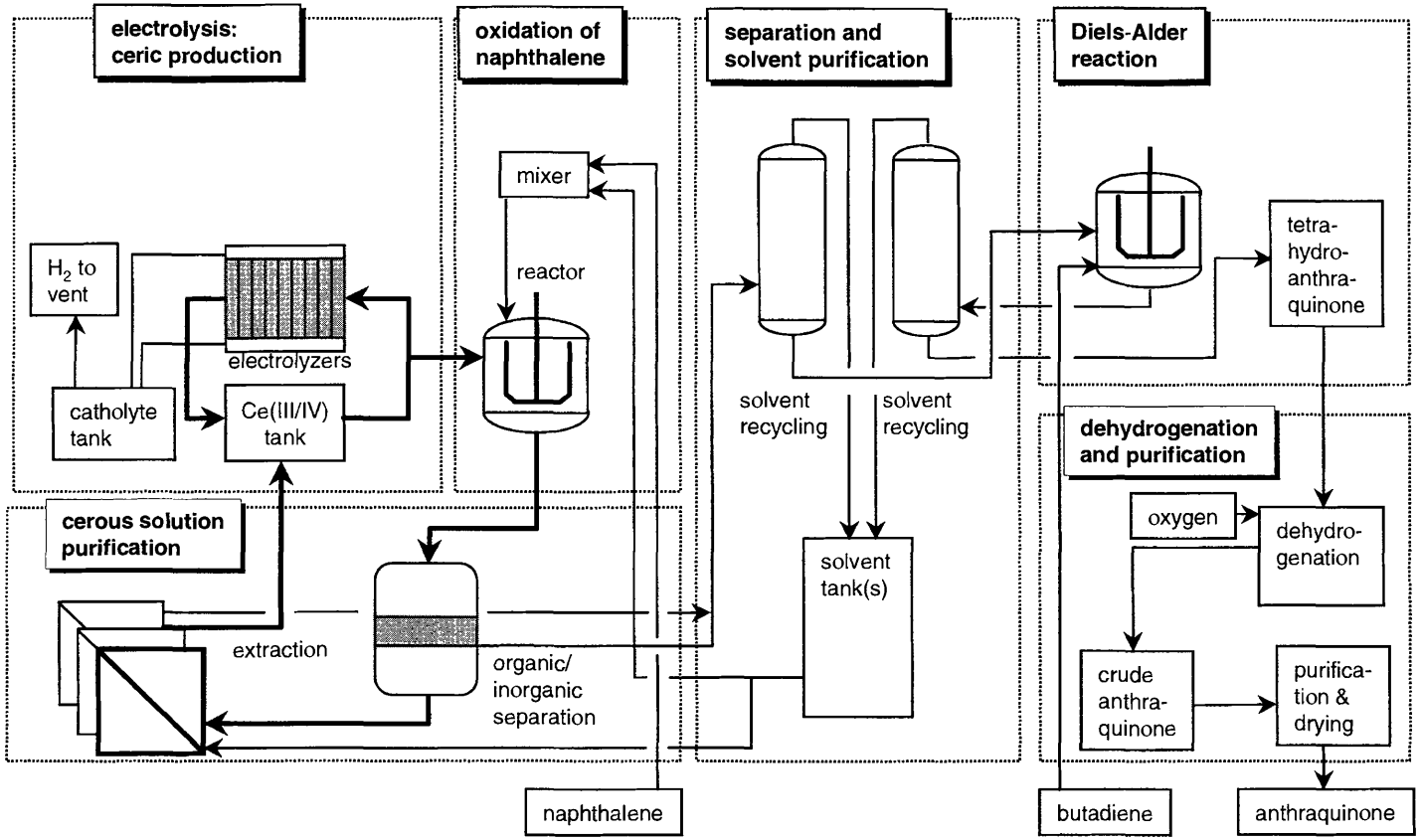


Figure 17. Indirect (in cell) electrochemical methoxylation of ketones.

The next step, the Diels–Alder reaction with butadiene, takes place at 95–120 psi pressure and a temperature of 90–120°C. The yield is 95% of crude tetrahydroanthraquinone. The solvent from this reaction has to be recycled.

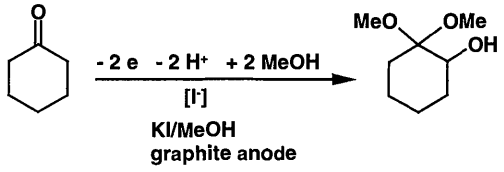
The last process step again includes several unit operations: dehydrogenation with oxygen, purification, and drying (Scheme 11b).

Hydro Quebec claims that the losses of both cerous salts and methanesulfonic acid are very low: Only 11 kg $Ce_2(CO_3)_2$ is required per metric ton of anthraquinone. The electricity consumption is 5130 kWh/metric ton of AQ. Investment costs are discussed as well.

The prospects of this process are extremely good from the electrochemical point of view. Taking into account the whole process and the prices of naphthalene and anthraquinone on the world market, the outlook is still good for large-scale plants, with a capacity of 5000 metric tons per year or more.

9. Acetoin/Adipoin

The anodic methoxylation of ketones is a recent commercial example for an indirect process in an undivided cell [107]. The process (Fig. 18) was developed for BASF's undivided capillary gap cells with bipolar graphite electrodes [108] (Scheme 12).



Scheme 12. Methoxylation of cyclohexanone.

The process parameters of the electrolysis step [107,108] are:

Ketone	20–35%
Base	KOH or NaOH, 2%
Potassium iodide	0.5–3%
Water	2–5%
Methanol	55–70%
Current density	3–5 A/dm^2
Temperature	15–30°C
Voltage per gap	5 V

The electrolyte is fed continuously into column 1. Methanol is removed and fed back into the electrolyte tank. The crude hydroxyketal is filtered and potassium iodide is recycled.

In a third process step, the hydroxyketal is purified by distillation (column 2). The hydroxyketal can either be sent to other chemical follow-up steps or be hydrolyzed.

The hydrolysis is part of the electrochemical reaction sequence; methanol from this step can be distilled in column 3 and recycled to the electrolyte tank.

The last unit operations depend on the specific nature of the hydroxyketone. In the case of acetoin, the purification consists of a fourth distillation. Because acetoin is a fragrance and flavor, it must be stored in dedicated storage facilities.

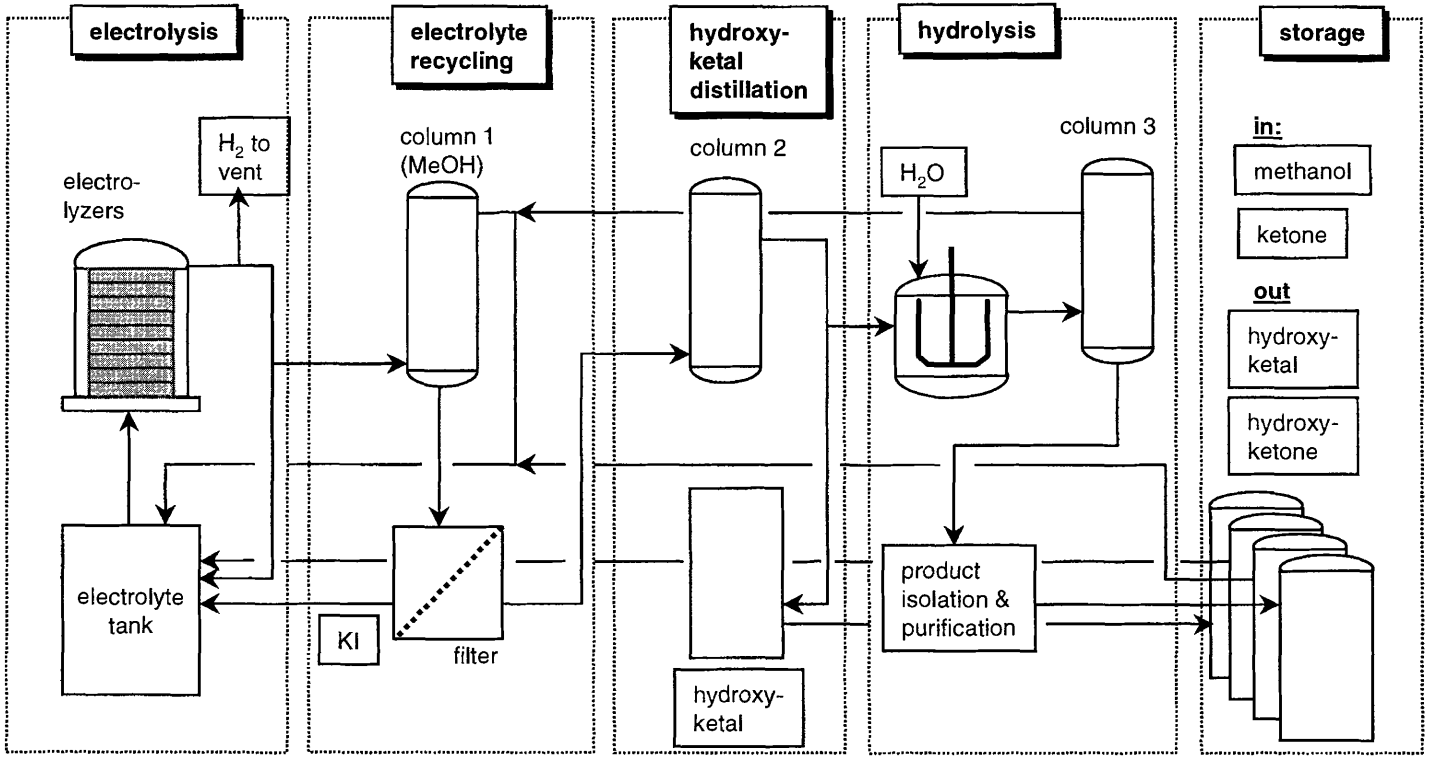
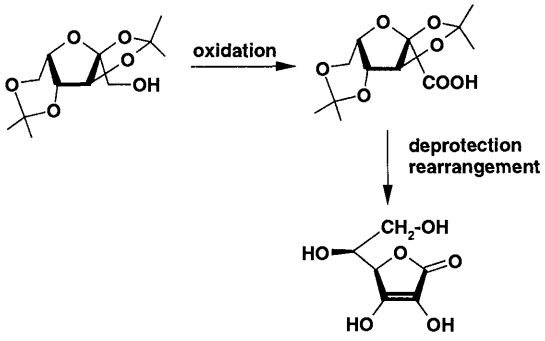


Figure 18. Indirect (ex cell) production of anthraquinones.

10. Diacetone–Ketogulonic Acid

The oxidation of diacetone-L-sorbose to diacetone-2-ketogulonic acid is an indirect process using NiOOH as electrocatalyst (Scheme 13). The protection of the starting material with acetone to produce 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose is done conventionally, as is the deprotection after the oxidation step.



Scheme 13. Oxidation of diacetone-L-sorbose.

The electrochemical process initially was developed by N. Ibl and coworkers at ETH, Zürich; it was technically applied for several years by Hoffmann La-Roche [109], and "it is said that Merck is using the reaction in the industrial production of Vitamin C" [91]. Hoffmann La-Roche used the "Swiss-roll" cell as electrolyzer (Fig. 19). Three-dimensional electrodes are discussed in Refs. 110 and 111.

Some details are given by Merck in Ref. 112. The electrochemical oxidation is performed in alkaline solution using nickel or nickel oxide electrodes [113]. Hydrogen evolved at the cathode can be used for the hydrogenation of D-glucose to D-sorbitol, the first step in the vitamin C synthesis by the Reichstein route. Obviously, Merck doesn't use electrodes with high specific areas but prefers to stop the electrolysis at a conversion rate of 90%. The oxidation is completed with sodium hypochlorite solution.

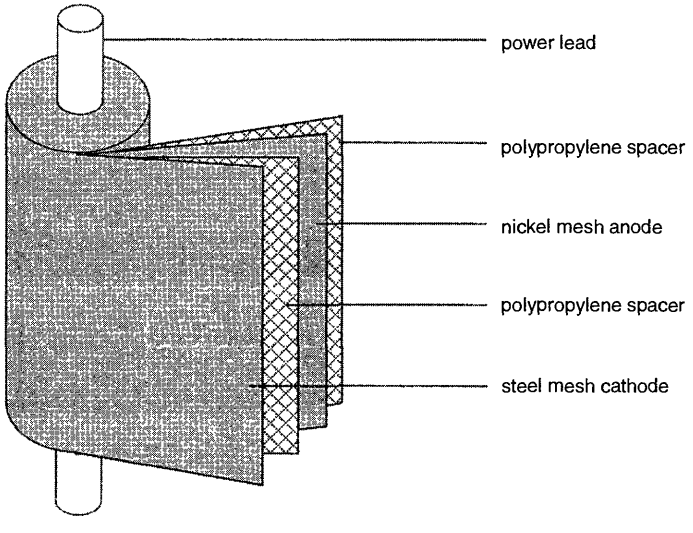


Figure 19. "Swiss-roll" cell: arrangement of the electrodes.

The market for vitamin C in 1995 was estimated at 60,000 metric tons [112]. E. Merck, Darmstadt, is one of the major producers of vitamin C. If the electrochemical route is in operation for the full capacity of Merck's production in Darmstadt, this electrosynthesis has the capacity of several thousand tons per year.

VI. CONDITIONS FOR THE REALIZATION OF ELECTROORGANIC PROCESSES IN INDUSTRY

Two periodicals try to focus on new opportunities for electrolytic processes [114,115]. They deal with technological improvements in electrochemical reactions; most of the reactions discussed are organic and many have been tested in pilot plants. Several authors have dealt with the question of success and failure of electrochemical processes. In the 1990s, the total market value for electroorganic products was US$0.5 billion, the overall market for all electrochemicals totalled US$12 billion [116]. This means that organics have a share of less than 5%. The prospects differ regionally: In India, for example, some processes with a capacity of 500 metric tons/year or less have been commercialized using cells developed by CERCI. This institute in Kairaikudi has a long tradition in electrochemical engineering. One example is that 500 metric tons/year of calcium gluconate is produced in a bipolar flow cell [117].

A. General Remarks

N. Weinberg, the great integrator in electrochemical process know-how, lists 17 unsuccessful organic electrochemical processes and discussed the reasons why they failed [118]. His eight reasons for the failure of electrochemical processes could also be criteria for the competitiveness of organic electrochemistry:

Corporate commitment: inadequate/adequate
Market: vanishing/promising
Timing: too early, too late/just in time
Economics: cost too hight/competitive
Catalytic route: superior/inferior
Environment: dangers/improvements
Technical factors: system not stable/system stable
Competition: others aggressive/ourselves aggressive

In 1988, D. Degner defined some semiquantitative success criteria [119] for electrochemical process parameters:

Material yield	(high)
Current efficiency	(> 50%)
Energy consumption	(< 8 kWh/kg)
Concentration of starting material	(> 10%)
Stability of electrodes	(> 1000 h)
Membrane life	(> 2000 h)
Workup conditions	(easy)
Recycling of supporting electrolyte	(possible)
Emissions	(low)

Authors of the 1990s feel that these conditions have become stricter today [5] and develop new rules. One "eternal" rule, derived from successes and failures with BASF projects [15] is:

If the ratio Ah/g rises to values greater than unity, the prospects will diminish quickly.

D. Pletcher discusses these problems in his lectures, "The Fundamentals of Electrosynthesis and Its Scale-Up" [120] and "Selling Electrochemical Technology: Why, How, When?" [121]. In Ref. 66, he illustrates his experience of many years with "factors important in the economics of organic electrosynthesis processes operated on various scales." Figure 20 reflects this outline from an industrial point of view.

The conditions for a successful realization differ greatly with the product capacity. Oxidations or reductions of chemicals of which less than 10 metric tons/year are produced probably never need an electrolysis because even very expensive chemicals like $LiAlH_4$ will be more convenient than electrochemistry if the redox step can be done in the companies' standard equipment. The costs for these chemicals are extremely dependent on the specific case.

Nevertheless, there is one good reason for dealing with this capacity. During the *development* of agrochemicals or pharmaceuticals [122], only some tons or some hundreds of kilograms are needed. In this stage, time is more decisive than chemical costs, even if chemicals are bought from laboratory chemical suppliers. Organic electrochemistry often has good assets in terms of selectivity and speed. The electrochemists' favorite opinion [123] that organic chemists turn to electrochemistry only after everything else has failed is disproved by the number of "piloted" examples in the literature. Even if the whole project fails or other methods are technologically superior, electrochemistry often plays the role of a door opener. This helps to improve the image of electrosynthesis.

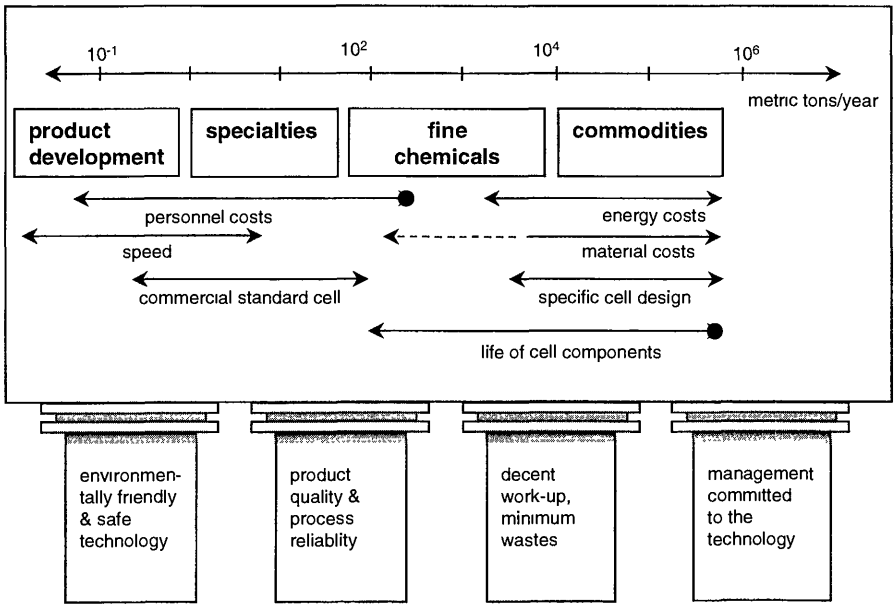


Figure 20. Factors important for successful electroorganic processes.

Speciality chemicals have, generally speaking, high personnel costs. Energy costs are not very important. A technology that can reduce personnel costs without incurring fixed costs in the form of high investment is favored. Electrochemistry has a good chance if production can be carried out alongside existing processes.

Fine chemicals, ranging from some hundred to some thousand tons per year, are usually cost sensitive in many directions. Here electrochemistry will find strong competition but also really good opportunities. If commercial cells and standard electrodes and membranes are available, this will be ideal. If the capacity is distinctly higher than 1000 metric tons/year, opportunities increase for suppliers of electrochemical equipment to develop a tailor-made system.

For *commodities*, it is nearly always necessary to use a specific cell design to minimize the energy demand. Current efficiency and product selectivity must be as high as possible. This has two very simple reasons: (1) The price difference between starting materials and product falls with capacity. So, contrary to Pletcher's analysis, chemical costs are more important for commodities than for specialities. (2) Wastes and emissions will be a focus in the discussions with the authorities.

Regardless of the scale, the success of organic electrochemistry is dependent on four additional factors:

1. Safety and environment
2. Quality and reliability
3. High selectivity
4. Management commitment

If one of these basics is missing, chances will soon near zero, even if the cost figures are promising. Here again another electrochemical prejudice has to be abandoned, namely, the belief that environmental factors support electrochemistry. The electron is not necessarily more environmentally friendly than hydrogen, oxygen, hydrogen peroxide, or chlorine. Here again the rule is clear: Only the total process counts.

B. Industrial Successes for Organic Electrochemistry

Table 1 (see 1274–1276) lists products that have been assigned to the group of industrial organic electrochemicals. The reason for this assumption is often not documented. Steckhan [67] and Pletcher [68] recently collected information on successful organic electrochemical processes. These compendia are based on older tables of M. Baizer, F. Beck, T. Beck [124], D. Danly and C. King [125], A. T. Kuhn, K. Scott [126], N. Weinberg, and others. Steckhan has made efforts to document the relevant literature for all these processes; Pletcher has collected information about the capacities of the processes. Both have tried to define a process status:

C: commercial
P: piloted
D: disrupted

Both have tried to check their results and to communicate their nonconfidential information [127]. A French bibliography compiled by Electricité de France and the book by A. T. Kuhn are helpful for checking older processes [128,129].

There are three organic electrochemcial *commodities*. ADN has one, and tetralkyllead has had only one, but big, application. Bleached montan waxes are sold by Clariant (Hoechst) for many applications [130].

Fine Chemicals: There are 20 anodic and cathodic processes for medium-volume products that have reached commercial status within the last 30 years. Roughly 50% survived. The number of products is much higher due to the great variety of fluorinated organics. This specific chemistry is reviewed in Chapter 25 of this book.

The evaluation of *specialities* is more complicated. Many of the cathodic and anodic processes have been abandoned; only about half a dozen are supposed to be operating. whether there are many more is open to speculation.

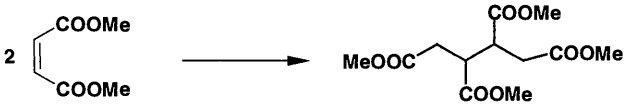
A great number of *development products* or developing processes are coming up. Some "classic" development products that are considered as milestones, even if they weren't successful, are also included in this list. Some recent examples of potentially new processes are given next.

C. Outlook

Although some authors see only limited signs of new industrial applications beside the existing US$11.8 billion market [131], there are new areas emerging.

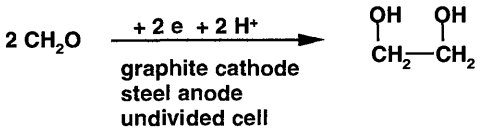
There is a trend toward chiral synthesis [132]: the Englehard company is said to have piloted the electrosynthesis of chiral diols. New reactor design for the epoxidation of olefins is under development on a pilot scale [133]. Gas diffusion electrodes, developed for fuel cells and inorganic processes, are finding their first applications in organic electrosynthesis [134–136]. Another area of more than laboratory interest is bioelectrochemistry [137] (see also E. Steckhan, Chapter 27 in this volume).

But new products, too, are ahead. Monsanto has developed a highly selective hydrodimerization of maleic acid esters [138] to prepare butanetetracarboxylic acid esters [139], a starting material for butanetetracarboxylic acid [140,141] (Scheme 14). BASF is continuously developing new specialities [142], especially for the capillary-gap cell. The methoxylation of ketones such as butanone and cyclohexanone has already been mentioned; other developments may be found in the patent literature [143].



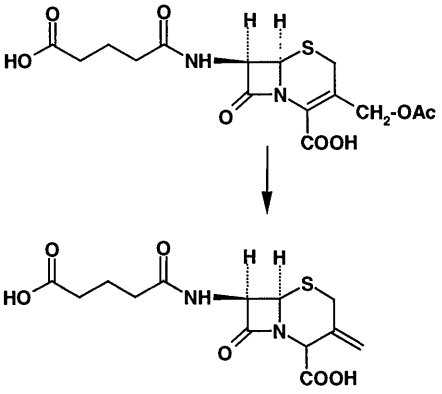
Scheme 14. Hydrodimerization of maleic esters.

The Electrosynthesis Company has piloted a "second-generation" hydrodimerization process to produce ethylene glycol from formaldehyde [144] (Scheme 15).



Scheme 15. Hydrodimerization of formaldehyde to ethylene glycol.

The Electrosynthesis Company, together with Schering Plough, has developed an electrochemical reduction step in the synthesis of ceftibuten [145] (Scheme 16). In the area of pharmaceutical intermediates, other opportunities are discussed [122].



Scheme 16. Intermediate for ceftibutene.

The review of the electrolytic industries for the year 1997 [146] reports the electrocatalytic hydrogenation of fatty acid esters like soybean oil [147] (see also Sec. II.B) and the hydrogenation of gluconic acid to arabinose as potential new commercially interesting candidates.

D. Pletcher concludes his outlook with a message: Electrochemical technology has much to offer in many fields. Be patient with our shortcomings, we can improve!

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Electrochemistry of Conducting Polymers

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I. INTRODUCTION

Conducting polymers have now been known for more than 20 years. In 1977 the American scientists Heeger and MacDiarmid discovered that doping polyacetylene (PA) with iodine endowed the polymer with metallic properties, including an increase in conductivity of 10 orders of magnitude [1]. The successful doping of PA—in electrochemical terminology the equivalent of oxidation or reduction—encourage the same scientists to test PA as a rechargeable active battery electrode [2]. Their promising results stimulated worldwide efforts to construct a polymer battery. In the course of these studies, conducting polymers with properties similar to PA were discovered, such as polyphenylene (PP) and polyphenylenevinylenes, as pure hydrocarbons, on the one hand, and polypyrrole (PPy) polythiophene (PTh), and polyaniline (PANI) on the other hand.

Nowadays, a great number of different monomers are known that form conducting polymers upon chemical or electrochemical preparation techniques. Such starting systems include substituted derivatives of the already mentioned hydrocarbons and heterocycles as well as specially tailored novel compounds, such as for the generation of small band-gap polymers with high transparency in the conducting state (Fig. 1).

There are several reasons why electrochemists are interested in this field. The method of choice for preparing conducting polymers, with the exception of PA, is the anodic oxidation of suitable monomer species such as pyrrole [3] or thiophene [4] or aniline [5]. Three aspects of electrosynthesis are of relevance for electrochemists. First, there is the deposition process of the polymers at the electrode surface, which involves nucleation and

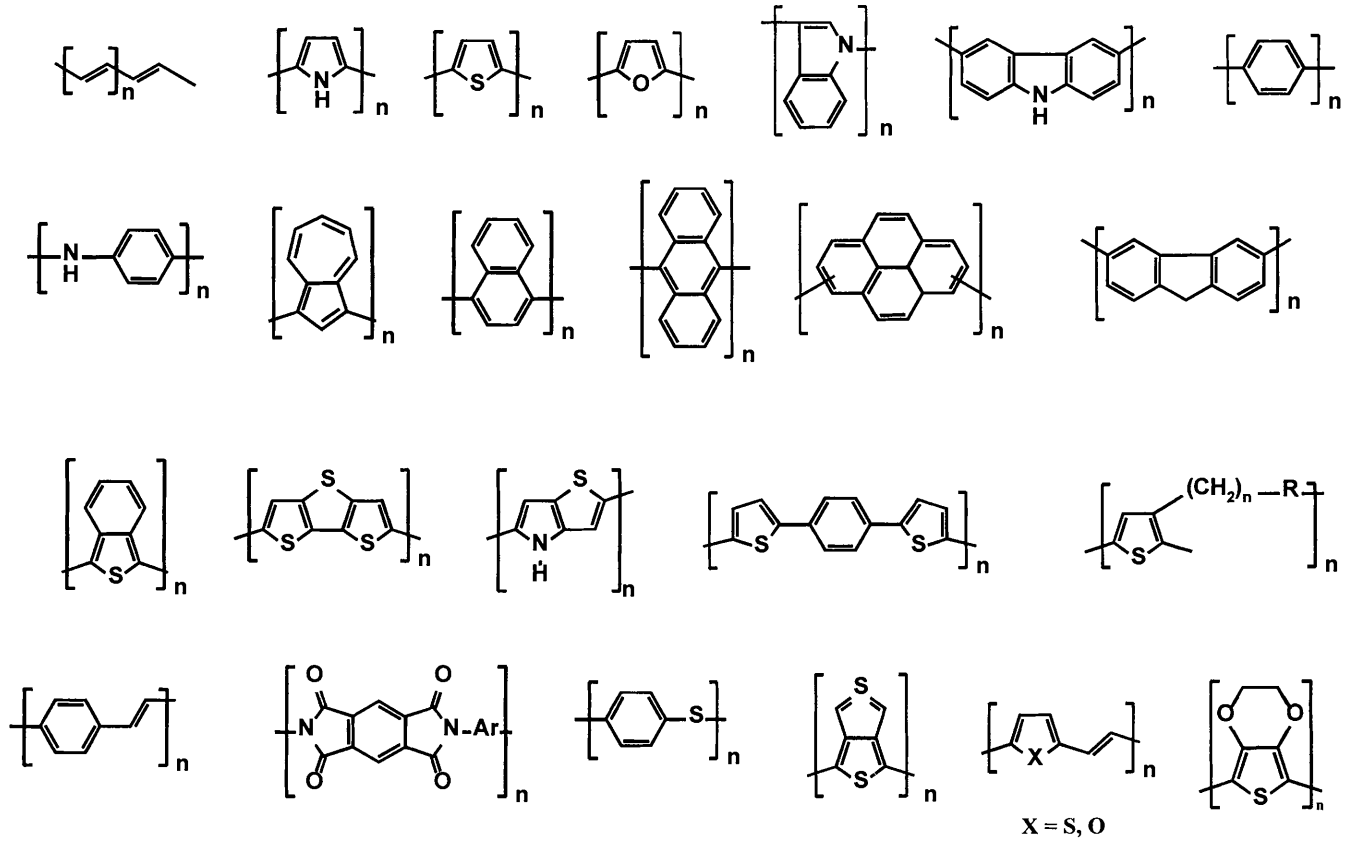


Figure 1. Monomeric building units of conducting polymers.

growth steps [6]. Second, to analyze these phenomena correctly, one has to know the mechanism of electropolymerization [7,8]. And third, there is the problem of optimization of the mechanical, electrical, and optical material properties produced by the special parameters of electropolymerization.

A central point of electrochemical research is the analysis of the doping mechanism. Even in the earliest stage of research it was clear that these processes were not comparable with the classic doping of typical semiconductors. Rather, they correspond to oxidation in the case of p-doping or reduction in the case of n-doping. Thus, in electrochemical terminology the doping process corresponds to a redox reaction. Especially for applications, it is important to know the phenomenological details of such redox reactions, for example, in which potential range the charging occurs and what is the maximum level of oxidation before the material starts degrading. Moreover, from the viewpoint of fundamental research, we should like to know the molecular details of the charge storage process; in recent years a lot of work has gone into explaining this phenomenon.

The huge efforts put into the basic research and development of conducting polymers are naturally related to hopes of feasible technical applications. Thus, conducting polymers are discussed as active battery electrodes [9], electrochromic displays [10], anticorrosives [11], sensors [12], electrocatalysts [13], or light-emitting materials (OLED) [14].

A basic property of all conducting polymers is the conjugation of the chain-linked electroactive monomeric units; that is, the monomers interact via a π-electron system. In this respect, they are fundamentally different from redox polymers. Although redox polymers also contain electroactive groups, the polymer backbone is not conjugated. Consequently, redox polymers are nonconductors. Hence, they are not included in this overview [15].

Given the different intentions and objectives of research into conducting polymers, it is inevitable that the relevant literature is widely dispersed and that some of it, especially proceedings of meetings, is difficult to find [16]. Accordingly, this chapter primarily reviews the electrochemical literature [17] on the subject of conducting polymers, emphasizing the general electrochemical characteristics of these materials. The large body of theoretical and experimental work on the charcterization of the electrical, magnetic, and optic properties of these materials receives only brief attention. The relevant information can be found in a number of review articles and monographs published in recent years [18].

II. ELECTROPOLYMERIZATION

A. Oligomerization in Solution

Electropolymerization of conducting polymers differs markedly from other polymerization reactions. In the normal electrochemically induced polymerization reactions, the electrode catalytically triggers chain growth and, consequently, the process requires little electricity [19]. By contrast, the anodic oxidation leading to conducting polymers involves a reaction sequence in which each coupling step has to be activated by two species. It has an electrochemical stoichiometry of 2.07 to 2.6 F/mol of reacting monomer [7,20]. It has been deduced from numerous measurements that the film-forming process needs only 2 F/mol, that is, 2 electrons/molecule, and the additional charge serves the partial, reversible oxidation (doping) of the polymer film. As the potential needed for monomeric oxidation is always significantly higher than the charging of the existing polymer, the two processes—film formation and its oxidation—occur simultaneously.

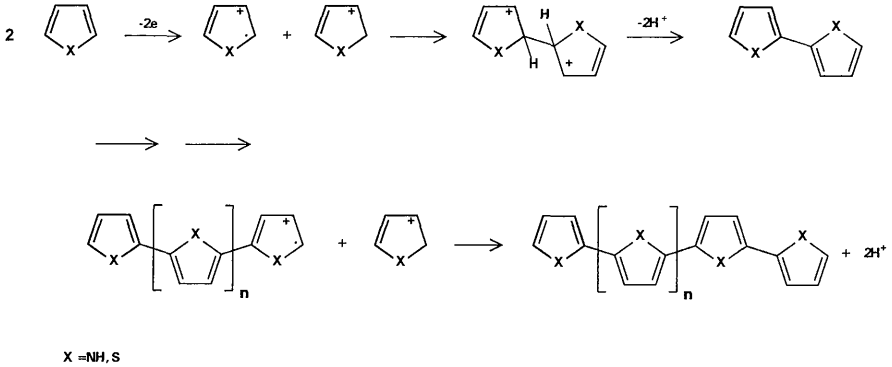
Taking this stoichiometry into account, the complete reaction equation for the polymerization of a suitable monomer HMH is:

$$(n+2)\,\mathrm{HMH} \rightarrow \mathrm{HM(M)}_n\mathrm{MH}^{(nx)+} + (2n+2)\mathrm{H}^+ (2n+2+nx)\,\mathrm{e}^- \quad (1)$$

where $(2n+2)$ electrons are used for the polymerization reaction itself, while the additional charging of the polymer film requires nx electrons. In general, x lies between 0.25 and 0.4. This means that every third to fourth monomeric subunit in the film is charged.

The mechanism of electropolymerization is still not fully understood. The one certainty is that in the very first step the neutral monomer is oxidized to a radical cation. It must have an oxidation potential that is accessible via a suitable solvent–electrolyte system, and should react more quickly with other monomers, that is, radical cations, than with other nucleophiles in the electrolyte solution. Therefore, as a general rule, polymerization without defects becomes less successful with increasing oxidation potential of the starting monomer, for example, in the order PPy > Th > benzene (Bz). As the nucleophilicity of the solvents commonly used in electropolymerization rises in the order $HF < CF_3COOH < SO_2 < CH_3NO_2 < CH_2Cl_2 < PC < CH_3CN < H_2O$, only pyrrole can be polymerized in water [21]. Even in the case of thiophene, small amounts of water are sufficient for nucleophilic addition to block further growth of the oligomer chain [22]. By contrast, benzene can be only partially polymerized in CH_3CN or PC, as the newly formed oligomers react with the solvent more readily than with the cations of the oligomeric intermediates. In dry SO_2, conductive polyparaphenylene films are formed in high yield [23].

In 1982, Diaz [7] suggested, by analogy to the long-known coupling reactions of radical cations in aromatic compounds, that in the polymerization of pyrrole the monomers dimerize at the α-position after oxidation at the electrode, and that protons are eliminated from the doubly charged dihydrodimer, forming the neutral species. As the dimer, on account of its greater conjugation, is more easily oxidized than the monomer under the given experimental conditions, it is immediately reoxidized to the cation. Chain growth should be accompanied by the addition of new cations of the monomeric pyrrole to the already charged oligomers. This, in turn, is followed by another proton elimination and the oxidation of the propagated oligomeric unit to a cation (Scheme 1).



Scheme 1. Classical formation mechanism of conducting polymers [7].

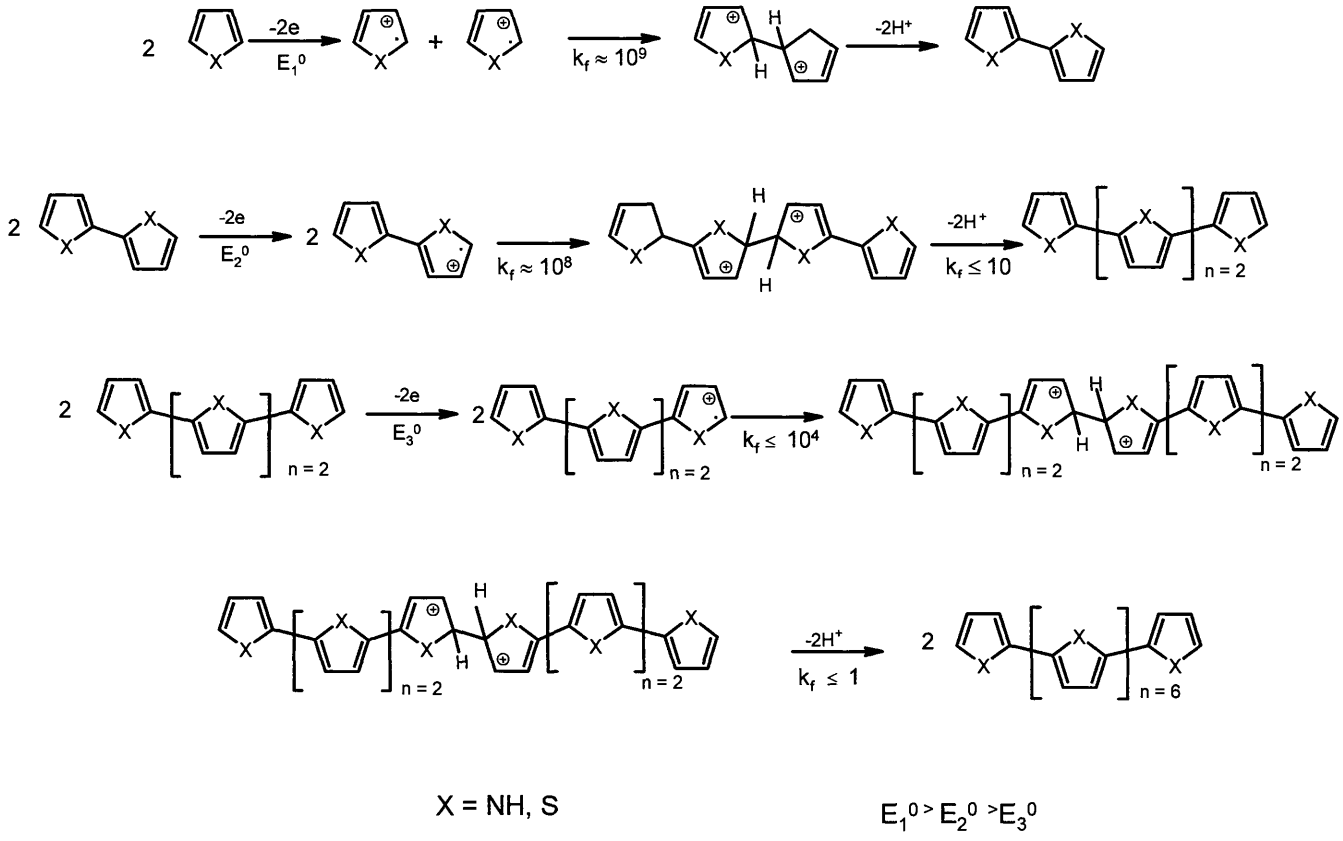
This classic chain propagation mechanism is still widely accepted in the literature [24]. However, recent studies using the so-called oligomer approach [25] have shown that this mechanistic view is far too simple. Obviously, after the formation of a dimer a sequence of subsequent "dimerization" steps leads to the formation of soluble oligomers with chain lengths normally ranging between four and eight units [26]. All these reactions preferably occur in solution without or with only small precipitation on the electrode. Subsequently, deposition and growth processes set in, triggered by nucleation reactions. They are strongly influenced by the concentration of the starting monomer, the temperature, and relevant electrochemical parameters such as the formation potential. Especially at high concentrations of monomer, the deposition may begin at a shorter chain length.

Quantitative investigations of the kinetics of these α-coupling steps suffered because rate constants were beyond the time scale of voltammetric experiments until ultramicroelectrodes and improved electrochemical equipment made possible a new transient method called "fast-scan voltammetry" [27]. With this technique, cyclic voltammetric experiments up to scan rates of $1\,\mathrm{MV\,s^{-1}}$ are possible, and species with lifetimes in the nanosecond scale can be observed. Using this technique, P. Hapiot et al. [28] were the first to obtain data on the lifetimes of the electrogenerated pyrrole radical cation and substituted derivatives. The resulting rate constants for the dimerization of such monomers lie in the order of $10^9\,\mathrm{M^{-1}\,s^{-1}}$. The same authors were also able to show that the radical cation of the pyrrole tetramer, by contrast, is rather stable [28]. This tendency of decreasing reactivity as a function of chain length is a general property of all chain-like conjugated oligomers [29]. Thus, in the series of unsubstituted thiophenes the radical cations of monomeric thiophene dimerize with a rate constant greater than $10^9\,\mathrm{M^{-1}\,s^{-1}}$, while the lifetimes of oligomer cation radicals increase with chain length [30]. For example, the rate constant for the dimerization of the unsubstituted thiophene tetramer is about $10^5\,\mathrm{M^{-1}\,s^{-1}}$ [30a,31], and that of the pentamer is below $10^4\,\mathrm{M^{-1}\,s^{-1}}$ [32].

From all these measurements, it is clear that the rate constants of the dimerization of chainlike conjugated oligomers, and of their coupling steps with the original monomer, decrease with increasing chain length. In addition, the rate of all these second-order reactions are a function of the concentrations of the reacting species. Therefore, as can be shown by simulations, a monomeric radical cation as starting species is far more likely to couple with monomeric radical cations than with radical cations of higher oligomers (Scheme 2).

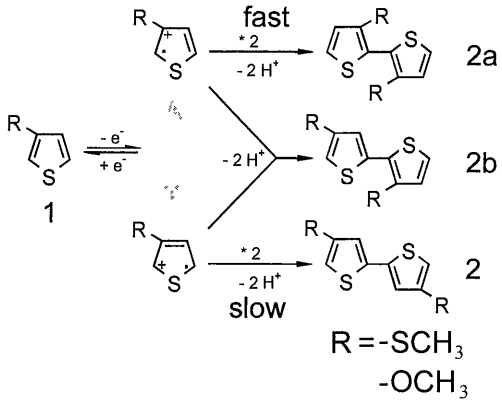
Studies by Heinze et al. on donor-substituted thiophenes [33] such as methylthio (= methylsulfonyl) or methoxy-substituted derivatives provide further clear evidence for this reaction pathway. They found, for instance, that 3-methylthiothiophene **1** undergoes a fast coupling reaction. However, deposition processes or insoluble film formation could not be detected in any experiments with this compound under any conditions, even at high concentrations. Similarly, the 3,3′-disubstituted bithiophene **2a** does not polymerize, but the anodic oxidation of 4,4′-dimethylthiobithiophene **2** produces an excellent yield of conducting polymer.

A careful analysis based on these experimental results excluded a chain propagation process [33a]. On account of the 3-position of the methylthio substituent in the thiophene ring, three isomeric dimers may be formed. The main reaction path can be deduced from the mesomeric forms of the radical cation $\mathbf{1}^{+\cdot}$. The two most important mesomeric structures are those with the unpaired electron in an α-position (**II**, **II**). Structure **I**, with the positive charge next to the methylthio sulfur, is preferred, because of the stabilizing +M effect of the methylthio substituent. Therefore, the 3,3′-connected dimer **2a** is the essential



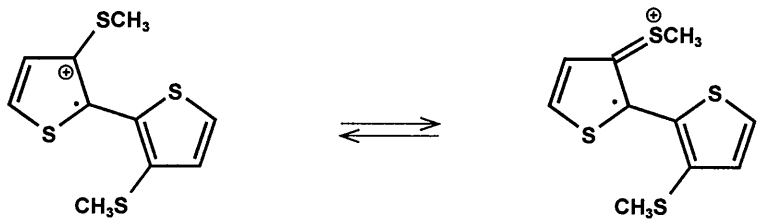
Scheme 2. "Dimerization" steps during oligomerization in solution as deduced from the oligomer approach.

product of the radical radical coupling process. Dimers **2b** and **2** are minor side products (Scheme 3).



Scheme 3. First coupling steps after the oxidation of 3-methylthiothiophene **1.**

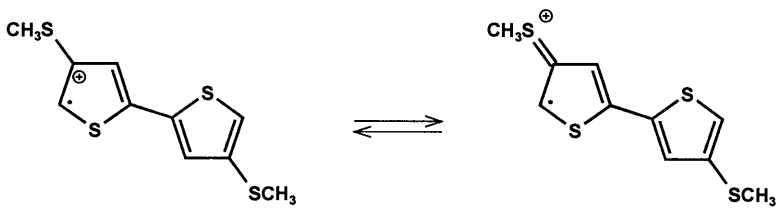
The main product initially formed, dimer **2a**, will undergo further slow coupling steps. At the given potential, dimer **2a** will immediately be oxidized to the corresponding monoradical cation. Again, the monoradical cation can be found in different mesomeric structures. The most reasonable notation has the positive charge next to the methylthio sulfur and the unpaired electron at the blocked inner α-position:



Most important mesomeric structure of the radical cation of **2a).**

Therefore, the reactivity of this species, similar to that of the 3,3′-dimethoxy-2,2′-bithiophene radical cation, is low, probably resulting in a rate constant for the dimerization of $< 10^4\,M^{-1}\,s^{-1}$ [33d]. The tetrameric product of the subsequent coupling is even more stable than the dimer, which means that the "polymerization" process stops at this level, or becomes very slow.

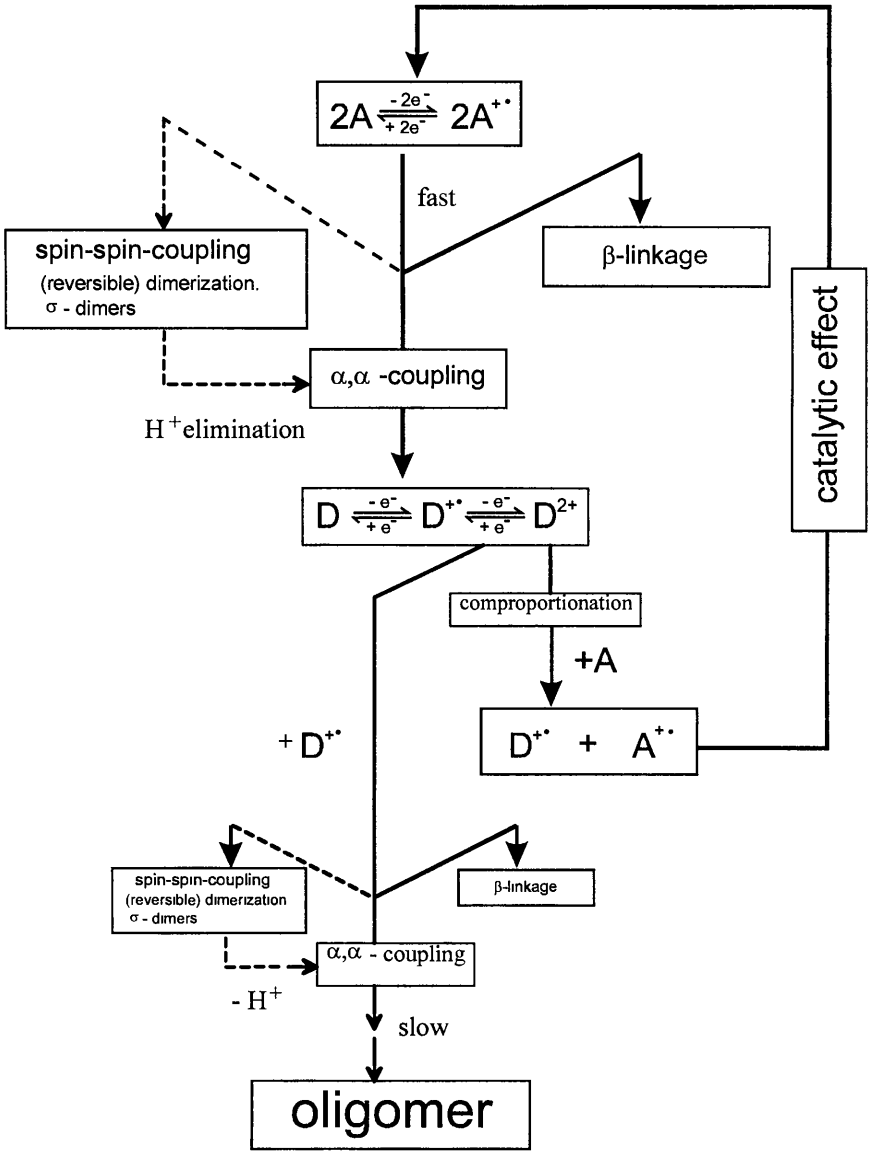
By contrast, the high polymerization tendency of dimer **2** is a result of the fact that the most important mesomeric structure has the unpaired electron at a nonblocked site. The coupling of the radicals is very fast, and the products of the coupling steps in turn have substitutents in "outer" β-positions of the oligomer, which makes it reactive.



All these findings prove that the electropolymerization mechanism of donor-substituted thiophenes does not involve a chain propagation process with successive coupling steps of the starting radical cation. By contrast, it must be concluded that oligomerization in solution preferably occurs via consecutive "dimerization" steps leading from a dimer to a tetramer and then to an octamer. In the case of a hypothetical chain growth reaction, the extremely high reactivity of $\mathbf{1}^{+\cdot}$ should trigger an almost perfect formation of a polymeric chain. However, this has never been observed.

It would be an oversimplification to assume that these simple coupling and electron-transfer reactions reflect all steps occurring in front of the electrode. In addition, parallel reactions such as homogeneous comproportionations ($D^{2+} + M \rightleftharpoons M^{+\cdot} + D^{+\cdot}$) autocatalytically produce radical cations of the lower oligomers [34]. Other possible side reactions are, for example, (reversible) dimerizations without elimination of protons or β-linkage reactions. Scheme 4 provides a corresponding representation of the oligomerization reactions in solution. Thus, Cava et al. could show that during oligomerization in solution branched β, β-coupling steps compete with the linear α, α-coupling [35]. In addition, their results reveal that the elimination of protons after the couipling of the radical cations may be slow. In this case, a charged σ-complex exists as a short-lived intermediate. In the case of the pyrrole oligomerization (dimer–tetramer), the deprotonation step is significantly slower than the radical–radical coupling step [28a], indicating that the stability of the σ-dimer increases as a function of chain length. Very recent data provide evidence that the positively charged σ-dimer of the thiophene octamer does not undergo a deprotonation step as long as the electrode potential does not exceed the redox potential of the octathiophene dication.

Recently, the discussion about the formation of π- or σ-dimers as intermediates of the oligomerization has intensified. Thus, on the basis of concentration- and temperature-dependent ultraviolet/visible (UV/VIS) and electron spin resonance (ESR) data, Miller et al. have suggested that the radical cations of substituted oligothiophenes may form π-dimers [36]. Other authors have subsequently reached similar conclusions [37]. In all cases, voltammetric analysis indicates the reversible formation of radical cations without chemical follow-up steps. Accordingly, it has been concluded that weakly interacting π-mers form rapidly and also decay relatively quickly in the experimental time scale. Very recent cyclic voltammetric studies of the oxidation of diphenylpolyenes, oligophenylenevinylenes, and oligothiophenes have indicated strong changes of the voltammetric response as a function of temperature, concentration, and scan rate. A detailed evaluation of all data gave clear evidence that the formation of the radical ions is followed by rapid reversible dimerization between oligomer chains, accompanied by the formation of a σ-bond [38]. Moreover, applying nuclear magnetic resonance (NMR) measurements, A. Merz et al. could show that the radical cations of 3,3′,4,4′-tetramethoxy-2,2′-bipyrrole reversibly dimerize and form a σ-dimer in solution, the equilibrium constant of which is temperature dependent [39]. It should be noted that the stability of the "σ-dimers" increases with chain length. Thus, for unsubstituted oligomers with a chain length greater than eight units, the elimination of protons after the coupling step between the charged species becomes extremely slow.



Scheme 4. Reaction scheme for the formation of conjugated oligomers in solution.

In the past, some authors [40] have questioned the radical–radical (RR) coupling mechanism on the ground that the strong coulomb repulsion between small cation radicals renders a direct dimerization of such particles improbable. Instead, they postulated a radical–substrate (RS) coupling. An electrophilic attack by the radical cation on the neutral monomer or oligomer produces the single-charged coupling product, which eliminates its protons only after a further charge transfer, becoming a neutral oligomer. However, the principal objection to the RR path—the strong coulombic repulsion between charged particles—is not convincing for reactions in solution. Using the Debye–Smoluchovski theory [41], it has been shown that even small molecules that are equally charged are able to dimerize at a diffusion-controlled rate [42]. Recently, applying the oligomer approach, several authors have demonstrated that the "dimerization" reactions of the heterocyclic monomers and oligomers involve coupling between two electrogenerated cation radicals rather than with the starting molecule [28c,32,33,38,39]. Careful quantitative kinetic studies of the coupling steps of oligomeric pyrroles and thiophenes have confirmed this mechanistic pattern [43].

B. Solid-State Electropolymerization

Despite the vast quantity of data on electropolymerization, relatively little is known about the processes involved in the deposition of oligomers (polymers) on the electrode, that is, the heterogeneous phase transition. Research—voltammetric, potential, and current-step experiments—has concentrated largely on the induction stage of film formation of PPy [6,44], PTh [22,45], and PANI [46]. In all these studies, it has been overlooked that electropolymerization is not comparable with the electrocrystallization of inorganic metallic phases and oxide films [47]. Thus, two- or three-dimensional growth mechanisms have been postulated on the basis that the initial deposition steps involve one- or two-electron transfers of a soluted species and the subsequent formation of ad-molecules at the electrode surface, which may form clusters and nuclei through surface diffusion. These phenomena are still unresolved.

Electropolymerization begins with the formation of oligomers in solution (Sec. II.A). Above a critical chain length, insoluble oligomers form, which deposit themselves on the electrode surface [48]. Two additional findings support this thesis. In potential-step experiments, optical signals indicating the deposition of oligomers on the electrode only change when the current on the i–t curve starts to rise again after the typical $t^{-1/2}$ drop. In potentiodynamic experiments the observed oxidation currents, as well as the visible changes on the electrode surface, are dependent on the scan rate. The slower the scan rate, the more visible is the electrode coating and the greater is the rise in the oxidation current [49]. The electrodeposition process can be also monitored by spectroelectrochemical in situ techniques [50]. Especially useful are ellipsometric studies [51] combined with time-resolved UV-visible spectroscopy [52,53]. Measurements of the deposition of oligothiophenes reveal that during the starting period of electrolysis, only species in the solution phase are generated, and that the growth of the nuclei is not a simple three-dimensional deposition process but a fairly complex one.

The literature contains descriptions of trace crossings or nucleation loops that normally appear on the reverse sweeps of the first cycle in all voltammograms, provided that the scan reversal lies close to the peak potential [44a]. This has been interpreted as the start of the nucleation process of the corresponding polymer. A strong argument for this assumption has been that this effect always appears in voltammetric experiments with freshly polished electrodes and only in the reverse sweep of the first cycle [6,44,54].

Such behavior is similar in this respect to the electrochemical deposition of metal on a foreign substrate, in which an overpotential is required for nucleation, after which further growth of the metallic layer occurs at the characteristic redox potential of the metal, leading to a trace-crossing in the reverse sweep. However, recent voltammetric studies have shown that such trace-crossings still appear even if deposition processes or insoluble film formation cannot be detected under any conditions, even at high concentrations [33a]. Moreover, the potentiodynamic electropolymerization of pyrrole at high concentrations produces the trace-crossing, even after the electrode has become completely polymer coated [55]. This is inconsistent with an interpretation based on the nucleation-and-growth mechanism.

By contrast, all experimental data supports the view that the additional anodic current observed in the reverse sweep results from slow follow-up reactions occurring in the diffusion layer in front of the electrode. Early in the 1970s, Feldberg [56] demonstrated the theoretical possibility of trace-crossing in ECE reactions involving slow rate constants for the chemical step. This is exactly what happens during the oligomerization of the monomeric starting species in solution. Trace-crossing results from the slow formation of a neutral tetramer or octamer ($k \approx 10^4\,M^{-1}\,s^{-1}$) in the diffusion layer and its subsequent oxidation to its mono- or dication.

Simulations that have been carried out for a vast number of different rate parameters and mechanistic variants show that only the slow second-order coupling steps between "dimers" and the subsequent slow elimination of protons can explain the trace-crossing (Fig. 2). In any case, the so-called nucleation loop in cyclic voltammetry is not the result of a nucleation step, but of slow, homogeneous follow-up reactions of soluble oligomers in the diffusion layer.

Galvanostatic, potentiostatic, or potentiodynamic techniques can be used to electropolymerize suitable monomeric species and form the corresponding film on the electrode. The potentiodynamic experiment in particular provides useful information on the growth rate of conducting polymers. The increase in current with each cycle of a multistep CV is a direct measure of the increase in the surface of the redoxactive polymer and, hence, a measure of relative growth rates (Fig. 3).

The relative growth rate per cycle v is calculated from the peak current of the respective polymer oxidation using Eq. (2):

$$v = k_{pa}^{pol}/(n-1) \tag{2}$$

where k is the proportionality constant. The parameter v is by its nature a function of the conditions of polymerization and thus must be standardized to v_0, in relation to which only one growth parameter may be changed [57]. Quartz microbalance measurements reveal that deposition occurs only in the potential range where the monomer and short oligomers are oxidized. No deposition is observed outside of this range. Surprisingly, lowering the temperature rasies the efficiency of deposition, owing to the fact that the solubility of the soluble oligomers decreases [58].

However, despite all these observations, it is still unclear which additional coupling steps take place after the nucleation of an oligomeric layer on the electrode. In the literature, experimental data have been presented to support the view that with the formation of an oxidized "prefilm" that the process gradually transforms into one in which chain growth can take place on the surface immediately by coupling of the monomer cation radical and the oxidized chain in the film [59]. However, the assumption of heterogeneous coupling of monomers or dimers with the existing layer of oligomers seems rather improb-

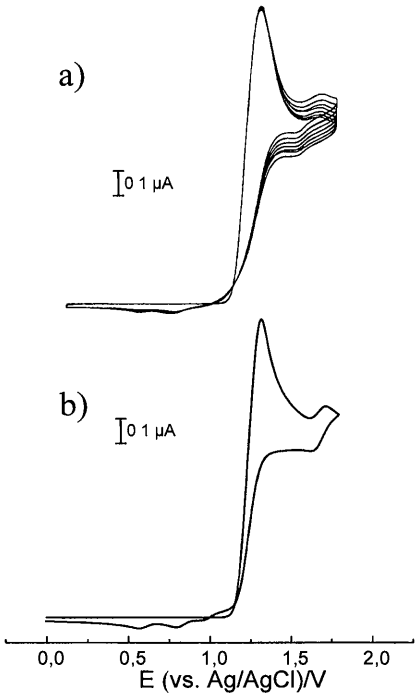


Figure 2. Multisweep cyclic voltammetry for the oxidation of **1** in $CH_2Cl_2 + 0.1\,M$ $TBAPF_6$ $c = 0.001\,M$, $v = 0.1\,V\,s^{-1}$: (a) experiment, (b) simulation (k_f for the formation of the tetramer $1000\,M^{-1}\,s^{-1}$). From Ref. 33a.

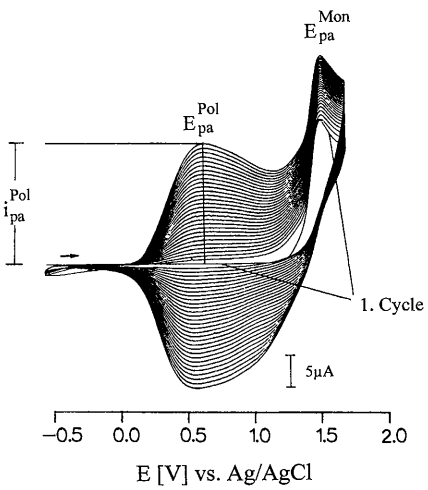


Figure 3. Potentiodynamic growth of a polypyrrole film in acetonitrile (+1% H_2O), $v = 0.02\,V\,s^{-1}$, $T = 24°C$, number of cycles $n = 30$, $E_{pa}^{mon} = 15\,V$ vs. Ag/AgCl, $E_{pa}^{pol} = 0.62\,V$ vs. Ag/AgCl.

able, as the oligomers in the film are not reactive and the rate constants for the dimerization of monomers or dimers are very high.

A few years ago, solid-state voltammetric measurements on sexiphenylene layers revealed for the first time that the material "polymerizes" upon p-doping in the solid state on the electrode [60]. It was show that sexiphenylene dimerizes at low oxidation potentials, while at high potentials long chains are produced and cross-linking steps become more and more predominant [61]. Since then, further solid-state experiments with monodisperse oligothiophenes have confirmed these early results and provided new insights into the general polymerization mechanism of conducting polymers [62].

The application of low-temperature voltammetry to octathiophene (H-T_8-H), for instance, allows the reversible generation of trications or even tetracations. This stability disappears when the temperature is raised. If, in the case of H-T_8-H, the switching potential is set in the ascent of the anodic trication wave, two new waves appear and gradually increase, while the original signals for redox processes of the starting material decrease (Fig. 4).

The resulting isopotential point confirms that H-T_8-H reacts to produce a new electroactive species without side reactions. The optical absorption of the electrochemically generated product is red-shifted and its cathodic peak potentials upon discharging (reduction) lie negative to those of the educt, indicating that the product consists of larger molecules with a more extended redox system. If experiments are carried out at higher sweep rates ($v > 100\,\mathrm{mV\,s^{-1}}$), broad waves are observed during the cathodic reverse scan at potentials around 0 V. This is typical for the discharging of protons formed during the process. The coulometric analysis of the voltammograms shows that one charge is lost per

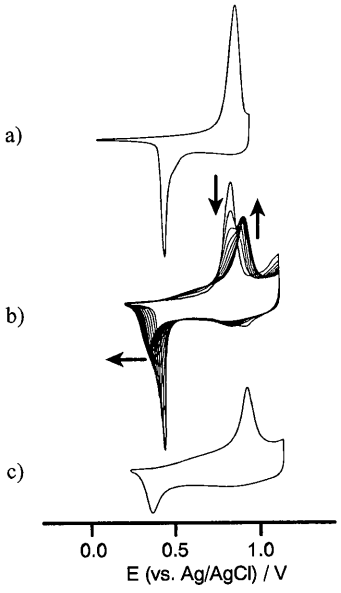


Figure 4. Potentiodynamically generated solid state coupling of octathiophene: (a) H-T_8-H, (b) oligomerization, (c) H-T_{16}-H. The resulting sexidecithiophene forms a stable σ-"dimer" after oxidation. Experimental conditions: $CH_2Cl_2/TBAPF_6$, $T = 268\,\mathrm{K}$. From Ref. 62.

molecule (by proton cleavage) in the condensation reaction. The average functionality of a monomer unit, f, has been calculated from coulometric data. The resulting values of $f < 2$, together with all other observations, give clear evidence that the short-chain H-T_8-H dimerizes quantitatively in this solid-state reaction, forming an isomer of sedecimthiophene. Analogous reactions have been observed for other short-chain oligomers, such as sexithiophene or sedecimphenylene, leading to dodecathiophene and -phenylene. All these materials can be polymerized further at higher formation potentials. The number of coupling steps depends strongly on the applied potential. At the end of such processes the voltammograms have the typical shape of those of conducting polymers in general; that is, they exhibit the characteristic current plateau and high current waves at the onset of charging and the end of discharging. Under these conditions, the average functionality may be larger than the limiting value for infinite chains ($f = 2$). From this, however, it must be concluded that chain-lengthening steps as well as coupling reactions between the chains take place, leading to a network with an intact π-system. All these experiments give no indication of a polymer of ininite length. Based on infrared (IR) data, Furukawa et al. concluded from studies of thiophene oxidation that the degree of polymerization is rather low, ranging from 10 to 35 [63]. For the conjugation length of PTh, a number of ~ 11 has been estimated [64].

III. STRUCTURE OF CONDUCTING POLYMERS

Besides synthesis, current basic research on conducting polymers is concentrated on structural analysis. Structural parameters—for example, regularity and homogeneity of chain structures, but also chain length—play an important role in our understanding of the properties of such materials. Research on electropolymerized polymers has concentrated on polypyrrole and polythiophene in particular and, more recently, on polyaniline as well. Of the chemically produced materials, polyacetylene still attracts greatest interest. In the lst decade, the oligomer approach has been successfully applied to the study of physical and chemical properties of conducting polymers [25]. When monitoring the physical properties as a function of chain length, extrapolation leads to the properties of a defect-free polymer. Spectroscopic methods have proved particularly suitable for characterizing structural properties. These comprise surface techniques such as XPS, AES, or ATR, on the one hand, and the usual methods of structural analysis, such as NMR, ESR, and x-ray diffraction techniques, on the other hand.

PPy was the first conducting polymer to be structurally analyzed. The discovery that α, α'-disubstituted pyrrole did not polymerize led to the conclusion that the pyrrole units in PPy are α-linked [65]. Magic angle spinning ^{13}C-NMR data support the view that the pyrrole units bond chiefly in the α, α'-position, although α, β bondings are also found [66]. On the other hand, XPS measurements of PPy reveal that a full one-third of the pyrrole rings in a chain are irregularly bonded [67]. Very recent electrochemical studies have shown that the structure of polypyrrole strongly depends on the preparation conditions during electropolymerization [55,68]. In highly acidic solutions saturated pyrrolidine units are generated, which lead to the formation of a passivating film. At very positive formation potentials greater than 1.2 V versus Ag/AgCl a cross-linked material is generated, while at low oxidation potentials relatively short linear chains are produced.

Similarly, a chain structure with predominantly α, α'-coupling between the monomer units is postulated for polythiophene (PTh) on the basis of spectroscopic findings and mechanistic studies. IR measurements of uncharged, chemically produced examples in

particular clearly reveal that α,α'-bonding predominates in the polymers produced from α,α'-dibromothiophene, 2,2′-bithiophene or 3-methylthiophene [4,69]. The IR data correlate very well with ^{13}C-NMR measurements, which similarly confirm the dominance of α,α'-bonding in P3-MeTh [70]. In agreement with these findings, the electrochemical oxidation of 3,3′;5,5-′tetramethyl-2,2-′bithiophene unambiguously demonstrates that the nonblocked outer β-position is nonreactive [38c].

Chain length is another factor closely related to the structural characterization of conducting polymers. The importance of this parameter lies in the considerable influence of the electric as well as the electrochemical properties of conducting polymers. However, the molecular weight techniques normally used in polymer chemistry cannot be employed on account of extreme insolubility of the materials. A comparison between spectroscopic findings (XPS, UPS, EES) for PPy and model calculations has led some researchers to conclude that 10 is the minimum number of monomeric units in a PPy chain, with the maximum within one order of magnitude [67,71]. By electropolymerizing α,α'-tritium-labeled β,β'-dimethylpyrrole and comparing the tritrium activity in the monomer and the polymer, Nazzal and Street obtained molecular weights that indicate chain lengths of between 100 and 1000 pyrrole units [72]. By contrast, the oligomer approach has shown that oligomerization in solution produces soluble oligomers with chain lengths between 8 to 12 units. During solid-state polymerization in dependence on the applied electrode potential, linear chains up to 30–60 units as well as cross-linked networks are generated [26,61].

IV. CHARGE STORAGE MECHANISM IN CONDUCTING POLYMERS

Conducting polymers, provided they are chemically produced, are initially insulators. Their metal-like properties, that is, their high conductivity and optic reflectivity, only become obvious after "doping." Even in the earliest stages of research on these materials, it was clear that these processes were not comparable with the classic doping of inorganic semiconductors. Rather, they correspond to oxidation in the case of p-doping or reduction in the case of n-doping. Suitable redox reagents are either chemical electron acceptors, such as iodine, or electron donors, such as potassium naphthalide; or the process may be electrochemically induced via an electrochemical cell. Because of the redox reaction, the polymer chain is negatively charged in the case of reduction and positively charged in the case of oxidation. To maintain electroneutrality, the appropriate counterions diffuse into the polymer during charging and out of the polymer during discharging.

The knowledge that conducting polymers can be charged, that is, oxidized and reduced, raised the question of possible applications, such as the construction of a polymer battery, at an early stage [73]. But basic research was long unable to explain the charge storage mechanism. Theoretical concepts that describe the voltammetric response during charging and discharging of redox-active films were developed more than two decades ago [74]. In the ideal case, reversible cyclic voltammograms should show completely symmetrical and mirror-image cathodic and anodic waves with identical peak potentials and current levels (Fig. 5).

The current in the reversible case is then:

$$i = \frac{n^2 F^2 A \exp\Theta v \Gamma_T}{RT(1+\exp\Theta)^2} \tag{3}$$

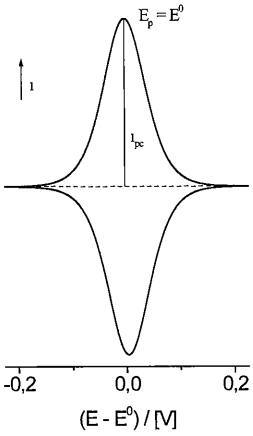


Figure 5. Theoretical cyclic voltammogram for a redox-active film with noninteracting sites.

where $\Theta = (nF/RT)(E - E^\circ)$, and $\Gamma_T = \Gamma_0 + \Gamma_R$ corresponds to the total surface covered with reduced and oxidized sites. The other parameters have their usual meanings. Apart from the mirror symmetry of the waves, it is also characteristic that, in contrast to measurements obtained with soluble redox systems, current i and the scan rate v are directly proportional to each other.

The preceding statements are valid for monomolecular layers only. In the case of polymer films with layer thickness into the micrometer range, as are usually produced by electropolymerization, account must also be taken of the fact that charge transport is dependent on both the electron-exchange reactions between neighboring oxidized and reduced sites and the flux of counterions in keeping with the principle of electroneutrality [75,76]. Although the molecular mechanisms of these processes are not yet understood in all their detail, their phenomenology can be adequately described by the laws of diffusion. All variants of the diffusion mass transport are possible from the finite limiting case to semi-infinite diffusion, depending on film thickness, the values of the formal diffusion coefficients, and the experimental time scales used. For voltammetric experiments, this implies that as the sweep rate increases there must be a shift from mirror symmetrical CV diagrams with i proportional to v to the classic, asymmetrical voltammograms with i proportional $v^{1/2}$.

Although the potentiodynamic charging and discharging of conducting polymers produces voltammograms of very different shape depending on type and polymerization conditions, one frequently finds CV diagrams (Fig. 6) with a very similar shape. This is particularly the case when polymeric films are produced under mild conditions at low formation potentials [4,5,10c,20,34,65]. Characteristic features of these systems are, in the case of the p-doping, a steep anodic wave at the start of charging, followed by a broad, flat plateau as potential increases. In the reverse scan a potential-shifted cathodic wave appears at the negative end of the capacitylike plateau, whose peak current corresponds to approximately half the value of the anodic peak.

The conspicuous separation between the cathodic and anodic peak potentials (hysteresis) was initially interpreted in terms of the simple theory of redox polymers as a kinetic effect of slow heterogeneous charge transfer; the thermodynamic redox potential

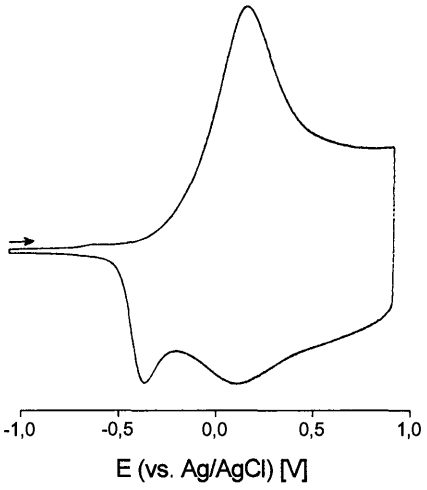


Figure 6. Cyclic voltammogram for the oxidation of polymethoxythiophene, $v = 0.5\,\mathrm{mV\,s^{-1}}$, $T = 298\,\mathrm{K}$.

of the whole system was calculated from the mean value between E_{pa} and E_{pc} [5,7a,77]. As a simplification, it was assumed that the interaction between the charged oligomeric segments was negligible. These redox data correlate well with potential values obtained by extrapolation from quantum mechanical calculations [78] and redox potential measurements [29,79,80] on oligomers of defined chain length. As expected, with increasing conjugation length the respective oxidation and reduction potentials shift toward lower energy values. However, the small discrepancy between the measured and the extrapolated E_{pa} values gave rise to the opinion that the conjugation length of the neutral polymer covered only 50 to 10 monomeric units [79].

Furthermore, from quantum-mechanical findings it was concluded that the onset potentials measured in the polymers reflected only the initial ionization of such systems and that further ionization steps had been linked to structural changes in the system [78]. Substitution effects, too, influence the position of the oxidation potentials of the polymers. Although electron-donating substituents lower oxidation potentials just as they do in the monomers, the electron-withdrawing substituents raise them. The fact that in the majority of cases there is a linear relation between the oxidation potentials for the monomers and the polymers shows that the substituents' effects are primarily of an electronic nature [71,81,82]. Feldberg and Rubinstein [83] offered another explanation for the typical separation between anodic and cathodic peak potentials of conducting polymers. In their opinion, the hysteresis is not due to a classic square scheme involving a heterogeneous and homogeneous kinetics but to N-shaped free-energy curves as a consequence of phase transitions in the polymer.

Another concept has been developed on a refined model based on two-step redox systems typical for organic compounds [84]. This concept treats a polymer chain with the degree of polymerization n as x weakly interacting segments containing k monomeric units, each of which can be charged up to a diionic state in two redox steps with different potentials ($1 < k \ll n, xk = n$).

$$M_n \underset{E_1^\circ}{\overset{-xe}{\rightleftharpoons}} (M_k^{1+})_x \tag{4a}$$

$$(M_k^{1+})_x \underset{E_2^\circ}{\overset{-xe}{\rightleftharpoons}} (M_k^{2+})_x \tag{4b}$$

This concept implies negligible interaction energies between the segments; consequently, the essential determinant of the position of the redox potentials must be the structure of the so-called effectively conjugated segments (ECS) [85].

In principle, such propositions resemble the bipolaron model, which presents the solid-state physicist's view of the electronic properties of doped conducting polymers [86]. The model was originally constructed to characterize defects in inorganic solids. In chemical terminology, bipolarons are equivalent to diionic states of a system ($S = 0$) after oxidation or reduction from the neutral state. The transition from the neutral state to the bipolaron takes place via the polaron state (= monoion, $S = \frac{1}{2}$, ESR signal) and, thus, corresponds sequentially as well to redox transitions observed in two-step redox systems. In contrast to normal redox processes, however, additional local distortions occur in the chain during the charging of the polymer. Already in the first step, the formation of polarons, there is a gain of relaxation energy E_{rel}. This is released by structural relaxation after ionization, for which a vertical Franck–Condon-like ionization energy E_{IP-v} is necessary. E_{rel} corresonds to the bonding energy of the polaron [86]. The structural relaxation causes a local distortion of the chain in the vicinity of the charge, whereby the twisted benzoidlike structure of the affected segments transforms into a quinoidlike structure in which the single bonds between the monomeric units shorten and assume doubling-bonding character.

Removing a second electron from the polymer segment results not in two polarons, but in the bipolaron, which is predicted to be energetically more favored than the polaron. The reason for this lies in the respective structural relaxations: That for the bipolaron is considerably greater than that for the polaron. The ionization energy required to remove a second electron decreases, or the electron affinity for taking up a second electron increases. In addition, it is assumed that the locally distorted bipolaron state comprises only four or five units of a chain segment (Fig. 7). The energy gain of the bipolaron compared to two polarons is said to be about 0.45 eV in the case of polypyrrole [87] and 0.35 eV in the case of polyparaphenylene [86a]. In terms of redox energies, this means that the redox potentials E_2° for bipolaron formation should be much lower than the potential E_1° for polaron formation. The model is based on the ideal assumption that the chain length of the linear polymer is infinite, which results, as far as electronic properties are concerned, in a band structure. During charging, polaron and bipolaron states develop in the band gap region, which leads to characteristic optical transitions.

Although the intermediate existence of polarons (= radical ions) has been unequivocally proved by ESR measurements and optical absorption spectra, up to now the existence of bipolarons has been only indirectly deduced from the absence of the ESR signal and the disappearance of the visible polaron band from the optical absorption spectra [88,89]. On the other hand, spin-free—diionic charge—states in aromatics, whose optical properties bear a remarkable resemblance to the predictions of the bipolaron model, have long been known [90]. Theoretical calculations of optical transitions in conjugated (chainlike) systems show that transitions of radical ions or diions are in principle similar to those predicted by the bipolaron model [91]. A strong argument against the validity of the bipolaron model is the fact that conductivity in highly doped polymers

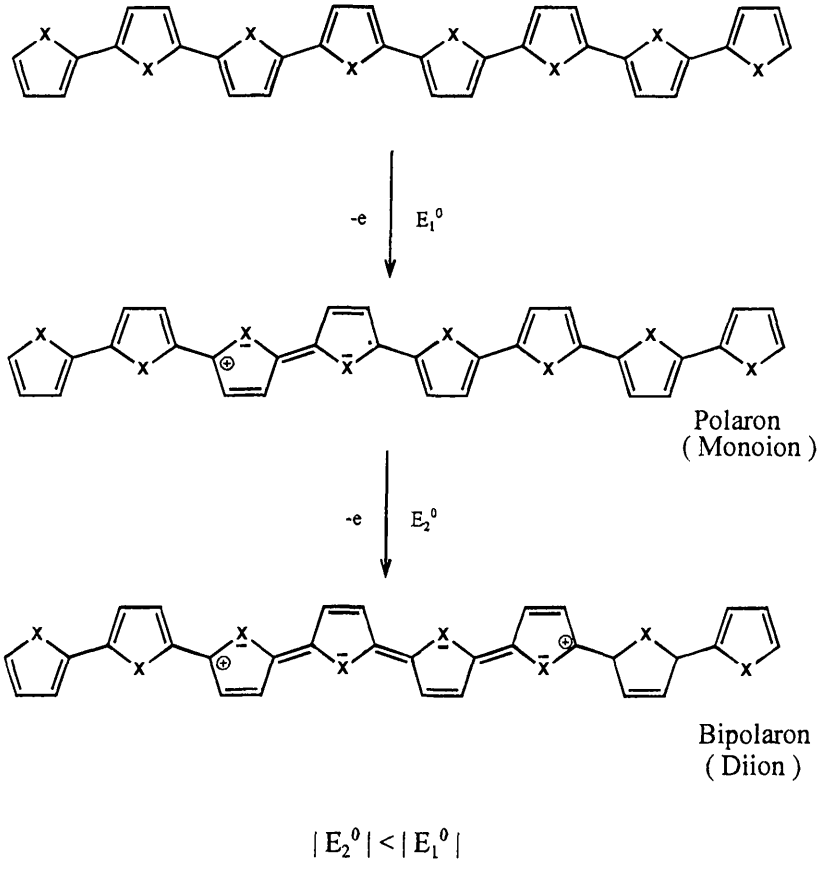


Figure 7. Formation of the bipolaron (= diion) state in PPy or PTh upon oxidation: In the model, it is assumed that the ionized states are stabilized by a local geometrical distortion from a benzoidlike to a quinoidlike structure. Hereby one bipolaron should thermodynamically become more stable than two polarons despite the coulombic repulsion between two similar charges.

decreases drastically [92]. According to the predictions of the model, the conductivity should increase at a higher doping level, owing to better overlap between the bipolaron and the valence band [86c]. So far, electrochemical measurements have not provided any direct proof for the formation of a bipolaron state in conjugated oligomers and polymers. However, electrochemical and ESR spectroscopic studies by Nechtschein et al. indicate that the bipolaron state is not much more stable than the polaron state [93].

A major barrier to a conclusive interpretation of voltammetric data on conjugated conducting polymers was the lack of measurements for well-defined model systems. A very important step was the measurement of charging/discharging behavior of oligomers of the phenylenevinylene type [80a,94] as well as of conjugated oligomers in different chainlike series [25,62,95] (see also Chapter 6). All these data clearly demonstrate that the redox behavior of such oligomers and polymers depend on the chain length of the systems (Fig. 8). They complement theoretical and experimental results already presented in the older literature [78,79,96].

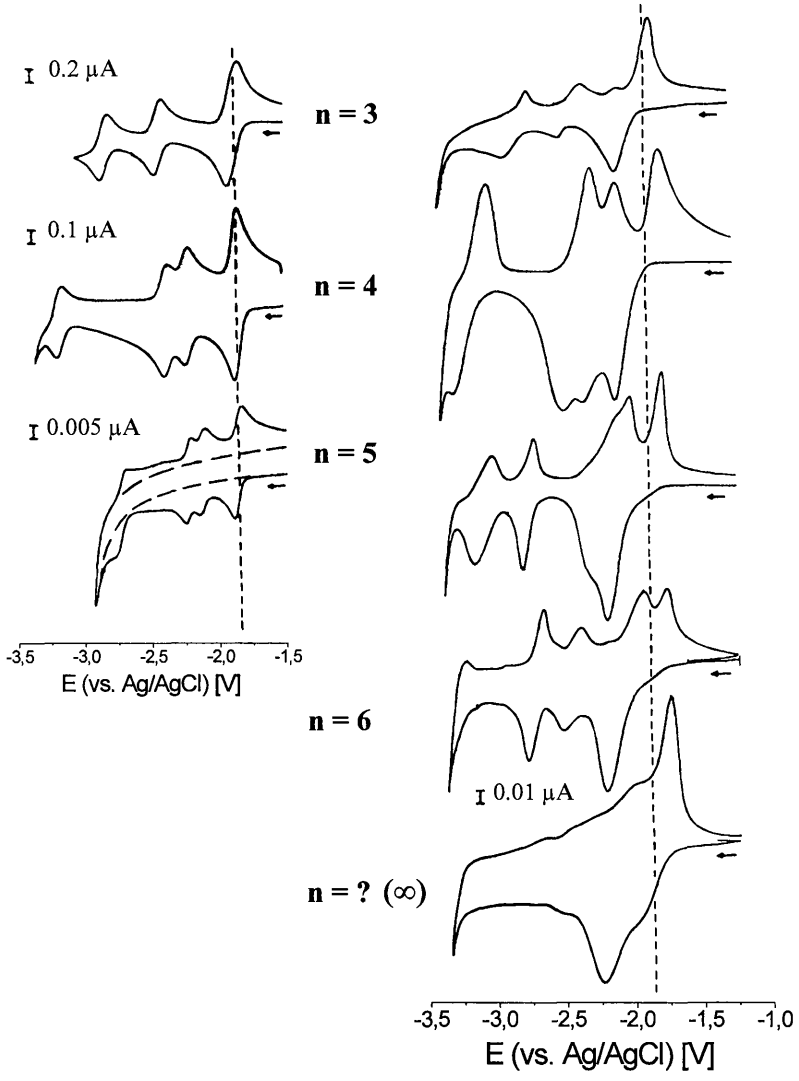


Figure 8. Reduction of oligophenylenevinylenes in solution (left) and in the solid state (right). From Ref. 80b.

The following trends have been established: First, with increasing chain length, redox states of identical charge (e.g., mono- and diion) shift toward lower energies. Obviously, the redox energies of different states gradually approach a common convergence limit with increasing chain length. Second, adding successive monomeric subunits in the molecular chain enlarges the number of accessible redox states, and third, the energy gap widens considerably between the lowest and the highest charged states. This is a consequence of the coulombic repulsion created by every new excess charge introduced into the system and contradicts the predictions of the bipolaron model. Moreover, in experiments in solution the stabilization of diionic states does not increase relative to monoionic states. All experimental data reveal—in excellent agreement with quantum-

mechanical calculations—that the generation of higher redox states essentially requires more or at least the same energy (in the case of long conjugated chains with $n \geq 8$) than the formation of the monoionic (polaron) state.

For real polymer systems—characterized by a more or less broad distribution of molecular weight and, depending on the conditions of formation, various structural defects—this means that at the start of charging there is a high density of virtually degenerated redox states, which generates the peak-shaped anodic wave. As potential increases, the density of the redox states decreases but remains finite within the experimentally accessible potential range. This explains the broad, plateau-like waves that are so often characteristic of the potential range following the peak-like main wave in voltammetric experiments. Unequivocal experimental evidence for this interpretation has been obtained from voltammetric measurements carried out under solid-state conditions on a series of oligophenylenevinylenes [80b]. The voltammograms clearly show that with increasing chain length the waves of succeeding redox steps superimpose and finally yield peak-shaped voltammograms involving the broad current plateau at higher charging levels (Fig. 8).

It is interesting to note that all the solid-state voltammograms in this experiment, both of the monodisperse oligomers and the polymer, again show the same hysteresis as has been observed for many polymers such as PPy or PTh (see Fig. 6). Originally, these phenomena were interpreted as redox-related structural changes within the solid film. It was assumed that during charging the polymeric chains stabilized through transition from a benzoid into a quinoidlike structure and became planar and that, therefore, the discharging process occurs at a considerably lower potential. Obviously, this seemed to be the missing link in the evidence of the bipolaron model [60,62,95b,95c,97].

However, quite another picture results from recent studies of soluble oligomers, which clearly show that their oxidized species reversibly dimerize and form energetically stabilized σ-intermediates [38,39]. Depending on the structure of the at least doubly charged "σ-dimers," their discharging occurs at considerably lower potentials than oxidation (or reduction) of the neutral starting compound, producing a strong hysteresis between charging and discharging of the respective oligomers. During the discharging process the σ-bonds between the chains break, and the system relaxes into its aromatic ground state. Even for small equilibrium constants between dimer and monomer ($K < 100$) under solid-state conditions, a predominant amount of the charged species is transformed into the "dimeric" state, owing to the high surface concentrations of the oligomers or polymers. Therefore, voltammetric solid-state experiments always show the characteristic hysteresis between charging and discharging. There is no doubt that σ-dimers are formed, not π-dimers, as postulated in the literature some years ago [98]. They are the key intermediates of the radical-radical coupling mechanism (see Scheme 2). In the past, it was assumed that the deprotonation of such intermediates is fast, leading to a rearomaticized coupling product. All recent measurement carried out with linear thiophene oligomers reveals that the deprotonation rate constant becomes considerably smaller than the coupling rate constant as the chain length oligomer increases [99]. Thus, the hexathiophene, and even more so the octathiophene, coupling products are stable as long as the oligomers are only weakly charged (≈ 0.1). Besides the hysteresis, these new findings explain all important electrochemical, electronic, and optical properties of conducting polymers. They overcome the massive, and frequently criticized, inconsistencies of the bipolaron model [36,62,102]. A major advantage of this new view on the properties of conducting polymers is its excellent agreement with findings in (physical) organic chemistry, without reference to models correlated with periodic lattice properties as applied in the case of

crystalline solids. It should be kept in mind that conducting polymers are amorphous materials.

Closely connected with the problems of the charge-storage mechanisms is the question of to what extent one must and can distinguish between faradaic and capacitive processes during charging and discharging [7a,33c,103–105]. Feldberg, in particular, holds that it is hardly possible to draw such a distinction, and that the capacitive charge portion is proportional to the amount of the oxidized polymer [106]. He concludes from a comparison with optical data that the faradaic oxidation processes in CV experiments are essentially limited to the range of the "peak-shaped" anodic wave, whereas the adjoining broad anodic tail represents the large double-layer capacity of the system. The solid-state experiments just mentioned provide strong evidence that the current plateau is due to faradaic processes [80b]. Similar conclusions must be drawn from charging/discharging experiments with poly(4,4′-dimethoxybithiophene), in which, at the end of the anodic charging in the plateaulike region, the current drops to almost zero [33c].

A further characteristic for charge storage in conducting polymers is the amount of doping and insertion. This gives the mole fraction of the corresponding monomers, whose charge is compensated by incorporated counterions; in the case of p-doping (oxidation), the counterions are anions. The doping level is determined either by elementary analysis or by coulometric measurements. However, these measuring techniques may produce different results, as the elementary analysis cannot distinguish an additional solvent portion or organic co-ions such as tetraalkylammonium ions, and coulometry also includes the capacitive charging. The optimum doping level for PPy or PTh is about 0.33, but can have very much lower values. This depends, inter alia, on structure and the applied charging potential, but is also influenced by environmental parameters such as the solvent or supporting electrolyte [107–111].

From the respective doping levels one can deduce that, on the oxidation of PPy, and often on that of PTh as well, every third or fourth heterocycle is charged, whereas in the case of PPP, provided that the experiments take place in common solvents such as propylene carbonate, only every sixth monomeric unit is charged [109]. By contrast, if one uses SO_2, a solvent with low nucleophilicity, PPP can be reversibly oxidized to a doping level of 0.24, which corresponds formally to a charge on every fourth monomer unit [112]. The differences in chargeability of PPP and PPy are explained by the high oxidation potential of PPP. This significantly increases the reactivity of this system towards the solution and other nucleophilic impurities. One should note that polymers such as PA and PPP can be more highly charged by reduction (n-doping) than by oxidation.

Moving to a higher doping level, such as 0.5, forces a charge in every second monomeric subunit, which, of course, induces a coulombic repulsion. Therefore, to achieve this, a higher electrode potential must be applied. And this, normally, results in overoxidation effects [113]. Through the overoxidation process a degradation of the polymer occurs, often induced by nucleophilic solvents such as water or nitriles. Therefore, overoxidized materials can be discharged only to a limited extent, which is a serious drawback for applications.

As already mentioned, the principle of electroneutrality must be fulfilled in charged polymers. Consequently, in freshly prepared p-doped polymers, anions must compensate the positive charges within the polymeric chains. However, spectroelectrochemical studies [114], electrochemical quartz microbalance (EQMC) measurements [115], and SIMS and XPS measurements [116] on the mechanism of ion transport during charging and discharging of conducting polymers prove that discharging involves not only the expulsion of

anions but also the incorporation of cations. In the case of small anions, this cation exchange mechanism is surprising. Recent results on structural peculiarities of PPy during charging [55,68] indicate that PPy chains "dimerize" upon oxidation of the neutral chains, forming σ-bonds between the chains, and that, therefore, immobile localized charges are generated, which in turn prevent any movement of the anionic counterions [117]. In consequence, during the first discharging process mobile anions slowly diffuse out of the film; in the second step cations are incorporated into the polymer, forming ion pairs with the immobile anions [Eq. (5)].

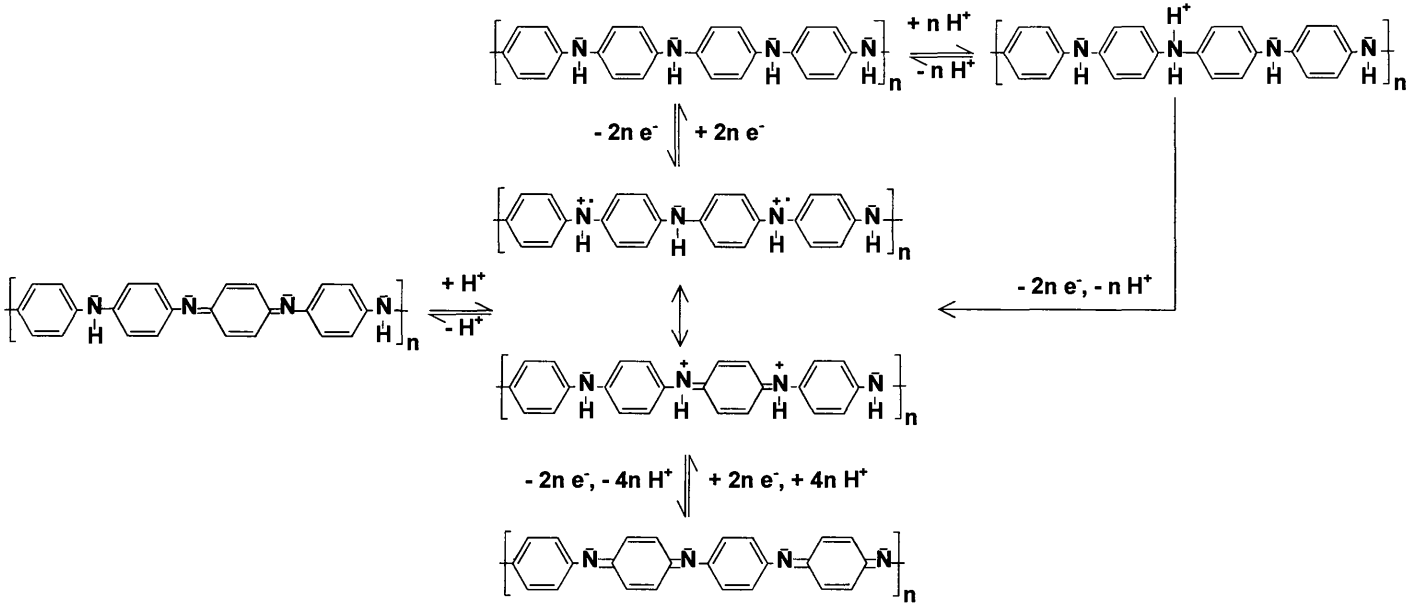
$$[(PPy)_4^+A^-] + (n-m)e^- \longrightarrow m(PPy)_{4n}^{m+}mA^- + (n-m)A_{sol}^- \tag{5a}$$

$$[(PPy)_{4n}^{m+}mA^-] + me^- + mM^+ \longrightarrow (PPy)_{4n} + m[M^+, A^-]_{film} \tag{5b}$$

Using polymeric or large anions during electropolymerization, a pure cation transport generally results upon anodic charging and discharging [118]. This has been confirmed by in situ monitoring of the mass charge during electrochemical switching using a quartz crystal microbalance [119].

Electrochemical measurements of polyaniline (PANI) produce a picture of the charge storage mechanisms that differs fundamentally from that obtained using PPy or PTh (Scheme 5). In the cyclic voltammetric experiment one observes two reversible waves in the potential range between -0.2 and $+1.2$ V versus SCE. Above $+1.0$ V, the current tends to zero. Capacitive currents and overoxidation effects, as in the case of PPy or PTh, do not occur [120]. The striking changes in the charge, characteristic of polyaniline compared with PPy and PTh, are largely explained by the nitrogen atoms capturing a considerable part of the coulombic interaction between the charged centers.

PANI is usually produced by the anodic oxidation of aniline in acidic aqueous solution [5,121], but can also be produced by chemical oxidation [120b,122]. Hence, it is not surprising that the oxidation of PANI is pH dependent and that therefore, in addition to electron-transfer processes, proton-transfer reactions occur during charging. Although it is usually assumed that PANI has a chains tructure (emeraldine) with head–tail connections between the aniline units [123], the existence of cyclic structures has also been postulated in the literature [124]. However, the synthesis and the characterization of monodisperse aniline oligomers support the view of a linear chain in the nonoxidized state [123]. It is generally accepted that there are different, possibly coexisting forms of polyaniline, including benzoid and quinoid rings, free amines (NH), imines, and protonated amines and imines [125]. Depending on the pH value of the solution, different protonated structures are formed. In the most simple case it is assumed that polycationic states are formed in the first step [126]. In the second step, which correlates with the second oxidation peak in the CV diagram, protons are eliminated and additional electrons are abstracted. This corresponds with MacDiarmid's observations, which show that the second redox step is strongly pH dependent [120b]. Shacklette et al. [127] showed in a very thorough study of the phenyl-end-capped tetramer of oligoaniline that the first oxidation step involves a 2e-transfer step, leading to the emeraldine salt form in which 50% of the nitrogens are oxidized. The second oxidation wave also indicates a 2e step and varies with pH at a rate of approximately 120 mV/pH, which suggests a deprotonation of four protons. In this case the resulting species should be the pure imine form.



Scheme 5. Redox steps during charging/discharging of PANI.

V. APPLICATIONS

The starting point for applications was the discovery that PA can function as an active electrode [2] in a rechargeable polymer battery. Since then, the prospects of technical applications have grown considerably. Apart from the battery electrode, conducting polymers are discussed as potential electrochromic displays, antistatic materials, anticorrosives, electrocatalysts, and light-emitting materials. The most advanced developments are the battery [73,128], antistatic materials [129], and light-emitting devices [130].

The attraction in the development of a rechargeable polymer battery lies in the specific weight of polymers, which is considerably lower than that of ordinary inorganic materials, as well as the potential environmental benefit. At the beginning of the battery research, the polyacetylene cell was most extensively studied [2,9]. However, due to its chemical instability, it has virtually no commercial prospects. A promising candidate for a polymer battery that does not possess the typical disadvantages of polyacetylene is PPy [107b,131]. Its open circuit voltage lies near 3.5 V versus Li^+/Li. Charge capacity is about 70 to 85 $A\,h\,kg^{-1}$, and the effective energy density reaches values of 40 to 60 $W\,h\,kg^{-1}$. A crucial disadvantage of PPy is that during discharging cations are incorporated into the polymeric layer, which leads to consumption of the electrolyte and stops the charging/discharging process in thin-layer cells. The reason for this phenomenon lies in structural pecularities of PPy, which forms σ-dimers during charging, producing immobile positive charges correlated with immobile anions [115c,132].

An important problem encountered with polymer electrodes is that of overoxidation. It occurs after reversible charging of an electrode with high oxidation potentials and leads to the degradation of the polymer. The results of thorough studies [113,133] show that such degenerative mechanisms are promoted by the nucleophilicity of the solvent.

Apart from polymer batteries, applied research on conducting polymers has reached an advanced stage in the fields of electrochromic displays [10,134], antistatic layers [129], and light-emitting devices [130]. Electrochromic displays are based on an electrochemical reaction of a material that displays a visual charge upon changing its redox state. The advantages of using electrochromic displays (ECD) are their ease of preparation and the uniformity of the prepared films. Furthermore, ECDs have no limited visual angle, but continue to exhibit a memory function even after the driving voltage has been removed. Erasing and rewriting can be performed almost at will. The suitability of PPy, PTh, and PANI as electrochromic displays has been intensively studied. PANI appears to be particularly promising, as its color changes during oxidation range from yellow through green, blue, and violet to brown [121c,135].

Baytron®, a conducting polymer [136] derived from 3,4-ethylenedioxythiophene, is a commercially available product that can be used as an antistatic or electrostatic coating of plastics and glass. Moreover, it has successfully been applied as counterelectrode in capacitors and as a hole-injection layer in organic light-emitting diodes [137].

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Abbreviations and Symbols

ELECTRODES

DME	Dropping mercury electrode
DSA	Dimensionally stable anode
HMDE	Hanging mercury drop electrode
NHE	Normal hydrogen electrode
OTE	Optically transparent electrode
OTTLE	Optically transparent thin-layer electrode
RDE	Rotating disc electrode
RRDE	Rotating ring-disc electrode
SCE	Saturated calomel electrode

TECHNIQUES

ATR	Attenuated total reflectance spectroscopy
CA	Chronoamperometry
CPE	Controlled potential electrolysis
CPSV	Convolution potential sweep voltammetry
CV	Cyclic voltammetry
DCV	Derivative cyclic voltammetry
DPSCA	Double potential step chronoamperometry
ESR	Electron spin resonance spectroscopy
IRS	Internal reflection spectroscopy
LSV	Linear sweep voltammetry
MSRS	Modulated specular reflectance spectroscopy
OCR	Open-circuit relaxation
RSS	Rapid scan spectroscopy
SRS	Specular reflectance spectroscopy

SOLVENTS

AN	Acrylonitrile
AcOH	Acetic acid
Ac_2O	Acetic acid anhydride
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EtOH	Ethanol
HFP	1,1,1,3,3,3-Hexafluoropropane-2-ol

HMPA	Hexamethylphosphoramide
MeCN	Acetonitrile
MeOH	Methanol
NMP	N-Methylpyrrolidone
PC	Propylene carbonate
Py	Pyridine
TFA	Trifluoroacetic acid
TFAn	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran

CHEMICALS, LIGANDS, RADICALS

Ac	Acetyl
acac	Acetylacetone
aib	Tripeptide of α-aminoisobutyric acid
Ant	Anthracene
Ar	Aryl
bipy	2,2′-Bipyridine
Boc	t-Butoxycarbonyl
Bu	Butyl
Bz	Benzyl
Cbz	Benzyloxycarbonyl
COT	Cyclooctatetraene
Cp	Cyclopentadiene
Cyclam	1,4,8,11-tetraazacyclotetradecane
Dim	Diimine
dppe	1,2-bis(diphenylphosphino)ethane, $(Ph_2PCH_2)_2$
dppp	1,2-bis(diphenylphosphino)propane, $(Ph_2PCH_2)_2CH_2$
E^+	Electrophile
EGB	Electrogenerated base
Et	Ethyl
$FADH_2$	Flavine adenine dinucleotide (reduced form)
FAD	Flavine adenine dinucleotide (oxidized form)
FMN	Flavine mononucleotide
Fc	Ferrocenyl
H_2P	Porphyrin
H_2OP	Octaethylporphyrin
Me	Methyl
MP	Metalloporphyrin
MTPP	Tetraphenylmetalloporphyrin
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NADH	Nicotinamide adenine dinucleotide (reduced form)
$NADP^+$	Nicotinamide adenine dinucleotide phosphate (oxidized form)
NAD^+	Nicotinamide adenine dinucleotide (oxidized form)
Naph	Naphthalene
Nu	Nucleophile
Pa	Polyacetylene
Pc	Phthalocyanine
Ph	Phenyl
phen	1,10-Phenanthroline
PQQ	Pyrroloquinoline quinone
Pr	Propyl

R	Alkyl
Sal	Salicylaldehyde
Salen	bis-salicylaldehydeethylenediamine
TBA	Tetrabutylammonium
TEA	Tetraethylammonium
THP	Tetrahydropyran
TMA	Tetramethylammonium
TPA	Tetrapropylammonium
TTF	Tetrathiafulvalene
Z	Benzyloxycarbonyl

STANDARD SUBSCRIPTS

an	anodic
cat	cathodic
d	diffusion
eq	equilibrium
f	forward
b	backward
l	limiting
p	peak
O, R	pertaining to the oxidized, reduced species

ELECTRIC, KINETIC AND THERMODYNAMIC SYMBOLS

A	Electrode surface area
A_{ff}	Affinity (in eV)
a_s	Equivalent radius of species S
C	Concentration (see also (S))
C^b	Concentration in the bulk solution
C^0	Initial concentration of the starting material
C_s	Concentration of species S (see also (S))
$C_x = \ldots$	Concentration at $x = \ldots$
D	Diffusion coefficient; average diffusion coefficient
D_s	Diffusion coefficient of species S
e_{metl}	Electron in metal phase number 1, etc.
E	Electrode potential vs. a given reference electrode
ΔE_f^{act}	Activation energy of a reaction between encounter pairs
E^{in} (or E^{fin})	Potential energy of the electron for any state of the initial (or final) system
E_j	Junction potential
E^0 (or E_1^0)	Standard reduction potential (relative to the half reaction 1)
E_E^0	Standard reduction potential of an electrode E
E^0O/R	Standard reduction potential relative to the half reaction: $0 + ne \rightleftharpoons R$
$E^{0'}$ (or $E_1^{0'}$)	Formal potential (relative to the half reaction 1, etc.)
E_p	Peak potential in CV
$E_{p/2}$	Half-peak potential in CV
E_w	Any characteristic potential pertaining to a given electrochemical wave
$E_{1/2}$	Half-wave potential
E	Potential energy of the electron in the initial or final systems at the transition state

f_s	Activity coefficient of species S
F	Faraday
ΔG_r^f (or ΔG_p^f)	Free energy of formation of the reactant (for product) encounter pair
ΔG^0	Standard free energy change in a specified reaction
$\Delta G^{0'}$	Standard free energy change between encounter pairs
ΔG^0_{red} (or G^0_{ox})	Standard free energy change for the considered half-reaction in the direction of reduction (or oxidation)
$\Delta G^0_{s,solv1}$	Standard free energy of solvation for species S in solvent 1, etc.
$\Delta G^0_{s,rel}$	Standard free energy of relaxation of an excited species S in gas phase
ΔG^s	Free energy change for species S between the end of the diffuse layer and the electron transfer site
$\Delta G^{\ddagger}_{exp}$	Experimental (apparent) activation free energy
$\Delta G^{\ddagger}_f$ (or $\Delta G^{\ddagger}_b$)	Overall free activation energy for the forward (or backward) reaction
$\Delta G^{\ddagger 0}$	Intrinsic activation barrier
h	Planck constant
i	Current
i^{lim}	Limiting current in steady state methods
I_p	Ionization potential (in eV)
J (or J(x))	Overall flux of particles through an elementary surface perpendicular to the x axis, at x
J_{conc}	Flux of particles through an elementary surface perpendicular to the x axis, arising from convection
J_{dif}	Flux of particles through an elementary surface perpendicular to the x axis, arising from diffusion
J_{migr}	Flux of particles through an elementary surface perpendicular to the x axis, arising from convection
k	Boltzmann constant
k	Rate constant
k^{ap}	Apparent rate constant
k_f^{act} (or k_b^{act})	Rate constant of the forward (or backward) reaction between encounter pairs, for an adiabatic electron transfer
k_f^{dif} (or k_b^{dif})	Overall diffusion limited forward (or backward) rate constant
k_{elec}	Apparent first order rate constant equivalent to an electrolysis
K_f (or k_b)	Measured forward (or backward) rate constant
k^0	Intrinsic standard heterogeneous rate constant
k_t^0	True standard heterogeneous rate constant
K_{dif}^r (or k_{dif}^p)	Diffusion rate constant for the formation of the reactant (or product) pair
k_z	Rate constant for the reaction involving the transfer of a Z moiety
k_1	Rate constant number 1, etc.
$k_f^{\ddagger}$ (or $k_b^{\ddagger}$)	Apparent forward (or backward) activation rate constant
K	Equilibrium constant
K_a	Acidity dissociation equilibrium constant
K_a'	Formal acidity dissociation equilibrium constant
K_c (or K_p)	General kinetic term of consumption (or production) for the considered species
K_J	Dimensionless kinetic term for consumption and production for the considered species
L	Mean distance covered by a particle during a specified time period
l	Any specified length . Free motion length for a "random walking" particle
M (or m_S)	Molar mass (of species S)
n (or n_1)	Number of electrons exchanged (for the half-reaction 1, etc.)
n_{ap}	Apparent number of electrons exchanged
n_{op}	Refractive index of the solvent

N_A	Avogadro's number
N	Number of nuclear degrees of freedom
N_S (or N)	Number of molecules (of species S)
p_1	Competition parameter number 1, etc.
P_e	Probability of electron tunnelling between the initial and final systems
q_i	i^{th} nuclear coordinate (i = 1, N)
q_i^m (or q_i^{fin})	Equilibrium value of the i^{th} nuclear coordinate (i = 1, N) in the initial (or final system)
q_i	Value of the i^{th} nuclear coordinate (i = 1, N) in the initial and final system, at the transition state
Q	Charge consumed (coulombs)
Q_t	Charge consumed after a period t of electrolysis
r	Distance between reactant, or product, centers in the encounter pairs
r_o	Radius of a disc electrode; smaller dimension of an electrode
R	Gas constant
R (or R_Ω)	Resistance of a solution
R_i (or $R_{\Omega i}$	Electrical potential drop arising from ohmic phenomena
s	Dimensionless concentration of species S
S_{gas}	Species S in gas phase
S_0	Species S at the end of the diffuse layer
S_{solv}	Species S solvated
(S)	Activity of species S
[S]	Concentration of species S
$[S]_{bulk}$	Concentration of species S in the bulk solution
$(S)_x = \ldots$	Activity of species S at $x = \ldots$
$[S]_x = \ldots$	Concentration of species S at $x = \ldots$
$[S]_{yield}$	Yield of species S
S_ϕ	Species S at the electron transfer site
ΔS	Entropy change
ΔS_{pair}	Entropy of formation of a pair electrode/molecule
ΔS_{rot}	Entropy of formation of a molecular pair (rigid rotator)
S^*	Excited species S in gas phase Isotopically labeled species S
t	Current time; time period
T	Absolute temperature
v(x)	Velocity of a fluid along the x axis
V	Volume of the bulk solution
V_i	Stabilization energy at the transition state
Wr (or W_p)	Energy of formation of a reactant (or product) encounter pair
$W_r^{(x)}$ (or $W_p(x)$)	Energy of formation of a loose reactant (or product) encounter pair, x being the distance between centers of the molecules
$W_\delta^{non\text{-}eq}$	Energy required to produce a non-equilibrium polarization of the solvent, corresponding to a virtual charge δ transferred
W_δ^{eop}	Energy required to produce an optical equilibrium polarization of the solvent corresponding to a charge δ transferred
W_δ^{es}	Energy required to produce a static equilibrium polarization of the solvent corresponding to a charge δ transferred
X	Coordinate along the x axis; normalized reaction coordinate; distance between the centers of reacting molecules; distance from the electrode surface
X_o	Double layer thickness
X_ϕ	Distance of the electron transfer site, from the electrode surface
$X^\ddagger$	Normalized reaction coordinate value at the transition state
Y	Dimensionless space variable
z (or z_s)	Charge of species S

Z	Collision frequency (homogeneous)
Z_{an}	Anodic faradaic impedance
Z_{cat}	Cathodic faradaic impedance
Z_{el}	Collision frequency (heterogeneous)

GREEK SYMBOLS

α	Transfer coefficient (heterogeneous)
β	Brönsted coefficient (homogeneous)
β_{exp}	Measured Brönsted coefficient
δ	Virtual fractional charge transferred; diffusion layer thickness
δ_{conv}	Stagnant layer thickness
δ^{in} (or δ^{fin})	Virtual fractional charge transferred in the initial (or final) system
$\overline{\Delta^2}$	Average square displacement of a particle during a specified time period
ε_{op}	Optical dielectric constant
ε_s	Static dielectric constant
Θ	Characteristic time of an electrochemical method; duration of an experiment
π	Transmission coefficient
κ	Proportionally constant between velocity of a particle and the force applied to it
K (kappa, versal)	Dimensionless equilibrium constant
λ	Dimensionless homogeneous rate constant
λ (or λ^{xy})	Reorganization energy (relative to the X/Y homogeneous couple)
λ_i (or λ_i^{xy})	Inner-shell reorganization energy (relative to the X/Y homogeneous couple)
λ_o (or λ_0^{xy})	Outer-shell reorganization energy (relative to the X/Y homogeneous couple)
λ_i^s	Inner-shell reorganization energy relative to species S
λ^{el}	Reorganization energy relative to a heterogeneous electron transfer
λ_i^{el} (or λ_o^{el})	Inner- (or outer-) shell reorganization energy relative to a heterogeneous electron transfer
Λ	Dimensionless heterogeneous rate constant
μ	Chemical potential
μ^o	Standard chemical potential
ν	Sweep rate in CV or LSV (Vs^{-1})
ξ	Dimensionless potential
τ	Dimensionless time. Duration of free motion for a "random walking" particle
ϕ	Potential difference between the anode and the cathode
ϕ_A	Potential difference between the auxiliary electrode and the solution
ϕ_{an}	Potential difference between the anode and the solution
ϕ_{cat}	Potential difference between the cathode and the solution
ϕ_{CE}	Potential difference between the counter electrode and the solution
ϕ_{Ref}	Potential difference between the reference electrode and the solution
ϕ_s	Potential difference between the electron transfer site and the solution
ϕ_W	Potential difference between the working electrode and the solution
ϕ_Ω	Potential drop due to ohmic phenomena
Ψ	Dimensionless current
ω	Rotation frequency of an RDE
Ω_i	Reduced force constant relative to the i^{th} nuclear coordinate
Ω_i^{in} (or Ω_i^{fin})	Force constant relative to the i^{th} nuclear coordinate in the initial (or final) system
Ω_o	Reduced force constant relative to the oscillator equivalent to the outer-shell medium

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