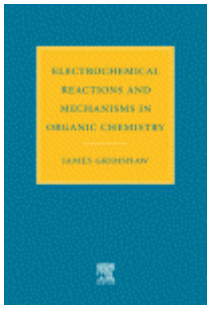


Electrochemical Reactions and Mechanisms in Organic Chemistry

Elsevier, 2000
Author : James Grimshaw
ISBN: 978-0-444-72007-8

PREFACE

This book is concerned with reactions carried out at an electrode on a preparative scale. The impact of organic electrochemistry on synthetic organic chemistry has a long history beginning with the Kolbe reaction, which is still in the repertoire in first year teaching. In the early 1900's electrochemical methods for the oxidative or reductive transformation of functional groups were actively pursued.. They offer the advantage of having no spent oxidant or reductant for disposal. However electrochemical processes fell out of favour in the face of conventional chemical reactions because the outcome from electrochemistry was often far from predictable. Now that the mechanisms of these processes are generally well understood, many of the former pitfalls can be avoided.

Electrochemical processes use the electron as a reagent and so avoid a chemical oxidant or reductant. The environmental impact of electrochemistry needs to be assessed by looking at the global cell reaction. In the electrochemical cell, every oxidation step at the anode must be accompanied by a reduction at the cathode. During an oxidation, whatever is evolved at the cathode is in effect a spent reagent. The cathode reaction can be controlled to give a desirable product, even hydrogen for use as a fuel. During a reduction process this spent reagent is produced at the anode. It can be oxygen, which is vented to the atmosphere. Control of the reaction at the counter electrode gives to electrochemical processes the advantage of being non-polluting, relative to corresponding steps using a chemical reagent.

The discovery of the Baizer hydrodimerization process for preparation of adiponitrile from acrylonitrile led to a resurgence of interest in organic electrochemistry. This process synthesises adiponitrile at the cathode and the spent reagent is oxygen evolved at the anode. Its immense technical success prompted extensive investigations into reaction mechanisms in organic electrochemistry with a view to improving the old functional group interchange reactions. At the same time new reactions of potential use in organic synthesis have been discovered. In parallel with these investigations, significant improvements have been made in the design of electrochemical cells both for laboratory and for industrial scale use.

Electrons are transferred at an electrode singly, not in pairs. The primary reactive species to be generated is either a delocalised radical-ion or a radical formed by cleavage of a σ-bond, together with an ion. The first formed radicals can be further converted to ions by electron transfer. Thus organic electrochemistry involves a study of the reactions of both radical and ionic intermediates. Electron transfer at the electrode is a surface reaction while intermediates undergo chemical reactions in the bulk solution. An appreciation of the existence of these two types of often competing processes is required to understand the outcome of organic electrochemical reactions.

Recent work has developed reactions for carbon-carbon bond formation or cleavage and has introduced new routes for the introduction of functional groups, all of which are attractive to those planning synthesis on both laboratory and industrial scales. The mechanisms of these processes are now generally well understood.

This book aims to be more than just an introduction to such current areas of research. It is intended also to show how the subject of Organic Electrochemistry is integrated across the spectrum of oxidation and reduction by a general set of mechanisms. The discussion centres around reactions on a preparative scale and on the mechanisms governing the outcome of such processes. The book will be of interest to inquisitive final year undergraduates, research students and research directors both in academia and in the fine chemicals industry. An understanding of general organic chemistry is assumed. Physical chemistry has to be introduced into a discussion on electrode kinetics and this area is kept to a minimum. Discussions on the preparation and properties of radical-ions are also necessary since these are the first reactive species produced at an electrode.

The redox properties of an electrode are determined by its potential measured relative to some reference electrode. Many different reference electrodes are used in the literature. In order to make cross comparisons easily, most of the electrode potential quoted for reactions have been converted to the scale based on the saturated calomel electrode as reference. Electrode materials and electrolyte solutions used by the original workers are quoted. In many cases, the electrodes could be fabricated from more modern materials without affecting the outcome of the reactions. In the not too distant past perchlorate salts were frequently used as electrolytes. This practise must be discouraged for preparative scale reactions because of the danger of an explosion when perchlorates and organic compounds are mixed. Alternative electrolytes are now readily available.

I acknowledge many discussions over the years with research students and with the international research community on problems in organic electrochemistry. The assistance given to me by Sheila Landy and her staff of the Science Library in Queen's University is gratefully acknowledged. Finally, I thank my wife for her help and her patience in dealing with all the disruptions to normal life which writing this book has caused.

James Grimshaw,
Belfast, July 2000

CHAPTER 1

ELECTROCHEMICAL OXIDATION AND REDUCTION OF ORGANIC COMPOUNDS

General Technique

During an electrochemical reaction, electrons are transferred between a molecule of the substrate and the electrode. Electrons are always transferred singly and the substrate first is converted to an intermediate with an unpaired electron. Transformation of this reactive intermediate to the final product involves a sequence of bond forming or bond cleaving reactions and frequently further single electron transfer steps. The complete electrochemical reaction vessel requires both an anode and a cathode. Only one of these electrodes, the working electrode, is involved with the chemical reaction of interest, oxidation at the anode or reduction at the cathode. The second electrode is the counter electrode and usually some simple inorganic reaction occurs here, such as hydrogen evolution if this is a cathode or oxygen evolution if this is an anode. The space between the anode and cathode is filled with an ionised salt solution and charge passes through the solution between the electrodes by migration of ions.

The simplest design of electrochemical cell has two electrodes dipping into the solution containing the substrate and the supporting electrolyte. A cell of this type is suitable for the Kolbe oxidation of carboxylate ions (see p. 316) where the anode reaction is given by Equation 1.1 and the cathode reaction is the evolution of hydrogen (Equation 1.2). Both the substrate and the hydrocarbon product are inert

$$2\,C_6H_{13}CO_2^- - 2e \longrightarrow C_6H_{13}{-}C_6H_{13} + 2\,CO_2 \qquad \text{Eq. 1.1}$$

$$2\,H^+ + 2e \longrightarrow H_2 \qquad \text{Eq. 1.2}$$

towards reduction at the cathode.

For many processes, however, it is necessary to employ a divided cell in which the anode and cathode compartments are separated by a barrier, allowing the diffusion of ions but hindering transfer of reactants and products between compartments. This prevents undesirable side reactions. Good examples of the need for a divided cell are seen in the reduction of nitrobenzenes to phenylhydroxylamines (p. 379) or to anilines (p. 376). In these cases the reduction products are susceptible to oxidation and must be prevented from approaching the anode. The cell compartments can be divided with a porous separator constructed from sintered glass, porous porcelain or a sintered inert polymer such as polypropene or polytetra-

fluoroethene. Another type of separator uses woven polytetrafluoroethene cloth which has been exposed to a soluble silicate and dilute sulphuric acid so that silicic acid precipitates into the pores [1]. On a laboratory scale porous porcelain and sintered glass are the most commonly used materials.

On an industrial scale, ion-exchange membranes are most frequently used for the separator material [2]. Cationic and anionic types are both available and a sulphonated polytetrafluoroethene cation exchange resin, which can withstand aggressive conditions, is frequently used. Arrangements for sealing this type of separator into a laboratory scale glass cell are also available.

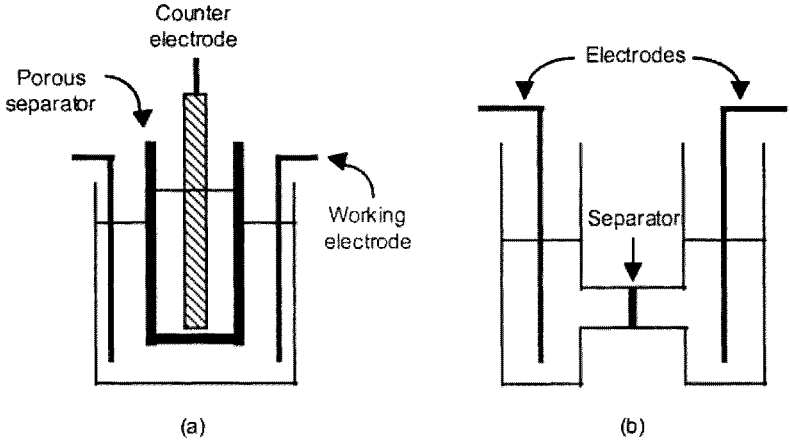


Figure 1.1. Cells used for laboratory scale electrochemical preparations: (a) a beaker-type cell; (b) an H-type cell.

General purpose laboratory scale glass cells are either of the beaker-type (Figure 1.1a) or the H-type (Figure 1.1b). The early pioneers of organic electrochemistry used beaker-type cells, with cylindrical symmetry, and the separator was either a porous porcelain pot or a sintered glass disc [3]. Designs for beaker-type cells in more modern materials have been described [4]. The H-type cell can be designed to use either one or two sintered glass separators [5]. Oxygen must be excluded from the cathode compartment during electrochemical reduction otherwise current is consumed by the reduction of oxygen to water and the highly reactive superoxide anion is generated as an intermediate. A flow of inert gas is maintained in the cathode compartment. It is not essential to exclude oxygen during electrochemical oxidation but usually a flow of inert gas is maintained in the anode compartment so as to dilute any oxygen, which is evolved. A stirring device is necessary to decrease the thickness of the diffusion layer around the working electrode.

The voltage drop across a working electrochemical cell is not uniformly distributed. This is shown schematically in Figure 1.2. A large proportion is due to the electrical resistance of the electrolyte and the separator. This, of course, can be decreased by a suitable cell design. The voltage drop across the working electrode solution interface determines the rate constant for the electrochemical reaction. It is

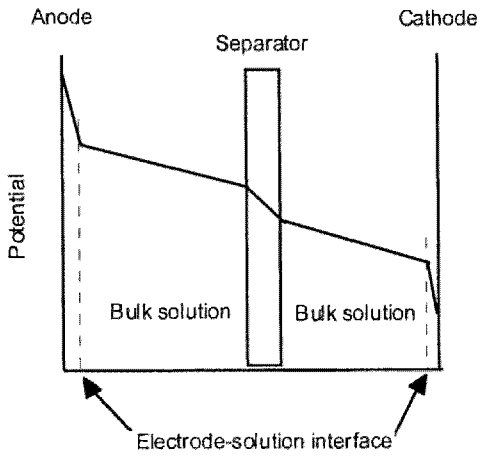


Figure 1.2. Distribution of potential across a working electrochemical cell. The potential drop across the working electrode-solution interface drives the cell reaction.

often advantageous to maintain a constant potential drop across this interface to control the rate of unwanted side reactions. The working potential is measured relative to a reference electrode and probe, placed close to the working electrode surface. An aqueous saturated calomel electrode is the most frequently used reference. The relative potentials of other reference half-cells are given in Table 1.1. The reference electrode dips into a salt bridge containing the electrolyte used in the main electrochemical cell. The salt bridge can be terminated either by a thin Luggin-Harber capillary [6] placed close to the working electrode or by a plug of porous Vycor glass [7] or an inert fibre [8]. For non-aqueous electrochemistry IUPAC recommends the ferrocene-ferricinium couple as an internal reference standard of potential [9]. It is suitable for use in linear sweep and cyclic voltammetry but not for preparative scale experiments. The couple has potentials of +0.69 and +0.72 V *vs.* nhe in acetonitrile and dimethylformamide respectively [10].

There is a potential drop V across the solution between the layer around the working electrode and the tip of the reference probe. This is related to the separation distance d by Equation 1.3 where i is the current flowing through the cell and κ is the specific conductivity of the electrolyte. The reference electrode probe is

placed as close as possible to the working electrode in order to minimise this volt-

$$V = \frac{i}{\kappa} d \qquad \text{Eq.1.3}$$

age drop. The voltage drop is termed the iR-drop and in preparative electrochemistry using currents of 10^{-1} A, or more, it is not negligible [11].

TABLE 1.1

Potentials of some reference electrodes relative to either the standard hydrogen electrode or the saturated calomel electrode. Further data in ref. [17].

Electrochemical cell	Potential / V	Ref.
(Pt)/H_2, H_3O^+ (a = 1) ‖ KCl (satd.) / AgCl (satd.) /Ag	0.199	[12]
(Pt)/H_2, H_3O^+ (a = 1) ‖ KCl (1.0 M) / Hg_2Cl_2 (satd.) / Hg	0.283	[12]
(Pt)/H_2, H_3O^+ (a = 1) ‖ KCl (satd.) / Hg_2Cl_2 (satd.) / Hg	0.244	[12]
Aqueous sce ‖ 0.1 M $NaClO_4$ in CH_3CN ‖ 0.01 M $AgNO_3$ in CH_3CN / Ag	0.253	[13]
Aqueous sce ‖ 0.1 M Et_4NClO_4 ‖ Me_2CHO NaCl(satd.), $CdCl_2$ (satd) / Cd, Hg	-0.737	[14]
Aqueous sce ‖ 0.1 M Bu_4I in 0.1 M Bu_4NI in Me_2NCHO / AgI (sat.) / Ag	-0.32	[15]
Aqueous sce ‖ 0.1 M Et_4NI in Me_2CHO / AgI (satd.) / Ag	-0.638	[16]

The overall rate of an electrochemical reaction is measured by the current flow through the cell. In order to make valid comparisons between different electrode systems, this current is expressed as current density, j, the current per unit area of electrode surface. The current density that can be achieved in an electrochemical cell is dependent on many factors. The rate constant of the initial electron transfer step depends on the working electrode potential. The concentration of the substrate maintained at the electrode surface depends on the diffusion coefficient, which is temperature dependent, and the thickness of the diffusion layer, which depends on the stirring rate. Under experimental conditions, current density is dependent on substrate concentration, stirring rate, temperature and electrode potential.

Conditions of constant potential are frequently employed in laboratory scale experiments. In these experiments, the current through the cell falls with time due to depletion of the substrate. Under conditions of constant diffusion layer thickness, the current i_t at time t is given by Equation 1.4 [17] where D is the diffusion coeffi-

$$i_t = i_0 \exp\left(-\frac{DA}{V\delta} t\right) \qquad \text{Eq.1.4}$$

cient of the active species, A is the electrode area, V is the solution volume and δ is the diffusion layer thickness. Controlled potential bulk electrolysis resembles a first-order reaction in that the current decays exponentially with time, eventually reaching a background level.

Chemical yields from an electrochemical reaction are expressed in the usual way based on the starting material consumed. Current efficiency is determined from the ratio of Coulombs consumed in forming the product to the total number of Coulombs passed through the cell. Side reactions, particularly oxygen or hydrogen evolution, decrease the current efficiency.

On a large scale, it is more difficult to maintain constant electrode potential and conditions of constant current are employed. Under these conditions, as the concentration of the substrate falls, the voltage across the cell rises in order to maintain the imposed reaction rate at the electrode surface. This causes a drop in current efficiency towards the end of the reaction, since as the working electrode potential rises, either oxygen or hydrogen evolution becomes significant.

Electrochemical reactions require a solvent and electrolyte system giving as small a resistance as possible between the anode and cathode. Protic solvents used include alcohol-water and dioxan-water mixtures and the electrolyte may be any soluble salt, an acid or a base. During reaction, protons are consumed at the cathode and generated at the anode so that a buffer will be required to maintain a constant pH. Aprotic solvents are employed for many reactions [18], the most commonly used being acetonitrile for oxidations and dimethylformamide or acetonitrile for reductions. In aprotic solvents, the supporting electrolyte is generally a tetra-alkylammonium fluoroborate or perchlorate [19]. The use of perchlorate salts is discouraged because of the possibility that traces of perchlorate in the final product may cause an explosion.

The designs of some early electrochemical cells for industrial use were based on the beaker-type laboratory cell. One improvement to mass transport conditions was to rotate the working electrode, which decreases the thickness of the diffusion layer [20]. As small a gap as is practical between the working electrode and the counter

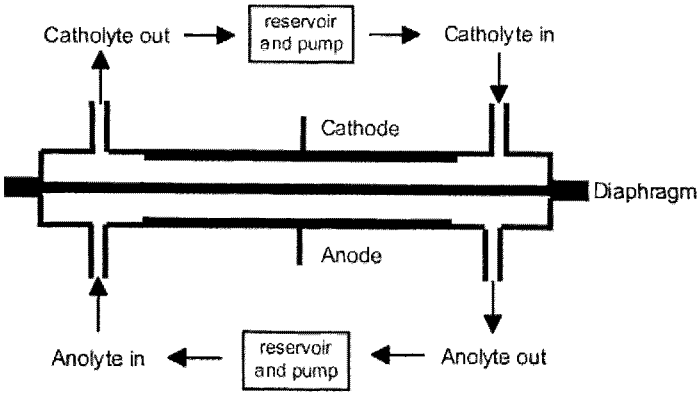


Figure 1.3. The narrow gap electrochemical cell. For large-scale work, several cells are connected in parallel from the same reservoirs.

electrode is necessary to decrease the voltage drop across the whole cell and reduce heating of the electrolyte due to passage of current. Cells with the basic design shown schematically in Figure 1.3 are available commercially. Each compartment contains only a small volume of electrolyte so both the anode and cathode compartments are connected to larger volumes of solutions, which are pumped continuously around the cell. Electrolyte flow also decreases the thickness of the diffusion layer. Cells can be connected in parallel to give a large overall electrode area. Starting from this basic design concept, many cells have been constructed to improve current efficiency in a particular reaction and some of these are described later.

Anode and Cathode Materials

Working electrode materials are selected to provide good electron transfer properties towards the substrate while showing high activation energy for electron transfer in the principal competing reaction. The most significant competing reactions in the presence of water are evolution of oxygen at the anode and hydrogen at the cathode. Accessible electrode potential ranges for some working electrode, solvent combinations are given in Table 1.2. The oxygen and hydrogen evolution reactions occur in several steps involving both bond cleavage and bond formation processes. At many electrode surfaces each reaction requires a potential substantially removed from the equilibrium reaction potential to drive the process at a significant rate. This difference between a working potential and the equilibrium potential is called the overpotential.

TABLE 1.2
Useable electrode potential range for some electrode-solution combinations

Electrode material	Solvent	Electrolyte $LiClO_4$		Electrolyte Et_4NClO_4	
		Cathodic V *vs.* sce	Anodic V *vs.* sce	Cathodic V *vs.* sce	Anodic V *vs.* sce
Pt	H_2O	-1.1	+1.8	-1.1	+1.8
Pt	CH_3CN	-3.2	+2.7	-3.0	+2.7
Pt	Me_2CHO	-3.3	+1.5	-2.7	+1.8
Hg	H_2O	-2.3	+0.4	-2.7	+0.4
Hg	CH_3CN	-1.8	+0.8	-2.8	+0.8
Hg	Me_2CHO	-1.8	+0.4	-2.8	+0.2
C	H_2O	-1.0	+1.0	-2.8	

Smooth platinum, lead dioxide and graphite are anode materials commonly used in electrooxidation processes. All show large overpotentials for oxygen evolution in aqueous solution. Platinum coated titanium is available as an alternative to sheet platinum metal. Stable surfaces of lead dioxide are prepared by electrolytic oxidation of sheet lead in dilute sulphuric acid and can be used in the presence of sulphuric acid as electrolyte. Lead dioxide may also be electroplated onto titanium anodes from lead(II) nitrate solution to form a non-porous layer which can then be used in other electrolyte solutions [21].

Mercury, lead, cadmium and graphite are commonly used cathode materials showing large overpotentials for hydrogen evolution in aqueous solution. Liquid mercury exhibits a clean surface and is very convenient for small-scale laboratory use. Sheet lead has to be degreased and the surface can be activated in an electrochemical oxidation, reduction cycle [3, 22]. Cadmium surfaces are conveniently prepared by plating from aqueous cadmium(II) solutions on a steel cathode.

Synthetic graphite is available in many forms for use as electrode material. A polycrystalline pyrolytic graphite is prepared by thermal decomposition of hydrocarbon vapours on a hot surface. It has the carbon ring planes oriented to a high degree parallel with the original surface for deposition. Less well oriented graphites with the crystalline phase embedded in a non-porous but amorphous carbon are prepared by the pyrolysis of carbonaceous materials. This type of material includes carbon-fibre, which is woven into a carbon felt, and a non-porous glassy carbon. Glassy carbon can be fabricated into plate form or as a solidified foam, termed reticulated carbon, with a large surface area and allowing free flow of electrolyte. Reticulated carbon and carbon felt allow electrochemical transformation at low current density to be completed on a shorter time scale because of their large surface area. This is important when further chemical reactions of the product can occur during the electrochemical process [23].

Surfaces of synthetic diamond, doped with boron, are electrically conducting and show promise as very inert electrode materials [24]. Boron carbide (B_4C) has been used as an anode material but this cannot be conveniently prepared with a large surface area [25].

Platinum and carbon are frequently used as counter electrode materials for both anode and cathode. Platinum is resistant to corrosion while carbon is cheap and can be discarded after use. Nickel is a suitable counter cathode material in aqueous solution because of the low overpotential for hydrogen evolution. Titanium coated with platinum and then over coated with ruthenium dioxide is a stable counter anode material with a low overpotential for oxygen evolution.

The separator is often the weakest component in any electrochemical cell. There are also difficulties in employing ion-exchange diaphragms in aprotic media. Particularly with large industrial cells, it is advantageous to devise reaction conditions that allow the use of an undivided cell. One solution to these problems for an electrochemical reduction process employs a sacrificial anode of magnesium, alumin-

ium or zinc in a single compartment cell when the most favoured anode reaction becomes oxidation of the metal to an anion [26, 27]. Zinc and magnesium ions formed in this way are beneficial to cathodic reactions which involve alkyl and aryl halides (p. 134) [28, 29]. On a laboratory scale, the sacrificial anode is a rod of metal concentric with a cylindrical working cathode. Tetraethylammonium fluoride can be added to the electrolyte to precipitate magnesium ions as the fluoride [30]. A V-shaped narrow gap cell (Figure 1.4) has been devised for use on an industrial scale using a magnesium sacrificial anode which fits into a stainless steel working cathode [31]. The combination of a working magnesium cathode and a sacrificial magnesium anode is used for the reduction of functional groups such as carboxylic

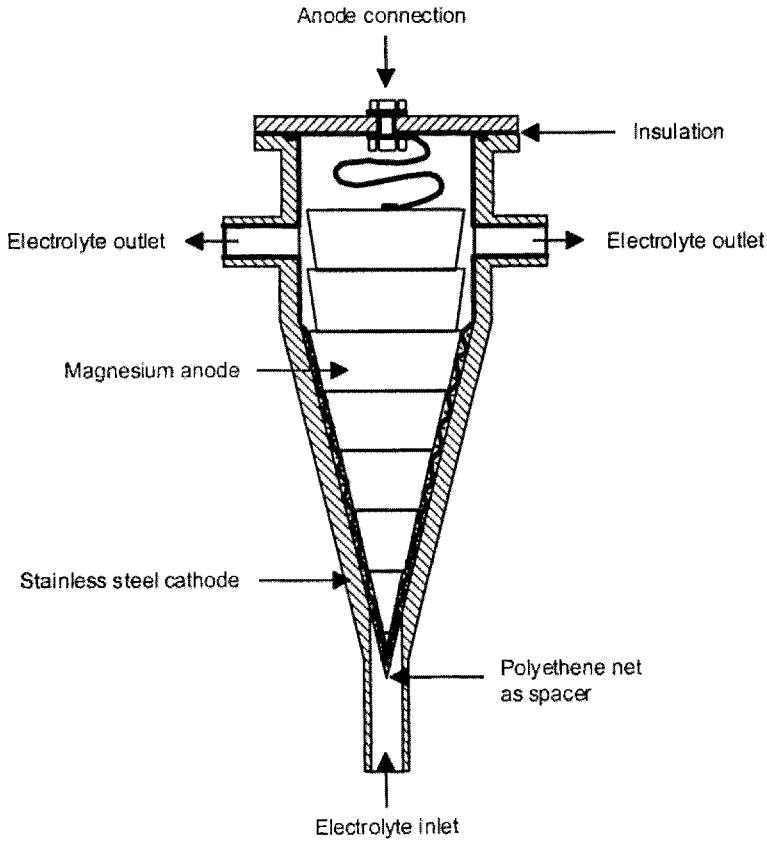


Figure 1.4. An undivided electrochemical cell fitted with a sacrificial magnesium anode. Diagram adapted from Ref. [31].

ester and the benzene ring requiring very negative cathode potentials. This combination is used in a single compartment cell with *tert.*-butanol as solvent [32,33].

Anode and cathode materials, including platinum, corrode slowly. One advantage of this corrosion is that it maintains a fresh active electrode surface. Fouling of the electrode surface by polymeric deposits can be a problem because this blocks the electron transport process. In the majority of electroorganic reactions, the working electrode is an inert material. Electron transfer generates a radical-ion species with sufficient lifetime to migrate away from the electrode surface. Further reactions then generate more reactive free radical species and these undergo terminal reactions before they are able to react with the electrode surface. Reactions of σ-type free radicals with metals including mercury and lead are well known [34]. In a few electrochemical reactions, the initial electron transfer step does generate a σ–radical at the electrode surface and organometallic compounds are formed. Examples include the reduction of ketones in acid solution at mercury, lead or cadmium (Chapter 8) and the reduction of alkyl halides at mercury (Chapter 4).

Kinetics of Electron Transfer

Electrons are transferred singly to any species in solution and not in pairs. Organic electrochemical reactions therefore involve radical intermediates. Electron transfer between the electrode and a π-system, leads to the formation of a radical-ion. Arenes, for example are oxidised to a radical-cation and reduced to a radical-anion and in both of these intermediates the free electron is delocalised along the π–system. Under some conditions, where the intermediate has sufficient lifetime, these electron transfer steps are reversible and a standard electrode potential for the process can be measured. The final products from an electrochemical reaction result from a cascade of chemical and electron transfer steps.

Knowledge of the variation of electron transfer rate with electrode potential is important for the understanding of electrochemical reactions. The first experiments in this area were prompted by the observation that nitrobenzenes and aromatic carbonyl compounds are reduced in acid solution with little competition from the hydrogen evolution process. This is the case even though the electrode potential is more negative than the value calculated for the reversible evolution of hydrogen in the same solution. The kinetics of hydrogen evolution have been examined in detail.

From experiments on the evolution of hydrogen at various metal cathodes in dilute sulphuric acid, Tafel in 1905 observed that an extra driving force was required to cause electrolysis to proceed at appreciable rates, expressed by the current density j [35]. The overpotential η is the difference between the working electrode potential and the reversible reaction potential and was related to current

$$\eta = a + b\log(j) \qquad \text{Eq.1.5}$$

density by Equation 1.5 where a and b are constants for a particular metal. The value of a varied widely with the metal used and was very small for mercury and lead. The value of b is proportional to absolute temperature and was found to be approximately 2.3x2RT/F for all the metals studied. Recent determinations of the Tafel constants are listed in Table 1.2. Mercury, lead and cadmium are commonly used as cathode materials in the electrochemical reduction of organic compounds. These metals adsorb hydrogen atoms very weakly and the rate-controlling step for hydrogen evolution is the formation of this adsorbed hydrogen.

TABLE 1.3
Constants in the Tafel Equation 1.5 for evolution of hydrogen. Units of current density are A cm^{-2}. Ref. [36].

Cathode material	a / V	b / V	$-\log(j_o/A\ cm^{-2})$
Pb	1.52 – 1.56	0.11 – 0.12	12.67 – 14.18
Hg	1.415	0.116	12.20
Cd	1.40 – 1.45	0.12 – 0.13	10.77 –12.08
Sn	1.25	0.12	10.77 – 12.08
Zn	1.24	1.12	10.33
Cu	0.77 – 0.82	0.10 – 0.12	6.15 – 8.20
Fe	0.66 – 0.72	0.12 – 0.13	5.08 – 6.00
Ni	0.55 – 0.72	0.10 – 0.14	3.93 – 7.20
Pt	0.25 – 0.35	0.10 – 0.14	1.79 – 3.50

Butler in 1924 developed the idea that the Nernst equilibrium potential for an electrochemical process is the potential at which the forward and back reactions proceed at the same rate [37]. Following this, Bowden and Rideal [38] introduced the term j_o as the value of the forward and back current density at the reversible Nernst potential and wrote the Tafel equation in the form of Equation 1.6.

$$\eta = b(\log j - \log j_o) \qquad \text{Eq.1.6}$$

The charge transfer coefficient, α, was introduced by Erdey-Gruz and Volmer in 1930 as being the proportion of the overpotential assisting electron transfer in the

$$\log(j) = \log(j_o) - \frac{\alpha\eta F}{RT} \qquad \text{Eq.1.7}$$

$$j = -nFk^{\circ}C\exp\left(-\frac{\alpha\eta F}{RT}\right) \qquad \text{Eq.1.8}$$

rate determining stage. They replaced Tafel's constant b by the expression $RT/\alpha F$.

Variation of the forward reaction rate for the reduction of protons then takes the form of Equation 1.7 or Equation 1.8. Here, n is the number of electrons transferred in the overall reaction, k° is the rate constant at the equilibrium potential and C the reactant concentration.

For a general electrochemical process:

$$Ox + ne \underset{k_{ox}}{\overset{k_{red}}{\rightleftharpoons}} Red$$

when the potential is disturbed from the equilibrium value, the potential-dependent

$$j = nF\,k^\circ\,C_{red}\exp\left(\frac{\beta\eta F}{RT}\right) - nF\,k^\circ\,C_{ox}\exp\left(-\frac{\alpha\eta F}{RT}\right) \qquad \text{Eq.1.9}$$

rate-equation takes the form of Equation 1.9 where β is the charge transfer coefficient for the oxidation step. Equation 1.9 is referred to as the Butler-Volmer equation for electrochemical kinetics. Since at the equlibrium potential there is no net current flow, it follows that the two transfer coefficients are related by Equation 1.10.

$$\alpha = 1 - \beta \qquad \text{Eq. 1.10}$$

Equation 1.7 for the reduction of protons at a mercury surface in dilute sulphuric acid is followed with a high degree of accuracy over the range $-9 < \log|j| < -2$ [39]. A schematic Tafel plot is shown in Figure 1.5. At large values of the overpotential, one reaction dominates and the polarization curve shows linear behaviour. At low values of the overpotential, both the forward and back reactions are important in determining the overall current density and the polarization curve is no longer linear.

Linear kinetic behaviour according to the Tafel equation indicates a linear free energy relationship between activation energy and driving force for the reaction and the value of α is defined by Equation 1.11. Methods based on polarography or linear sweep voltammetry are available for the determination of α in the electron

$$\frac{d(\log|j|)}{dE} = -\frac{\alpha F}{2.3\,RT} \qquad \text{Eq.1.11}$$

transfer reactions of organic compounds. In many cases, including the reduction of nitrocompounds in aprotic media and the reduction of benzaldehyde in aqueous alkaline solution, the value of α is dependent on potential and Butler-Volmer kinetics are not observed [40]. An understanding of this behaviour and also the examples where α is independent of potential, is achieved in the Marcus theory of electron transfer kinetics [41, 42].

In polar media, electron transfer is associated with a marked change in the solvation shell of the species concerned. This strong solvation interaction between ions and solvent dipoles mediates electron transfer between the electrode and an electroactive species, and between two components of a redox system. Fluctuations in the solvent shell change the potential energy of the reactant and the product.

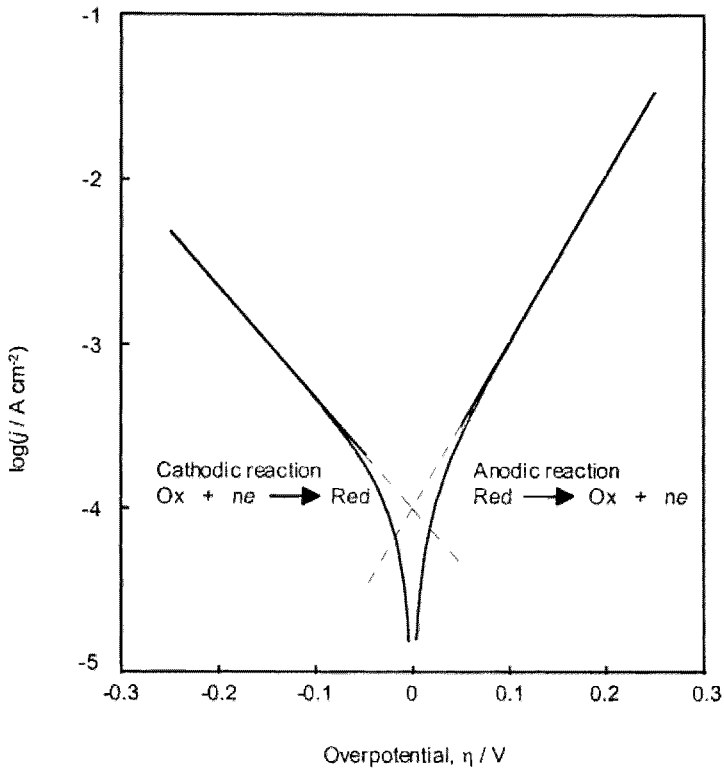


Figure1.5. Tafel diagram for the cathodic and anodic processes with $\alpha = 0.4$ and $j_o = 10^{-4}$ A cm^{-2}. Oxidised and reduced species are in equal concentrations.

Marcus theory assumes that these solvent shells vibrate harmonically and with identical frequency so that the potential energies of both components in a redox couple can be represented by identical but mutually shifted parabolae. Only electrons from the Fermi level in the electrode and from the ground state of the redox system in solution participate in the redox process.

The potential energy profile for an electrode reaction is shown in Figure 1.6. The reactant curve denotes the initial state of the system. The product curve denotes the final state of the system where the energy minimum is shifted by a value

corresponding to the difference ΔE_e between the initial and final energies of the

$$\Delta E_e = F\eta \qquad \text{Eq.1.12}$$

electronic system. This dependes on the applied electrode overpotential (Equation 1.12). The reaction coordinate represents solvent fluctuations. The intercept of the two curves corresponds to the transition-state for electron transfer and the coordinates of this point can be found by algebraic manipulation of the equations for the two curves. Equating the activation free energy, $\Delta G^{\ddagger}$ with the energy required to reach this point leads to Equation 1.13, where E_r is termed the re-organisation energy of the system and is not dependent on ΔE_e.

$$\Delta G^{\ddagger} = \frac{(E_r + \Delta E_e)^2}{4E_r} \qquad \text{Eq.1.13}$$

At high inert electrolyte concentration, when the effect of the electrical double

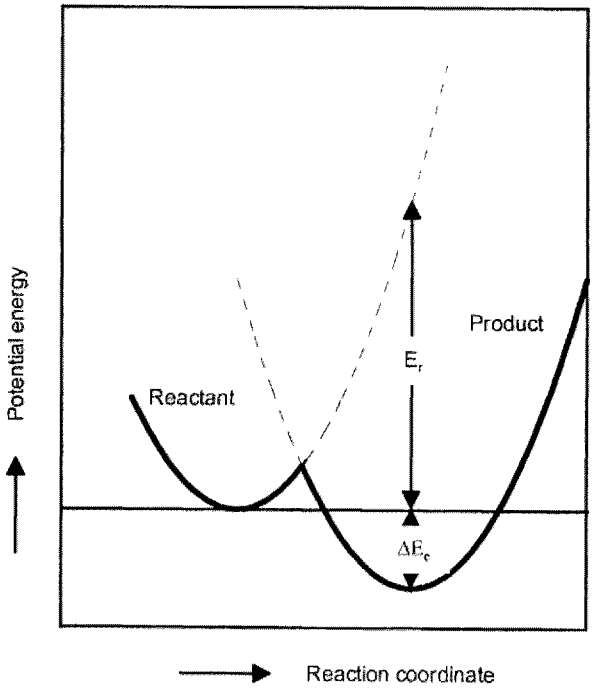


Figure 1.6. Dependence of the potential energy on the reaction coordinate during electron transfer. ΔE_e is the change in electronic energy from the ground state of the system and E_r the reorganization energy.

layer can be neglected, the rate constant k for a cathodic reaction is given approximately by Equation 1.14, where r_s is the mean of the radii of the oxidised and re-

$$k = r_s \rho \varpi \kappa \exp\left(-\frac{\Delta G^{\ddagger}}{RT}\right) \qquad \text{Eq.1.14}$$

duced forms of the species, ρ is the number of electronic states per unit area of the conductivity band of the electrode, ω is the vibrational frequency associated with the solvent sheath and κ is the transmission coefficient with a value of unity for an adiabatic process. This leads to Equation 1.15 for the variation of j with overpotential for a cathodic reaction and Equation 1.16 expresses the charge transfer coefficient as defined by Equation 1.11.

$$|j| = r_s \rho \varpi \kappa \exp\left[-\frac{(E_r + F\eta)^2}{4RTE_r}\right] . C_{ox} \qquad \text{Eq.1.15}$$

$$\alpha = \frac{1}{2} + \frac{F\eta}{2E_r} \qquad \text{Eq.1.16}$$

The Marcus approach predicts a parabolic dependence of log(k) and log $|j|$ on the overpotential together with a linear dependence of the transfer coefficient on overpotential. Values of α for an electron transfer process can be obtained from linear sweep voltammetry data (p. 17) and for a simple, single electron transfer process the variation with potential is as predicted by the Marcus approach [40]. Even when the overall process is chemically irreversible, the initial electron transfer step can be reversible and rate controlling. Where values of α show a linear dependence on electrode potential, extrapolation will give the potential at which $\alpha = 0.5$ [43]. According to the theory presented above, the overpotential for the process at this point is zero so this extrapolated potential is the standard electrode potential for the electron transfer process. The value of $\alpha = 0.5$, at the standard potential, is associated with the assumption of a single harmonic oscillator with the same frequency in the initial and final states of the electrode reaction.

For some important irreversible electrochemical reactions, electron transfer is concerted with a bond cleavage step. This is the case with the hydrogen evolution process where electron transfer to the hydroxonium ion is concerted with hydrogen-oxygen bond cleavage. In the reduction of alkyl halides, electron transfer is concerted with hydrogen-halogen bond cleavage. These reactions are controlled by the bond stretching process and not by solvent reorganization alone. They show Tafel behaviour with a linear dependence of log(k) on overpotential and a transfer coefficient independent of potential.

Analytical and Spectroscopic Techniques

Examination of the behaviour of a dilute solution of the substrate at a small electrode is a preliminary step towards electrochemical transformation of an organic compound. The electrode potential is swept in a linear fashion and the current recorded. This experiment shows the potential range where the substrate is electroactive and information about the mechanism of the electrochemical process can be deduced from the shape of the voltammetric response curve [44]. Substrate concentrations of the order of 10^{-3} molar are used with electrodes of area 0.2 cm^2 or less and a supporting electrolyte concentration around 0.1 molar. As the electrode potential is swept through the electroactive region, a current response of the order of microamperes is seen. The response rises and eventually reaches a maximum value. At such low substrate concentration, the rate of the surface electron transfer process eventually becomes limited by the rate of diffusion of substrate towards the electrode. The counter electrode is placed in the same reaction vessel. At these low concentrations, products formed at the counter electrode do not interfere with the working electrode process. The potential of the working electrode is controlled relative to a reference electrode. For most work, even in aprotic solvents, the reference electrode is the aqueous saturated calomel electrode. Quoted reaction potentials then include the liquid junction potential. A reference electrode, which uses the same solvent as the main electrochemical cell, is used when mechanistic conclusions are to be drawn from the experimental results.

Two classes of voltammetry experiment are particularly useful for examining the electrochemical behaviour of a substrate. In the first, a controlled relative movement of the electrode and solution is maintained. Polarography at a dropping mercury electrode and voltammetry at the rotating disc electrode belong to this category. In the second, the electrode and solution are maintained still. The technique of cyclic voltammetry belongs to this second category.

Polarography at a dropping mercury electrode has the longest history of these techniques. Heyrovsky developed it around 1922 [45]. The working electrode is a mercury drop formed by allowing mercury to flow through a capillary under constant pressure. In modern equipment the drop is detached mechanically after a fixed time interval. The current due to any electrochemical reaction increases with the drop area and falls to zero as the drop is detached (Figure 1.7). Older equipment used a damped galvanometer to measure the current flow and afforded a graph of current versus potential with a rhythmic wave pattern due to the periodic drop fall. Modern equipment senses the current for a defined short period before the drop fall. A slow potential sweep is applied to the dropping mercury electrode. A curve of current versus electrode potential is thus built up from a series of observations, each at a clean mercury surface of always the same area. Reduction processes can be examined but oxidative processes are generally not accessible at the mercury surface because the metal itself is oxidises to mercury(I).

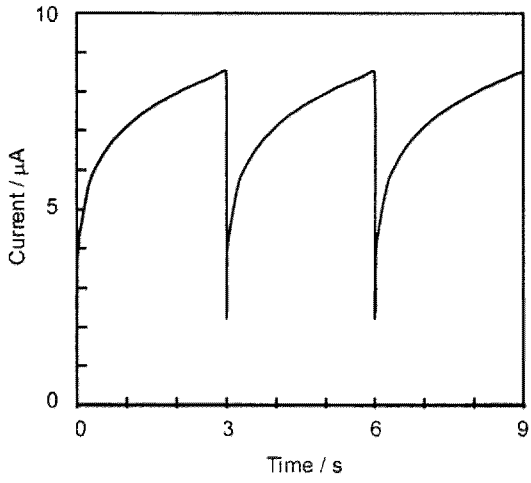


Figure 1.7. Current versus time profile for an electrochemical reaction under polarographic conditions at a dropping mercury electrode, drop time 3 s.

Following historic precedence, the polarogram is displayed as in Figure 1.8 with more negative potential to the right and higher negative reducing currents upwards. The diffusion limited plateau current i_d is proportional to the concentration of the electroactive substrate. The half-wave potential $E_{½}$, defined as the potential where $i = i_d/2$, is characteristic of the electrochemical reaction. Where two or more consecutive polarographic steps occur at different potentials, the currents due to each step are additive. A slow increase in the background current with potential is observed due to charging of the mercury-solution interface, which acts like a condenser. The potential window for observations with polarography is limited on the anodic side by the oxidation of mercury and on the cathodic side by the reduction of ions in the supporting electrolyte. Commonly used solvent supporting electrolyte systems are aqueous buffers with added ethanol or an aprotic solvent such as dimethylformamide or acetonitrile and a tetraalkylammonium salt.

The current density during polarography is of the order of 10^{-6} A cm^{-2} and for electrochemical reactions where j_o is large, equlibrium is established between the oxidised and reduced forms of the substrate, at the potential of the electrode surface according to the Nernst equation.

$$Ox + ne \rightleftharpoons Red$$

In these cases the polarographic wave follows equation 1.17 where κ_{ox} and κ_{red} are the mass transfer coefficients of the two species. Usually κ_{ox} and κ_{red} are approximately equal so that for a reversible polarographic wave, the half-wave potential is

equal to the redox potential of the substrate relative to the reference electrode used. The plot of $\ln[(i_d - i)/i]$ versus E is linear with a slope of nF/RT.

$$E = E^{\circ} + \frac{RT}{nF}\ln\left(\frac{\kappa_{red}}{\kappa_{ox}}\right) + \frac{RT}{nF}\ln\left(\frac{i_d - i}{i}\right) \qquad \text{Eq.1.17}$$

In an irreversible reaction, the rate controlling process is usually a single electron transfer step with a rate determined by Equation 1.8. The corresponding polarographic wave is then described by Equation 1.18 where k_{conv} is the rate constant for electron transfer at the potential of the reference electrode. For an irreversible

$$E = E^{\circ} + \frac{RT}{\alpha F}\ln\left(\frac{k_{conv}}{\kappa_{ox}}\right) + \frac{RT}{\alpha F}\ln\left(\frac{i_d - i}{i}\right) \qquad \text{Eq.1.18}$$

process, the plot of $\ln[(i_d - i)/i]$ versus E now has a slope of $\alpha F/RT$ and the value of α at a given potential can be determined by constructing tangents to the curve. This plot is linear only when α is independent of potential. The mass transfer coefficient is dependent on the rate at which the mercury drop expands into the solution so

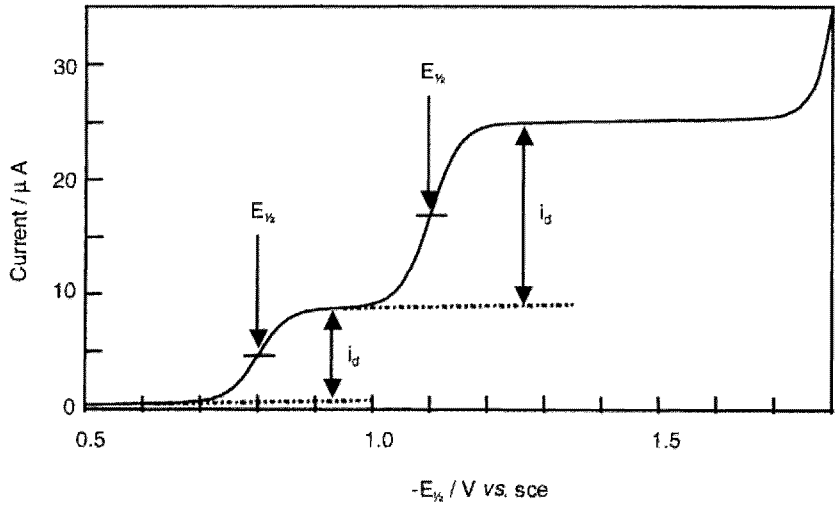


Figure 1.8. Polarogram from a substrate showing two polarographic waves. The wave at −1.8 V is due to reduction of ions in the supporting electrolyte.

that the value of $E_{½}$ for an irreversible reaction depends on the characteristics of the dropping mercury electrode.

The rotating disc electrode is constructed from a solid material, usually glassy carbon, platinum or gold. It is rotated at constant speed to maintain the hydrodynamic characteristics of the electrode-solution interface. The counter electrode and reference electrode are both stationary. A slow linear potential sweep is applied and the current response registered. Both oxidation and reduction processes can be examined. The curve of current response versus electrode potential is equivalent to a polarographic wave. The plateau current is proportional to substrate concentration and also depends on the rotation speed, which governs the substrate mass transport coefficient. The current-voltage response for a reversible process follows Equation 1.17. For an irreversible process this follows Equation 1.18 where the mass transfer coefficient is proportional to the square root of the disc rotation speed.

Voltammetry experiments in the second class use a stationary electrode-solution interface. In the course of the experiment, a diffusion layer is allowed to grow around the working electrode without disturbance. The working electrode can be a hanging mercury drop or a stationary disc of carbon, platinum or gold. There are practical advantages in making this disc as small as is possible which have led to the development of ultramicro electrodes. The currents passed at an ultramicro electrode are so low that a potential drop due to resistance of the solution can be neglected, which greatly simplifies control of electrode potential.

The technique of cyclic voltammetry is conveniently applied at these stationary electrodes [46]. The electrode potential is scanned with time between two limits in a triangular fashion depicted in Figure 1.9. The scan rate can be between mV s^{-1}

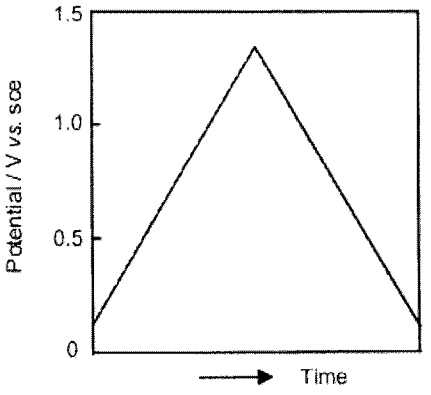


Figure 1.9. Typical potential-time sweep applied during cyclic voltammetry. This was used to generate the data for Figure 1.10.

and kV s^{-1}. The voltammetry response is plotted according to rational convention with anodic potential to the right and anodic current upwards [47]. This is the opposite of the convention used to plot polarographic curves. For a reversible process the cyclic voltammogram has the appearance of Figure 1.10a, which illustrates oxidation of a substrate. As the potential is swept in a positive direction and oxidation of the substrate commences, the layer around the electrode becomes depleted and substrate diffuses from the bulk of the solution. The diffusion layer around the

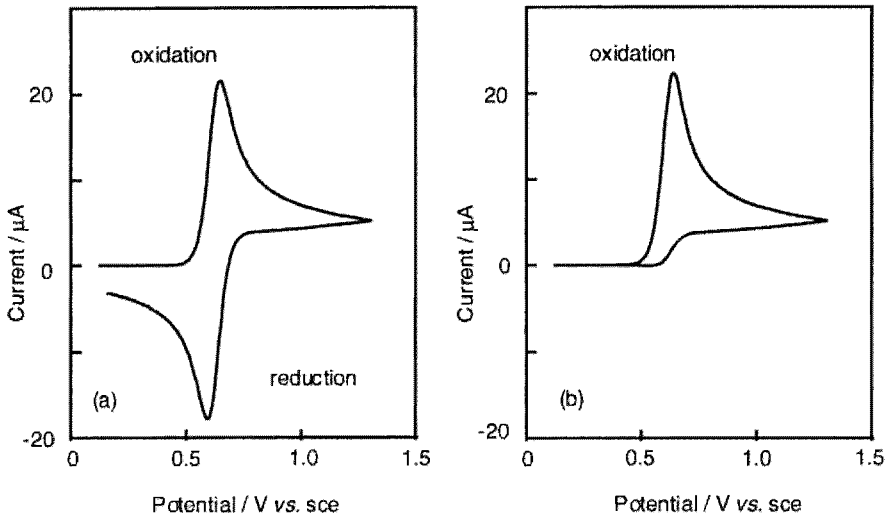


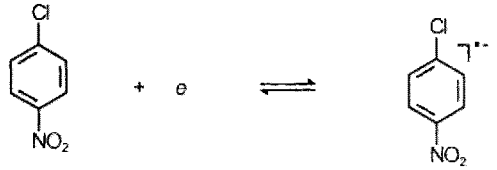
Figure 1.10. Current-potential responses from cyclic voltammetry of an oxidisable substrate: (a) reversible oxidation with $E^{\circ} = 0.62$ V *vs.* sce; (b) irreversible oxidation process.

electrode eventually becomes so depleted of substrate that the current flow passes through a maximum and the falls to a value which can be sustained by diffusion of substrate from the bulk of the solution. Within the diffusion layer, the substrate is replaced by oxidation product. Upon reversal of the direction of potential sweep, this accumulated oxidation product is reduced back to the substrate. A peak in the negative reduction current is seen as the concentration of the oxidised substrate becomes depleted. A small additional current is observed as a consequence of charging the electrode-solution interface like a condenser. The electrochemical reactivity of the substrate is characterised by the anodic peak potential E_{pa} for an oxidation process and the cathodic peak potential E_{pc} for a reduction process. During a reversible process, which has a large value for the exchange current density, Nernstian equlibrium between the reduced and oxidised forms is maintained at the potential of the electrode surface. In these cases, the peak potentials are independ-

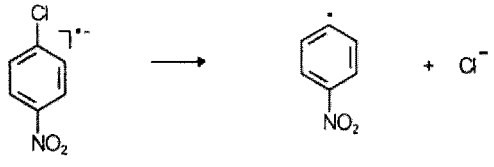
ent of scan rate and the redox potential for the couple, relative to the reference electrode used, is the average of E_{pa} and E_{pc}. The anodic peak current i_{pa} and the cathodic peak current i_{pc} are proportional to the concentration of substrate and i_{pa}/i_{pc} is approximately one. Currents are proportional to the square root of the scan rate.

The voltammogram for an irreversible oxidation process is shown in Figure 1.10b. The anodic peak is visible but there is no corresponding cathodic peak and now the peak potential depends on scan rate.

Cyclic voltammetry is useful in defining the electroactive region of a substrate prior to preparative scale reaction. The technique has also been used extensively for the elucidation of reaction mechanism in electrochemistry [48, 49]. A simple example of this application is in the reduction of aryl halides in aprotic solvents. Overall the process is irreversible and results in the replacement of halogen by hydrogen. The first step in the process involves addition of an electron to the substrate to form a radical-anion (Equation 1.19) and this stage is reversible. The next step is cleavage of the carbon-halogen bond (Equation 1.20) which is an irreversible process. Subsequent steps lead to replacement of the halogen substituent by hydrogen. At sufficiently fast scan rates only the reversible reaction of Equation 1.20 can be detected and a cyclic voltammogram with related cathodic and anodic peaks is observed. As the scan rate is decreased, the anodic peak height decreases because, during the time period of the scan, decomposition of the radical-anion



Eq. 1.19



Eq. 1.20

according to Equation 1.20 becomes important. Finally at the slowest scan rates, reduction of the substrate becomes irreversible and a new reversible process is detected due to reduction of the nitrobenzene produced. The rate constant for Equation 1.20 is deduced from the experimental data [50]. In the general case, the sweep rate applied during cyclic voltammetry is adjusted so that the influence of the individual reaction steps causes a significant change in the shape of the current-time response. A reaction mechanism must then be proposed to account for these changes.

The validity of a reaction mechanism is tested by digital simulation of the cyclic voltammograms [51, 52] obtained under a variety of scan rates and substrate concentrations. Simultaneous partial differential equations are written to describe electron transfer between the electrode and the substrate and changes in concentration due to chemical reaction of intermediates. Further differential equations account for the diffusion of substrate and reaction intermediates under a concentration gradient. In order to simulate the reaction steps, the solution is divided into compartments separated by a distance Δx sufficiently small that $\Delta c/\Delta x$ can be equated with $\partial c/\partial x$ where Δc is a concentration difference between two adjacent compartments. Concentration changes in compartments are then calculated at successive intervals of time Δt, sufficiently small that $\Delta c/\Delta t$ can be equated with $\partial c/\partial t$. During each time interval the electrode potential changes and changes in concentration in the first compartment occur due to the passage of electrons. In all compartments changes in concentration occur due to chemical reaction and due to diffusion of species under concentration gradients. An iterative technique allows the voltammogram to be constructed. Changes are made to reaction rate constants to achieve the best fit with experimental voltammograms.

The first intermediate to be generated from a conjugated system by electron transfer is the radical-cation by oxidation or the radical-anion by reduction. Spectroscopic techniques have been extensively employed to demonstrate the existance of these often short-lived intermediates. The life-times of these intermediates are longer in aprotic solvents and in the absence of nucleophiles and electrophiles. Electron spin resonance spectroscopy is useful for characterization of the free electron distribution in the radical-ion [53]. The electrochemical cell is placed within the resonance cavity of an esr spectrometer. This cell must be thin in order to decrease the loss of power due to absorption by the solvent and electrolyte. A steady state concentration of the radical-ion species is generated by application of a suitable working electrode potential so that this unpaired electron species can be characterised. The properties of radical-ions derived from different classes of conjugated substrates are discussed in appropriate chapters.

Reactive intermediates can be characterised through their uv-visible spectra by carrying out the electrochemical experiment in an optically transparent thin-layer electrode (OTTLE) [54, 55]. In its basic design, this electrochemical cell has for the working volume a narrow gap between quartz plates. This gap contains the working electrode, made from either a semi-transparent mini-grid constructed from gold wire, or a semi-transparent vapour-deposited layer of doped tin oxide or a metal such as platinum and gold. The cell dips into a larger bulk of solution containing the counter electrode and the reference electrode. Light shines through the arrangement of quartz plates and working electrode and spectra are taken with a diode-array spectrometer. The cell design allows complete electrolysis in seconds of the working electrolye volume trapped between the quartz plates. Intermediates can be detected and in some cases their decay followed by spectroscopy. Spectra of

radical-cations and radical-anions have been obtained in this way [56, 57] and many examples are noted in later chapters.

Pulse Radiolysis

Pulse radiolysis using a high energy radiation source offers a way by which the first electron transfer step in an electrochemical reaction can be made to proceed in homogeneous solution at the diffusion controlled rate limit. Radical-anions as well as radical-cations can be generated by the appropriate choice of reaction conditions. The kinetics of the decay of this reactive species can then be followed in a direct manner [58, 59], usually by monitoring changes in the uv-spectrum of the solution. The technique complements cyclic voltammetry by allowing faster reaction rate constants to be determined, including diffusion controlled rate constants. The most convenient source of high-energy radiation is a mono-energetic pulse obtained from either a Van der Graaff generator or a Lineac Ion Accelerator.

A solution of the substrate is subjected to a microsecond or nanosecond pulse of high-energy radiation. Energy is transferred to the solvent molecules causing the ejection of electrons of lower energy which rapidly lose their excess energy and form solvated electrons. An equal number of positive ions must be formed and these decay to give solvated protons. Radicals also form by homolytic bond cleavage processes of the solvent molecules. These species are all formed initially along the tracks of high-energy particles in regions called spurs. Some of the species combine with each other within the spurs and the rest diffuse into the bulk of the solvent to form a homogeneous solution.

Many pulse radiolysis experiments have use water as the solvent. Here, the solvated electron, solvated protons, hydrogen atoms and hydroxyl radicals are generated. Isopropanol and *tert.*-butanol can be added to remove selectively hydrogen atoms and hydroxyl radicals giving radicals which are inert under the reaction conditions. The hydrated electron itself is specifically scavenged by nitrous oxide, which does not react with hydroxyl radicals and hydrogen atoms. Sodium formate scavenges both hydroxyl radicals and hydrogen atoms to form the carbon dioxide radical-anion. Using these reagents in combination, it is possible to generate solutions containing only the solvated electron, carbon dioxide radical-anion or the 2-hydroxypropan-2-yl radical, all of which are powerful reducing agents operating by electron-transfer.

The most powerful reducing agent is the solvated electron with a reduction potential of –3.05 V *vs.* sce [60]. The LUMO of ethene is too high in energy to permit electron attachment to this molecule but introduction of an electron withdrawing substituent such as carbonyl or nitrile lowers the energy of the LUMO sufficiently that the rate of electron attachment becomes close to diffusion control [61]. Benzene reacts with solvated electrons more slowly than the diffusion controlled limit

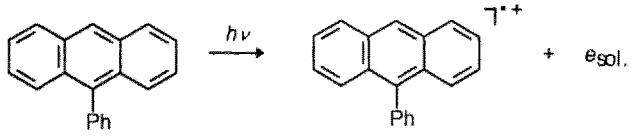
but the rate of reaction of benzene derivatives is raised to near diffusion control by the introduction of electron withdrawing substituents [62].

Peroxydisulphate ions are reduced by solvated electrons to give the sulphate radical-anion which is a powerful oxidising agent, functioning by single electron transfer to form sulphate dianion. Thus irradiation of solutions containing peroxydisulphate and an alkyl or alkoxybenzene gives the substrate radical-cation in a diffusion-controlled reaction [63].

High-energy irradiation of the lower alcohols gives solvated electrons, solvated protons and radicals [64]. Solvated electrons are also obtained by irradiation of the aprotic amide solvents [65] frequently used in organic electrochemistry and by the irradiation of hexamethylphosphoric triamide [66]. N-Methylpyrrolidone which has properties similar to dimethylformamide, is a useful solvent for the generation of solvated electrons because the reaction between electrons and protons is relatively slower than with dimethylformamide [67].

Pulse radiolysis experiments, which generate the solvated electron, also generate an equivalent amount of solvated protons. These two species react at the diffusion-controlled rate to generate hydrogen atoms. Because these two species are present in very low concentration, preferential reaction of the solvated electron occurs with an organic substrate in concentrations around 10^{-3} molar. Electron attachment to the substrate proceeds at almost the diffusion controlled rate. Decay of the electron attachment product is then followed by uv-spectroscopy. First order rate constants for the decay of radical-anions can be determined in the range of 10^{1} to 10^{7} s^{-1}. For faster reactions, electron attachment becomes the rate-limiting step. Bimolecular reactions of radical-ions are usually examined as pseudo-first order reactions by addition of an excess of the second reagent. The maximum lifetime of a species formed on electron attachment to an organic substrate is determined by the rate of the second order reaction with solvated protons generated during the radiolysis.

A laser flash technique can be used to generate radical-cations and follow the kinetics of their reaction with nucleophiles [68, 69]. The experimental technique



Eq. 1.21

resembles that of pulse-radiolysis. Anthracenes, for example, are photoionized by nanosecond laser flash in acetonitrile (Equation 1.21). When the concentration of radical-anions is kept very low, the rate of the diffusion controlled back reduction is decreased so that reaction of the radical-anion with an added nucleophile can be followed.

References

[1] P. W. Staal, *US* 3424659 (1969); *Chem. Abstr.*, 1969, **71**, 9128.
[2] G. Richter, *Chem. Ing. Tech.*, 1975, **47**, 909.
[3] J. Tafel, *Ber.*, 1900, **33**, 2209
[4] C. Moinet and D. Peltier, *Bull. Soc. chim. France.*, 1969, 690.
[5] L. Meites, *Anal. Chem.*, 1955, **27**, 1116.
[6] F. Harber, *Z. physikal. Chem.*, 1900, **32**, 208.
[7] W. N. Carson, C. E. Michelson and K. Koyama, *Anal. Chem.*, 1955, **27**, 472.
[8] P. Arthur, D. S. Rulison and K. D. Berlin, *Anal. Chem.*, 1968, **40**, 1389.
[9] G. Gritzner and J. Kuta, *Pure Appl. Chem.*, 1984, **56**, 461.
[10] W. C. Barrette, H. W. Johnston and D. T. Sawyer, *Anal. Chem.*, 1984, **56**, 1890.
[11] S. Barnatt, *J. Electrochem. Soc.*, 1961, **108**, 102.
[12] D. J. G. Ives and G. J. Janz (Editors.), *Reference electrodes*, Academic Press, New York, 1961.
[13] R. C. Larson, R. T. Iwamoto and R, N.. Adams, *Anal. Chim. Acta*, 1967, **25**, 371.
[14] C. W. Manning and W. C. Purdy, *Anal. Chim. Acta*, 1970, **51**, 124.
[15] B. Lamm and K, Ankner, *Acta Chem. Scand. B*, 1978, **32**, 193.
[16] J. Voss, K. Thimm and L. Kistenbrügger, *Tetrahedron*, 1977, **33**, 259.
[17] J. J. Lingane, *Anal. Chim. Acta*, 1948, **2**, 584.
[18] Nonaqueous solvents for electrochemical use: C. K. Mann in Electroanalytical chemistry (A. J. Bard Editor) Vol.3, pp. 57-127, Marcel Dekker Inc., New York, 1969.
[19] H. O. House, E. Feng and N. P. Peat, *J. Org. Chem.*, 1971, **36**, 2371.
[20] H. V. Udupa and K. S. Udupa, *Tech. Chem. (N. Y.)*, 1982, **5**, 385; *Chem. Abstr.*, 1982, **97**, 30175.
[21] Badische Anilin und Soda-Fabrik, *Fr. Pat.*, 1534453 (1969); *Chem. Abstr.*, 1969, **71**, 45113.
[22] K. H. Slotta and G. Haberland, *Z. anorg. Chem.*, 1933, **46**, 770.
[23] C. Moinet, *J. de Physique [4]*, 1994, **4**, 175.
[24] G. M. Swain, *J. Electrochem. Soc.*, 1994, **141**, 3382.
[25] T. R. Mueller and R. N. Adams, *Anal. Chim. Acta*, 1961, **25**, 482.
[26] G. Silvestri, S. Gambino, G. Filardo and A. Gullota, *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 979.
[27] O. Sock, M. Troupel and J. Périchon, *Tetrahedron Letters*, 1985, **26**, 1509.
[28] J. Chaussard, M. Troupel, Y. Robin, G. Jacob and J. P. Jubesz, *J. Appl. Electrochem.*, 1989, **19**, 345.
[29] T. Ohno, H. Aramaki, H. Nakahiro and I. Nishiguchi, *Tetrahedron*, 1996, **52**, 1943.
[30] M. Genesty, C. Thobie, A. Gautier and C. Degrand, *J. Appl. Electrochem.*, 1993, **23**, 1125.
[31] J. Chaussard, M. Troupel, Y. Robin, G. Jacob and J. P. Juhasz, *J. Appl. Electrochem.*, 1989, **19**, 345.
[32] T. Shono, H. Masuda, H. Murase, M. Shimomura and S. Kashimura, *J. Org. Chem.*, 1992, **57**, 1061.
[33] T. Shono, M. Ishifune, H. Kinugasu and S. Kashimura, *J. Org. Chem.* 1992, **57**, 5561.
[34] F. A. Paneth and K. F. Herzfeld, *Z. Elektrochem.*, 1929, **62**, 1335.
[35] J. Tafel, *Z. physikal. Chem.*, 1905, **50**, 641.

[36] Hydrogen overvoltage and adsorption phenomena, Part III: L. I. Krishtalik in Advances in electrochemistry and Electrochemical Engineering (P. Delahay Editor) Vol. 7, pp. 283-339, Interscience, New York, 1970.
[37] J. A. V. Butler, *Trans. Faraday Soc.*, 1924, **19**, 729.
[38] F. P. Bowden and E. K. Rideal, *Proc. Roy. Soc. A*, 1928, **120**, 59.
[39] F. W. Bowden and EK. E. W. Grew, *Faraday Soc. Discuss.*, 1947, **1**, 86.
[40] J.-M. Savéant and D. Tessier, *Faraday Discuss. Chem. Soc.*, 1982, **74**, 57.
[41] R. A. Marcus, *Ann. Rev. Phys. Chem.*, 1964, **15**, 155.
[42] J. Koryta, J. Dvorak and L. Kavan, *Principles of Electrochemistry*, John Wiley and Sons, New York, 2nd edition, 1993, p.266.
[43] K. Daasbjerg, H. Jensen, R. Benassi, F. Taddei, S. Antonello, A. Gennaro and F. Moran, *J. Am. Chem. Soc.*, 1999, **121**, 1750.
[44] Z. Galus, *Fundamentals of electrochemical analysis*, Ellis Horwood Ltd., Chichester, 2nd edition, 1994.
[45] J. Heyrovsky, *Chem. Listy*, 1922, **16**, 173; *Phil. Mag.*, 1923, **45**, 303.
[46] D. H. Evans, *Chem. Rev.*, 1990, **90**, 739.
[47] Analytical Chemistry Division, IUPAC Commission on Electroanalytical Chemistry, *Pure Appl. Chem.*, 1976, **45**, 131.
[48] Conformational change and isomerization associated with electrode reactions: D. H. Evans and K. M. O'Connell in Electroanalytical Chemistry (A. J. Bard Editor) Vol. 14, pp. 113-207, Marcel Dekker Inc., New York, 1986.
[49] C. Amatore A. Jutand and L. Mottier, *J. Electroanal. Chem.*, 1991, **306**, 125.
[50] Electrochemical reactions: C. P. Andrieux and J.-M. Savéant in Investigation of Rates and Mechanisms of Reactions (C. F. Bernasconi Editor), Vol. 6, 4/E, part 2, pp. 305-309, Wiley, New York, 1986.
[51] A general method for solving electrochemical diffusion-kinetic problems: S. W. Feldberg in Electroanalytical Chemistry (A. J. Bard Editor), Vol. 3, pp. 119-296, Marcel Dekker Inc., New York, 1969.
[52] D. Britz, *Digital simulation in electrochemistry*, Springer-Verlag, Berlin, 1981.
[53] B. Kastening, *Chem. Ing. Tech.*, 1970, **42**, 190.
[54] T. Kuwana and W. R. Heineman, *Acc. Chem. Res.*, 1976, **9**, 241.
[55] E. A. Blubaugh and L. M. Doane, *Anal. Chem.*, 1982, **54**, 329.
[56] T. Osa and T. Kuwana, *J. Electroanal. Chem.*, 1969, **22**, 389.
[57] E. Steckhan and D. A. Yates, *Ber. Bunsenges. phys. Chem.*, 1977, **81**, 369.
[58] L. M. Dorfman in Techniques of chemistry (A. Weissberger Editor) Vol.VI, Investigation of rates and mechanisms of reactions Part II (G. G. Hammes Editor) 3rd Edition, p. 463, Wiley, New York, 1974
[59] Electron Transfer reactions studied using pulsed high-energy radiation: J. Grimshaw in Royal Society of Chemistry, Specialist Periodical Reports, Electrochemistry, Vol. 10, p.p. 151-170, 1985.
[60] J. H. Baxendale, *Radiation Res. Suppl.*, 1964, **4**, 139.
[61] G. V. Buxton, P. G. Ellis and T. F. W. McKillop, *J. Chem. Soc. Faraday Trans. 1*, 1979, **75**, 1050.
[62] M. Anbar and E. J. Hart, *J. Am. Chem. Soc.*, 1964, **86**, 5633.
[63] P. O'Neill, S. Steenken and D. Schulte-Frohlinde, *J. Phys. Chem.*, 1975, **79**, 2773.
[64] S. Arai and L. Dorfman, *J. Chem. Phys.*, 1964, **41**, 2190.

[65] S. C. Guy, P. P. Edwards and G. A. Salmon, *J. Chem. Soc. Chem. Commun.*, 1982, 1257.
[66] H. Nauta and C. van Huis, *J. Chem. Soc. Faraday Trans. 1*, 1972, **68**, 647.
[67] J. Grimshaw, J. R. Langan and G. A. Salmon, *J. Chem. Soc. Faraday Trans.* 1994, **90**, 75.
[68] M. S. Workentin, L. J. Johnston and D. D. M. Wayner, *J. Am. Chem. Soc.*, 1994, **116**, 8279.
[69] M. S. Workentin, V. D. Parker, T. L. Morkin and D. D. M. Wayner, *J. Phys. Chem. A*, 1998, **102**, 6503.

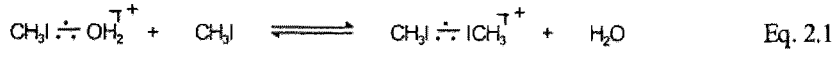
CHAPTER 2

OXIDATION OF ALKANES, HALOALKANES AND ALKENES

Radical-Cations

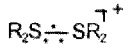
Oxidation of alkanes involves the removal of an electron from either a carbon-hydrogen or a carbon-carbon σ-bond. These are dissociative processes where the radical-cation cannot be detected as an intermediate in either fluorosulphuric acid or acetonitrile.

Oxidation of iodoalkanes involves removal of an electron from the halogen non-bonding orbital. The radical-cations of primary and secondary alkyl iodides can be identified in aqueous solution by their absorption spectra and have half-lives of microseconds [1]. They are formed during pulse radiolysis of the iodoalkane in aqueous solution in the presence of nitrous oxide. This system generates hydroxyl radicals, which remove an electron from the iodine atom lone pair. Iodoalkane radical-anions complex with the lone-pair on other heteroatoms to form a $2\sigma/1\sigma^*$ three-electron bond. In aqueous solution, the radical-cation of iodomethane is involved in an equlibrium indicated by Equation 2.1.

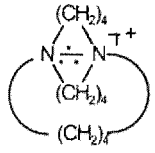


Eq. 2.1

Related three-electron bond radical-cations **1** are formed from dialkyl sulphides by oxidation with hydroxyl radicals generated using pulse radiolysis [2]. An isoelectronic three-electron bond between two nitrogen atoms in **2** is formed by reduc-



1

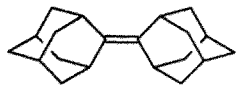


2

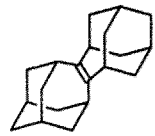
tion of the hydrazine dication with sodium in liquid ammonia. This species is sufficiently stable to be sublimed in vacuum as the tetrafluoroborate salt [3].

Electrochemical oxidation of alkenes results in the removal on one electron from the alkene function to give a π-radical-cation where the electron deficiency is delocalised over the conjugated system. The majority of alkene radical-cations cannot be characterised because they readily lose an allylic proton in aprotic sol-

vents or react with any nucleophile present in solution. Important exceptions are the radical-cations of the rigid adamantane derivatives **3** and **4**, which persist in aprotic solvents for several hours. In these molecules, the allylic carbon-hydrogen bonds lie in the same plane as the alkene bond. This prevents overlap between the



3



4

stretching σ-bond and the π-system so that no low energy transition state is available for bond cleavage. The alkene - radical-cation redox potentials of **3** and **4** in acetonitrile are 1.45 and 1.35 V *vs.* sce respectively [4].

Oxidation of Alkanes

Alkanes are functionalised by anodic oxidation in acetonitrile, methanol, acetic acid and more acidic solvents such as trifluoracetic acid and fluorosulphuric acid. Reaction requires very positive electrode potentials (see Table 2.1) and platinum has generally been used as anode materials in laboratory scale experiments. On a larger scale carbon is used as anode material. The first stage in these reactions in-

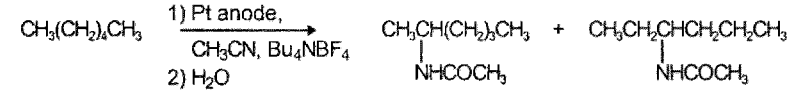
TABLE 2.1
Half-peak potentials ($E_{p/2}$) from cyclic voltammetry of alkanes and alkenes in acetonitrile

Substrate	$E_{p/2}$ V *vs.* sce	Ref.
Hexane	3.10	[5]
Octane	3.10	[5]
Methyl hexanoate	3.08	[11]
Adamantane	2.70	[8]
1,1,2-Trimethylcyclopropane	2.30	[11]
1,1,2,2-Tetramethylcyclopropane	2.05	[11]
2-Methylbut-2-ene	1.96	[11]
2,3-Dimethylbut-2-ene	1.74	[11]

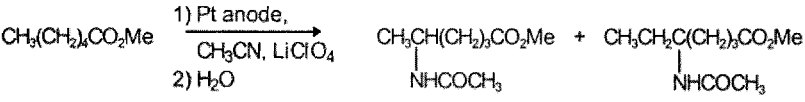
volves removal of an electron from either a carbon-carbon or a carbon-hydrogen σ-bond, with simultaneous bond cleavage. A need to form the most stabilised carbon

radical and carbonium ion determines which of the bonds in the substrate is preferentially cleaved. Carbon radicals are then oxidised to the carbonium ion at the potentials required for the first electron transfer. Products are formed by further reactions of these carbonium ions.

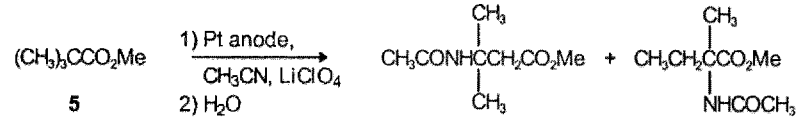
In acetonitrile, carbonium ions combine with the solvent to form a nitrillium ion. The latter reacts with added water to form the N-substituted acetamide, often in good yield [5, 6, 7]. Thus electrochemical oxidation of alkanes in acetonitrile is a route for the introduction of an amino-substituent. Some carbonium ions are inefficiently quenched by acetonitrile and eliminate a proton to form an alkene. This alkene is readily oxidised at the anode potentials used and oxidation products contribute to electrode fouling. Pulsing of the anode potential to +0.3 V *vs.* sce helps to



Ref. [1]



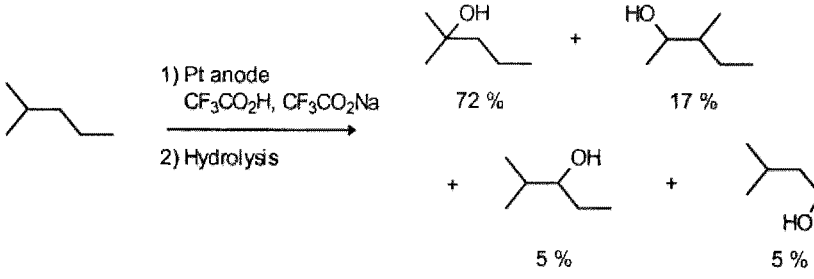
Ref. [10]



Ref. [11]

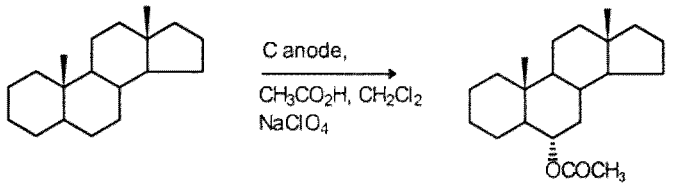
prevent this fouling of the anode surface [5, 8]. In acetic acid and trifluoroacetic acid, the carbonium ion is quenched by reaction with the carboxylate anion. Electrochemical oxidation in these solvents is a route for the introduction of a hydroxyl substituent [5, 9].

Oxidation of alkanes such as *n*-hexane never gives products from a primary carbonium ion, the *sec.*-carbonium ion intermediates are always formed in preference



Ref. [9]

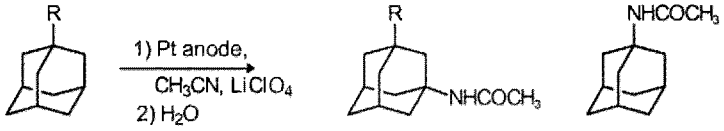
both in acetonitrile [5] and in trifluoroacetic acid [10]. An electron withdrawing alkanoate function directs oxidation towards a remote site, but primary carbonium ions are never formed so long as another site exists for oxidation. In the case of



Ref. [10]

methyl pivalate **5**, a methyl group is the only site available for attack and products obtained are derived from the rearranged carbonium ion [11]. Electrochemical oxidation of steroids in acetic acid – dichloromethane give high selectivity for functionalisation in the 6-position [10].

Cleavage of carbon-carbon bonds is illustrated by the electrochemical oxidation of some adamantane derivatives. In this series of substrates **6**, there is competition

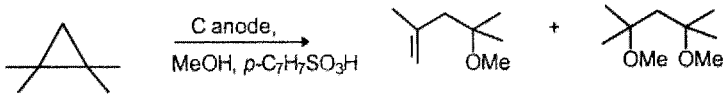


6

R =	% yield	% yield
Et	0	77
Pr^i	9	75
Bu^t	62	7
CO_2Me	64	0

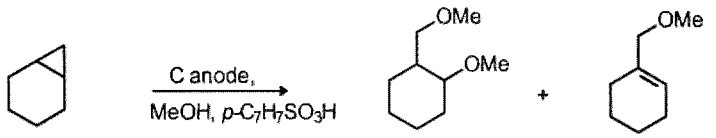
between bridgehead carbon-hydrogen bond cleavage and carbon-carbon bond cleavage [8]. The latter process occurs particularly when a *tert*-butyl carbonium ion can be formed.

Cyclopropanes are oxidised at less positive potentials than *n*-alkanes. Carbon-carbon bond cleavage occurs. When methanol is the solvent, the carbonium ion formed by bond cleavage reacts to form a methyl ether. The remaining carbon



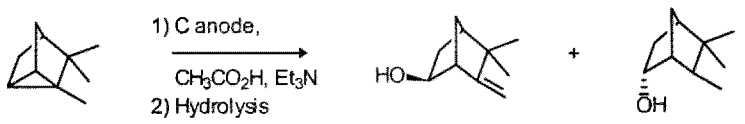
radical is the oxidised to a carbonium ion which undergoes further reactions [12, 13]. In the case of substrate **7** two *sec*-carbonium ion centres are formed initially and the isolated products arise from a Wagner-Meerwein skeletal rearrangement at

one of these carbonium ion centres. Tricyclene **8** is converted into a secondary al-



7

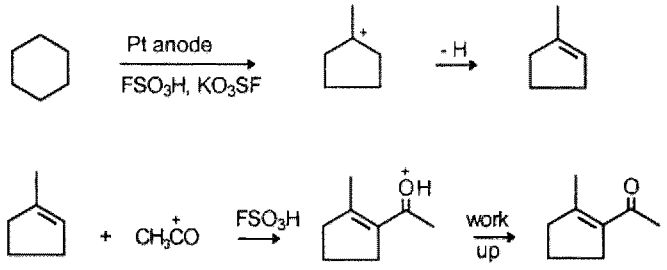
cohol by anodic oxidation in acetic acid and the related conversions of cyclofenchene and longicyclene occur in 77-85 % yields [14]. The *exo*-alcohol derived from



8 75 % 8 %

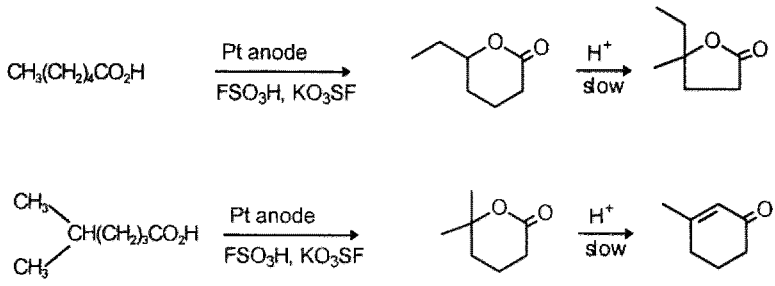
tricyclene is a valuable perfumary agent. Its preparation on a semi-pilot plant scale in an undivided cell using a carbon anode and a stainless steel cathode has been achieved starting with commercial tricyclene containing some camphene.

Use of the strong acid, fluorosulphuric acid, has been explored as a solvent for the electrochemical oxidation of alkanes. Carbonium ion intermediates can undergo extensive rearrangement in this medium. Also, fluorosulphate ion is a very poor nucleophile. Carbonium ions lose a proton under these conditions to form an alkene. When a carboxylic acid is present in the solution, these alkenes are trapped in an electrophilic reaction with the acyl carbonium ion generated from the carboxylic acid by the action of fluorosulphuric acid. Anodic oxidation of cyclohexane in fluorosulphuric acid containing acetic acid gives the ketone **9** and isobutane undergoes a related reaction [15].



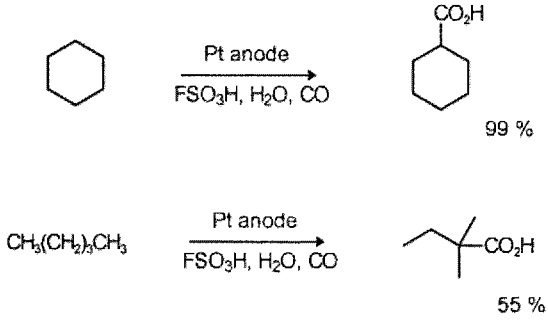
9

Slow acid catalysed transformation of the initial oxidation products is illustrated by the anodic oxidation of alkanoic acids in fluorosulphuric acid [16]. Carbonium



Ref. [16]

ions formed by the oxidation of alkanes in aqueous fluorosulphuric acid are efficiently trapped by carbon monoxide under pressure to form carboxylic acids. Extensive skeletal rearrangement of carbonium ion intermediates often occurs during this process [17].



Ref. [17]

Hydrocarbons undergo related reactions in the super-acid media, such as fluorosulphuric acid and antimony pentachloride. It has been suggested that the initial one-electron processes during the electrochemical oxidation of alkanes in fluorosulphuric acid involve a protonated carbon-hydrogen bond with formation of a carbon radical and release of two protons [15].

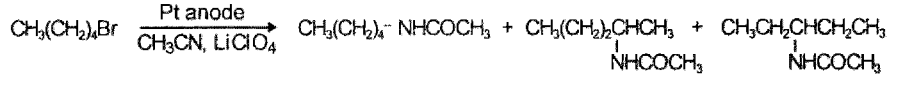
Oxidation of Haloalkanes

Electrochemical oxidation of alkyl bromides and iodides leads to loss of a non-bonding electron from the halogen substituent, followed by cleavage of the carbon-halogen bond to form a carbonium ion and a halogen atom. The products isolated are formed by further reactions of the carbonium ion while two of the halogen at-

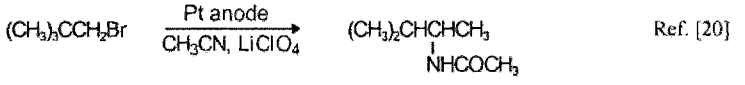
oms combine to form the halogen molecule. Radical-cations from primary alkyl iodides are detectable as very short-lived intermediates [1]. Preparative scale electrochemical oxidation reactions are carried out in acetonitrile where the carbonium ion reacts with one molecule of solvent to form a nitrillium ion. The latter is quenched by water to give the N-alkylacetamide.

Molecular iodine is oxidised in acetonitrile at about the same potential as alkyl iodides. It forms iodine(I), co-ordinated with one molecule of acetonitrile [18]. Iodine(I) will oxidise alkyl iodides to form a carbonium ion and molecular iodine. Thus the iodine generated during electrochemical oxidation of an alkyl iodide can function as an electron transfer agent in the latter stages of reaction [19].

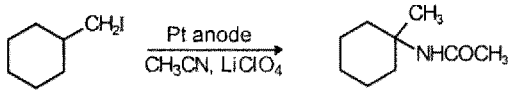
Interaction between the radical-cations of primary alkyl halides and acetonitrile is on the verge of S_N2 *versus* S_N1 type reactivity. Some product is formed by direct substitution, but rearrangement also occurs to give the most stable carbonium ion [20, 21]. Thus 1-bromopentane yields a mixture of three N-pentylacetamides on



30 % 33 % 33 %

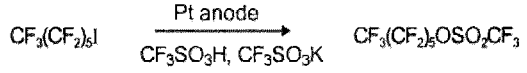


Ref. [20]

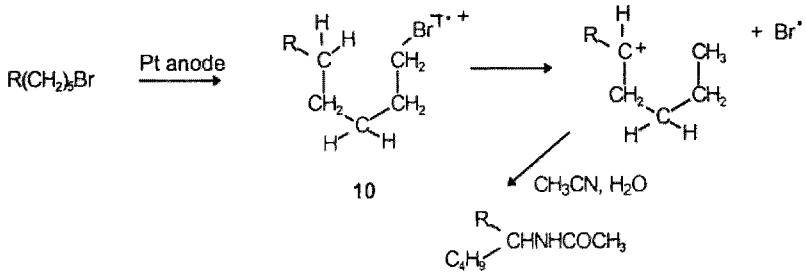


Ref. [21]

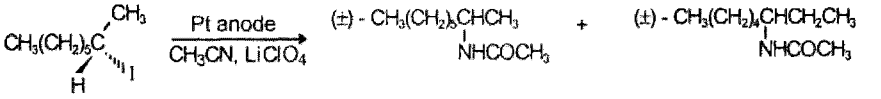
oxidation in acetonitrile. This reactivity is in contrast with that of carbonium ions generated by oxidation of primary alkylcarboxylates (see p. 322). The latter intermediates show entirely S_N1 type reactivity and give rise only to products formed from a 1,2-hydride shift step [22]. The anodic oxidation of perfluoroalkyl iodides proceeds without a carbonium ion migration step [23].



In addition to 1,2-hydride shifts, the 1,5-hydride shift is favoured [24] in the decomposition of radical-cations of long chain alkyl halide such as **10**.



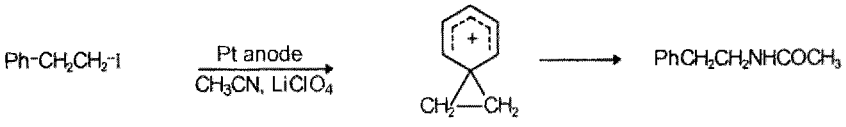
Reaction between acetonitrile and the radical-cations of secondary alkyl halides is almost entirely S_N1 in character. Both direct substitution and 1,2-hydride shift reactions occur and the products from a chiral alkyl halide such as 2-iodooctane, are almost totally racemised [25].



53 % 26 %

Ref. [25]

Deuterium labeling experiments show that oxidation of 2-phenylethyl iodide proceeds through the bridged carbonium ion **11** [21]. Both iodocyclobutane and

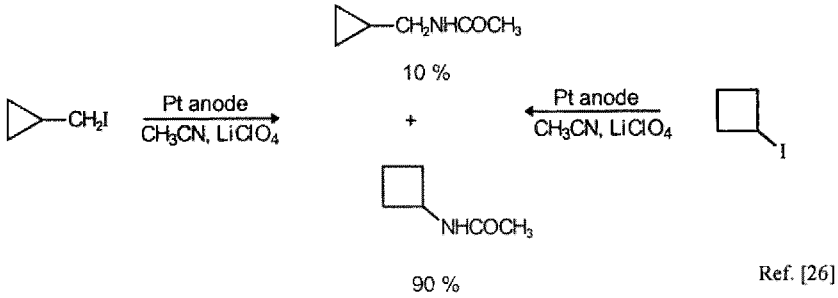


11

iodomethylcyclopropane yield the same mixture of N-cyclopropylmethyl- and N-cyclobutyl-acetamides after electrochemical oxidation [26]. This reaction proceeds through an equlibrium mixture of cyclopropylmethyl and cyclobutyl carbocations.

The oxidation potential of the carbon-bromine bond is close to that for the bridgehead carbon-hydrogen bond in adamantane. Thus, 2-bromoadamantane in acetonitrile undergoes mainly oxidation at the bridgehead positions, retaining the

bromine atom to afford a mixture of N-(2-bromoadamantyl)acetamides. Only 5 %



Ref. [26]

of N-(2-adamantyl)acetamide is formed in the process. In contrast, 2-iodoadamantane gives 98 % of N-(2-adamantyl)acetamide along with a negligible amount of bridgehead substitution products [27].

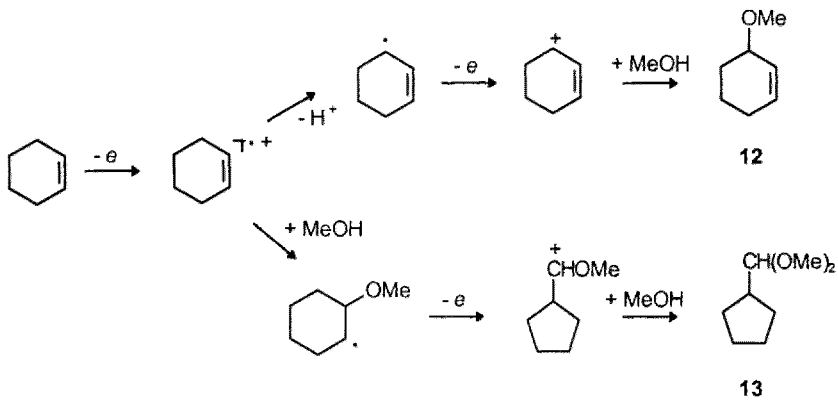
Oxidation of Alkenes

Alkenes are electrochemically oxidised in nucleophilic solvents such as alcohols, acetic acid or acetonitrile using an undivided cell and the products isolated result from quenching of intermediate carbonium ions by nucleophiles. Most alkene hydrocarbons show a single two-electron wave at a rotating disc electrode due to the formation of the radical-cation and its subsequent reactions. The oxidation potentials of alkenes are made less positive by alkyl substitution. Enol ethers are more easily oxidised than unsubstituted alkenes and conjugation with an aryl ring or another alkene bond also makes the oxidation potential less positive. Representative peak potentials found by linear sweep voltametry of dilute solutions of alkenes at a glassy carbon electrode are given in Table 2.2.

The radical-cation reacts with the nucleophile to form a radical intermediate, which is then oxidised to the carbonium ion, usually at a potential less positive than that required for the first electron transfer process. However, enol ethers show two one-electron waves on linear sweep voltammetry. The first wave is due to the formation of the radical-anion and the second wave to oxidation of carbon radical intermediates to the carbonium ion.

Products from the electrochemical oxidation of cyclohexene (Scheme 2.1) illustrate the general course of reaction [28, 29]. The radical-cation either undergoes loss of an allylic proton or reacts, at the centre of highest positive charge density, with a nucleophile. Either reaction leads to a carbon radical, which is oxidised to the carbonium ion. A Wagner-Meerwein rearrangement then gives the most stable carbonium ion, which subsequently reacts with a nucleophile.

The relative importance of these two pathways for radical-cation decomposition depends on the nucleophilicity of the solvent and on the structure of the alkene



Scheme 2.1. Steps in the electrochemical oxidation of cyclohexene using methanol as solvent.

substrate. Oxidation of cyclohexene in methanol containing sodium methoxide gives both **12** and **13** in similar amounts while **12** becomes the major product in tetrahydrofuran – 1 M-methanol with sodium perchlorate as supporting electrolyte. Analogous cyclohexene-3-yl ethers have been prepared using this strategy [29].

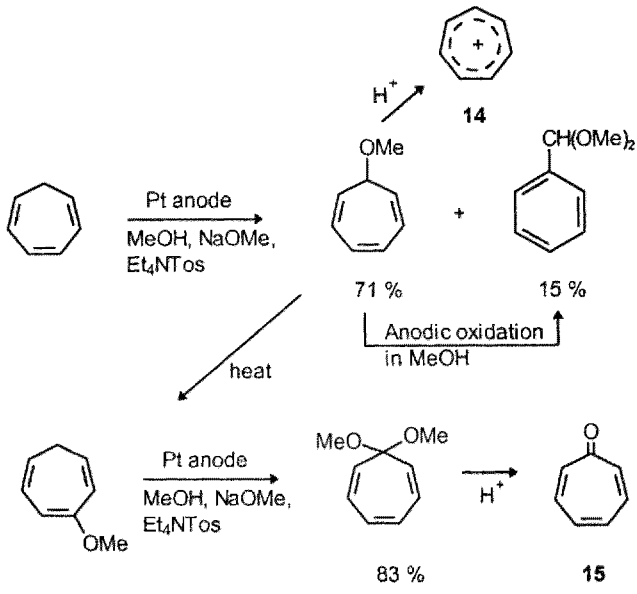
TABLE 2.2

Peak potentials from linear sweep voltammetry of alkenes at a glassy carbon anode in methanol, sodium perchlorate. Sweep rate 20 mV s^{-1}

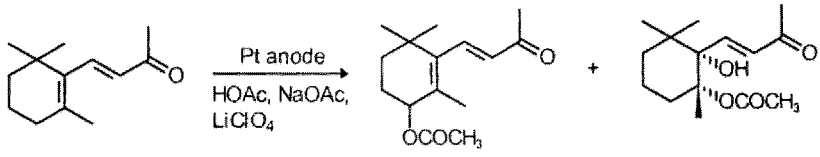
Substrate	E_p /V *vs.* sce	Ref.
1,3-Butadiene	1.95	[43]
2-Methylbutadiene	1.85	[43]
1,3-Pentadiene	1.43	[43]
2,4-Hexadiene	1.23	[43]
2,5-Dimethyl-2,4-hexadiene	1.04	[43]
1,3-Cyclohexadiene	1.31	[43]
Cycloheptatriene [a]	1.31, 1.61	[43]
Styrene	1.63	[38]
Ethyl vinyl ether	1.67	[38]
1-Ethoxy-1-hexene [a]	1.23, 1.58	[38]
1-Acetoxy1,3-butadiene	1.39	[43]

Footnote: (a) Shows two one-electron waves.

Electrochemical oxidation of cycloheptatriene gives products principally by loss of a proton from the radical-anion. The reactions afford a route to the preparation of tropyllium **14** and tropone **15** [30, 31]



Allylic acetoxylation of alkenes is achieved using acetic acid with sodium acetate as solvent and nucleophile. Cyclohexene gives 1-acetoxycyclohexene as the

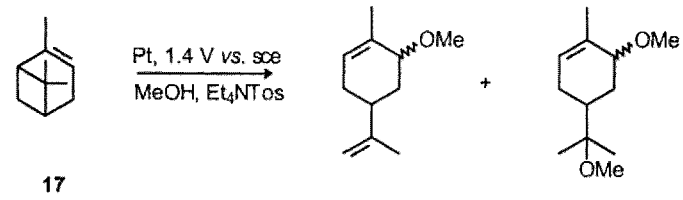


16

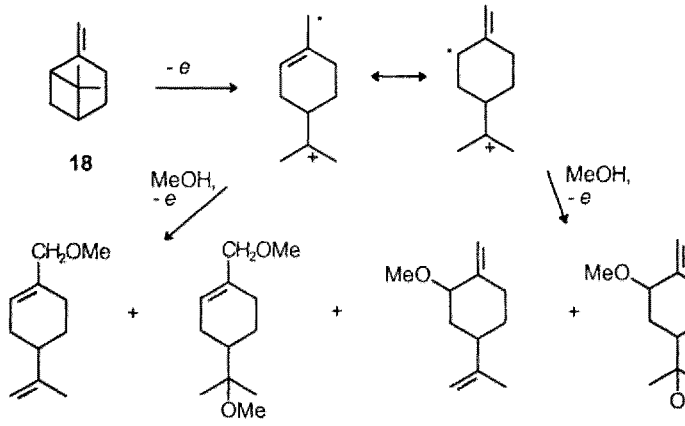
principal product [32]. In the case of β-ionone **16** the major product is formed by allylic axidation. The minor diol monoacetate results from reaction between the radical-anion and acetate ion as nucleophile followed by anchimeric assistance of the acetate carbonyl oxygen during oxidation of the carbon radical to the carbonium ion to give an intermediate *ortho*-ester [33].

Electrochemical oxidation in methanol of both α-pinene **17** and β-pinene **18** leads to opening of the four membered ring by cleavage of one allylic carbon-

carbon bond [34]. Some products from β-pinene have a methoxy-substituent on the cyclohexane ring, indicating that carbon-carbon bond fragmentation occurs from



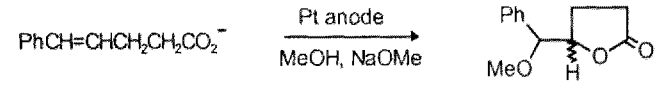
17



18

the radical-anion to give a *tert.*-carbocation and an allylic radical. Oxidation of the radical leads to an allylic carbocation with two centres for nucleophilic attack. The equivalent series of reaction steps for chiral α-pinene will lead to racemic products, but so far the stereochemistry of this process has not been examined.

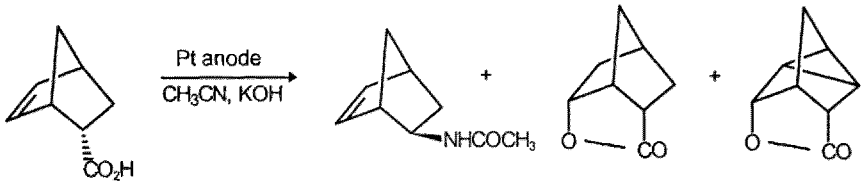
The oxidation potential for the alkene bond is close to that for a carboxylate ion. In the styrene derivative **19**, the alkene moiety is preferentially oxidised and intramolecular capture of a carbocation leads to a lactone product [35]. The tetrasub-



19

stituted alkene bond is also oxidised in preference to a carboxylic acid group [36]. Disubstituted alkenes show a balance of reactivity between the alkene bond and a

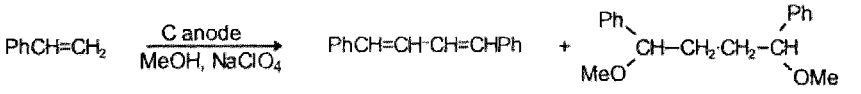
carboxylic acid function. *Endo*-norbornene-2-carboxylic acid **20** gives lactone products by oxidation of the alkene bond and also a Kolbe type product by oxida-



20

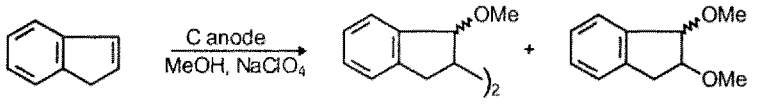
tion of the carboxylate group [37]. Many alkene carboxylic acids show only typical Kolbe oxidation of the carboxylate (see p. 316).

An electron donating substituent such as phenyl and methoxy will polarise electron density on the radical-anion of an alkene in favour of more positive charge density on the carbon atom bearing this substituent with more free electron density on the other carbon atom. This promotes dimer formation by linkage through atoms with free electron density. Styrene is oxidised at a graphite anode in methanol



Ref. [38]

to dimeric products and the oxidation of styrene in aqueous acetonitrile affords 2,5-diphenyltetrahydrofuran [38]. However indene **21** shows a tendency to form dimer

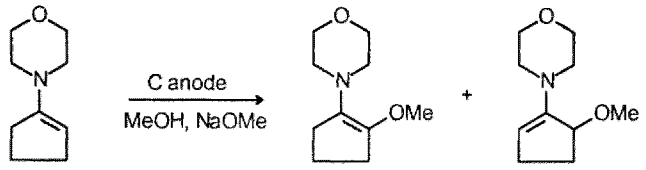


21 30 % 29 %

in favour of dimethoxylation of the alkene bond [39]. Electrochemical oxidation of diphenylacetylene gives a mixture of benzil, resulting from dimethoxylation of the acetylenic bond, and 1,2,3,4-tetraphenylbut-2-en-1,4-dione, resulting from a radical dimerization process [40].

Vinyl ethers also form dimeric products in methanol in the presence of a weak base such as 2,6-lutidine [41], which accepts protons liberated during the reaction. Some dimethoxylation of the alkene bond also occurs under these conditions. In

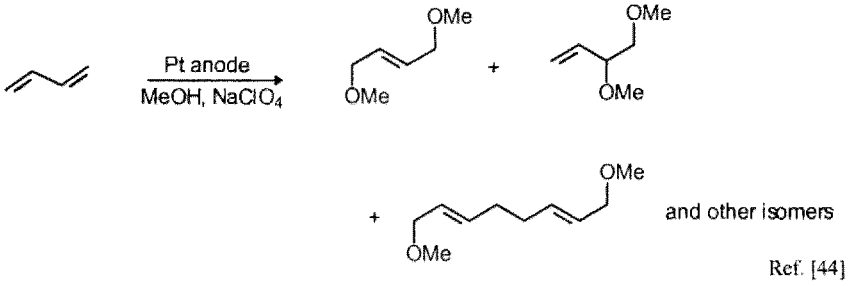
the presence of sodium methoxide as a strong nucleophile, high yields of the dimethoxylated product result [42]. Enamines such as **22** also undergo α-methoxylation at a carbon anode in methanol containing sodium methoxide[42].



22

Sodium iodide is proposed as a good supporting electrolyte for the dimerization of enol ethers in methanol [41]. The electrolyte is readily oxidised to iodine so that the first reaction of the vinyl ether will be iodomethoxylation [43]. Since the electrochemical reaction is carried out in an undivided cell, reduction of the iodo intermediate at the cathode can give the dimeric product (see p. 99).

Butadienes give a complex mixture of methoxylated products by electrochemical oxidation in methanol with sodium perchlorate as supporting electrolyte [44]. Dimethoxybutenes are formed together with dimers from reaction of methoxybutenyl radicals. A platinum anode gives the highest yields of monomeric products while graphite anodes yield only dimeric products. This is a distinction from the

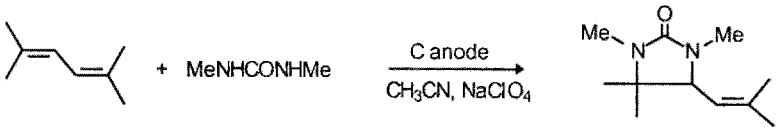


Ref. [44]

Kolbe oxidation of carboxylate ions to radicals with loss of carbon dioxide (p. 312). The latter process gives highest yields of dimeric product at a platinum anode and only monomeric products from oxidation of the radical centre at a carbon anode. Oxidation of butadiene in methanol containing benzoic acid, at a smooth platinum anode, gives 45 % of the but-3-ene-1,4-diol diester [45].

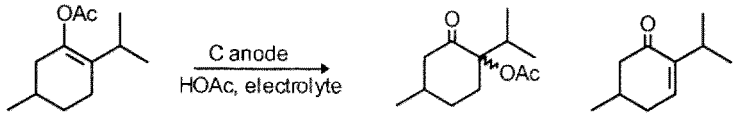
Electrochemical oxidation of alkyl substituted butadienes in the presence of dimethylurea as a 1,3-bidentate nucleophile, leads to formation of a five membered ring heterocycle [46]. Unsymmetrically substituted butadienes show no regiospeci-

ficity in this reaction while butadiene does not react, being less readily oxidised than dimethylurea.



Ref. [46]

Electrochemical oxidation of enol acetates in an undivided cell gives monomeric products in parallel with the reactions of simple alkenes [47, 48]. Thus, in the reaction of menthol enol acetate **23**, the α-acetoxyketone product arises from nucleophilic attack of acetate ion on the radical-cation while the enone product



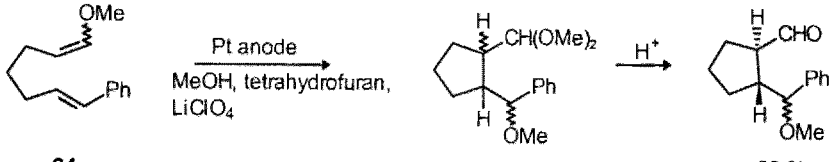
23

Et_4NTos	0 %	90 %
KOAc	60 %	25 %

arises by loss of a proton from the radical-cation. The relative proportion of the two products can be change in favour of the α-acetoxyketone by addition of acetate ions to the reaction mixture. In the absence of acetate ions, good yields of the enone are obtained.

Intramolecular Cyclization

Intermolecular coupling of a vinyl ether with styrene at a carbon anode in methanol is successful, giving a mixture of the cross coupled product and the two homocoupled products [49]. Intramolecular coupling between an enol ether and an alkene centre, as in **24** and **25**, proceeds to give the cyclized product in good yield [50]. Five and six membered rings can be constructed in this way. An easily oxidised vinyl ether group is necessary to initiate the reaction and the second alkene

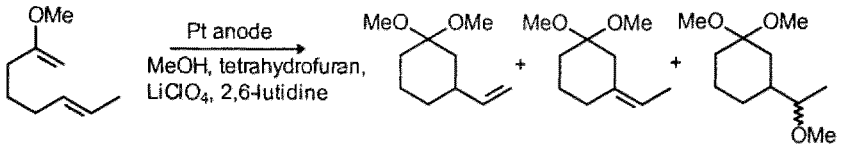


24

80 %

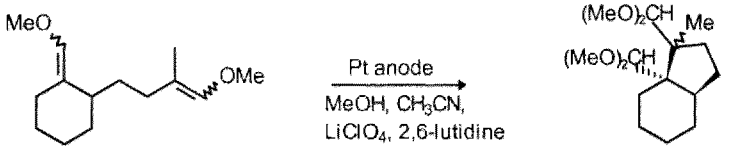
may be either an isolated group or conjugated to a benzene ring. Cyclization occurs by reaction of the vinyl ether radical-cation with the second alkene function. Reac-

tion of **24** is directed towards a five-membered ring because of the phenyl substitu-



25

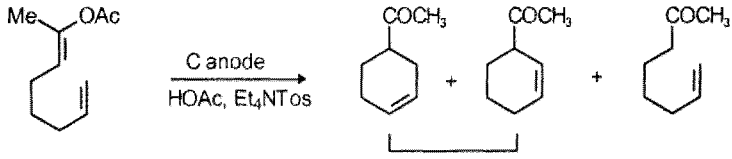
ent which stabilise the radical intermediate. Silyl vinyl ethers are also suitable as the initiating group for these processes [51]. Reaction of the radical-cation from one vinyl ether group onto a second vinyl ether is also regioselective. This is again because the second alkene is able to stabilise the radical intermediate formed in the cyclization step [52]. Cyclization of **26** generates a five-membered ring, which for



26 44 %

steric reasons is *cis*-fused to the existing six-membered ring. Two quaternary carbon centres are also formed in the process.

Enol acetates such as **27** will also undergo oxidative cyclization onto an alkene centre, but hydrolysis of the starting material to the ketone occurs at a comparable rate [53].

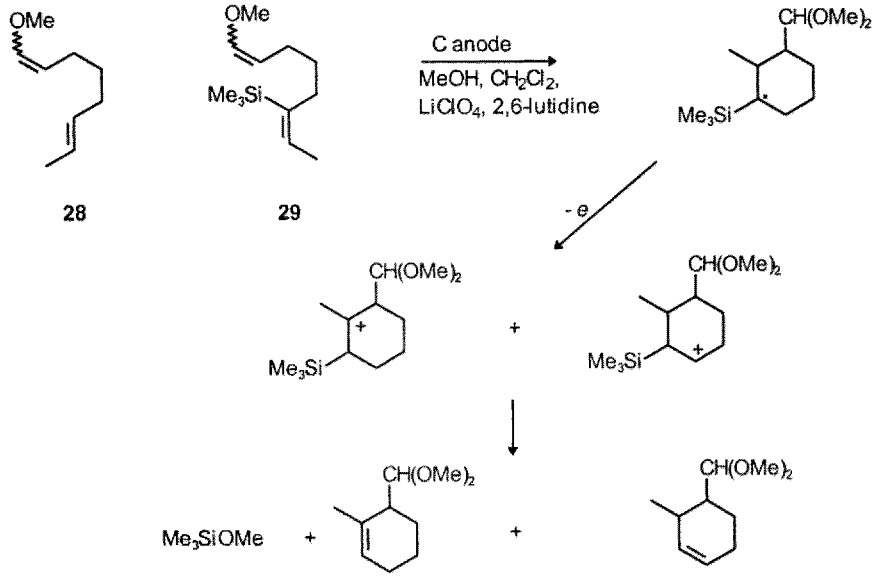


27 35 % 25 %

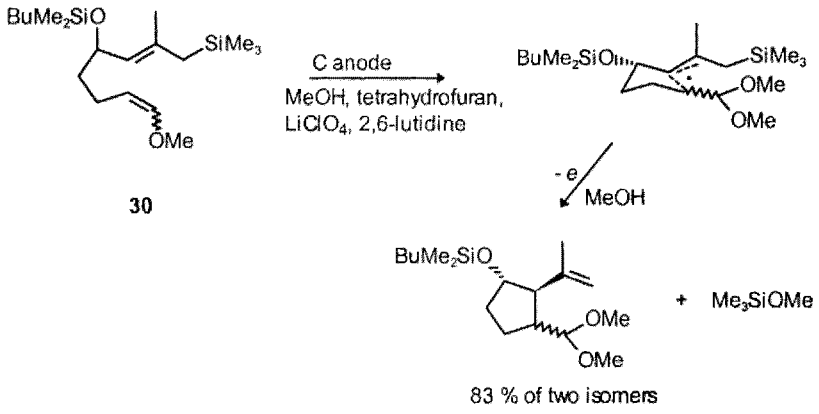
The electrochemical cyclization of enol ethers in methanol uses an undivided cell and 2,6-lutidine is added as a proton scavenger. Acid catalysed hydrolysis of the enol function is thus avoided. An advantage is gained by diluting the methanol with a non-nucleophilic co-solvent. This lowers the extent of dimethoxylation of

the enol ether function, which is a competing reaction [52]. Reticulated vitreous carbon, followed by platinum is the most satisfactory anode material.

Trialkylsilyl substituents have proved very useful for directing the course of cyclizations involving vinyl ethers. The trialkylsilyl group stabilises a radical centre but destabilises a carbonium ion next to the silicon atom. An example of the di-



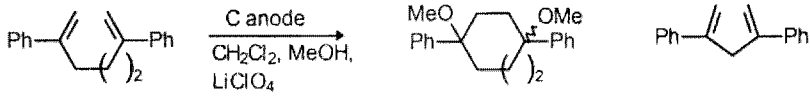
recting effect is provided by a comparison between the reactions of **28** and **29**. Oxidative cyclization of compound **28** leads to a mixture of five-membered and six-membered ring products, whereas **29** yields only six-membered ring products [54]. The carbon-carbon bond-forming step involves radical addition to the alkene



bond and in the case of compound **29** gives the silicon stabilised intermediate radical. Further oxidation to the carbonium ion also involves a proton shift and then elimination of the trimethylsilyl group.

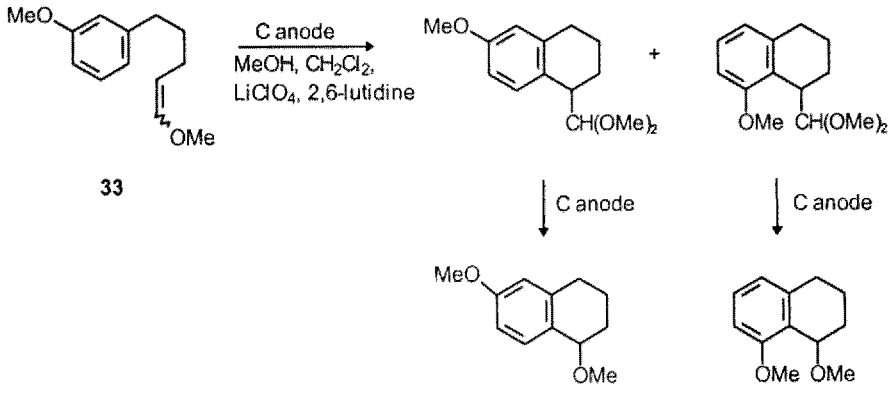
Allylsilanes offer a means of directing an elimination from the final carbonium ion generated after the cyclization step [55, 56]. The reaction of compound **30** illustrates this point. In the final stage, rapid elimination of the trimethylsilyl group prevents solvolysis of the carbonium ion and directs the forming alkene bond. Stereoselectivity in ring closure is also illustrated. This arises through kinetic control of the cyclization step. The favoured transition-state has minimum interaction between groups in the forming ring structure [56].

Intramolecular cyclization can also be initiated from the radical-cation of a styrene residue [57]. Oxidative cyclization of **31**, n = 1 and **31**, n = 2 give five and seven membered ring products respectively but in contrast **32** failed to yield a five membered ring product, giving only intractable mixtures. This difference in reactivities can be explained in terms of Baldwin's rules where the *5-endo-trig* cyclization of the radical-cation from **32** is disfavoured [58].



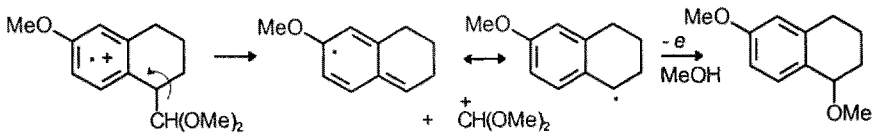
31 **32**

Vinyl ether radical-cations also react in a radical substitution fashion with an adjacent electron rich benzene ring [59]. However the reaction products from simple examples such as **33** themselves readily undergo a further anodic oxidation



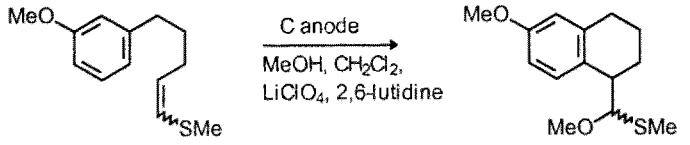
33

coupled with an elimination step the mechanism of which is shown in Scheme 2.2. A complex mixture of products results.



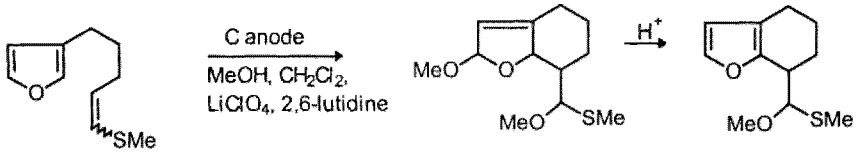
Scheme 2.2. Radical-cation fragmentation following the cyclization of substrate **33**

The second competing fragmentation reaction can be avoided by using a vinyl sulphide substrate **34**. Vinyl sulphides have a lower oxidation potential compared

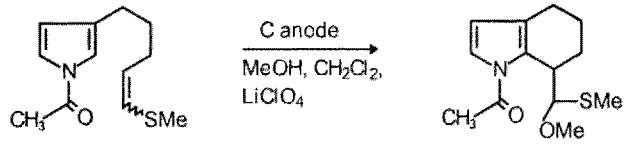


34 38 %

to vinyl ethers and so long as unreacted substrate remains in the mixture, over oxidation of the product is avoided [59] Furan and pyrrole rings also take part in related radical substitution processes initiated by the oxidation of a vinyl sulphide.



54 %



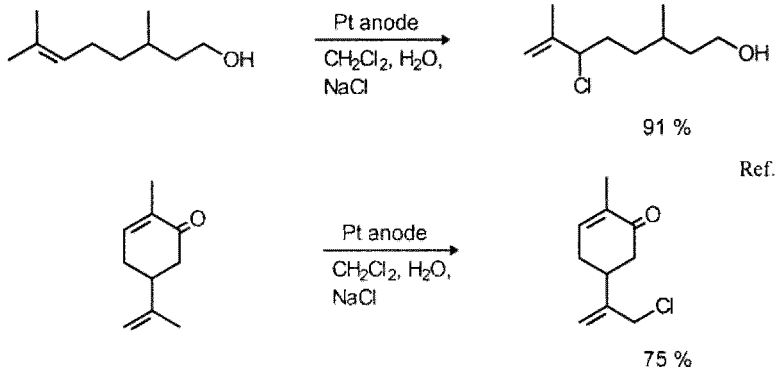
Ref. [59]

66 %

Electrochemically Generated Reagents for Alkenes

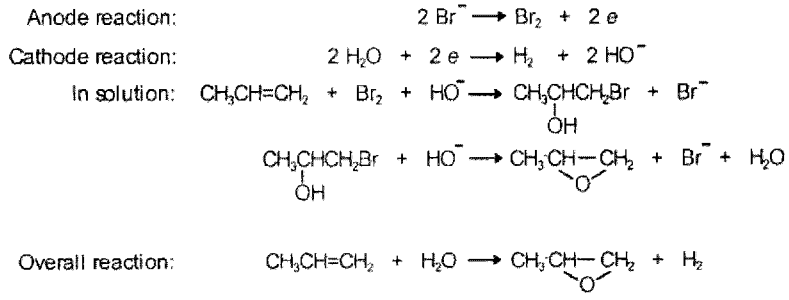
Electrochemical generation of chlorine in a reaction mixture affords a simple means for controlling the rate of addition of this reagent. The route has proved use-

ful for promoting the ene-chlorination of alkenes in an inert solvent [60]. This process is carried out in a two-phase system of aqueous sodium chloride and a solution of the alkene in dichloromethane. An emulsion of the two phases is flowed between platinum electrodes, generating chlorine, which diffuses into the organic phase. The ene-chlorination step then occurs in the organic phase. In aqueous solu-



tion with no organic phase present, electrochemically generated chlorine reacts with alkenes to give the chlorohydrin. The preparation of 2,3-dichloropropanol from allyl chloride on a technical scale has been investigated using this route with dilute hydrochloric acid as electrolyte [61].

A process, which uses propene bromohydrin as an intermediate, has been extensively studied as a route for the conversion of propene to propylene oxide [62, 63]. The electrolyte is an aqueous solution of sodium bromide saturated with propene gas. An undivided flow cell fitted with a graphite anode is used. Overall, propylene oxide and hydrogen are generated in the sequence of cell reactions given in Scheme 2.3.

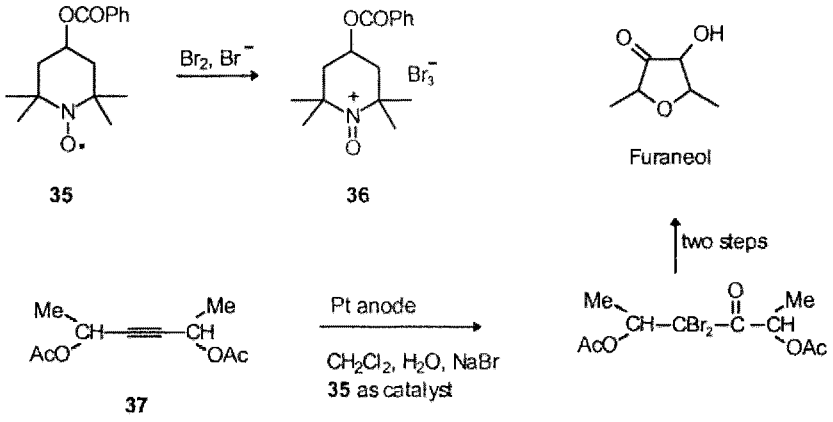


Scheme 2.3. Electrochemical conversion of propene to propylene oxide in an undivided cell, catalysed by bromide ions.

Bromide ions serve as a catalyst, although in practice there is some loss due to the formation of bromate in side reactions. The process has also been run with a feed of oxygen through a porous cathode, which eliminates the liberation of hydrogen and decreases the overall cell voltage.

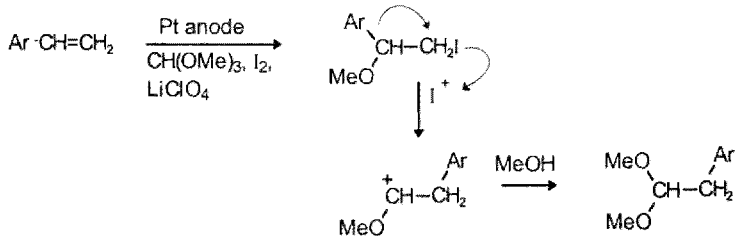
Laboratory scale bromination of alkenes in homogeneous solution using an undivided cell is adaptable to the formation of epoxides, bromohydrins or dibromides depending on the conditions [64]. Epoxides are generated using an initially neutral solution and a low concentration of bromide ions. The reaction sequence is similar to that of Scheme 2.3. Formation of bromohydrins requires dilute hydrobromic acid as the supporting electrolyte. Dibromides are obtained using a concentrated solution of sodium bromide as electrolyte.

Electrochemical bromination of long chain alkenes in a two-phase water-organic medium presents a difficulty because the bromine, which is generated, is held in the aqueous phase as the tribromide ion. A catalytic amount of the nitroxyl **35** acts



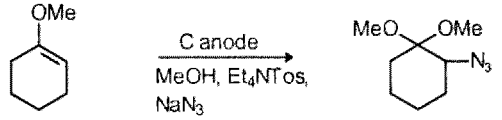
to generate a phase transfer agent when it is oxidised by bromine and forms the ion pair **36**. The system can be used to form alkene dibromides. In another general reaction, this system interacts with propargyl acetates to give an α,α′-dibromoketone and with the example of **37**, affords a facile synthesis of the flavouring agent furaneol [65]. Neighbouring group participation by the acetoxy function in the initial bromination step is responsible for the introduction of a carbonyl oxygen function.

Iodine is oxidised to iodine(I) at an anode and use has been made of this reagent for the conversion of styrenes to the phenylacetaldehyde dimethyl acetal [66]. Iodine functions as a catalyst in this process. However, a moderate concentration of iodine is required to suppress the direct oxidation of the styrene to give 1,2-dimethoxylated products.



Ref.[66]

Azide ions are oxidised at low positive potentials and generate azide radicals. Azide radicals will add to an alkene. Thus the anodic oxidation of enol ethers in

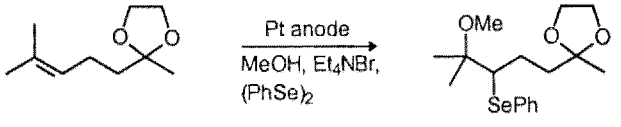


83 %

Ref. [67]

methanol containing sodium azide gives the α-azidoacetal [67]. The azide ion is more readily oxidised than the enol ether group. A divided cell is however required since azides are reduced at the cathode.

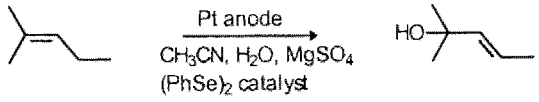
Electrochemical catalytic cycles allow the efficient use of diphenyl diselenide in the oxyselenation of alkenes. In the presence of bromide ions, the electrochemically generated bromine forms phenylselenium bromide which reacts with the alkene regenerating bromide ion [68]. In the absence of bromide ions and at more



80 %

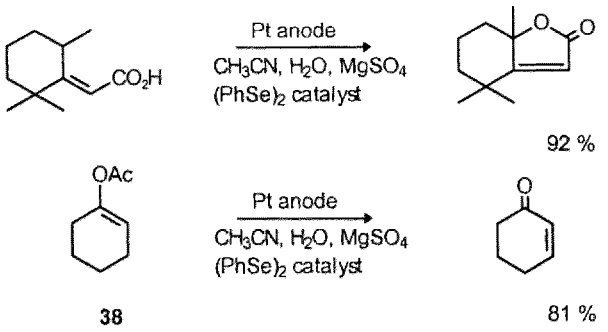
Ref. [68]

anodic potentials, diphenyl diselenide is oxidised in aqueous acetonitrile to form an electrophilic selenium intermediate, which adds to the alkene bond. Further oxidation of this phenyl alkyl selenium intermediate to the selenoxide occurs at the anode potentials used and this step is followed by elimination of PhSeOH. Overall,



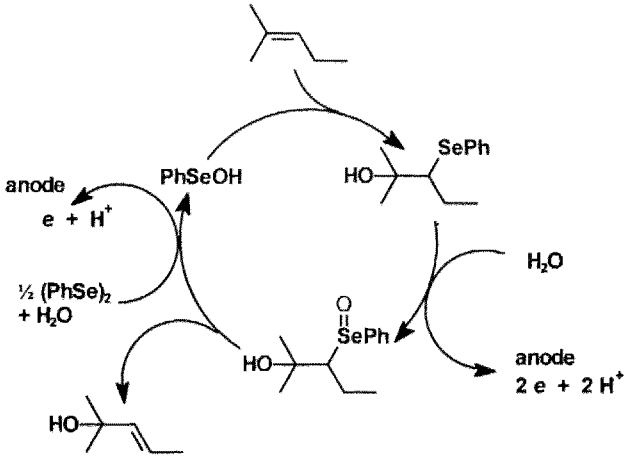
Ref. [69]

the alkene is transformed into an allyl alcohol through the reaction cycle in Scheme 2.3 and only a catalytic amount of diphenyl diselenide is necessary [69]. Magne-



Ref. [69]

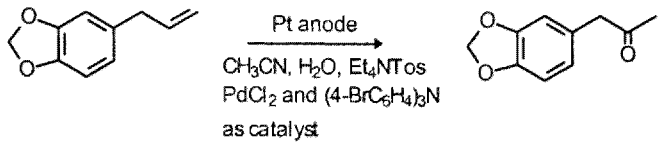
sium ions are necessary to promote the reaction. Enol acetates, such as **38** are converted to conjugated enones by a similar route.

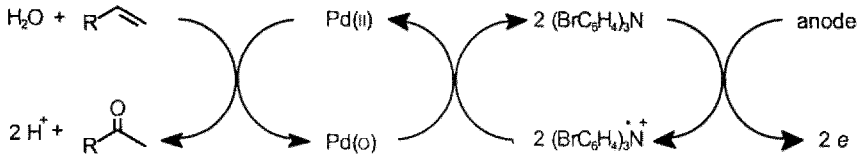


Scheme 2.3. Catalytic cycle for the allylic hydroxylation of alkenes by anodic oxidation in the presence of diphenyl diselenide.

Anodic oxidation is used to promote the recycling of palladium(II) in the Wacker process for the conversion terminal alkenes to methyl ketones. Completion of the catalytic cycle requires the oxidation of palladium(O) back to the palladium(II) state and this step can be achieved using an organic mediator such as tri(4-bromophenyl)amine. The mediator is oxidised at the anode to a radical-cation and

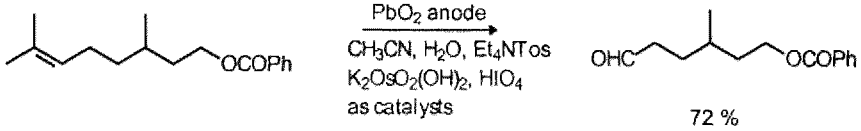
this oxidises palladium(0) in homogeneous solution. Reaction is achieved in an undivided cell with platinum electrodes [70]. Long chain alk-1-enes however undergo alkene bond migration catalysed by palladium(II), leading to a mixture of ketones as the final oxidation product.





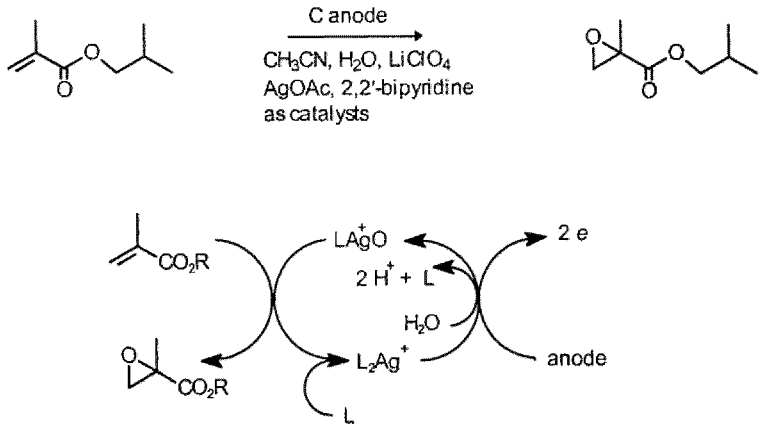
Scheme 2.4. Double catalytic cycle for the electrochemical conversion of alk-1-enes to methyl ketones

Fission of carbon-carbon double bonds with the combined use of an osmium catalyst and periodate as a comsumable reagent is an alternative to ozonolysis. In this process a catalytic amount of osmium is oxidised to osmium(VIII) by preiodate and converts the alkene to a glycol which is then cleaved by the periodate. In the electrochemical modification of this process, which uses a divided cell and aqueous acetonitrile as solvent, periodate is also used in catalytic amounts and is regenerated from the formed iodate by oxidation at a lead dioxide anode [71]. Lead dioxide is known to be a catalytic anode material for oxidation of iodate to periodate [72].



Ref. [71]

The Sharpless asymmetric dihydroxylation of alkenes usually employs a stoichiometric amount of iodine or potassium ferricyanide to re-oxidise the osmium centred intermediates in the catalytic cycle [73]. Either reagent can also be used in catalytic amounts and re-oxidised electrochemically at an anode [74, 75].



Scheme 2.5. Catalytic cycle for the electrochemical epoxidation of alkenes using silver(I)bis(2,2′-bipyridine).

Electrochemical epoxidation of alkenes can be achieved using a silver(I) bis-(2,2′-bipyridine) catalyst which is generated *in situ* in acetonitrile containing a little water by the addition of silver acetate and 2,2′-bipyridine. The silver is anodically oxidised to a silver(III)oxo(2,2′-bipyridine) complex which transfers oxygen to the alkene bond in a chemical step, Scheme 2.5. Both simple alkenes and conjugated alkenes can be epoxidised by this route [76].

References

[1] H. Mohan and K.-D. Asmus, *J. Chem. Soc. Perkin Trans. 2*, 1987, 1795.
[2] M. Göbl, M. Bonifacic and K.D. Asmus, *J. Am. Chem. Soc.*, 1984, **106**, 5984.
[3] R. W. Alder and R. B. Sessions, *J. Am. Chem. Soc.*, 1979, **101**, 3651.
[4] F. Gerson, J. Lopez, R. Akaba and S. F. Nelsen, *J. Am. Chem. Soc.*, 1981, **103**, 6716.
[5] D. B. Clarke, M. Fleischmann and D. Pletcher, *J. Chem. Soc. Perkin Trans. 2*, 1973, 1579.
[6] T. M. Siegel, L. L. Miller and J. Y. Becker, *J. Chem. Soc. Chem. Commun.*, 1974, 341.
[7] F. Vincent, R. Tardivel, P. Mison and P. von Raugé Schleyer, *Tetrahedron*, 1977, **33**, 325.
[8] V. R. Koch and L. L. Miller, *J. Am. Chem. Soc.*, 1973, **95**, 8631.
[9] H. P. Fritz and T. Würminghausen, *Z. Naturforsch. B*, 1977, **32**, 241.

[10] A. Hembrock, H.-J. Schäfer and G. Zimmermann, *Angew. Chem. Int. Ed. Engl.*, 1985, **24**, 1055.
[11] L. L. Miller and V. Ramachandran, *J. Org. Chem.*, 1974, **39**, 369.
[12] T. Shono and Y. Matsumura, *Bull. Chem. Soc. Japan*, 1975, **48**, 2361.
[13] P. G. Gassman and R. Yamaguchi, *Tetrahedron*, 1982, **38**, 1113.
[14] T. Uchida, Y. Matsubara, I. Nichiguchi, T. Hirashima, T. Ohnishi and K. Kanehara, *J. Org. Chem.*, 1990, **55**, 2938.
[15] J. Bertram, J. P. Coleman, M. Fleischmann and D. Pletcher, *J. Chem. Soc. Perkin Trans. 2*, 1973, 374.
[16] D. Pletcher and C. Z. Smith, *J. Chem. Soc. Perkin Trans. 1*, 1975, 948.
[17] J. P. Coleman, *J. Electrochem. Soc.*, 1981, **128**, 2561.
[18] L. L. Miller and B. F. Watkins, *J. Am. Chem. Soc.*, 1976, **98**, 1515.
[19] L. L. Miller and B. F. Watkins, *Tetrahedron Letters*, 1974, 4495.
[20] J. Y. Becker, *J. Org. Chem.*, 1977, **42**, 3997.
[21] A. Laurent, E. Laurent and R. Tardivel, *Tetrahedron*, 1974, **30**, 3423.
[22] J. M. Kornprobst, A. Laurent and E. Laurent-Dieuzeide, *Bull. Soc. chim. France*, 1968, 3657.
[23] A. Germain and A. Commeyras, *Tetrahedron*, 1981, **37**, 487.
[24] J. Y. Becker, *Tetrahedron Letters*, 1978, 1331.
[25] L. L. Miller and B. F. Watkins, *Tetrahedron Letters*, 1974, 4495.
[26] E. Laurent and R. Tardivel, *Tetrahedron Letters*, 1976, 2779.
[27] F. Vincent, R. Tardival and P. Mison, *Tetrahedron*, 1976, **32**, 1681.
[28] A. J. Baggaley and R. Brettle, *J. Chem. Soc. C*, 1968, 2055.
[29] K. C. Möller and H.-J. Schäfer, *Electrochim. Acta*, 1997, **42**, 1971.
[30] T. Shono, T. Nozoe, H. Maekawa and S. Kasimura, *Tetrahedron Letters*, 1988, **29**, 555.
[31] T. Shono, H. Maekawa, T. Nozoe and S. Kashimura, *Tetrahedron Letters*, 1990, **31**, 895.
[32] T. Shono and A. Ikeda, *J. Am. Chem. Soc.*, 1972, **94**, 7892.
[33] A. Guirado, G. P. Moss and J. H. P. Utley, *J. Chem. Soc. Chem. Commun.*, 1987, 41.
[34] T. Shono, A. Ikeda, J. Hayashi and S. Hakozaki, *J. Am. Chem. Soc.*, 1975, **97**, 4261.
[35] F. M. Banda and R. Brettle, *J. chem. Soc. Perkin Trans. 1*, 1975, 1907.
[36] C. Adams, N. Jacobsen and J. H. P. Utley, *J. Chem. Soc. Perkin Trans 2*, 1978, 1071.
[37] E. Laurent and M. Thomalla, *Bull. Soc. chim. France*, 1977, 834.
[38] E. Steckhan and H. Schäfer, *Angew. Chem. Int. Ed. Engl.*, 1974, **13**, 472.
[39] R. Engels, H. J. Schäfer and E. Steckhan, *Liebigs Ann. Chem.*, 1977, 204.
[40] M. Cariou, *Tetrahedron*, 1991, **47**, 799.
[41] D. Koch, H. Schäfer and E. Steckhan, *Chem. Ber.* 1974, **107**, 3640.
[42] T. Shono, Y. Matsumura, H. Hamaguchi, T. Imenichi and K. Yoshida, *Bull. Chem. Soc. Japan*, 1978, **51**, 2179.
[43] A. J. Birch, J. Grimshaw and H. R. Juneja, *J. Chem. Soc.*, 1961, 5194.
[44] H. Baltes, E. Steckhan and H. J. Schäfer, *Chem. Ber.*, 1978, **111**, 1294.
[45] L. V. Aniskova, A. G. Dubinin, L. A. Mirkind and M. Ya. Fioshin, *Zh. Org. Khim.*, 1973, **9**, 425.
[46] H. Baltes, L. Stork and H. J. Schäfer, *Angew. Chem. Int. Ed. Engl.*, 1977, **16**, 413.
[47] T. Shono, Y. Matsumura and Y. Nakoyawa, *J. Am. Chem. Soc.*, 1974, **96**, 3532.
[48] T. Shono, M. Okawa and I. Nishiguchi, *J. Am. Chem. Soc.*, 1975, **97**, 6144.
[49] H. J. Schäfer and E. Steckhan, *Tetrahedron Letters*, 1970, 3835.

[50] M. Hudson, M. R. Marzabaldi, K. D. Moeller and D. G. New, *J. Am. Chem. Soc.*, 1991, **113**, 7372.
[51] K. D. Moeller, M. R. Marzabadi, D. G. New, M. Y. Chiahg and S. Keith, *J. Am. Chem. Soc.*, 1990, **112**, 6123.
[52] K. D. Moeller and L. V. Tinao, *J. Am. Chem. Soc.*, 1992, **114**, 1033.
[53] T. Shono, I. Nishiguchi, S. Kashimura and M. Okawa, *Bull. Chem. Soc. Japan*, 1978, **51**, 2181.
[54] C. M. Hudson and K. D. Moeller, *J. Am. Chem. Soc.*, 1994, **116**, 3347.
[55] L. V. Tinao-Wooldridge, K. D. Moeller and C. M. Hudson, *J. Org. Chem.*, 1994, **59**, 2381.
[56] D. A. Frey, J. A. Marx and K. D. Moeller, *Electrochim. Acta*, 1997, **42**, 1967.
[57] M. Kimura, M. Nakashima and Y. Sawaki, *Denki Kagaku*, 1997, **65**, 676.
[58] J. E. Baldwin, *J. Chem. Soc. Chem. Commun.*, 1976, 734.
[59] D. G. New, Z. Tesfai and K. D. Moeller, *J. Org. Chem.*, 1996, **61**, 1578.
[60] S. Torii, K. Uneyama, T. Nakai and T. Yasuda, *Tetrahedron Letters*, 1981, **22**, 2291.
[61] C. Comninellis and E. Plattner, *J. Appl. Electrochem.*, 1982, **12**, 253.
[62] A. Mangi and C. W. Oloman, *J. Appl. Electrochem.*, 1987, **17**, 532.
[63] J. M. McIntyre (to Dow Chemical Co.), *U.S. Pat.*, 4726887; *Chem. Abstr.*, 1988, **108**, 205249.
[64] S. Torii, K. Uneyama, H. Tanaka, T. Yamanaka, T. Yasuda, M. Ono and Y. Kohmoto, *J. Org. Chem.*, 1981, **46**, 3312.
[65] T. Inokuchi, S. Matsumoto, M. Tsuji and S. Torii, *J. Org. Chem.*, 1992, **57**, 5023.
[66] T. Shono, Y. Matsumura, S. Katoh, K. Iteda, T. Fugita and T. Kamada, *Tetrahedron Letters*, 1989, **30**, 5309.
[67] K. Fujimoto, Y. Tokuda, Y. Matsubara, H. Maekawa, T. Mizano and I. Nishiguchi, *Tetrahedron Letters*, 1995, **36**, 7483.
[68] S. Torii, K. Uneyama and M. Ono, *Tetrahedron Letters*, 1980, **21**, 2741.
[69] S. Torii, K. Uneyama, M. Ono and T. Bannou, *J. Am. chem. Soc.*, 1981, **103**, 4606.
[70] T. Inokuchi, L. Ping, F. Hamaue, M. Izawa and S. Torii, *Chem. Letters*, 1994, 121.
[71] H. Tanaka, R. Kikuchi, M. Baba and S. Torii, *Bull. Chem. Soc. Japan*, 1995, **68**, 2989.
[72] A. Hickling and S. D. Richards, *J. Chem. Soc.*, 1940, 256.
[73] H. C. Kolb, M. S. VanNiewenhze and K. B. Sharpless, *Chem. Revs.*, 1994, **94**, 2483.
[74] S. Torii, P. Liu and H. Tanaka, *Chem. Letters*, 1995, 319.
[75] S. Torii, N. Bhuvaneswari, C. Amatore and A. Jutand, *J. Org. Chem.*, 1996, **61**, 3055.
[76] C. Kandzia and E. Steckhan, *Tetrahedron Letters*, 1994, **35**, 3695.

CHAPTER 3

REDUCTION OF ALKENES AND CONJUGATED ALKENES

Alkenes and Phenylalkenes

In general the isolated alkene bond is not reducible under electrochemical conditions. The major exception to this rule is tetrakis(trifluoromethyl)ethene in which the substituents are strongly electron withdrawing by the inductive effect. Alkene conjugation lowers the energy level of the lowest π^*-orbital so that polyenes and phenylethenes become reducible in the accessible potential range. Some relevant half-wave potentials are collected in Table 3.1. Reaction involves the addition of one electron to form the delocalised radical-anion. The radical-anions of conjugated alkenes are stable on the time scale of cyclic voltammetry. Addition of a second electron occurs at more negative potentials. Compounds where the alkene function is conjugated to an electron withdrawing π-system such as carbonyl or nitrile are more easily reduced to the radical-anion and the electrochemical reactions of these systems will be considered later in this chapter.

TABLE 3.1

Alkenes: Influence of conjugation on the polarographic half-wave potential for one-electron addition

Substrate	$E_{½}$ / V *vs.* sce	Solvent	Ref.
$(CF_3)_2C=C(CF_3)_2$	-0.445	Dimethylformamide	[1]
Cycloheptatriene	-2.6	Dimethylformamide	[2]
β-Carotene	-1.63	Tetrahydrofuran	[3]
$PhCH=CH_2$	-2.58	Dimethylformamide	[4]
$Ph_2C=CH_2$	-2.43	Dimethylformamide	[5]
trans-PhCH=CHPh	-2.17	Dimethylformamide	[5]
$Ph_2C=CHPh$	-2.04	Dimethylformamide	[5]
PhCH=CHCH=CHPh	-1.85	Dimethylformamide	[6]

Radical-anions from *cis*- and *trans*-stilbene are distinct species with individual uv- and esr-spectra [7]. The *cis*-form is metastable and slowly converts to the *trans*-form. The kinetic features of this interconversion have been studied by generating the *cis*-stilbene radical-anion in hexamethylphosphoramide by photochemically assisted electron transfer from a second radical-anion of less negative

reduction potential [8]. Isomerization involves electron transfer to the stilbene radical-anion from another radical-anion as electron donor, to give the stilbene dianion. The latter exists in an orthogonal form and collapses with donation of one electron to some acceptor molecule, yielding mainly *trans*-stilbene radical-anion.

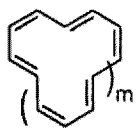
Cycloalkenes of the *anti*-Hückel type, where the number of conjugated π-electrons is $4n$ (n is an integer), take up a total of two electrons on reduction in aprotic solvents. The resulting di-anions have $(4n + 2)$ π–electrons and are relatively stable in the absence of proton donors. The Hückel $(4n + 2)$ systems are generally planar whereas the anti-Hückel systems are generally folded. In the case of cyclo-octatetraene, the reorganization energy associated with flattening the ring system contributes to slow electron-transfer leading to formation of the radical-anion [9]. Some $4n$ type cycloalkenes are more nearly planar and for these, the redox potential of the radical-anion is less negative than that of the hydrocarbon. Reduction then affords the dianion and no radical-anion intermediate can be detected [10, 11].

TABLE 3.2

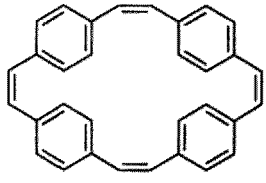
Polarography of anulenes with $4n$ conjugated π–electrons

Substrate	$E_{½}$ V *vs.* sce		Solvent	Ref.
	1st wave	2nd wave		
Cyclooctatetraene	-1.65	-1.95	Dimethylformamide	[12]
1,3,5,7-tetraphenyl-cyclooctatetraene	-1.706 [a]		Tetrahydrofuran	[10]
[12]-Annulene **1**	-1.35 [b]	-2.00 [b]	Dimethylformamide	[13]
[16]-Annulene **2**	-1.14	-1.52	Dimethylformamide	[14]
[2_4]-Paracyclophane-tetraene **3**	-1.69 [a]		Dimethylformamide	[11]

Footnotes: a: A single two-electron wave is found;
b: Measured *vs.* mercury pool as reference



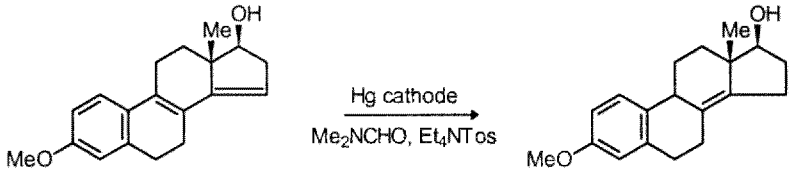
1, m = 1
2, m = 2



3

Reduction of polyenes in dimethylformamide leads to dihydro compounds as the first isolated products by addition of two electrons and two protons [15, 16].

However, too few examples are available to allow a general prediction of the position for hydrogen attachment. Electrochemical reduction of 1,4-diphenylbutadiene gives products from both 1,2- and 1,4-attachment of hydrogen [6]. The 1,2-addition product predominates in absence of a good proton donor because electrochemically generated base catalyses isomerisation of the 1,4-addition product. Reduction of a steroid diene **4** gives the 1,4-addition product [17].

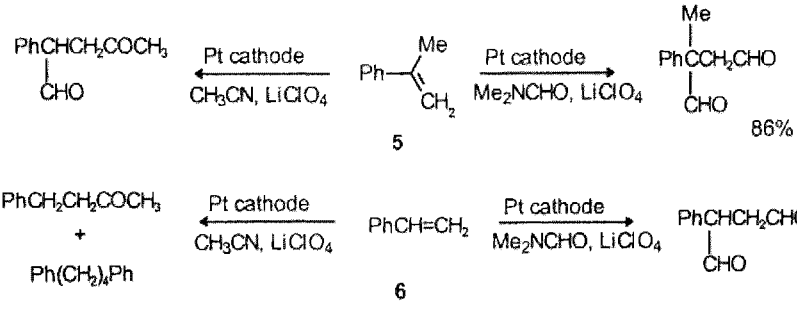


4

Stilbene derivatives are reduced in dimethylformamide to the dihydrocompound and in a number of cases [6,18] the mechanism is known to involve accumulation of the radical-anion in solution. This disproportionates to the starting material and the dianion, which is protonated.

Alkene Radical-Anions as Nucleophiles

Radical-anions derived from styrene derivatives are nucleophilic in character. Electrochemical reduction of α-methylstyrene **5** gives the radical-anion intermediate, which in the absence of other electrophiles is sufficiently nucleophilic to attack dimethylformamide or acetonitrile [19]. The radical-anion from styrene **6** under-

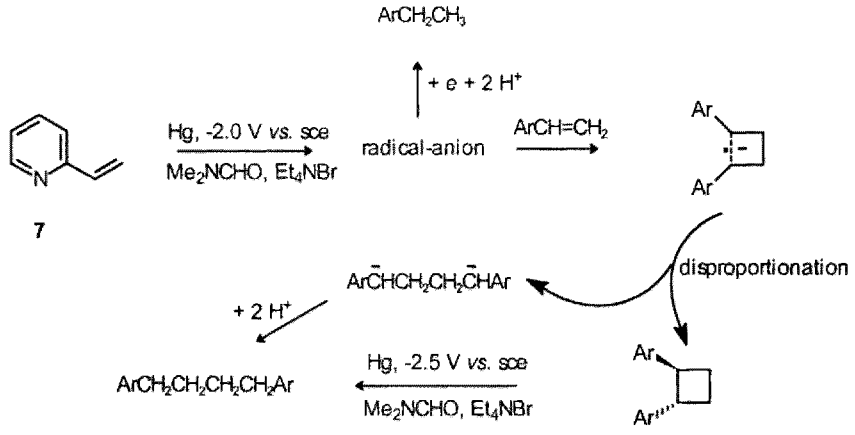


5

6

goes a related reaction with the solvent in competition with formation of 1,4-diphenylbutane [19]. 1,1-Diphenylethene however yields only 1,1-diphenylethane and 1,1,4,4-tetraphenylbutane on reduction in dimethylformamide [20].

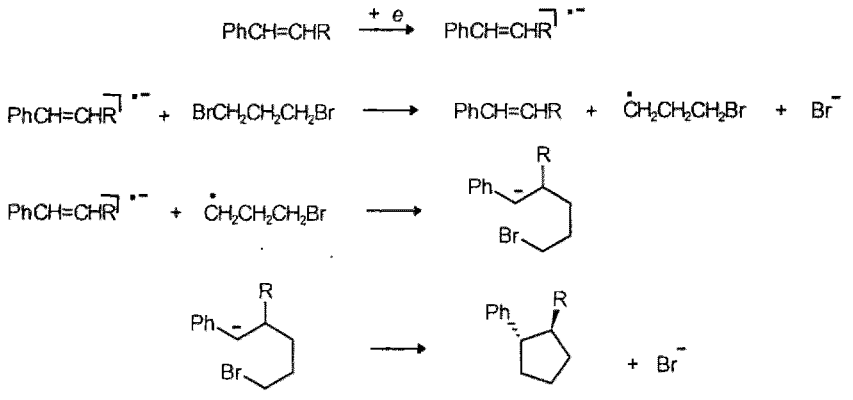
The formation of butanes by reduction of arylethenes may arise by radical-radical coupling of two radical-anions giving a dianion, which is then protonated. An alternative route is by nucleophilic addition onto one neutral molecule of the radical-anion, followed by further reduction and protonation. In support of this alternative, cyclobutanes have been isolated from electrochemical reduction of phenylvinylsulphones [21] and vinylpyridines [22]. A mechanism for the latter process is illustrated for the case of 2-vinylpyridine **7**. Nucleophilic attack of a radical-anion on the substrate gives an intermediate and this disproportionates to form the cyclobutane and a 1,4-diarylbutane. Cyclobutanes are themselves reduced with ring opening to form the 1,4-diarylbutane.



Arylalkenes [23] and alkenes with electron withdrawing substituents [24] can be bis-alkylated across the alkene bond by electrochemical reaction with dihaloalkanes giving 3- to 6-membered carbocyclic products in good yields. The best reaction conditions use an undivided cell with a nickel cathode and a sacrificial aluminium anode in dimethylformamide or N-methylpyrrolidone containing a tetraalkylammonium salt. Anodically generated aluminium ions are essential for the reaction. 1,2-Disubstituted alkenes, regardless of their stereochemistry, are converted to the *trans*-substituted cycloalkane.

In these reactions (Scheme 3.1), the first electron addition is to the alkene giving a radical-anion. This interacts with the alkyl halide to transfer an electron, in a process driven by simultaneous cleavage of the carbon-halogen bond. The alkyl radical formed in this manner adds an alkene radical-anion [25]. Aluminium ions generated at the anode are essential to the overall process. They coordinate with the intermediate carbanion, which then interacts with the second halogen substituent in an S_N2 process to form the carbocycle.

Reaction with the appropriate α,ω–dihalide gives rise to 4-, 5- or 6-membered rings. Three-membered rings are formed by a similar reaction between the alkene

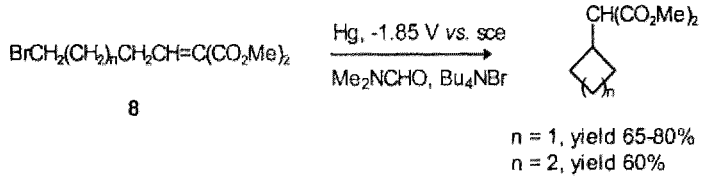


Scheme 3.1. Reductive alklyation of phenylalkenes.

and dichloromethane in an undivided cell [24].

The intramolecular reaction of activated alkenes of the type **8** leads to the formation of 5- or 6-membered rings [26] and has been carried out only at a mercury cathode in a divided cell. In these processes, the activated alkene radical-anion is formed at a less negative potential than that required for cleavage of the carbon-bromine bond. Cyclization then occurs by nucleophilic substitution.

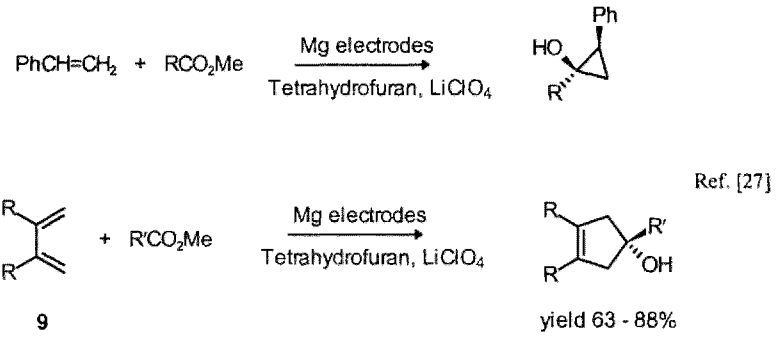
Cyclo-coupling between arylalkenes and an aliphatic ester function is achieved by electrolysis in tetrahydrofuran using cathode and anode both of magnesium in an undivided cell. The first electron addition is to the arylalkene. The bond forming steps involves nucleophilic attack by radical-anions or dianions derived from the alkene. Magnesium ions generated at the anode are essential to the process. The



8

n = 1, yield 65-80%
n = 2, yield 60%

related cyclo-coupling of 1,3-dienes **9** with esters proceeds in good yield. These reactions involve the alkene radical-anion [27]. Benzoate esters do not take part in any of these processes because they are reduced to the radical-anion in preference



and at lower potentials than the arylalkene or the diene.

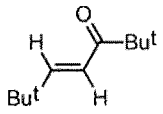
The radical-anions from from alkenes with electron withdrawing substituents will add to carbon dioxide [28]. This process involves the alkene radical-anion, which transfers an electron to carbon dioxide for which $E^{\circ} = -2.21$ V *vs.* sce [29]. Further reaction then occurs by combination of carbon dioxide and alkene radcal-anions [30]. The carbanion centre formed in this union may either be protonated or react with another molecule of carbon dioxide. If there is a suitable Michael acceptor group present, this carbanion undergoes an intramolecular addition reaction

Activated Alkenes – Introduction

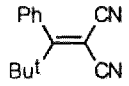
Conjugation with an electron-withdrawing group substantially lowers the energy of the lowest unoccupied molecular π-orbital, which results in less negative reduction potentials for the alkene system. The class of compounds is referred to as activated alkenes. Polarographic half-wave potentials for some activated alkenes in aprotic solvents are listed in Table 3.3

Dimerization is the characteristic reaction of radical-anions from activated alkenes. The rate constants for dimerization are high and the conjugate acids from such alkene radical-anions in many cases have low pKa values and. The data in Table 3.4 were obtained by following the changes in uv-absorbance after pule-radiolysis of the substrate in an aqueous buffer. Attachment of a solvated electron leads to the radical-anion. Changes in the initial absorbance with pH lead to determination of the pK_a value, while the dimerization rate can be determined from changes in absorbance over a longer time scale. Radical-anions from esters and amides are pro-

tonated first on oxygen. Bulky substituents on the alkene bond increase the lifetime of the radical-anion in aprotic solvents and the radical-anions derived from **10** and **11** persist for seconds in aprotic aolvents when tetraalkylammonium counter ions are present [31,34]. In the presence of sodium or lithium ions, these radical-anions decay rapidly.



10



11

TABLE 3.3
Polarographic half-wave potentials for activated alkenes in aprotic solvents

Substrate	$E_{1/2}$ / V *vs.* sce	Solvent	Ref.
CH_2=CHCN	-1.94	Dimethylformamide	[32]
PhCH=CHCN	-1.784	Dimethylformamide	[28]
CH_2=$CHCO_2$Me	-2.10	Acetonitrile	[28]
PhCH=$CHCO_2$Me	-1.781	Dimethylformamide	[30]
E-MeO_2CCH=$CHCO_2$Me	-1.35	Dimethylformamide	[33]
Z-MeO_2CCH=$CHCO_2$Me	-1.53	Acetonitrile	[28]
Bu^tCH=CHCOBu^t	-2.224	Dimethylformamide	[34]
PhCH=CHCOBu^t	-1.707	Dimethylformamide	[35]
PhCH=CHCOPh	-1.34	Dimethylformamide	[36]

Development of the industrial process for electrochemical conversion of acrylonitrile to adiponitrile led to extensive investigation into the mechanism of the dimerization process. Reactions of acrylonitrile radical-anion are too fast for investigation but the dimerization step, for a number of more amenable substrates, has been investigated in aprotic solvents by electrochemical techniques. Pulse-radiolysis methods have also been used to study reactions in aqueous media.

TABLE 3.4
Properties of radical-anions determined by pulse radiolysis in buffered aqueous solution

Substrate [S]	Bimolecular rate constant (/ M^{-1} s^{-1}) for		pK_a for [HS•]	Ref.
	decay of [S•⁻]	decay of [HS•]		
Z-$MeO_2CCH{=}CHCO_2Me$	2.5×10^8	-[a]	4.8	[37]
E-$MeO_2CCH{=}CHCO_2Me$	2.9×10^8	7.0×10^8	2.8	[37]
$PhCO_2Me$	-	-	5.5	[38]
$CH_2{=}CMeCONH_2$	1.3×10^{6} [b]	4.0×10^9	8.0	[39]
$PhCONH_2$	-	-	7.7	[40]
PhCN	-	-	7.2	[41]

Footnotes: (a): Reaction too fast to measure.
(b): 1st order decay (/ s^{-1}).

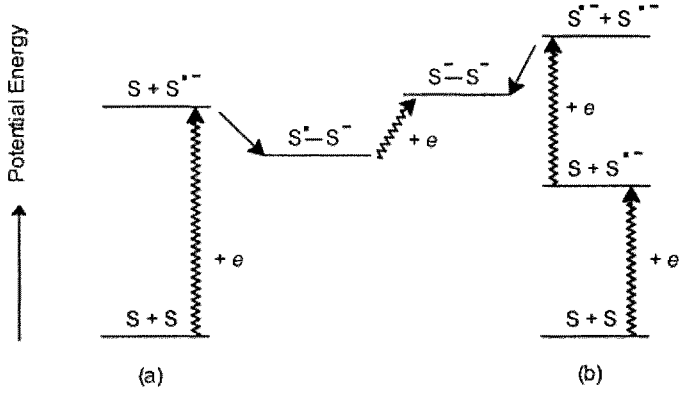
Activated Alkenes – Dimerization in Aprotic Media

Investigations into the mechanism of dimerization in aprotic solvents has been restricted to those activated alkenes reacting with bimolecular rate constants up to 10^6 M^{-1} s^{-1}. Protonation of the radical-anion by residual water is generally not important. Traces of water, particularly in the cases of alkenoate esters, do however increase the dimerization rate and act by solvating the ionic centre [42, 43]. The rate constant for a particular reaction also depends on the nature of the counter ion, being of the same order of magnitude with various tetraalkylammonium ions but much larger with lithium or sodium ions [44, 45].

The decay of a radical-anion can be followed directly by generating the intermediate within the cavity of an esr spectrometer through application of a controlled potential pulse to the cathode of a thin electrochemical cell [46]. Loss of the radical-anion is then followed by decay of the esr signal. Decay is second order in radical-ion concentration for dimethyl fumarate ($k = 160$ M^{-1} s^{-1}) and for cinnamonitrile ($k = 2.1 \times 10^3$ M^{-1} s^{-1}) in dimethylformamide with tetrabutylammonium counter ion. Similar values for these rate constants have been obtained using purely electrochemical techniques [47].

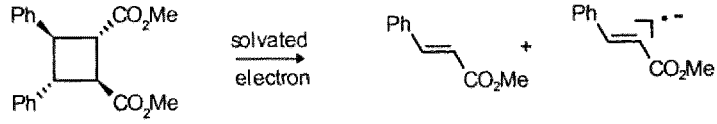
Electrodimerization of activated alkenes in aprotic solvents occurs by radical-ion, radical-ion coupling. There is ample evidence for steric inhibition to this process. In contrast to the low reactivity of **11**, 4-methylbenzalmalononitrile radical-ion dimerises with a rate constant of 5.8×10^6 M^{-1} s^{-1} in dimethylformamide containing tetraalkylammonium ions [48]. Dimethyl maleate radical-anion dimerises faster than dimethylfumarate radical-anion by a factor of 10^3 in dimethylformamide [49].

In a previous section (p. 57) experimental evidence for the electrodimerization of vinylpyridines by a radical-ion, substrate coupling mechanism was presented. A diagrammatic representation (Scheme 3.1) of the pathway for this and for the radical-anion, radical-anion coupling mechanism illustrates the particular situations under which each mechanism operates. When the free energy of formation of the radical-anion is large sufficient energy is available to drive the radical-ion, substrate coupling. Otherwise energy to drive the coupling process can only be obtained by combining the resources of two lower energy radical-anions. Where there is substantial steric hindrance, as with **10** and **11**, neither of the dimeric species $S^{\cdot}$-S^{-} nor S^{-}-S^{-} will form because strain energy contributes to raising their free energy of formation to a level greater than that available from the combined resources of two radical-anions.



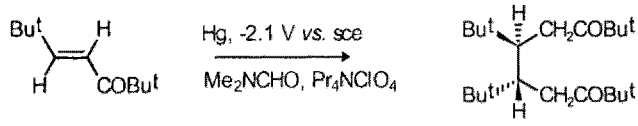
Scheme 3.1. Schematic energy level diagram comparing (a) the radical-anion substrate and (b) the radical-anion radical-anion coupling routes for the electrodimerization process. Wavy lines indicate an electron transfer step.

The fragmentation of radical-anions from 1,2-diarylcyclobutanes is also controlled by the free energy of the arylalkene radical-anion, which can be formed in a two carbon-carbon bond cleavage. The radical-anion from **12**, generated by pulse-radiolysis, fragments to methyl cinnamate and methyl cinnamate radical-anion [50]. Here the free energy change is sufficient to allow cleavage of two carbon-carbon bonds. In contrast, the radical-anion from 1,2-dipyrid-2-ylcyclobutane (see p. 57) undergoes cleavage to a 1,4-dipyridylbutane species having separated radical and ionic centres [22]. The free energy change here is only able to accommodate one carbon-carbon bond cleavage.

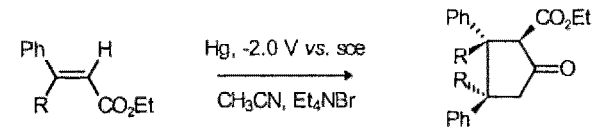


12

Reduction in aprotic solvents may be accompanied by side reactions due to the alkaline conditions developed around the cathode. Preparative work is thus limited to substrates undergoing these unwanted side reactions relatively slowly. Reductive dimerizations in aprotic solvents show a high degree of stereoselectivity in favour of carbon-carbon bond formation to yield the (±)-isomer. A templating action is brought about either by co-ordination to a lithium or sodium ion of two reacting



Ref. [34]

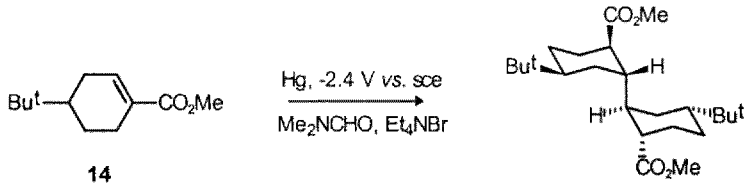


Ref. [53, 54]

13

radical-anions [34, 51], or by association between two radical-anions and a molecule of water [43]. Radical-anions are not sufficiently basic to be protonated by traces of water in aprotic solvents. The dimerization of cinnamate esters is followed by an intramolecular Diekmann cyclization step to form a cyclopentanone **13** [52, 53]. The stereochemistry of the product is rigorously established for **13**, **R** = **H**, and a similar result is inferred for the other derivatives. In the case of a cyclohexenecarboxylate **14**, stereoelectronic control of radical-anion interaction leads to a highly specific axial coupling of the cyclohexane rings [54].

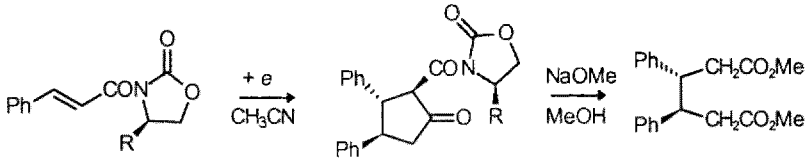
The hydrodimerization of cinnamate esters formed with a chiral alcohol leads to asymmetric induction at the carbon-carbon bond formation step. The ester with borneol gives a chiral cyclopentanone with greater than 95% enantiomeric excess [55]. A second approach towards achieving a chiral carbon-carbon bond formation has been to use the asymmetric oxazolidones **15** as substrates. These are reduced at



14

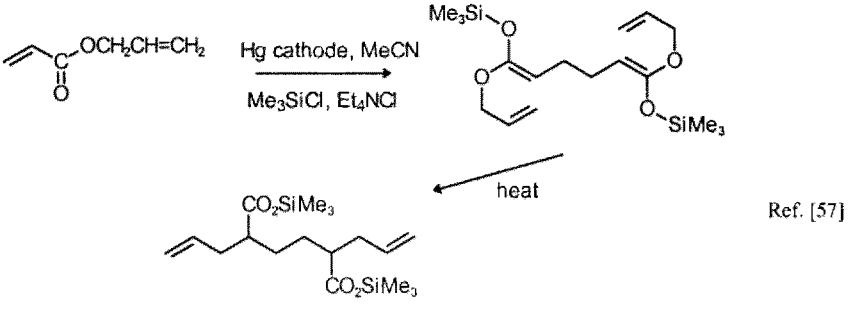
a lead cathode with a platinum anode in an undivided cell. The product can be transformed into an enantiomer of methyl 3,4-diphenyladipate [56].

The first formed enolate products from hydrodimerization of esters are trapped by reaction with added chlorotrimethylsilane. By starting with allyl esters, this hy-



15

drodimerization process has been combined with an *in situ* Claisen rearrangement, thus incorporating the allyl group into the dimer carbon chain [57].



Ref. [57]

Activated Alkenes – Dimerization in Protic Media

The formation of dimers by reduction of α,β-unsaturated ketones in aqueous media is well documented in the early literature of electrochemistry. Reductants include sodium or aluminium amalgams [58], dissolving zinc and a lead cathode in both acid and alkaline conditions [59,60]. Mixtures of dimers and dihydro derivatives were isolated. As the concept of the hydrodimerization of activated alkenes

developed, work concentrated on carrying out the process in aqueous solution. Several industrial groups realised that, if conditions could be found for the conversion of acrylonitrile to adiponitrile **16** in good yield, with minimum formation of propanonitrile, this would be a key step in a new low-cost process for the formation of Nylon-66 intermediates. Knunyants and Vyazankin [61] achieved moderate

$$2\ CH_2{=}CHCN + 2\ H^+ + 2\ e \longrightarrow NCCH_2CH_2CH_2CH_2CN$$

16

success using potassium amalgam as the reductant. These workers introduced the term hydrodimerization for the class of process to which the reduction of acrylonitrile belongs.

Baizer, working at the Monsanto Company, showed that good yields of adiponitrile are obtained from aqueous solutions by reduction at mercury or lead in the presence of a high concentration of quaternary ammonium salt [62]. Tetraethylammonium toluene-4-sulphonate was favoured as electrolyte. The first commercial plant operating the process was commissioned in 1965. It used a divided cell system with a lead cathode and aqueous tetraethylammonium ethylsulphate as electrolyte, with the addition of acid to regulate the pH. A lead anode with an anolyte of dilute sulphuric acid was employed.

It is commercially advantageous to operate cells with no diaphragm since the cell diaphragm is the weakest point in the system. Achievement of this aim rests upon finding an anode reaction that destroys neither the substrate nor the product. Russian workers [63] showed that up to 90 % yields of adiponitrile can be obtained at a graphite cathode in an undivided cell with an iron oxide anode, provided that phosphate and tetraalkylammonium ions are present. Further research contributions from Monsanto, BASF and Japanese companies led to the present system for hydrodimerization of acrylonitrile using an undivided cell [64,65].

The most efficient system devised by Monsanto uses electrodes fabricated from carbon steel plate, electro-coated on one face with cadmium. These are stacked in parallel so that the electrolyte can be pumped through the gap between successive plates. Overall the system forms a series of electrochemical cells with a cadmium cathode and a carbon steel anode. Each plate of metal forms the cathode of one cell and the anode of the next in the stack. Electric current is passed across the stack. The electrolyte contains phosphate and borate salts as corrosion inhibitors, EDTA to chelate any cadmium and iron ions generated by corrosion together with hexamethylenebis(ethyldibutylammonium) phosphate to provide the necessary tetraalkylammonium ions. This electrolyte circulates through the cell from a reservoir and there is provision for the introduction of acrylonitrile and water as feedstock. The overall cell reaction is:

$$4\ CH_2{=}CHCN + 2\ H_2O \longrightarrow 2\ NCCH_2CH_2CH_2CH_2CN + O_2$$

and oxygen is evolved at the anode. Adiponitrile, being relatively insoluble in water, accumulates as an upper layer in the electrolyte reservoir from where it is continuously bled off. A portion of the electrolyte is also continuously bled off to allow removal of any propanonitrile by distillation and the recovery of dissolved cadmium and iron. Conducting salt is recovered and returned to the system. It is found advantageous to allow slight corrosion of the electrodes because this maintains a clean and active surface.

Fumaronitrile, which is reduced at less negative potentials than acrylonitrile, has been used as a model compound for kinetic investigation into hydrodimerization in aqueous solution [66]. In unbuffered lithium chloride solution, fumaronitrile shows one two-electron polarographic wave. Progressive addition of aliquots of a surfactant cause a gradual decrease in the height of this wave and the simultaneous appearance of a second more negative reduction wave until eventually two one-electron waves are observed. The role of these additives is to displace adsorbed water from the electrode surface. Adsorbed water molecules are considerably more acidic than bulk water and will protonate the radical-anion intermediate. By analogy with benzonitrile radical-anion (Table 3.4), fumaronitrile radical-anion is expected to have a pK_a value around 7. When no surfactant is present, the radical-anion is protonated at the electrode surface. The radical formed by this process at the electrode surface accepts a further electron and a proton to yield succinonitrile. When surfactant is present, the radical-anion passes into the bulk of the solution where it dimerises to a dianion, which is protonated. Introduction of high concentrations of phosphate buffer, pH 7, promotes protonation of the radical-anion in the bulk solution and suppresses the dimerization step.

The dichotomy between one-electron and two-electron reactions is also seen in the reduction of N-ethylmaleinimide in 95 % ethanol containing aqueous buffers [67]. At pH < 4, one two-electron polarographic wave is observed (Figure 3.1) and reduction leads to N-ethylsuccinimide. At pH > 5, two one-electron polarographic waves are seen and reduction at the potential of the first wave leads to a hydrodimer. In aqueous solution N-methylmaleinimide radical-anion has pK_a of 2.85 (Table 3.4) so the change in polarographic behaviour of the N-ethyl compound with pH seen in 95 % ethanol at pH 4 is due to acid-base behaviour of the radical-anion. In acid solution, the radical-anion is protonated rapidly, the resulting radical being further reduced, whereas at the higher pH values, radical-anions survive to dimerise.

The hydrodimerization reaction at mercury or lead in aqueous dimethylformamide containing tetraalkylammoniun salts has been examined for a range of α,β–unsaturated amides, esters and nitriles, see Table 3.5. Reactions are carried out at controlled potential at the plateau of the first polarographic wave and the solution becomes alkaline due to base generated at the cathode. Protonation of the radical-anion is discouraged and dimerization leads to a mixture of *meso*- and (±)-products by formation of a β,β-linkage. With a large excess of water present, the

radical-anions are well solvated and the templating action of a trace of water (see p. 63) is swamped. Hydrodimerization of N,N-dimethylcinnamamide is claimed to

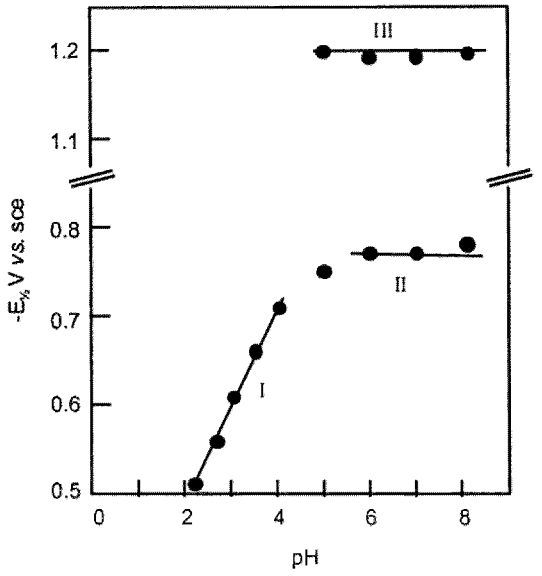
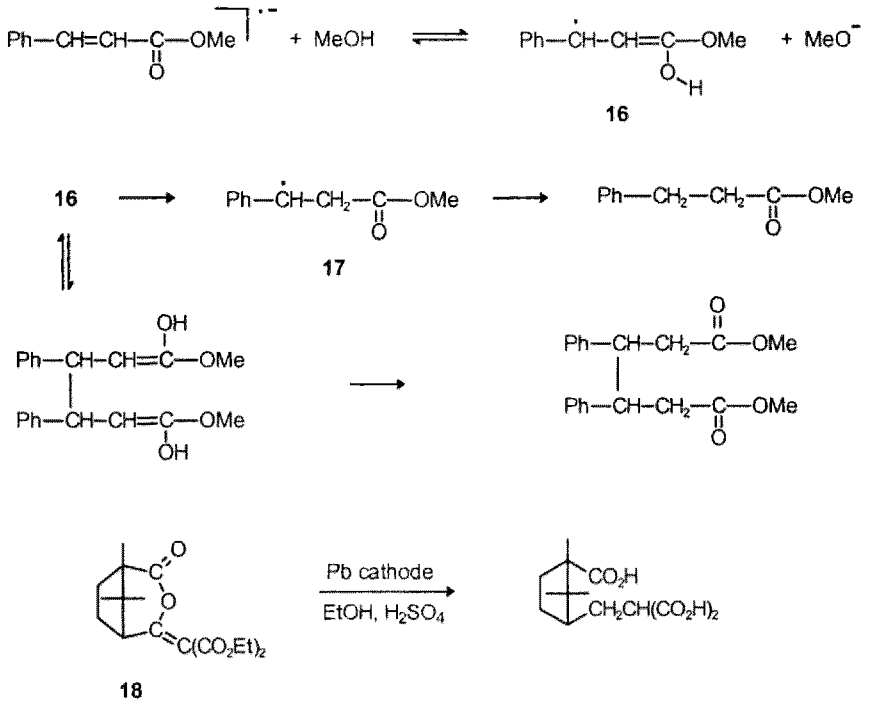


Figure 3.1 . Changes with pH of the half-wave potential ($E_{½}$) for the polarographic waves of N-ethylmaleinimide in alcoholic aqueous buffers. Wave I is due to a two-electron process, waves II and III are each due to one-electron processes. Data from ref. [67].

form the α,α-linkage, but the structure of the product is not well established. Also, reduction of the cinnamamide **15** in tetrahydrofuran with lithium ions present leads to a mixture of the meso- and (±)-isomers of 3,4-diphenyladipic acid diamide [56].

Electrochemical reduction of methyl cinnamate in methanol affords a mixture of the saturated ester and the *meso*- and (±)-hydrodimers [68]. Loss of the initially formed radical-anion follows a first order rate law [69]. The rate-determining step becomes protonation of the radical-anion to give an allyl radical **16**, which is reduced only at a more negative potential. Dimerization of the allyl radical leads to the hydrodimers. The tautomeric alkyl radical **17** is more easily reduced than the starting ester and is converted to the saturated ester. The tautomerism **16** to **17** becomes very fast in acid solution so that methyl dihydrocinnamate becomes the major product from reduction of methyl cinnamate in an aqueous buffer of pH 4 [70]. Hydrodimerization of dimethyl maleate in methanol, at a pH where the rate of enol-keto tautomerization is slowed down, has been developed to a pilot scale process [71]. The ester **18** derived from camphoric anhydride is reduced in acid solution to give the dihydrocompound [72]. Reduction of the sterically hindered

norbornenedicarboxylate **19** gives only the dihydro derivative in both acid and alkaline solution [73].

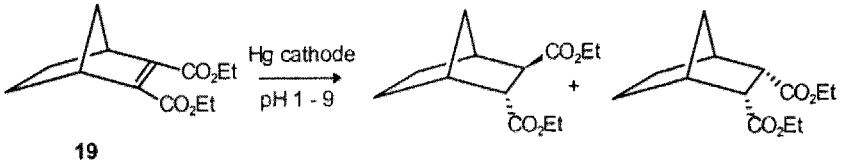


16

17

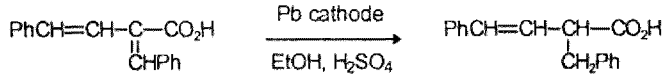
18

Electrochemical reduction of conjugated alkenoic acids in alkaline solution generally leads to the dihydrocompound and negligible amounts of the hydrodimer are formed. Examples include the conversion of maleic or fumaric acid to succinic



19

acid [74] and the conversion of cinnamic acid to dihydrocinnamic acid at a mercury cathode [75]. The dihydrocompound is also usually obtained by reduction in acid solution, for example with maleic or fumaric acids [76]. The advantage of this electrochemical method lies in its selectivity in the presence of non-conjugated alkene bonds, for example in the reduction of **20** where one alkene bond is not reduced [77]. The reaction will tolerate a halogen substituent in 2-chlorocinnamic acid [78] and the cyano substituent in 2-cyanocinnamic acid [79]. No stereoselec-



20

tivity is shown in the reduction of cyclohexen-1,2-dicarboxylic acid to cyclohexane-1,2-dicarboxylic acid [80]. The few examples of hydrodimerization of alkenoic acids include reduction of sorbic acid in dioxan, sulphuric acid at a mercury cathode [81] and of cinnamic acid under similar conditions [68].

TABLE 3.5

Hydrodimers from the controlled potential reduction of activated alkenes in aqueous dimethylformamide containing tetraethylammonium toluene-4-sulphonate Ref. [82].

Substrate	Hydrodimer Product	Yield / %
PhCH=CHCN	$PhCH(CH_2CN)_2$	87
$(CH_3)_2C=C(CH_3)CN$	Dihydrocompound formed	
$CH_2=CHCH=CHCN$	$NC(CH_2)_6CN$ (after hydrogenation)	50
PhCOCH=CHCN	$NCCH(CH_2COPh)_2$	55
$PhCOCH=CHCO_2Et$	$PhCOCH_2CH(CO_2Et)_2$	77
$NCCH=CHCO_2Et$	$NCCH(CH_2CO_2Et)_2$	84
$PhCH=CHCONMe_2$	$PhCH_2CH(CONMe_2)_2$	82

α,β-Unsaturated Aldehydes and Ketones

Only non-enolizable eneones give satisfactory yields of hydrodimer on reduction in aprotic solvents [83]. A suitable aqueous buffer is needed with enolizable eneones to control base catalysed side reactions of condensation and oligomerisation. The polarographic behaviour of eneones in buffers is illustrated using cyclo-

hexenone (Figure 3.2) [84, 85]. Mesityl oxide shows similar behaviour [86]. A one-electron wave is seen in acid solution and the half-wave potential varies with

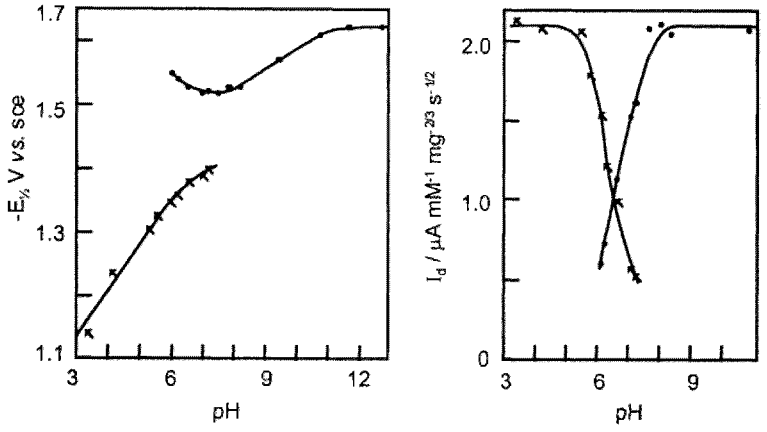


Figure 3.2. Variation of half-wave potential ($E_{½}$) and diffusion current constant (I) for the two polarographic waves of cyclohexenone in aqueous buffers. Data from ref. [84].

pH. Early workers considered this behaviour due to equlibrium preprotonation of the eneone followed by one-electron addition. However when electron and proton addition occur simultaneously, this is equivalent to the following two equlibria being established in the layer close to the electrode:

$$C{=}C{-}C{=}O + e \rightleftharpoons C{=}C{-}C{=}\overline{O}^{\bullet -}$$

$$C{=}C{-}C{=}\overline{O}^{\bullet -} + H^{+} \rightleftharpoons \dot{C}{-}C{=}C{-}OH \longleftrightarrow C{=}C{-}\dot{C}{-}OH$$

Protonation of the radical-anion occurs on oxygen to give an enol-radical. The latter species is a resonance hybrid. It takes part in a fast irreversible radical-radical dimerization step and since the species has two potential radical sites, three structural isomers of the hydrodimer can be formed. The main product is formed from a transition state with minimum steric hindrence between the radical centres.

Around pH 6-8, two polarographic waves are seen and the sum of the two wave heights corresponds to a one-electron process. The first wave is due to the two reactions above and decreases in height because protons are in low concentration and do not diffuse sufficiently fast to the electrode surface. The second wave is due to formation of the radical-anion followed by proton transfer from a general acid present as a component of the buffer. In alkaline solution, the concentration of acid component in the buffer decreases and this wave moves towards more negative potentials. Finally, $E_{½}$ becomes independent of pH in very alkaline solution where

$pH > pK_a$ for the enol-radical. From independent work [87], the pK_a of the conjugate acid from the radical-anion of propenal is 9.6.

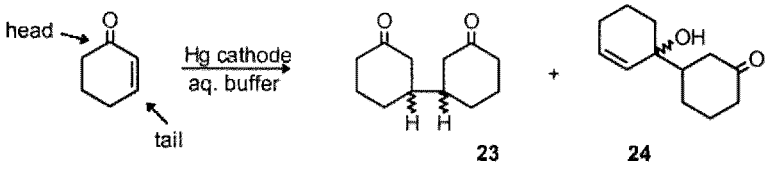
This explanation for the two polarographic waves seen in Figure 3.2 suggests that the region of transition between the two waves will be sensitive to buffer concentration and composition. Such effects are seen in the polarography-pH profiles of steroid enones, some of which [88] show behaviour like that of cyclohexenone while others show only a linear variation of half-wave potential over the whole pH range of 2 – 11 [89, 90].

The enone **21** shows two waves in acid solution, each due to one-electron addition [91]. The first wave is due to the reactions discussed above. The further wave

21 **22**

at more negative potentials is due to reduction of the enol-radical, followed by protonation. Conjugation with the benzene ring lowers the redox potential for this process so that it becomes observable within the accessible potential window. The half-wave potential for this second electron addition is almost independent of pH while for the first electron addition the potential becomes more negative with increasing pH. The two waves eventually coalesce above pH 8 to a single two-electron wave. In the case of 1,3-diphenylpropenone **22**, two separate one-electron waves are found over the entire pH range [92]. The first wave is equivalent to the behaviour of cyclohexenone while the wave at more negative potentials is due to reduction of the enol-radical.

Preparative scale reduction of cyclohexanone affords principally the tail-to-tail hydrodimer **23** and some of the head-to-tail isomer **24** [93]. The proportions vary with pH, and no head-to-head pinacol has been isolated. Both *meso*- and (±)-forms

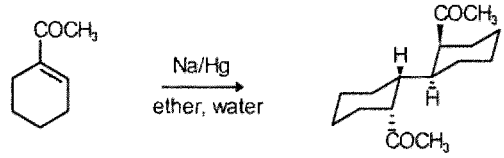


23 **24**

pH 1	74 %	26 %
pH 13	90 %	10 %

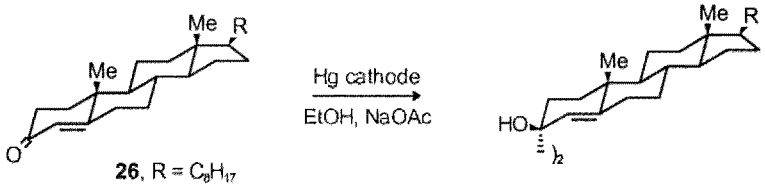
of the tail-to-tail isomer are found with the *meso*-form predominating. Tail-to-tail hydrodimers are known from reduction, in buffer mixtures, of other cyclohexenones including isophorone,which gives mainly the *meso*-product [94], carvone [95, 96] and piperitone [97]. In many cases the stereochemistry of the products have been elucidated [98] but data on relative yields are not available. Cyclopente-

nones also afford the tail-to-tail hydrodimer with the *meso*-form predominating [99]. Reduction of 1-acetylcyclohexenone by sodium amalgam also affords the tail-to-tail *meso*-hydrodimer **25** [100]

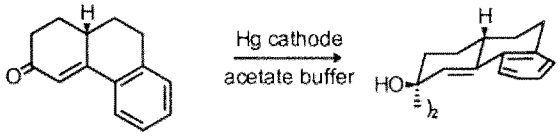


25

Reduction of steroid enones like cholestenone **26**, with a rigid ring conformation, leads to head-to-head pinacol dimers because of steric hindrance at the alternative dimerization site, and reaction occurs through the α–face of the radical intermediate [101, 102]. The α–face is opposite to the angular methyl substituent



26, R = C_8H_{17}



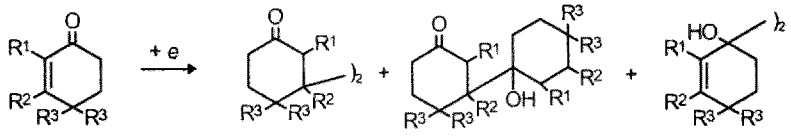
27

on ring-A. The steroid analogue (±)-**27** gives only one pinacol isomer on electrochemical reduction. This is formed by union, through the α–face, of two radical intermediates, each of which is derived from a molecule of enone with the same absolute stereochemistry [103]. The product is therefore a single racemate and arises through a transition state, which maximises overlap of π–systems and minimises interactions of the σ–skeleton.

Steric considerations, which influence the relative proportions of the three hydrodimers, are demonstrated by the reduction of substituted cyclohexenones **28** in acetonitrile (Table 3.6). The ratio of products is influenced by steric hindrance at the radical centres and also depends on the concentration of water in the solvent.

In the non-cyclic alkenone series, regioselectivity in the hydrodimerization step is not well controlled. Dissolving metal reducing agents such as sodium amalgam,

and zinc or magnesium in acid, have frequently been used. These yield the same products as electrochemical reduction and some control in favour of the head-to-



28 **29** **30** **31**

head pinacol hydrodimer can be achieved by reduction with dissolving zinc in acetic acid [104].

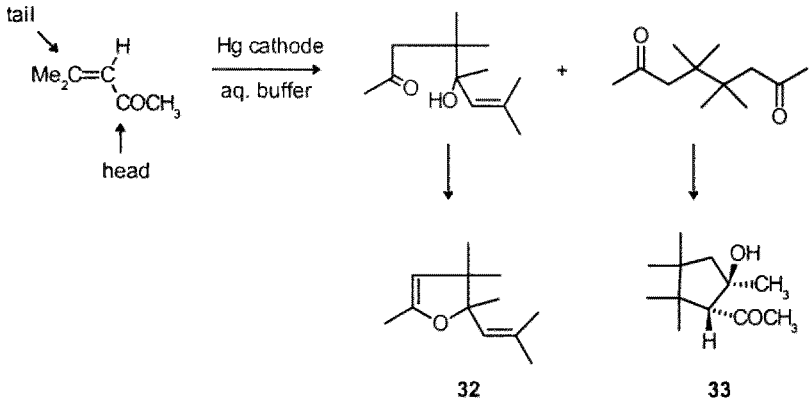
TABLE 3.6

Products from reduction of cyclohexenones **28** at a mercury cathode in acetonitrile with tetrabutylammonium fluoroborate as supporting electrolyte, from ref. [105].

Substrate **28** with	Water / %	Product yields / **29**	**30**	**31**
$R^1 = R^2 = R^3 = H$	0	97		
	5	97		
$R^1 = R^2 = H$, R^3 =Me	0	52	11	16
	5	28	4	67
$R^1 = R^2$ = Me, R^3 = H	0	10	40	50
	5		10	90
R^1 =H, R^2 =R^3 = Me	0	10	60	30
	5		45	50

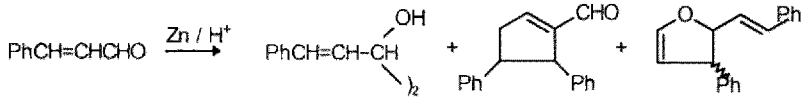
Mesityl oxide at a mercury cathode in acetate buffer affords a mixture of tail-to-tail and head-to-tail hydrodimers. The initally formed reduction products undergo further reactions so that **32** and **33** are isolated [106, 107, 108]. A low yield of the head-to-head glycol has been isolated from some reactions [109, 110, 111]. The structures of these products were confirmed in 1955 [112]. Methyl vinyl ketone yields a mixture of tail-to-tail and head-to-head hydrodimers [113].

Addition of chromium(III) [114] or tin(II) [115] ions to the electrolyte strongly favours the formation of head-to-head pinacols from the reduction of enones. It is believed that these ions direct the dimerization step by coordination through the oxygen centre



32 **33**

Some control of regioselectivity in favour of the tail-to-tail hydrodimer can be achieved with a phenyl substituent in the tail position and any group other than hydrogen in the head position. Reduction of cinnamaldehyde **34** shows poor regio-

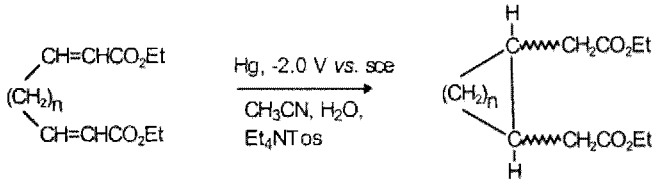


34 *meso-* + (±)- *cis-* + *trans-*

and stereo-selectivity, affording all three types of hydrodimer [116]. Here the tail-to-tail and head-to-tail hydrodimers undergo further condensation under the reaction conditions to yield the isolated products. In contrast, benzalacetone under the same reaction conditions as cinnamaldehyde affords 80 % of the tail-to-tail *meso*-hydro-dimer [117], and reduction of 1,3-diphenylpropenone gives a mixture of the tail-to-tail *meso*- and (±)-hydrodimers [118, 119].

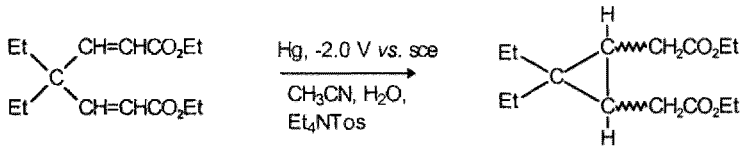
Intramolecular Cyclization

Intramolecular carbon-carbon bond formation during reduction of a molecule possessing two activated alkene groups offers a synthetic route to cyclic structures.



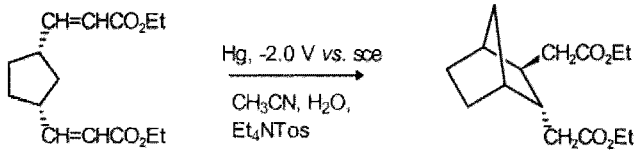
35

Electrochemical reduction of a homologous series of unsaturated esters **35** at a mercury cathode in aqueous acetonitrile gives satisfactory yields for four to six membered ring structures (Table 3.7) [120]. Cyclization under these conditions is not stereoselective. Attempts to prepare rings of larger size lead to mixtures of oligomers by the intramolecular dimerization process and slow addition of the substrate to the catholyte does not improve yields of cyclic products. Very high yields of the three membered ring compound **36** can be obtained and it has long been



36

known that dialkyl substitution favours cyclopropane formation; the Thorpe-Ingold



37, yield 37 %

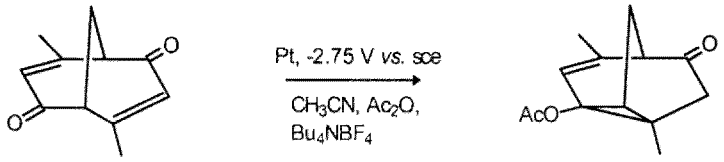
effect [121]. Electrochemical cyclization has been applied to the construction of the norbornane skeleton **37** and to the synthesis of heterocyclic compounds using appropriate analogues of **35**.

TABLE 3.7

Intramolecular cyclization of bis(activate alkenes) by reduction at a mercury cathode in aqueous acetonitrile containing tetraethylammonium toluene-4-sulphonate. Data from ref. [120].

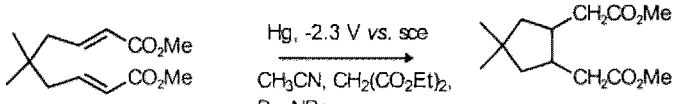
Substrate **35**, n =	Ring Size	Yield / %	Substrate **35**, n =	Ring Size	Yield / %
2	4	41	5	7	10
3	5	100	6	8	0
4	6	90	8	10	0

The substrates discussed in the previous paragraph show two overlapping polarographic waves and reduction at the plateau of the more negative wave gives the



38, $E_{½}$ = -1.67 and -2.76 V *vs.* sce

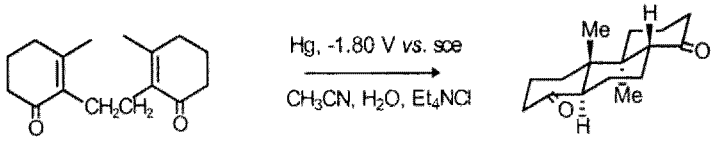
best yields [122] of cyclized product. For compound **38**, the enone functions are in close proximity and the molecule shows two distinct one-electron polarographic waves. Cyclization occurs only during reduction at the potential of the more negative wave when the molecule forms a bis radical-anion [123]. Reduction at the potential of the less negative wave gives oligomers by intermolecular hydrodimerization. In all of these processes, intramolecular cyclization probably occurs by radical-anion, radical-anion reaction followed by a protonation step.



39, *trans* : *cis* = 7.5:1
with Ce(III), *trans* : *cis* = 14.8:1

Diethyl malonate has been proposed for use as a proton source in these cyclization reactions [124]. It is not a sufficiently strong acid to protonate the radical-anion rapidly. However it irreversibly protonates the enol intermediate generated after carbon-carbon bond formation. In one case, control of stereochemistry in favour of the *trans*-sunstituted five membered ring **39** was achieved by the addition of cerium(III) ions [124].

In the case of the bis-enone **40**, the two functions are reduced at almost the same

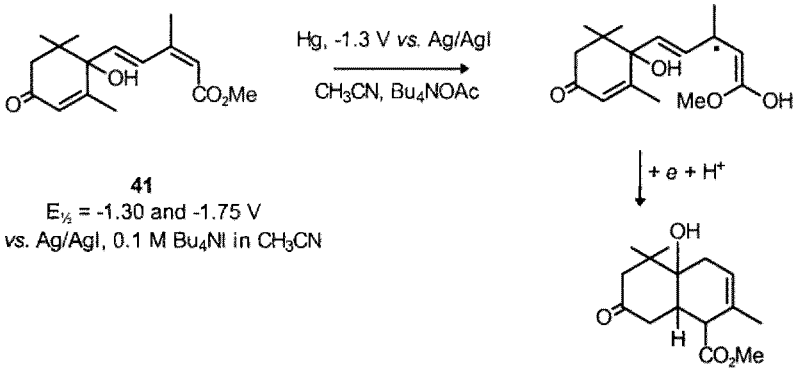


40

yield 81 %

potential and the cyclization process occurs in good yield [125]. Abscisic acid

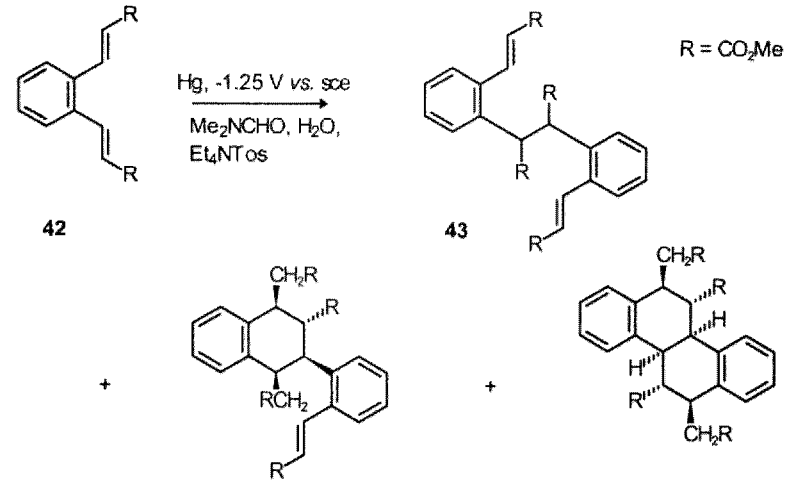
methyl ester **41** has two different activated alkene functions and shows two well seperated polarographic waves [126]. The wave at less negative potentials is asso-



41
$E_{½}$ = -1.30 and -1.75 V
vs. Ag/AgI, 0.1 M Bu_4NI in CH_3CN

ciated with the unsaturated ester function. Reduction at this potential causes an unusual cyclization where the α–carbon of the unsaturated ester becomes attached to the β–carbon of the enone. Cyclization is due to a Michael addition of the ester enol on the enone function.

The low yield of a four-membered ring product from **35**, n = 2 (Table 3.7) is reflected in the activity of substrate **42**, electrochemical reduction of which leads to

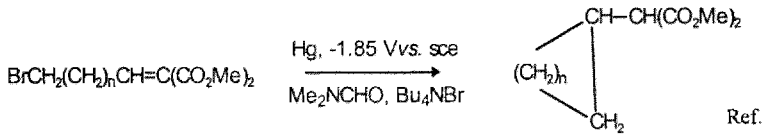


42 **43**

dimeric structures based on **43** and no four membered ring compound is isolated [127]. *Meso*-**43** was isolated. The other isolated dimeric products are formed from

(±)-**43** in an intramolecular Michael addition step which yields new six membered rings.

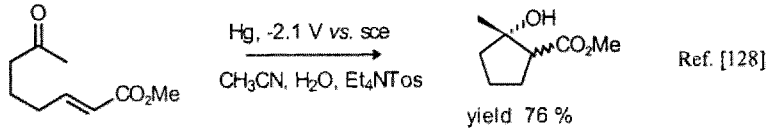
The radical-anions from enecarboxylates show nucleophilic reactivity on the β–carbon atom. Intramolecular carbon-carbon bond formation occurs when a suitably placed alkyl bromide, see p. 58 [26], or carbonyl [128] function is available. Related reactions are shown by the radical-anions from enenitriles [128]. The



Ref. [26]

n = 2, yield 65-80 %
n = 3, yield 60 %

overall process is one of hydrocyclization and is generally useful only for the con-

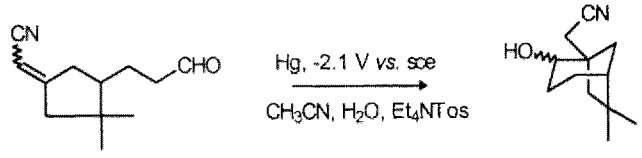


Ref. [128]

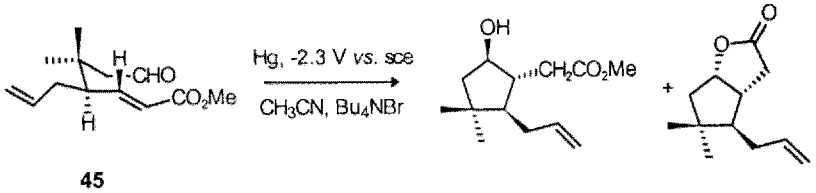
yield 76 %
trans : *cis* = 5.1:1

struction of five and six membered rings where there is negligible competition from the formation of a hydrodimer by the usual bimolecular process. These reactions take place in an initially neutral aprotic solvent and the mechanism is different from that of coupling between carbonyl compounds and alkenes in protic solvents (p. 80).

The hydrocyclization procedure has been used to construct a number of carbocyclic systems such as **44** and **45** and in general it shows little stereoselectivity. A



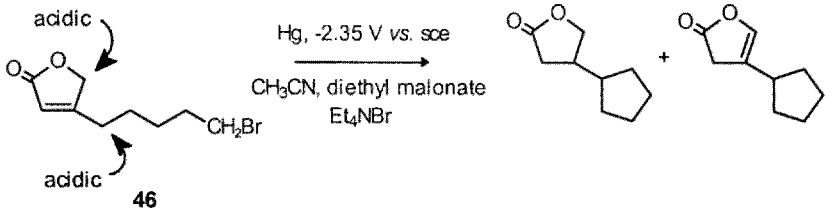
44, yield 73 %



45

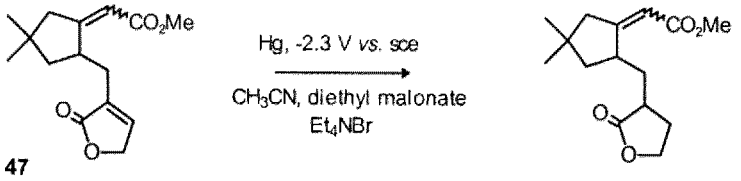
trans relationship between the allyl group and the ester function was however achieved in the case of **45** because the transition-state for reaction has a chair-like structure with a maximum of *pseudo*-equatorial substituents [129]. The stereochemistry of the forming hydroxyl group is however not controlled. Diethyl malonate has been found to be a very convenient proton source in these reactions. It protonates the alkoxide which is formed in the cyclization step but it is unlikely to protonate the radical-anion intermediates.

Anomalous reactions are reported for some butenolides. Thus compound **46** does not cyclize in the expected manner [130]. Formation of the observed products can be rationalised on the assumption that electrogenerated base can interact with



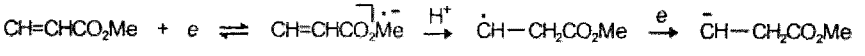
46

the protons labelled as acidic so as to generate an enolate. The exocyclic enolate then reacts with the bromine substituent to form a cyclopentane. The latter is either reduced to the dihydro compound, or alternatively the alkene bond migrates under base catalysis to form the second isolated product. Compound **47** does not cyclize during reduction at a potential required to form the cyclobutenolide radical-anion but instead is converted to the dihydro derivative [131]. Compound **48** is reduced at a less negative potential than for the previous example and forms a radical-anion on the alkylidene malonate ester function. This does cyclize although in a non-stereo-selective manner [131].

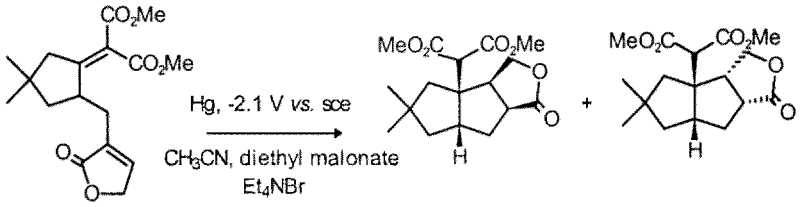


47

The mechanism for intramolecular hydrocyclization of enecarboxylates was originally thought to involve nucleophilic addition of the enecarboxylate radical-anion onto the ketone function [26]. A more recent suggestion is that a sequence of electron, proton, electron additions leads to the β-carbanion:



This intermediate is then involved in the cyclization step [132]. However, it has been shown in another series of experiments that enecarboxylate radical-anions dimerize rapidly before protonation when only traces of water are present [43]. On the basis of these findings, it seems more likely that, as originally proposed, intramolecular cyclization occurs at the level of the radical-anion, and that this process is faster than the alternative bimolecular dimerization.



48 ratio 1:1, total yield 90 %

Mixed Hydrocoupling Reactions

Controlled current reduction of a mixture of two activated alkenes will yield a mixture of the two possible hydrodimers together with the hydrocoupled product, provided that the reduction potentials of the two substrates are not too far apart [133]. This can be a useful synthetic route to the hydrocoupled product provided that the other products are themselves valuable. Thus, reduction of a mixture of 1-cyanobutadiene with excess acrylonitrile, followed by catalytic hydrogenation of the products, gives a synthesis of 1,6-dicyanohexane with adiponitrile as the side product [133].

Examples are known of hydrocoupling between methyl acrylate and ketones in both protic and aprotic solvents. Reaction in acid solution is thought to involve reduction of the protonated ketoneto a radical, which adds to acrylate. In aprotic solvents, the ketone is more difficult to reduce and electron addition occurs on methyl acrylate. Modest yields of coupling product, dimethylbutanolide, are obtained from acetone and methyl acrylate in dimethylformamide [134]. Better results are obtained by reduction of methyl acrylate and an exces of the carbonyl compound in dimethylformamide in the presence of chlorotrimethylsilane [135]. This process is useful for the synthesis of butenolides and some examples are given in Table 3.8.

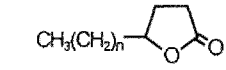
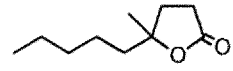
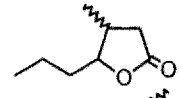
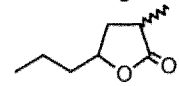
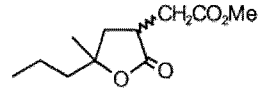
Asymmetric Reduction

Coumarin shows a one-electron wave on polarography in aqueous buffers and the half-wave potential is independent of pH [136]. Reduction at a mercury cathode affords the *meso*- and (±)-isomers of the 4-coupled hydrodimer. Reduction of

4-methylcoumarin has been an important test case for diversion of the hydrodimerization step in favour of formation of the dihydrocompound in a reaction having the potential for asymmetric synthesis.

TABLE 3.8

Mixed hydrocoupling reactions in dimethylformamide, containing chlorotrimethylsilane, at a lead cathode with tetrathylammonium toluene-4-sulphonate electrolyte. The aldehyde or ketone is in five-fold excess. Ref. [135].

Ester	Aldehyde or Ketone	Butanolide Product	Yield / %
CH_2=CHCO$_2$Me	$CH_3(CH_2)_nCHO$		73 - 77
CH_2=CHCO$_2$Me	$CH_3CO(CH_2)_4CH_3$		76
CH_3C=CHCO$_2$Me	$CH_3(CH_2)_2CHO$		71
CH_2=CMeCO$_2$Me	$CH_3(CH_2)_2CHO$		54
CH_2=C(CO$_2$Me)CH$_2$CO$_2$Me	$CH_3CO(CH_2)_2CH_3$		86

Reduction of coumarin in aqueous methanol, pH 5-6, in the presence of alkaloids yields an increased amount of dihydrocoumarin. This is also the case for reduction of 4-methylcoumarin and now the 4-methyldihydrocoumarin isolated is optically active [137]. The enantiomeric excess and yield of dihydrocompound both depend on the alkaloid used (Table 3.9) and Low concentrations of alkaloid are effective in achieving asymmetric induction. Concentrations of codeine above 4 mM do not further influence either the yield of dihydrocompound or the degree of induction.

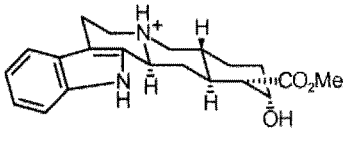
Systematic variation of the reaction conditions has increased the enantiomeric excess to 47.4 % in the presence of yohimbine [138]. Lowering both the cathode working potential and the pH improved the degree of asymmetric induction, and no further improvement in induction is achieved by raising the concentration of alkaloid above 0.4 mM. Enantioselectivity is due to an adsorbed layer of alkaloid and adsorption phenomena at the mercury water interface are dependent on the surface

potential. Values for the surface excess of a solute can be obtained from surface tension measurements at various potentials. The mercury solution interfacial tension is directly related to the natural capillary drop time. Yohimbine is strongly adsorbed at mercury in the region of –1.5 to-1.7 V *vs.* sce [139] and is effective in the asymmetric reduction of 4-methylcoumarin. Strychnine is not active in the same way since this alkaloid is only strongly adsorbed at mercury in the potential range —0.5 to –1.2 V and the surface excess falls to zero at –1.5 V *vs.* sce [140]. When 4-trifluoromethylcoumarin is used as the substrate, reduction proceeds at –1.2 V vs. sce and strychnine gives better enantiomeric excess in the dihydrocompound formed than does yohimbine [138]. Similarly for 4-carbethoxycoumarin reduced at –1.0 V *vs.* sce, up to 20 % enantiomeric excess for the dihydrocompound is obtained for reaction in the presence of strychnine or brucine while yohimbine yields zero enantiomeric excess [141].

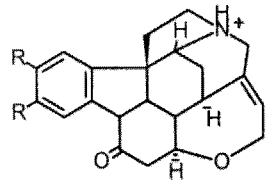
TABLE 3.9

Formation of the dihydrocoumarin by reduction of 4-methylcoumarin in the presence of alkaloids in aqueous methanol pH 5-6, mercury cathode potential –1.8 V *vs.* sce. Ref. [137].

Alkaloid	Concentration / mM	Dihydrocoumarin / %	Enantiomeric Excess / %
None		3.8	
Sparteine	5	3.5	17
Narcotine	5	9.6	15
Emetine	1.5	13.0	12
Codeine	5	28.0	12
Brucine	5	31.7	0
Yohimbine	2	56.6	12



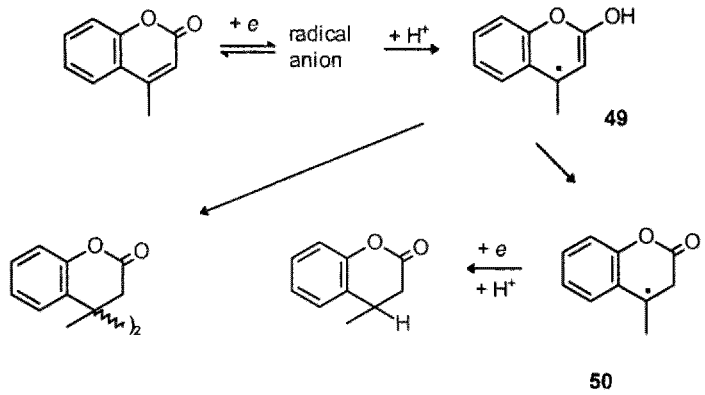
Yohimbine cation



R = H, Strychnine cation
R = OMe, Brucine cation

Reduction of 4-methylcoumarin in aqueous buffers employed for the asymmetric reduction resembles the reactions of methyl cinnamate (p. 67) The process leads

to a radical-anion which is rapidly protonated to form the radical-enol **49**. The latter species is only reduced at more negative potentials. In absence of the alkaloid it dimerises. The alkaloid has two functions. First it catalyses the enol to ketone conversion. The radical-carbonyl intermediate **50** is more easily reduced than the ini-



tial coumarin and accepts an electron to form the carbanion. Second, the adsorbed layer of alkaloid protonates the carbanion formed at the mercury surface and this step leads to the observed asymmetric induction. Thus alkaloids in general do catalyse the formation of dihydrocoumarin but a surface excess of alkaloid is required to achieve asymmetric induction [142].

Alkaloids lower the potential for hydrogen evolution at a mercury surface by a process in which the first step is reduction of the protonated alkaloid to give the nitrogen centred radical [143]. Hydrogen and the unprotonated alkaloid are formed by the interaction of two nitrogen centred radicals. The original mechanistic suggestion [137] for asymmetric induction involved hydrogen atom transfer from this nitrogen centered radical to the radical-carbonyl intermediate. It is not possible to exclude participation of this process within the mercury surface layer.

Electrocatalytic Hydrogenation

At surfaces of low hydrogen overvoltage in aqueous solution, the mechanism for reduction of alkenes changes [144]. The dominant electrochemical reaction becomes the generation of adsorbed hydrogen atoms and the alkene undergoes an electrochemical equivalent of catalytic hydrogenation. This process has been recognised for many years at cathodes of platinum, palladium or nickel black in aqueous acid or alkali. Examples include the hydrogenation of alkene bonds in crotonic acid [145] and sorbic acid [146] in dilute sulphuric acid.

The most effective cathode surface for the electrocatalytic hydrogenation of alkenes is based on Raney nickel [147]. Preparation of the surface involves elec-

troplating nickel from a solution in which Raney alloy (Ni 50%, Al 50%) particles are suspended so that some of the alloy becomes attached to the surface. Leaching out the aluminium with alkali then generates an active surface. Highest current efficiency for the hydrogenation reaction is achieved using an emulsion of the alkene substrate in water containing some surfactant. The system will allow the conversion of unconjugated alkenes, such as limonene, to the alkane [147] and it has been proposed as a route for the hydrogenation of soya bean oil to give a more saturated product without causing isomerization of *cis*-alkenes to the *trans*-alkene [148].

Enones are selectively hydrogenated electrochemically at the conjugated alkene bond. A high degree of selectivity is achieved at an electrodeposited nickel surface [149] and complete selectivity is found at electrodes either of compressed fractal nickel or compressed nickel boride (Ni_2B) [150, 151]. Excellent selectivity is also achieved at a catalytic surface prepared by electroplating palladium into a film of poly(pyrrole-viologen) [152].

The selective hydrogenation of enones is also achieved in a process employing an aluminium-nickel system. This process is electrochemical in nature but does not use an external electron source. Dissolving aluminium is used as the reducing agent with a catalytic amount of nickel chloride present in the tetrahydrofuran solvent. Finely divided nickel is deposited on the aluminium and this sets up local corrosion cells. Aluminium dissolves and the released electrons are transferred to nickel where protons are reduced to hydrogen. The hydrogen-nickel system then reduces the alkene bond in the enone [153].

References

[1] E. A. Polenov, V. V. Minin, S. R. Sterlin and L. M. Yagupol'skii, *Izv. Akad. Nauk SSSR Ser. Khim.*, 1978, 482.
[2] M. A. Fox, K. Din, D. Bixler and W. S. Allen, *J. Org. Chem.*, 1978, **44**, 3208.
[3] S.-M. Park, *J. Electrochem. Soc.*, 1978, **125**, 216.
[4] G. Filardi, S. Gambino, G. Silvestri, A. Gennaro and E. Vianello, *J. Electroanal. Chem.*, 1984, **177**, 303.
[5] T. Troll and M. M. Baizer, *Electrochim. Acta*, 1974, **19**, 951.
[6] T. R. Chen, M. R. Anderson and D. G. Peters, *J. Electroanal. Chem.*, 1986, **197**, 341.
[7] B. S. Jensen, R. Lines, P. Pagsberg and V. D. Parker, *Acta Chem. Scand. B*, 1977, **31**, 707.
[8] H. C. Wang, G. Levin and M. Szwarc, *J. Am. Chem. Soc.*, 1977, **99**, 2642.
[9] B. J. Huebert and D. E. Smith, *J. Electroanal. Chem.*, 1971, **31**, 333.
[10] R. D. Rieke and R. E. Copenhafer, *J. Electroanal. Chem.*, 1974, **56**, 409.

[11] K. Ankner, B. Lamm, B. Thulin and O. Wennerström, *Acta Chem. Scand. B*, 1978, **32**, 155.
[12] A. J. Fry and C. S. Hutchins, *J. Am. Chem. Soc.*, 1975, **97**, 218.
[13] J. F. M. Oth and G. Schröder, *J. Chem. Soc. B*, 1971, 904.
[14] J. F. M. Oth, G. Anthoine and J. M. Giles, *Tetrahedron Lett.*, 1968, 6265.
[15] V. G. Mairanovskii, L. A. Vakulova, N. T. Ioffe *et al.*, *Khim.-Farm. Zh.*, 1977, **11**, 111; *Chem. Abstr.*, 1978, **88**, 37999.
[16] N. A. Bogoslovskii, I. A. Titova, V. G. Mairanovskii *et al.*, *Khim.-Farm. Zh.*, 1977, **11**, 30; *Chem. Abstr.*, 1978, **88**, 62523.
[17] H. Kasch and K. Ponsold, *Ger. (East)*, 142344 (1980); *Chem. Abs.*, 1981, **95**, 81317.
[18] G. Farnia, F. Maran, G. Sandona and M. G. Severin, *J. Chem. Soc. Perkin Trans. 2*, 1982, 1153.
[19] Engels and H.-J. Schäfer, *Angew. Chem. Int. Ed. Engl.*, 1978, **17**, 460.
[20] M. Fruianu, M. Marchetti, G. Melloni, G. Sanna and R. Secber, *J. Chem. Soc. Perkin Trans. 2*, 1994, 2039.
[21] J. Delaunay, A. Orliac-Le Moing and J. Simonet, *New J. Chem.*, 1993, **17**, 393.
[22] R. G. Janssen, M. Motevalli and J. H. P. Utley, *J. Chem. Soc. Chem. Commun.*, 1998, 539.
[23] E. Leonel, J. P. Paugam, J.-Y. Nédélec and J. Périchon, *J. Chem. Res. S*, 1995, 278.
[24] Y. W. Lu, J.-Y. Nédélec J. C. Folest and J. Périchon, *J. Org. Chem.*, 1990, **55**, 2503.
[25] D. Occhialini, S. U. Pedersen and H. Lund, *Acta Chem. Scand.*, 1990, **44**, 715.
[26] S. T. Nugent, M. M. Baizer and R. D. Little, *Tetrahedron Lett.*, 1982, **23**, 1339.
[27] T. Shono, M. Ishifune, H. Kinugasa and S. Kashimura, *J. Org. Chem.*, 1992, **57**, 5561.
[28] D. A. Tyssee and M. M. Baizer, *J. Org. Chem.*, 1974, **19**, 2823.
[29] E. Lamy, L. Nadjo and J.-M. Savéant, *J. Electroanal. Chem.*, 1977, **78**, 403.
[30] L. Lamy, L. Nadjo and J.-M. Savéant, *Nouv. J. Chim.*, 1979, **3**, 21.
[31] L. A. Avaca and J. H. P. Utley, *J. Chem. Soc. Perkin Trans. 2*, 1975, 161.
[32] L. Lamy, L. Nadjo and J.-M, Savéant, *J. Electroanal. Chem.*, 1973, **42**, 189.
[33] A. V. Il'yasov, Yu. M. Kargin *et al.*, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1968, 736; *Chem. Abstr.*, 1968, **69**, 32452.
[34] K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger and D. K. Roe, *J. Am. Chem. Soc.*, 1970, **92**, 2783.
[35] J. Simonet, *Compt. rend. C*, 1966, **263**, 1546.
[36] C. Degrand and H. Lund, *Nouv. J. Chim.*, 1977, **1**, 35.
[37] E. Hayon and M. Simic, *J. Am. Chem. Soc.*, 1973, **95**, 2433.
[38] M. Simic and M. Z. Hoffman, *J. Phys. Chem.*, 1972, **76**, 1398.
[39] V. Madhavan, N. N. Lichtin and E. Hayon, *J. Am. Chem. Soc.*, 1975, **97**, 2989.
[40] E. Hayon, T. Ibata, N. N. Lichtin and M. Simic, *J. Phys. Chem.*, 1972, **76**, 2072.
[41] B. Chutny and A. J. Swallow, *Trans. Faraday Soc.*, 1970, **66**, 2847.
[42] V. D. Parker, *Acta Chem. Scand. B*, 1981, **35**, 279.
[43] I. Fussing, M. Güllü, O. Hammerich, A. Hussain, M. F. Nielsen and J. H. P. Utley, *J. Chem. Soc. Perkin Trans. 2*, 1996, 649.
[44] W. V. Childs, T. T. Malory, C. P. Keszthelyi and A. J. Bard, *J. Electrochem. Soc.*, 1971, **118**, 874.
[45] M. T. Hazelrig and A. J. Bard, *J. Electrochem. Soc.*, 1975, **122**, 211.
[46] I. B. Goldberg, D. Boyd, R. Hirasawa and A. J. Bard, *J. Phys. Chem.*, 1974, **78**, 295.
[47] V. J. Puglisi and A. J. Bard, *J. Electrohem. Soc.*, 1972, **119**, 829.

[48] L. Nadjo and J.-M. Savéant, *J. Electroanal. Chem.*, 1978, **91**, 189.
[49] L. S. R. Yeh and A. J. Bard, *J. Electrochem. Soc.*, 1977, **124**, 189.
[50] S. Takamuku, H. Kigawa, H. Suematsu, S. Toki, K. Tsumori and H. Sakurai, *J. Phys. Chem.*, 1982, **86**, 1861.
[51] J. P. Zimmer, J. A. Richards, J. C. Turner and D. H. Evans, *Anal. Chem.*, 1971, **43**, 1000.
[52] L. H. Klemm and D. R. Olson, *J. Org. Chem.*, 1973, **38**, 3390.
[53] I. Nishiguchi and T. Hirashima, *Angew. Chem. Int. Ed. Engl.*, 1983, **22**, 52.
[54] J. H. P. Utley, M. Güllü, C. I. Dematteis, M. Molevalli and M. F. Nielsen, *Tetrahedron*, 1995, **51**, 11873.
[55] J. H. P. Utley, M. Güllü and M. Montevalli, *J. Chem. Soc. Perkin Trans. 1*, 1995, 1961.
[56] N. Kise, S. Mashiba and N. Ueda, *J. Org. Chem.*, 1998, **63**, 2731.
[57] T. Troll and J. Wiedemann, *Tetrahedron Letts.*, 1992, **33**, 3847.
[58] C. Harries and F. Hübner, *Annalen*, 1897, **296**, 295.
[59] H. D. Law, *J. Chem. Soc.*, 1912, **101**, 1016.
[60] H. Hibbert and R. R. Read, *J. Am. Chem. Soc.*, 1924, **46**, 983.
[61] I. L. Knuyants and N. S. Vyazankin, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 1957, 238; *Chem. Abstr.*, 1957, **51**, 11235.
[62] M. M. Baizer, *J. Electrochem. Soc.*, 1964, **111**, 215.
[63] A. P. Tomilov, S. L. Varshavskii, I. L. Knunyants *et al.*, *Brit.* 1089707 (1968); *Chem. Abstr.*, 1968, **68**, 12503.
[64] F. Beck, *Angew. Chem. Int. Edn. Engl.*, 1972, **11**, 760.
[65] D. E. Danly, *J. Electrochem. Soc.*, 1984, **131**, 435C.
[66] M. R. Moncelli, F. Pergola, G. Aloisi and R. Guidelli, *J. Electroanalyt. Chem.*, 1983, **143**, 233.
[67] P. H. Zoutendam and P. T. Kissinger, *J. Org. Chem.*, 1979, **44**, 758.
[68] C. L. Wilson and K. B. Wilson, *Brit.*, 553675 (1943); *Chem. Abstr.*, 1944, **38**, 5227.
[69] I. Fussing, O. Hammerich, A. Hussain, M. F. Nielsen and J. H. P. Utley, *Acta Chem. Scand.*, 1998, **52**, 328.
[70] S. Ono and M. Uehara, *Nippon Kagaku Zasshi*, 1957, **78**, 929; *Chem. Abstr.*, 1960, **54**, 4486.
[71] E. A. Casanova, M. C. Dutton and D. J. Kalota, *J. Applied Electrochem.*, 1995, **25**, 479.
[72] A. Lapworth and F. A. Boyle, *J. Chem. Soc.*, 1920, **117**, 743.
[73] J. Sarrazin and A. Tallec, *Electrochim. Acta*, 1982, **27**, 95.
[74] A. Kekule, *Annalen*, 1864, **131**, 85.
[75] A. W. Ingersoll, *Org. Synth., Coll. Vol 1*, 1932, p. 304.
[76] J. F. Norris and E. O. Cummings, *Ind. Eng. Chem.*, 1925, **17**, 305.
[77] C. Mettler, *Ber.*, 1906, **39**, 2933.
[78] R. Beer and G. Lasch, *Monatsh.*, 1913, **34**, 1668.
[79] G. A. Edwards, *J. Chem. Soc.*, 1926, 813.
[80] R. Fujita and T. Sekine, *Denki Kagaku*, 1983, **51**, 681.
[81] K. B. Wilson and C. L. Wilson, *J. Chem. Soc.*, 1941, 874.
[82] J. Petrovich, M. M. Baizer and M. R. Ort, *J. Electrochem. Soc.*, 1969, **116**, 749.
[83] J. Simonet, *Compt. rend. C*, 1966, **263**, 1546.
[84] E. J. Denney and B. Mooney, *J. Chem. Soc. B*, 1968, 1410.

[85] E. Brillas and J. J. Ruiz, *J. Electroanal. Chem.*, 1986, **215**, 293.
[86] L. Holleck and S. Mahapatra, *J. Electroanal. Chem.*, 1972, **35**, 381.
[87] D. A. Nelson and E. Hayon, *J. Phys. Chem.*, 1972, **76**, 3200.
[88] P. Zumsn, J. Tenygl and M. Brezina, *Coll. Czech. Chem. Commun.*, 1954, **19**, 46.
[89] P. Kabasakalian and J. McGlotten, *J. Am. Chem. Soc.*, 1956, **78**, 5032.
[90] H. Lund, *Acta Chem. Scand.*, 1957, **11**, 283.
[91] M. A. Almiron, L. Camacho, E. Muñoz and J. L. Avila, *J. Electroanal. Chem.*, 1988, **241**, 297.
[92] A. Ryvolová-Kejharová and P. Zuman, *J. Electroanal. Chem.*, 1969, **21**, 197.
[93] E. Touboul, F. weishbuch and J. Wiemann, *Bull. Soc. Chim. France*, 1967, 4291.
[94] J. Simonet, *Compt. rend. C*, 1986, **267**, 1548.
[95] H. D. Law, *J. Chem. Soc.*, 1912, **101**, 1016.
[96] J. Grimshaw and J. Trocha-Grimshaw, *J. Chem. Soc. Perkin Trans. 1*, 1973, 2584.
[97] R. S. Hughesdon, H. G. Smith and J. Read, *J. Chem. Soc.*, 1923, **123**, 2916.
[98] J. Grimshaw and R. J. Haslett, *J. Chem. Soc. Perkin Trans. 1*, 1979, 395.
[99] J. Wiemann, P.-F. Casals and S. Risse, *Bull. Soc. Chim. France*, 1963, 1281.
[100] P.-F. Casals, *Bull. Soc. chim. France*, 1963, 253.
[101] P. Bladon and J. Redpath, *J. Chem. Soc.*, 1962, 2352.
[102] H. Lund, *Acta Chem. Scand.*, 1957, **11**, 283.
[103] E. Touboul and G. Dana, *Tetrahedron*, 1975, **31**, 1925.
[104] J. Wiemann and M. Jon, *Bull. Soc. chim. France*, 1958, 1125.
[105] P. Tissot, J. P. Surbeck, F. O. Gülaçar and P. Margaretha, *Helv. Chim. Acta*, 1981, **64**, 1571.
[106] C. Harries and F. Hübner, *Annalen*, 1897, **296**, 295.
[107] H. D. Law, *J. Chem. Soc.*, 1912, **101**, 1016.
[108] J. Wiemann and M. L. Bouguerra, *Ann. Chim. [14]*, 1967, **2**, 35.
[109] J. Wiemann and C. Glacet, *Compt. rend.*, 1948, **226**, 923.
[110] J. Wiemann and R. Nahum, *Compt. rend.*, 1954, **238**, 2091.
[111] M Kolobielski, *Bull. Soc. chim. France*, 1954, 1409.
[112] M. Kolobielski, *Ann. Chim. [12]*, 1955, **10**, 271.
[113] J. Wiemann and M. L. Bouguerra, *Ann. Chim. [14]*, 1968, **3**, 215.
[114] D. W. Sopher and J. H. P. Utley, *J. Chem. Soc. Perkin Trans. 2*, 1984, 1361.
[115] K. Uneyama, T. Tokunaga and S. Torii, *Bull. Chem. Soc. Japan*, 1987, **60**, 3427.
[116] J. Chuche and J. Wiemann, *Bull. Soc. chim. France*, 1968, 1497.
[117] I. K. Traore, B. Furth and J. Wiemann, *Compt. rend. C*, 1967, **264**, 1079.
[118] R. Pasternak, *Helv. Chim. Acta*, 1948, **31**, 753.
[119] L. R. Finch and D. E. White, *J. Chem. Soc.*, 1950, 3367.
[120] J. D. Anderson, M. M. Baizer and J. P. Petrovich, *J. Org. Chem.*, 1966, **31**, 3890.
[121] R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, 1915, **107**, 1080.
[122] J. P. Petrovich, J. D. Anderson and M. M. Baizer, *J. Org. Chem.*, 1966, **31**, 2897.
[123] J. M. Mellor, B. S. Pons and J. H. A. Stibbard, *J. Chem. Soc. Chem. Comm.*, 1979, 759.
[124] L. Moëns, M. M. Baizer and R. D. Little, *J. Org. Chem.*, 1986, **51**, 4497.
[125] L. Mandell, R. F. Daley and R. A. Day, *J. Org. Chem.*, 1976, **41**, 4087.
[126] B. Terem and J. H. P. Utley, *Electrochim. Acta*, 1979, **24**, 1081.
[127] J. Andersson, L. Eberson and C. Svensson, *Acta Chem. Scand. B*, 1978, **32**, 234.

[128] R. D. Little, D. P. Fox, L. Vashijfte, R. Dannecker, G. Sowell, R. L. Wolin, L. Moëns and M. M. Baizer, *J. Org. Chem.*, 1988, **53**, 2287.
[129] C. G. Sowell, R. L. Wolin and R. D. Little, *Tetrahedron Letters*, 1990, **31**, 485.
[130] M. A. Amputch and R. D. Little, *Tetrahedron*, 1991, **47**, 383.
[131] H. E. Bode, G. Sowell and R. D. Little, *Tetrahedron Letters*, 1990, **31**, 2525.
[132] A. J. Fry, R. D. Little and J. Leonette, *J. Org. Chem.*, 1994, **59**, 5017.
[133] M. M. Baizer, *J. Org. Chem.*, 1964, **29**, 1670.
[134] M. Nicolas and R. Pallaud, *Compt. rend. C*, 1968, **267**, 1834.
[135] T. Shono, H. Ohimizu, S. Kawakami and H. Sugiyama, *Tetrahedron Letters*, 1980, **21**, 5029.
[136] A. J. Harle and L. E. Lyons, *J. Chem. Soc.*, 1950, 1575.
[137] R. N. Gourley, J. Grimshaw and P. G. Miller, *J. Chem. Soc. C*, 1970, 2318.
[138] N. Schoo, and H.-J. Schäfer, *Annalen*, 1993, 601.
[139] M. Jubault, E. Raoult and D. Peltier, *Electrochim. Acta*, 1974, **19**, 865.
[140] R. Bennes, M. Jubault, M. Privat and P. Vandel, *Electrochim. Acta*, 1981, **26**, 1079.
[141] E. Raoult, J. Sarrazin and A. Tallec, *Bull. Soc. Chim. France II*, 1981, 420.
[142] M. F. Nielsen, B. Batanero, T. Löhl, H.-J. Schäfer, E.-U. Würthwein and R. Frölich, *Chem. Eur. J.*, 1997, **3**, 2011.
[143] S. G. Mairanovskii, *Russian Chem. Rev.*, 1964, **33**, 38.
[144] L. D. Burke C. Kemball and F. A. Lewis, *Trans. Faraday Soc.*, 1964, **60**, 913.
[145] S. Fokin, *Z. Elektrochem.*, 1906, **12**, 760.
[146] E. Issacs and C. F. Wilson, *J. Chem. Soc.*, 1936, 810.
[147] P. Chamberlin, L. Roger, J. Lessard, V. Beraud, J. Mailhot and M. Thomalla, *Can. J. Chem.*, 1995, **73**, 804.
[148] G. Y. Yusem and P. N. Pintauro, *J. Am. Oil Chemists Soc.*, 1992, **117**, 399.
[149] A. Bryan and J. Grimshaw, *Electrochim. Acta*, 1997, **42**, 2101.
[150] B. Mahdavi, P. Chambrion, J. Binette, E. Martel and J. Lessard, *Can. J. Chem.*, 1995, **73**, 846.
[151] P. Dabo, B. Mahdari, H. Menard and J. Lessard, *Electrochim. Acta*, 1997, **42**, 1457.
[152] L. Coche, B. Ehui, D. Limosin and J.-C. Moutet, *J. Org. Chem.*, 1990, **55**, 5905.
[153] B. K. Sarmah and N. C. Barua, *Tetrahedron*, 1991, **47**, 8587.

CHAPTER 4

REDUCTIVE BOND CLEAVAGE PROCESSES - I

Dissociative Electron Transfer

When a single electron is transferred to a molecule with no π-bonds, it is accommodated in the lowest energy antibonding σ–orbital. Mechanistic studies of these reactions have employed substrates where the antibonding orbital is associated with a carbon-halogen bond or an oxygen-oxygen bond. The substrates give polarographic waves at a mercury or glassy carbon electrode due to the irreversible reduction process. Electron addition is associated with an antibonding orbital so the σ-bond becomes unstable. Electron addition and bond dissociation become synchronous. The radical-anion is not a transient intermediate during electron addition to an alkyl σ-bond and notional standard redox potentials for these reactions are not directly measurable quantities.

Attempts to detect the radical-anions from alkyl halides by γ-irradiation in a low temperature glass, using esr spectroscopy, have generally been unsuccessful. Irradiation of the glass generates solvated electrons, which attach to the alkyl halide to generate an alkyl radical and halide ion. There is evidence for a weak interaction, but not bond formation, between alkyl radicals and bromide ion formed in acetonitrile at 77 K. In the more solvating methanol there is no interaction between radicals and bromide ions [1]. Trifluoromethyl halide molecules are the exceptions to this otherwise general behaviour. These give radical-anions on irradiation in methyltetrahydrofuran at 77 K with free electron density largely in the carbon-halogen σ*-orbital [2]. The trifluoromethyl radical is pyramidal so the tendency to complete separation from the halide ion is arrested in the glassy matrix. Alkyl radicals are planar, precluding any strong association with the halide ion.

Reaction rates for dissociative electron transfer processes are determined by the method of homogeneous electron transfer. The kinetic sequence is illustrated in Scheme 4.1. Linear sweep voltammetry is used to generate the radical-anion from

$$Ar + e \rightleftharpoons Ar^{\bullet -}$$

$$Ar^{\bullet -} + R\text{-}X \xrightarrow{k_{tr}} Ar + R^{\bullet} + X^{-}$$

Scheme 4.1 Dissociative electron transfer using an aromatic radical-anion as electron relay

an aromatic compound in the presence of the substrate for study. The aromatic

compound is chosen to have a redox potential less negative than the substrate reduction potential and the aromatic radical-anion is formed at the electrode surface. Electron-transfer, in solution, from the radical-anion to the substrate causes bond dissociation and also regenerates the aromatic compound. Thus there is an augmentation of the voltammetric peak due to reduction of the aromatic compound. A bimolecular rate constant for electron transfer from radical-anion to substrate can be extracted from the experimental data [3].

Rate constants in excess of 10^5 M^{-1} s^{-1} are determined by pulse-radiolysis methods [4, 5]. High-energy irradiation of a solution containing the substrate and an excess of the aromatic species, generates the aromatic radical-anion, The decay of this by electron transfer to the substrate is followed using uv-spectroscopy and affords a rate constant for the second-order process. Slow rates of electron transfer are determined by adding the substrate to a solution of the aromatic radical-anion and following the reaction by conventional methods.

In the ensuing discussion, the following symbols will be used:

k_{tr} = bimolecular rate constant for electron transfer between a radical-anion and the substrate;

α = transfer coefficient, defined by the expression $d \ln(k_{tr})/d E_D^\circ = \alpha F/RT$

k_i = unimolecular rate constant for intramolecular electron transfer;

E_D° = standard potential of the radical-anion electron donor;

E_A° = strandard potential of the substrate, electron acceptor.

A bank of data on dissociative electron transfer has been developed for purposes of investigating the influence of electron donor redox potential on the bond cleavage rate. Theoretical treatment of this relationship by the methods of molecular mechanics has been given [6] and quantum theory has also been applied to the problem [7]. The Marcus treatment of electron transfer from the aromatic radical-anion under the influence of solvent fluctuation is combined with the Morse treatment of C-X bond stretching. A Morse potential energy curve is adopted to describe the stretching of the C-X bond while the repulsive component of the Morse relationship is used to describe interactions between the two product species $R^{\cdot}$ and X^{-}. In this molecular mechanics approach, the point of intersection of the two Morse curves (Figure 4.1) is taken as the transition-state for bond cleavage. With these assumptions, an analytical solution is possible for the relationship between activation energy and driving force. This predicts a parabolic relationship between $\log(k_{tr})$ and E_D° for a given substrate undergoing dissociative electron transfer in reactions with different radical-anions. Monte-Carlo simulations suggest however that this extension of the Marcus equation should be treated with caution [8].

Experimental data (Figure 4.2) for the dissociative electron transfer between radical anions and the carbon-halogen bond in alkyl halides indicates a linear relationship between $\log(k_{tr})$ and E_D° over a wide range of reaction rates [5, 9]. Very fast reactions become controlled by the rate of diffusion of two species towards each other, when every close encounter gives rise to electron transfer. A parabolic

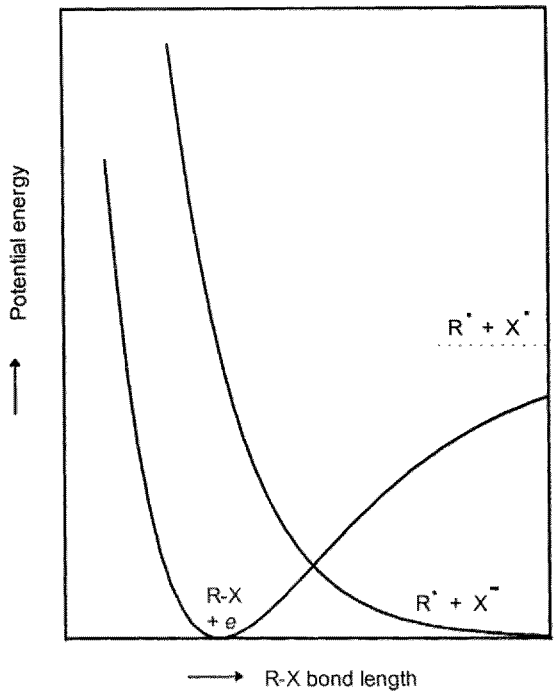
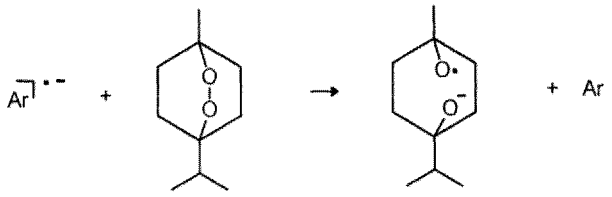


Figure 4.1. Profile of the free energy surface along the co-ordinate of the R-X bond at zero driving force; initial state R-X + electron donor; final state R• + X⁻.

relationship (Figure 4.3) is however seen for dissociative electron transfer between a radical-anion and the oxygen-oxygen bond of peroxides such as **1** [10].

It has been suggested that the reaction of alkyl halides is not purely of the electron transfer type and may include some S_N2 component, particularly where the



1

alkyl halide is less sterically hindered. The influence of this additional component of the reaction will be more pronounced for slower overall rates and have the effect

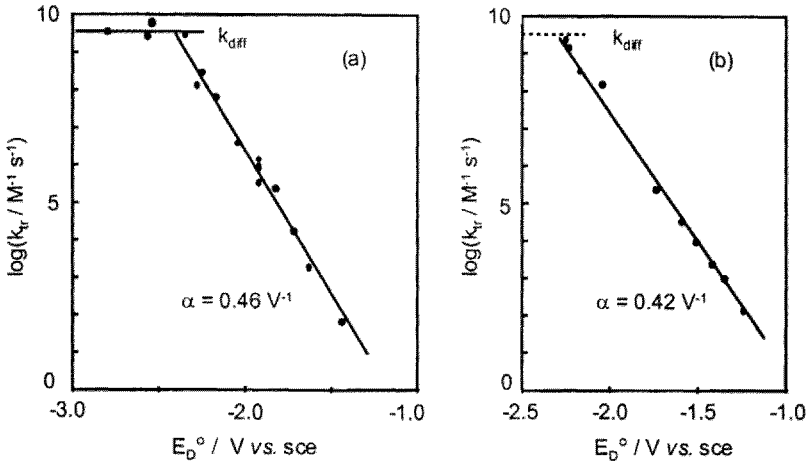


Figure 4.2. Dissociative electron transfer rates from aromatic anion-radicals to alkyl halides determined by cyclic voltammetry or by pulse-radiolysis; (a): iodobutane; (b): 1-iodo-1-methylpropane. Solvent N-methylpyrrolidone or dimethylformamide. Data from refs. [3,5].

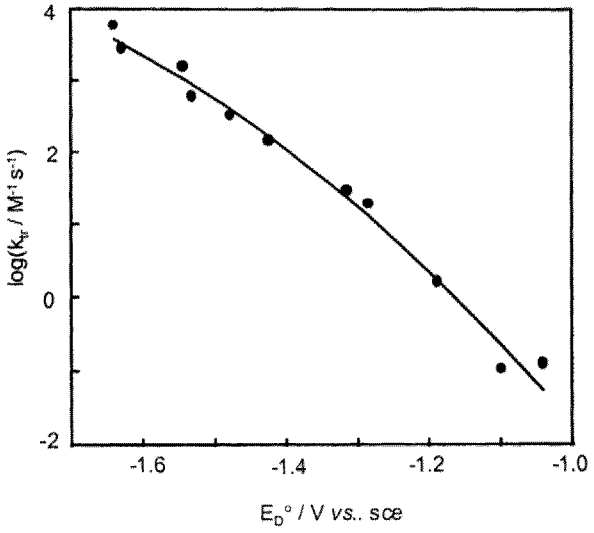
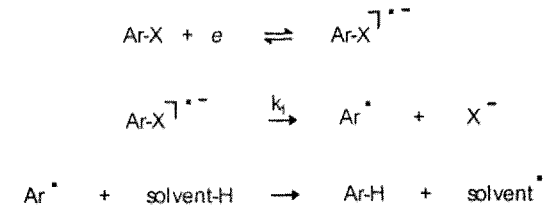


Figure 4.3. Rates of disociative electron transfer from aromatic radical-anions to the peroxide **2** measured in dimethylformamide by cyclic voltammetry. Data from ref. [9].

of increasing the observed reaction rate. Thus whereas the underlying electron transfer rate profile is parabolic, the overall observed rate profile becomes more linear [11]. Evidence for the existence of some S_N2 character in the dissociative electron transfer to alkyl halides comes from the reaction of anthracene radical-anion with (-)-2-bromooctane. 9-(2-Octyl)-9,10-dihydroanthracene is isolated with a low optical rotation, indicating that 8 % of the reaction proceeds with inversion of configuration at the 2-octyl centre. In reaction between (+)-2-octyl methanesulphonate and anthracene radical-anion, some 25 % of reaction proceeds via the S_N2 pathway [12].

In the case of dissociative electron transfer to aromatic compounds, electron transfer is not necessarily concerted with bond dissociation. The substrate π–radical-anion may be an intermediate whose existence can be demonstrated by fast scan cyclic voltammetry in aprotic solvents. At fast scan rates, reversible electron transfer occurs. At slower scan rates, the anodic peak height falls and a second reversible electron transfer step appears due to formation of the radical-anion of the compound formed by replacement of the substituent by hydrogen. Cleavage of the



Scheme 4.2. Intermolecular dissociative electron transfer.

radical-anion leaves an aryl σ-radical, which may abstract a hydrogen atom from the solvent (Scheme 4.2). Alternatively, this radical may react further by electron transfer, and protonation of the resulting carbanion [13]. First order rate constants for the intramolecular bond dissociation of radical-anions can be determined up to a maximum of about 10^6 s^{-1} [14]. Values are collected in Table 4.1 for the cleavage of aromatic carbon-halogen bonds and in Table 4.2 for the cleavage of aromatic carbon-nitrogen bonds in dimethylformamide. In acetonitrile, cleavage rate constants are lowered by approximately one order of magnitude [15]. Radical-anion lifetimes are prolonged by lowering the temperature [16, 17].

Intramolecular dissociative electron transfer in aryl halide radical-anions involves an interaction between the π-aromatic orbital and the σ-type carbon-halogen bond. These orbitals are orthogonal, but bending of the carbon-halogen bond allows the necessary interaction. Qualitatively, the influence of several factors on the bond cleavage rate can be discerned [18].

(a) For halogeno derivatives with the same aromatic structure, carbon-halogen bond cleavage rate increases in the order Cl<Br<I with the carbon-fluorine bond cleaving much more slowly than the carbon-chlorine bond. Thus the larger the carbon-halogen bond strength, the slower the cleavage rate.
(b) A more negative radical-anion redox potential leads to faster bond cleavage.
(c) Among structural isomers, faster cleavage rates are found for isomers with the halogen attached to a centre of higher free electron density in the radical-anion. However, a substituent *ortho* to the halogen group markedly increases the rate of bond cleavage over that predicted from the previous generalisation.

The relationships between rate of cleavage, bond strength and radical-anion redox potential can be combined in one concept. In this, cleavage rate is dependent on a reaction driving force, defined as the difference between the redox potential of the substrate radical-anion and the redox potential of the product anion in equilibrium with the corresponding radical (E° for bromine ion, bromine radical as an example).

TABLE 4.1
Unimolecular cleavage of haloaromatic radical-anions in dimethylformamide at 25 °C.

No.	Substrate	E° / V *vs.* sce	$\log(k_f/s^{-1})$	Ref.
1.	1-Chloronaphthalene	-2.26	7.2	[19]
2.	1-Bromonaphthalene	-2.19	7.8	[19]
3.	4-Fluorobenzonitrile	-2.35	1.04	[20]
4.	4-Chlorobenzonitrile	-2.08	8.2	[19]
5.	4-Chloroacetophenone	-1.90	5.5	[19]
6.	4-Bromoacetophenone	-1.84	7.5	[19]
7.	4-Chlorobenzophenone	-1.64	1.6	[21]
8.	4-Bromobenzophenone	-1.63	4.90	[22]
9.	3-Bromobenzophenone	-1.53	2.87	[22]
10.	4-Bromonitrobenzene	-0.98	-2.40	[23]
11.	4-Iodonitrobenzene	-1.00	-0.05	[23]
12.	3-Iodonitrobenzene	-0.94	-0.51	[23]
13.	2-Iodonitrobenzene	-0.95	4.90	[23]
14.	2,6-Dimethyl-4-iodonitrobenzene	-1.19	2.40	[23]
15	3-Nitrobenzyl chloride	-1.04	1.90	[24]
16	4-Nitrobenzyl chloride	-1.10	6.60	[24]

Cleavage of benzyl bonds is faster than cleavage of bonds to the aromatic ring because of overlap, in the transition-state, between the π–system containing the unpaired electron and the stretching σ–bond. Compare the reactivity of 4-

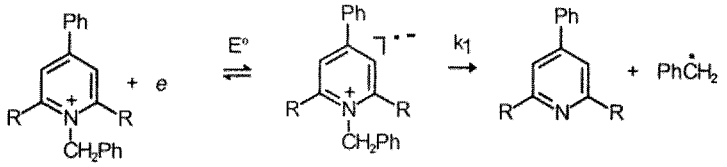
nitrobenzyl halides with 4-halonitrobenzenes listed in Table 4.1. The benzylic carbon-carbon bond in 1,2-diphenylethanes can also be reductively cleaved. For a large number of substituted 1,2 diphenylethanes, a Marcus type parabolic relationship is found between $\log(k_1)$ and the driving force as defined in the previous paragraph [25]. Rate constants for bond cleavage in this series of diphenylethanes range in value over 17 powers of ten.

The effect of *ortho*-substituents in increasing the bond cleavage rate illustrates the importance of bond bending modes in allowing interaction between the π^*- and the σ–type orbitals for development of the transition state for the process. A further illustration of the *ortho*-effect is given by the influence of 2,6-substituents on the rate of nitrogen-carbon bond cleavage (Table 4.2) in the radical-zwitterions derived from the 1-benzylpyridinium salts **2** [26]. More bulky substituents increase the cleavage rate.

TABLE 4.2

Effect of 2,6-substituents on the carbon-nitrogen bond cleavage rate in radical-zwitterions from 1-benzyl-4-phenylpyridiniums in dimethylformamide at 25 °C. Data from ref. [26].

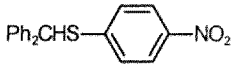
Compound **2**, R =	E° / V *vs.* sce	k_1 / s^{-1}
Me	-1.27	<0.02
Et	-1.27	0.48
Ph	-0.99	240



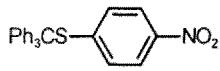
2

Resonance stabilization of the departing radical increases bond cleavage rate. This is illustrated by reactions of some thioethers of 4-nitrothiophenol. The radical-anion from the diphenylmethyl compound **3** has $k_1 = 16.4\ s^{-1}$ at 25 °C [27] compared to a value of $k_1 = 4.1 \times 10^5\ s^{-1}$ [28] for the triphenylmethyl compound **4**. Also the 1-alkylpyridinium salt analogues of **2** give stable radical-zwitterions whereas the 1-allylpyridinium salt analogues show nitrogen-carbon bond cleavage from the radical-zwitterion [26].

For some bond cleavage reactions associated with electron transfer to an aromatic π–system, the cleavage rate is so fast that the radical-anion intermediate can-



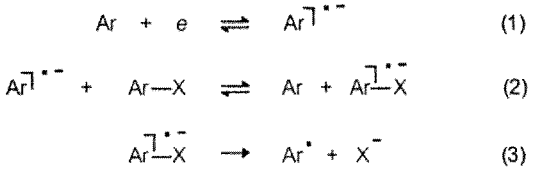
3



4

not be detected by cyclic voltammetry. Here, data for the bimolecular reaction rate between a stable radical-anion and the substrate can be obtained by the methods of homogeneous electron transfer. The overall reaction is shown in Scheme 4.3. Examples include carbon-halogen bond cleavage in chloro and bromo derivatives of benzene, naphthalene and pyridine, also a number of benzyl-X bonds.

Typical experimental results are illustrated in Figure 4.4 for carbon-bromine bond cleavage during the homogeneous electron transfer reaction of 2-bromopyridine [29]. The graph of $\log(k_{tr})$ *vs.* $E_D°$ shows two linear regions of differing slope. This results from the existence of an extremely short-lived substrate



(1)

(2)

(3)

Scheme 4.3. Intermolecular electron transfer driven by fast bond cleavage.

radical-anion [30, 31] and the potential energy diagram for the overall reaction can be illustrated in Figure 4.5(a). The free energy of activation, $\Delta G_3^{\ddagger}$, for bond cleavage reaction 3 in Scheme 4.3, is independent of the electron donor. However, the free energy of activation, $\Delta G_{-2}^{\ddagger}$, for back electron transfer, reverse step of reaction 2 in Scheme 4.3, does depend on the aromatic acceptor. For less negative values of $E_D°$ in Figure 4.4, $\Delta G_3^{\ddagger} > \Delta G_{-2}^{\ddagger}$ and electron transfer becomes a pre-equilibrium to the bond dissociation process. The slope of the graph becomes F/RT. For more negative values of $E_D°$, $\Delta G_{-2}^{\ddagger} > \Delta G_3^{\ddagger}$ and electron transfer is coupled to bond dissociation so that the slope of the graph in Figure 4.4 becomes αF/RT where the value of α is typically 0.5 or less.

When the molecule has an especially weak bond together with a higher energy π*-orbital, the potential energy scheme for bond dissociation can resemble Figure 4.5(b). The approaching radical-anion electron donor interacts directly with the

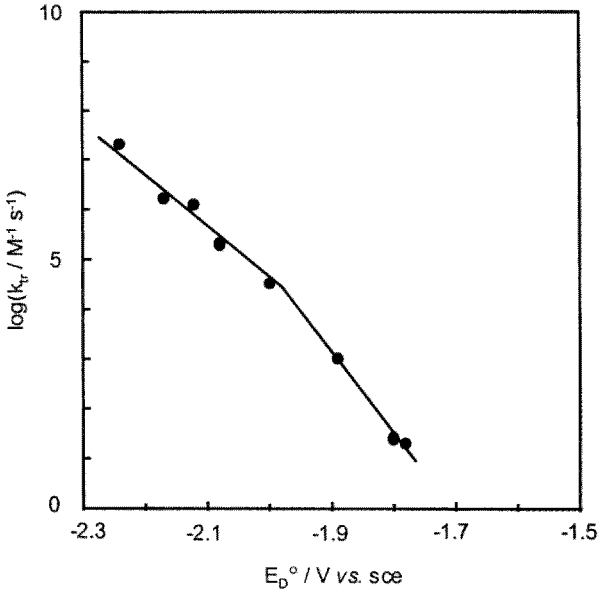


Figure 4.4. Homogeneous electrocatalytic reduction of 2-bromopyridine in dimethylformamide. Forward electron transfer rate constant *vs.* standard potential of the aromatic radical-anion donor. Data from ref.[29].

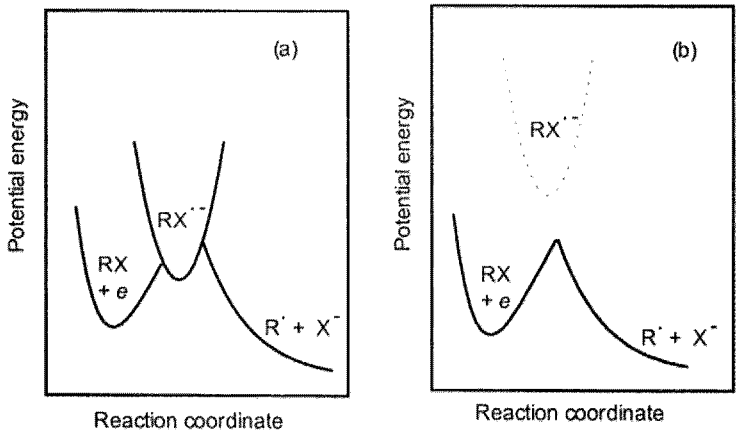


Figure 4.5. Potential energy diagrams for the homogeneous electron transfer reaction between an aromatic radical-anion and a second aromatic with a frangible R-X bond. (a) The situation where back electron transfer and bond cleavage have similar free energy of activation. (b) The situation where the RX radical-anion has high energy and the R-X bond has low dissociation energy.

dissociating σ-bond and the substrate π*-orbital is not involved in reaction. The mechanism has become identical to that described in Figure 4.1.

Homogeneous reductive cleavage of the sulphur-sulphur bond in some diphenyl disulphides by electron transfer from added radical-anions in the solution illustrate points from the two previous paragraphs [32]. Rate data for two diphenyl disulphides are given in Figure 4.6. The variation in electron transfer rate with electron

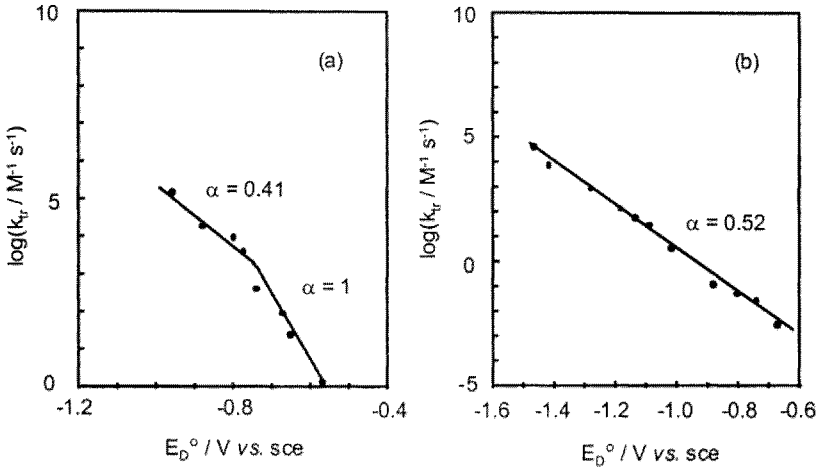


Figure 4.6. Homogeneous dissociative electron transfer reaction between aromatic radical-anions and (a) di-(4-cyanophenyl) disulphide, (b) diphenyl disulphide in dimethylformamide. Data from ref. [31].

donor redox potential for di-(4-cyanophenyl) disulphide shows two kinetic regions as the relative values of $\Delta G_2^{\ddagger}$ and $\Delta G_3^{\ddagger}$, for reactions in Scheme 4.3, change. The corresponding dissociative electron transfer with diphenyl disulphide shows only one kinetic regime associated with the potential energy diagram of Figure 4.5(b).

Reduction of Alkyl and Benzyl Halides

Reduction of alkyl and benzyl halides proceeds in two one-electron addition steps. The first detectable product is the alkyl or benzyl radical and this is reduced further to the carbanion. Some alkyl iodides show two polarographic waves corresponding to the two steps. Alkyl bromides show only one two-electron wave and alkyl chlorides are not reducible in the available potential window. Benzyl halides also show only one wave and benzyl chlorides are reducible in the available potential range. Reduction potentials measured in dimethylformamide are collected in

Table 4.3. They vary with the electrode material and with the tetraalkylammonium cation used. Early workers used mercury electrodes but mercury may be involved in the overall reaction. Glassy carbon is generally favoured as the electrode material. Reproducibility of data depends critically on methods used for cleaning the glassy carbon surface [33].

TABLE 4.3

Reduction potentials for alkyl and benzyl halides measured by cyclic voltammetry at 0.1 or 0.2 V s^{-1} with a glassy carbon electrode in dimethylformamide.

Substrate	Electrolyte	E_p / V *vs.* sce		n for first wave	Ref.
1-Iododecane[a]	Me_4ClO_4	-1.69	-2.22	1.0	[34]
1-Iodopentane	Me_4NClO_4	-2.18			[35]
1-Iodobutane	Bu_4NBF_4	-2.33		2.3	[3]
1-Bromopentane	Me_4NClO_4	-2.66			[35]
1-Bromobutane	Bu_4NClO_4	-2.85		2.2	[36]
2-Iodooctane[a]	Bu_4NClO_4	-1.96,	-2.42	1.0	[37]
2-Iodobutane	Bu_4NBF_4	-2.05,	-2.50	1.2	[3]
2-Bromooctane[a]	Me_4NClO_4	-2.24	-2.67	1.2	[37]
2-Bromobutane	Bu_4NBF_4	-2.63		2.0	[3]
2-Methyl-2-iodopropane	Bu_4NBF_4	-1.91,	-2.62	1.2	[3]
1-Iodonorbornane	Bu_4NClO_4	-2.22		1.8	[38]
1-Iodoadamantane	Bu_4NClO_4	-2.09		1.92	[39]
2-Bromo-2-methylpropane	Bu_4NBF_4	-2.51		1.9	[3]
1-Bromonorbornane	Bu_4NClO_4	-2.79		1.8	[38]
Benzyl bromide	Bu_4NBF_4	-1.71		2.0	[24]
Benzyl chloride	Bu_4NBF_4	-2.21		2.0	[24]

Footnote: (a) Half-wave potential from pulse polarography at a mercury electrode

The reduction potential for an alkyl or benzyl radical, relative to that of the carbon-halogen bond from which it is derived, is important in determining the isolated products. Products are derived either by radical or by carbanion chemistry. The half-wave potential for the second polarographic wave of alkyl halides is connected with reduction of the radical. Sophisticated methods have been devised for deducing radical reduction potentials in cases where this second wave is not seen. Values are collected in Table 4.4.

One approach to this problem [40, 41] generates the alkyl radicals by homogeneous electron transfer to an alkyl halide from an aromatic radical anion. These

radicals can either interact with a second radical-anion by carbon-carbon bond formation or be reduced by electron transfer. Competition ratios for the two reactions are derived by careful analysis of reaction products. Results from the reaction with a series of radical-anions of increasingly negative redox potential correspond to a redox titration of the alkyl radical from which the standard potential for the radical carbanion couple can be derived.

Benzyl radicals are generated, for polarographic investigation, by a photochemical route. Oxygen radicals are first generated by photolysis of di-*tert*-butyl peroxide and allowed to abstract a hydrogen atom from the appropriate toluene. Sinusoidal modulation of the light source generates a modulated concentration of radicals. Polarography at a gold mini-grid electrode, with phase sensitive amplification, then allows detection of the radicals even at very low concentrations. The signal is transformed into a conventional polarogram from which half-wave potentials are derived [42].

TABLE 4.4
Reduction potentials for aliphatic radicals

Radical substrate	E / V *vs.* sce	Method	Ref.
Methyl	-1.19	(a)	[41]
Primary radicals	-1.57 to –1.62	(a)	[40]
Dodec-1-yl	-2.12	(b)	[34]
Secondary radicals	-1.68 to –1.72	(a)	[40]
But-2-yl	-2.50	(c)	[36]
Tertiary radicals	-1.77	(a)	[40]
2-Methylprop-2-yl	-2.62	(c)	[36]
1-Adamantyl	-1.81	(a)	[41]
Benzyl	-1.43	(d)	[43]
4-Methylbenzyl	-1.62	(d)	[43]
4-Chlorobenzyl	-1.40	(d)	[43]
Ph_2CH	-1.47	(d)	[44]
$PhC(CH_3)_2$	-2.10	(d)	[44]

Methods used:

(a) E° values based on a redox titration with aromatic radical-anions in dimethylformamide.
(b) $E_{½}$ value from pulse polarography at a mercury electrode in dimethylformamide.
(c) E_p values from voltammetry at a glassy carbon electrode in dimethylformamide, sweep rate 0.1 or 0.2 V s^{-1}
(d) $E_{½}$ values from polarography at a gold grid in acetonitrile.

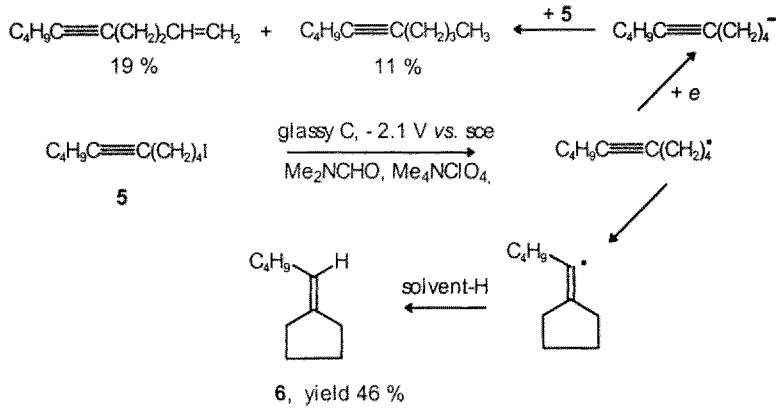
Alkyl radicals are planar while carbanions are pyramidal so reduction of radicals requires considerable reorganisation energy and the polarographic half-wave potentials are more negative than the standard redox potential. Benzyl radicals and benzyl carbanions are both planar so reduction of these radicals involves less reorganisation energy and their polarographic half-wave potentials are believed to be close to the standard reduction potential.

For primary alkyl iodides, the potentials of the two one-electron processes are close and under some conditions the two polarographic waves partially merge. Preparative scale reduction at a potential close to the foot of the polarographic wave yields products derived from the alkyl radical. The radical will attack a mercury cathode to generate a layer of RHg radicals which disproportionate to give the dialkylmercury. 1-Iododecane gives 100 % yield of didecylmercury at a mercury cathode. In the presence of N-methylformamide, substantial amounts of N-methyl-N-decyl-formamide are formed in a further radical reaction [45]. At the plateau of the polarographic wave, decane and decene are formed due to reduction of the radical to the carbanion. Decene is produced from the iodo compound in an elimination reaction by attack of the carbanion. Addition of 1,1,1,3,3,3-hexafluoropropan-2-ol or diethyl malonate as a proton source suppresses such elimination reactions [46]. Reduction of α-iodo-ω-hydroxyalkanes leads to coupling of electrochemically generated primary radicals. The process has been developed as a route to α,ω-alkanediols [47]. Reduction of 1-bromodecane, at any potential, yields decane and some 1-decene. The intermediate alkyl radical is reduced to the carbanion at the potential needed for reaction of the carbon-bromine bond [45].

For secondary alkyl iodides, the two one-electron polarographic waves are more separated. Reduction of 2-iodooctane at the potential of the first wave affords the dialkylmercury and 7,8-dimethyl-tetradecane by reactions of the *sec*-octyl radical. At the potential of the second wave only octane and octenes are isolated [37]. 2-Bromooctane shows only one polarographic wave and yields octane and octene on reduction at any potential [37]. Radicals generated by reduction of primary and secondary iodoalkanes will react with other cathode materials including tin, lead and thallium to form metal alkyls [48, 49].

tert-Butyl bromide and iodide show two one-electron polarographic waves at mercury. Reduction at the potential of the first wave yields an equimolar mixture of isobutane and isobutylene by disproportionation of the first formed *tert*-butyl radicals. A small amount of 2,2,3,3-tetramethylbutane is also formed by radical dimerization. Carbanions are not involved in the reaction because addition of water as a proton source does not suppress the formation of isobutylene. Reduction at the potential of the second wave gives principally isobutane [50]. Reduction of bridgehead *tert*-alkyl halides such as 1-iodonorbornane gives the corresponding cycloalkane and only traces of mercury compounds can be detected [38]. The bridgehead position is here constrained in a pyramidal shape, which causes the radical reduction potential to be close to the potential for carbon-iodine bond cleavage.

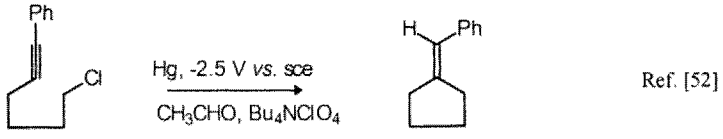
Radical intermediates are also trapped by intramolecular reaction with an alkene or alkyne bond. At a mercury cathode this process competes with formation of the dialkylmercury [51]. At a reticulated vitreous carbon cathode, this intramolecular cyclization of radicals generated by reduction of iodo compounds is an important process. Reduction of 1-iododec-5-yne **5** at vitreous carbon gives the cyclopentane



6, yield 46 %

product **6** in 46 % yield. At more negative potentials, further reduction of the radical is faster than cyclization so that reduction of 1-bromodec-5-yne at –2.6 V *vs.* sce yields only dec-5-yne and dec-1-en-5-yne [46].

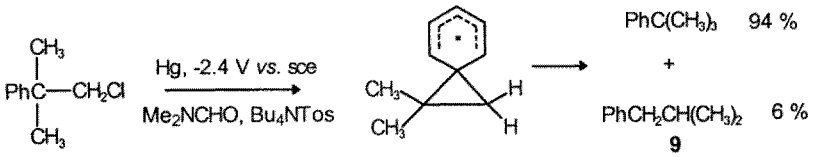
Primary and secondary chloroalkanes are generally not reducible within the available potential window. The exceptions to this rule involve some degree of neighbouring group participation. Reduction of 6-chloro-1-phenylhexyne involves



Ref. [52]

7, yield 81 %

initial attachment of an electron to the π^*-orbital of the benzene ring. Intramolecular electron transfer with carbon-halogen bond cleavage then occurs and the alkyl radical is formed in solution away from the electrode surface where it is unable to react with mercury. Intramolecular cyclization leads to the final product **7** in 81 % yield [52]. Reduction of the 6-bromo and 6-iodo analogues involves electron addition directly to the carbon-halogen bond and the formation of mercury compounds

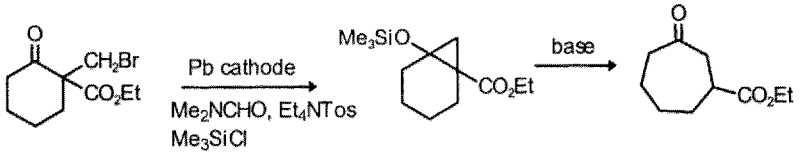


8 **9**

75 % yield hydrocarbons

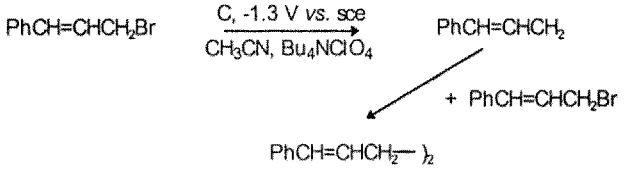
as well as the cyclization product [51]. Reduction of the chloro compound **8** must also involve the π–orbitals of the adjacent benzene ring. One of the products is the rearranged hydrocarbon **9**, which points to the involvement of radicals as intermediates [53].

Electrochemically generated carbanions are trapped by an adjacent carbonyl function in the presence of chlorotrimethylsilane. Subsequent reactions can lead to a ring enlargement process, for example the conversion of **10** to **11**, which has been demonstrated for 5, 6, 7 and 12 membered ring substrates in 62-76 % yields [54].



10 **11**

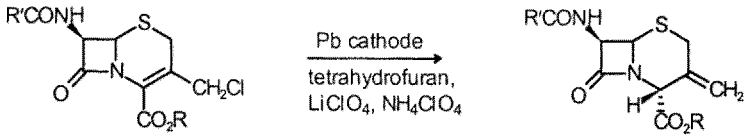
Reduction of allyl bromides and iodides at vitreous carbon in an aprotic solvent generally gives good yields of the dimer. This product arises by rapid substitution by the allyl carbanion, formed in an overall two-electron reaction, onto a second molecule of allyl halide [55, 56].



Ref.[56]

In the cases of a series of allyl chlorides derived from the antibiotic cephalosporin, reduction leads to a delocalised carbanion, which is protonated on the ester

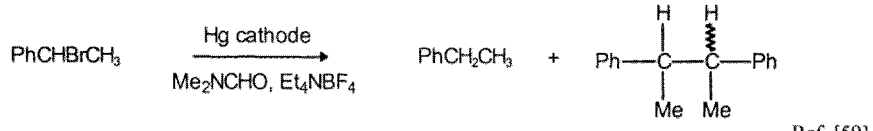
carbonyl oxygen. Enol to keto tautomerism then leads to the 3-methylenecepham



12

12 in 87 % yield [57].

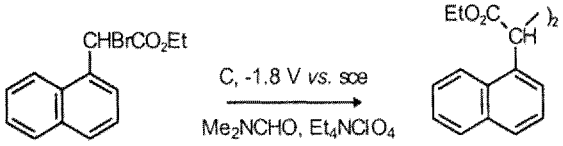
Benzyl radicals have a reduction potential only slightly more negative than the reduction potential of the corresponding benzyl bromide. At a mercury cathode in



potential -0.9 V *vs.* sce yield 17.6% 80 %
-1.7 V *vs.* sce yield 100 %

Ref. [59]

acetonitrile, benzyl bromide gives dibenzylmercury at the foot of the polarographic wave and toluene at the plateau of the wave [58]. 1-Bromo-1-phenylethane shows a related variation in reaction products with cathode potential [59]. Similarly, in the reaction of benzyl bromide at a mercury cathode using methanol as solvent, the radical products, bibenzyl and dibenzylmercury, are favoured at less negative cathode potentials. Electron withdrawing substituents such as *para*-nitro favour bibenzyl formation [60]. Radical dimerization is the usual reaction pathway for reduction of benzyl halides at a vitreous carbon cathode [61, 62].



yield 90 %, *meso* + (±)

Ref. [61]

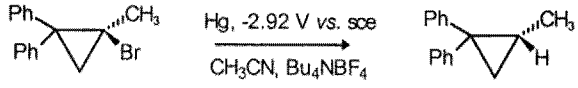
Benzhydryl chloride and bromide are both reduced at a more negative potential than that required for reduction of the benzhydryl radical. Reduction in dimethyl-

formamide at vitreous carbon gives both diphenylmethane and tetraphenylethane. The latter arises from an S_N2 reaction between diphenylmethyl carbanion and the substrate. Addition of diethyl malonate as a proton source suppresses the formation of tetraphenylethane [63].

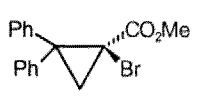
Benzyl and allyl chlorides undergo reactions characteristic of the carbanion after reduction in dimethylformamide in an undivided cell with a consumable magnesium anode. The cathode material is not critical. Glassy carbon, nickel and stainless steel have been used. Reaction with acid anhydrides give a ketone [64] while reaction with ketones gives the tertiary alcohol [65]. Magnesium ions generated at the anode have a stabilising effect on the carbanion intermediates but a true Grignard reagent is not formed and electricity is required for the reaction.

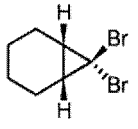
Reduction of chiral alkyl halides leads to hydrocarbons that are largely racemised. Examples are reactions of 6-chloro-2,6-dimethyloctane [66] and 1-deuterio-1-bromo-1-phenylethane [59]. Reduction of these halides in both protic and aprotic solvents leads to replacement of halogen by hydrogen with a low degree of inversion of configuration in the presence of tetraalkylammonium salts. Reduction of the 1-phenylethyl bromide in presence of lithium salts shows a low degree of retention of configuration. Asymmetry is partly retained by the carbanion intermediate, which forms a tight ion pair with the counter cation. The tetraalkylammonium ion shields one face of the carbanion and so directs protonation towards inversion of configuration. Where lithium ion is also co-ordinated to water as a proton source, this gives the hydrocarbon by retention of configuration.

Cyclopropyl carbanions are capable of maintaining their configuration whereas the σ-radical has been shown to reach inversion equlibrium with a rate constant of 10^{11} s^{-1}. The cyclopropyl bromide **13**, and the corresponding iodide, are reduced in a single two-electron polarographic wave and the S(+)-isomer yields the R(-)-hydrocarbon with 26% enantiomeric excess [67 ,68]. Such a substantial retention of configuration during reduction of the carbon-bromine bond indicates a very fast second electron transfer process. Results from reduction of the cyclopropyl bro-



13 26 % e.e.





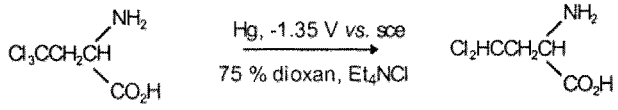
14 **15**

mide **14**, however, are less easy to interpret. The degree of retention, or inversion depends on the reduction potential and on the cation of the electrolyte. Tetraalkylammonium cations always favour inversion of configuration while ammonium cations favour retention. Sodium cations give increasing retention at more negative reduction potentials [69].

Reduction of geminal dibromocyclopropenes of the type **15** gives the *endo*-monobromo compound preferentially. In solvents containing a good proton donor, selectivity rises to 100% in favour of the *endo*-product [70]. The behaviour suggests that the bromocyclopropyl radical intermediates exist with a preference for *exo* arrangement of the radical centre, which is then reduced and protonated on the *exo*-side.

Reactions of the Trichloromethyl Group

The trichloromethyl group is strongly electron withdrawing and consequently the group is reducible within the accessible potential range. Addition of an electron results in carbon-chlorine bond fission and further reduction of the carbon radical to the carbanion. Further reaction takes several courses depending on the experimental conditions. Mercury is a frequently used cathode material even though it is known that mercury compounds can be formed during the reaction. Glassy carbon or carbon-felt are more satisfactory cathode materials for these processes. In the presence of an acid, the carbanion is protonated [71, 72].

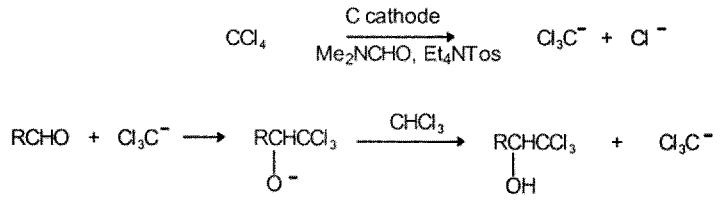


Ref. [71]

Electrochemical reduction in aqueous acid is useful in the treatment of waste liquors obtained from the formation of chloroacetic acid by chlorination of acetic acid. The liquors contain further chlorination products. These are reduced in an undivided cell at a magnetite cathode and a carbon anode to give excellent conversion to monochloroacetic acid [73].

In aprotic solvents, the carbanions, generated by reduction of carbon tetrachloride or ethyl trichloroacetate at mercury, can be trapped by reaction with an added carbonyl compound [74]. This reaction has been developed as a useful step in synthesis. Cathodic reduction of a system containing a catalytic amount of carbon tetrachloride, excess chloroform and an aldehyde leads to an effective ionic chain reaction sustained by trichlormethyl carbanions as indicated in Scheme 4.4. A carbon-felt cathode is used with dimethylformamide as solvent [75]. Aldehydes react with current efficiency of 700 %, which indicates a short chain reaction. Ketones

react only slowly with the carbanion and are not suitable substrates. The related

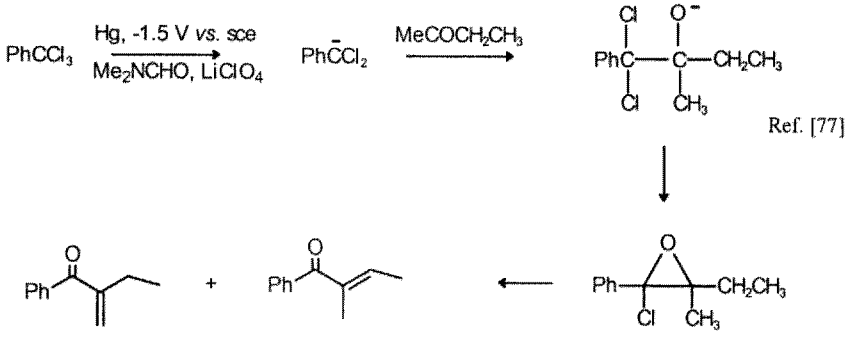


Scheme 4.4. Electrochemically induced ionic chain reaction between aldehydes and chloroform.

reaction with methyl trichloroacetate and methyl dichloroacetate is also effective with aldehyde substrates [76]. In this process, addition to α-branched aldehydes always shows excellent stereoselectivity where Cram's rule defines the preferred mode of attack of the carbanion. One example is given below.

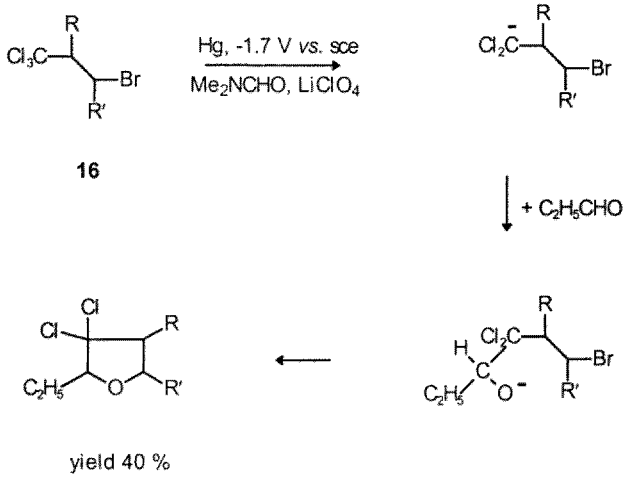
Ref. [76]

In the absence of a proton donor, the alkoxide ion generated by carbanion addition to the carbonyl function can interact with a carbon-halogen bond in the S_N2 displacement reaction. Reactions of this type have led to some novel carbon chain forming processes. Ketones are converted to homologated enones in good yield by



total yield 48 %

cathodic addition of followed by internal substitution and solvolysis reactions [77]. 3,3-Dichlorotetrahydrofurans are obtained by reductive addition of bromotrichloroalkanes **16** to carbonyl groups, followed by an internal substitution step [78].



16

Ref. [78]

yield 40 %

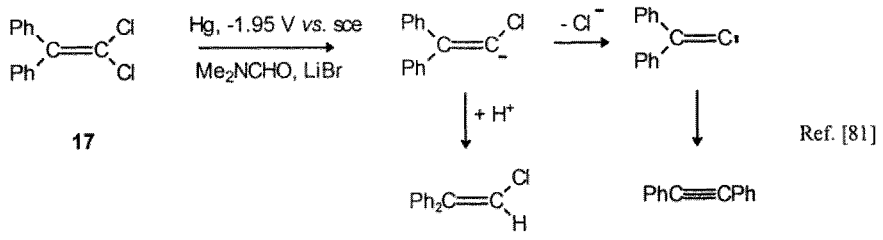
When no electrophile is present, reduction of carbon tetrachloride leads to dichlorocarbene by elimination of chloride ion from the trichloromethyl carbanion intermediate. Dichloromethane is the best solvent for this process [79]. The carbene is trapped by reaction with an alkene to form a dichlorocyclopropane (Table 4.5). Reduction of dibromodifluoromethane in the same solvent is a route to the difluorocarbene intermediate [80].

TABLE 4.5

Yields of dichlorocyclopropanes from reaction of alkenes with dichlorocarbene generated at a lead cathode in dichloromethane containing tetrabutylammonium bromide. Ref. [79].

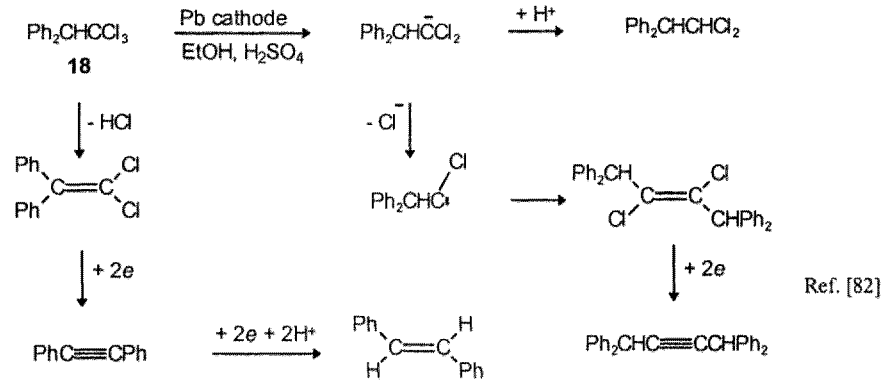
Alkene	Yield of dichlorocyclopropane / %
$Me_2C{=}CHMe$	80
$PhCH{=}CH_2$	65
$PhCH_2CH{=}CH_2$	67
$Me_2C{=}CMe_2$	82

Carbenes are generated during reduction of 1,1-diaryl-1,1-dihaloethenes **17** in the presence of lithium ions and conditions of high current density. Rearrangement of the carbene yields the diarylacetylene [81]. When 3 to 5 % water is present in



the electrolyte, protonation of the intermediate carbanion occurs before elimination to give the carbene. The only product under the latter conditions is the 1,1-diaryl-2-chloroethene.

Reduction of diphenyltrichloroethanes **18** in ethanol and sulphuric acid gives the dichloro compound at room temperature by protonation of the dichlorocarbanion intermediate. At the boiling point of the solution, an acetylene is formed in good yield [82, 83]. In the latter reaction, a chlorocarbene intermediate dimerises and the reductive elimination of the vicinal chlorine atoms forms the alkyne group (see p. 115). A side product is the stilbene. This arises by solvolysis of the substrate to form diphenyldichloroethene and then reduction of this intermediate, as described in the previous paragraph, to give diphenylethyne. Under the reaction conditions,

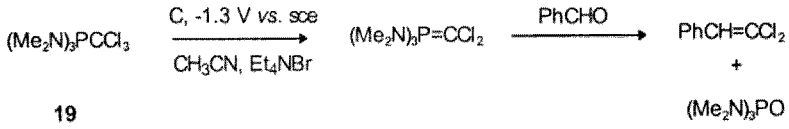


this ethyne is reduced to stilbene.

Electrochemically induced Wittig reactions can be achieved by reduction of trichloromethylphosphorus compounds in the presence of carbonyl compounds. Carbon-felt or glassy carbon are the best cathode materials to use, although many of the early experiments used mercury. Trichloromethylphosphonates give only modest yields of the alkene from reaction with an aldehyde in the Wittig-Horner process at a mercury cathode [84, 85]. Better yields are obtained in an undivided cell with a carbon-felt cathode and a sacrificial aluminium anode [86]. The best yields are obtained in a Wittig reaction between the phosphonium salt **19** and an aldehyde (see Table 4.6). Ketones give negligible yields. The process can be operated in acetonitrile in a divided cell with a carbon-felt cathode or in an undivided cell with a sacrificial aluminium anode [87].

TABLE 4.6
Yields of alkenes from the electrochemical Wittig reaction between phosphonium salt **19** and aldehydes from Ref. [87].

Aldehyde	Yield of alkene / %
Benzaldehyde	83
Pyridine-3-aldehyde	75
Thiophene-2-aldehyde	73
Cinnamaldehyde	86
Hexanal	75
Phenylethanal	63
Cyclopropanaldehyde	50



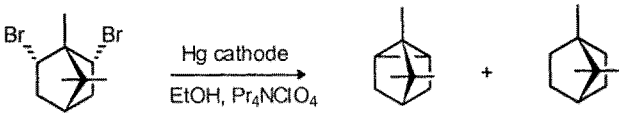
19

Reductive Cyclization of α,ω-Dihaloalkanes

The formation of cyclopropane by reduction of 1,3-dibromopropane was discovered in 1887. Dissolving metals, in particular zinc dust in ethanol, were employed as an electron source [88]. Electrochemical reduction in dimethylformamide at a mercury cathode has been found to give good yields of cyclopropane [89, 90]. 1,3-dibromo, 1,3-diiodo and 1-chloro-3-iodopropane all give greater than 90 % yield of cyclopropane, the other product being propene.

Since chloroalkanes are not reduced at the cathode potential used, it is concluded that these reactions involve generation of a carbanion by dissociative electron transfer to the most easily reduced carbon-halogen bond followed by S_N2 attack of this carbanion on the second carbon-halogen bond [91].

Cyclopropane ring formation under electron transfer conditions shows no stereoselectivity. Reduction in dimethylformamide of pure *meso*- or (±)-2,4-dibromopentene gives the same mixture of *cis*- and *trans*-1,2-dimethylcyclopentane [92]. *Cis*- and *trans*-1,3-dibromocyclohexane are both satisfactory substrates for formation of bicyclo[3.1.0]hexane and either isomer of 1,3-dibromocyclopentane affords bicyclo[2.1.0]pentane [93]. *Endo*-2,*endo*-6-dibromobornane **16** gives a mixture of tricyclene and bornane on electrochemical

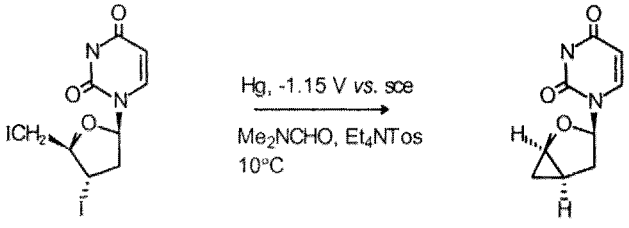


16

reduction in either ethanol or dimethylformamide [94] and *endo*-2-Bromobornane is an intermediate in the formation of bornane.

Most of the cyclopropane ring forming reactions can be accommodated in the mechanism that involves a carbanion in S_N2 displacement of the second halogen atom. An exception is the reactions of 2,6-dibromobornane, which cannot accommodate the transition state stereochemistry necessary for an intramolecular S_N2 displacement. Also, the original preparation of cyclopropane in good yield by dissolving metals in a protic solvent is unlikely to involve carbanions. When the reacting orbitals are parallel, addition of the second electron and carbon-carbon bond formation are likely to be synchronous. If these orbitals are not aligned, reduction leads to a diradical after which the carbon-carbon bond is formed.

Cyclopropane ring formation has been achieved by electrochemical reduction of the nucleoside derivative **17** [95]. Very highly strained cyclopropanes **18** [90] and



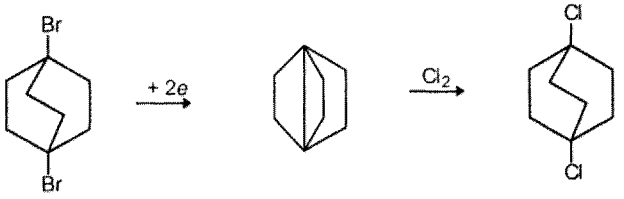
17

19 [96] are formed from the appropriate dibromide. [3.1.1]Propellane **19** can be

18 **19**

isolated but other propellanes are formed by the electrochemical process are too unstable for isolation. Thus, reduction of the dibromide **20** at a mercury cathode is

20



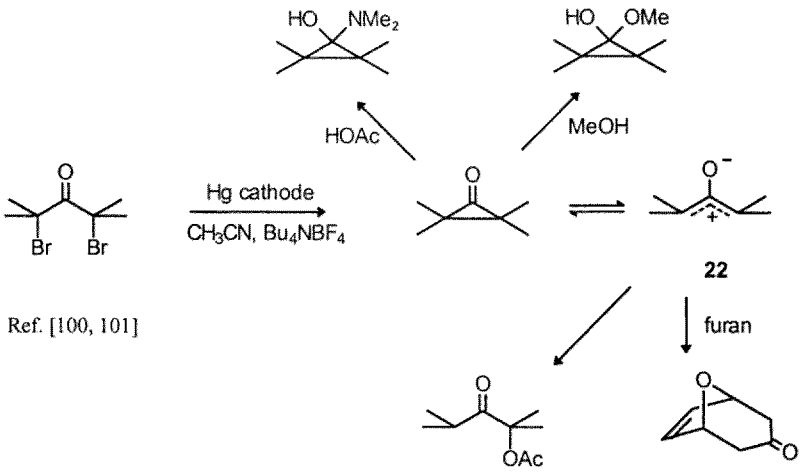
21

a three-electron proces and di-norbornylmercury is isolated [97]. Here the propellane is formed in a two-electron process but is reduced further in a one-electron process to the norbornyl radical, which reacts with mercury. [2.2.2]Propellane **21** exists in solution at –25 °C but cannot be isolated. It was detected by reaction with chlorine to give a dichloro derivative with ring opening [98].

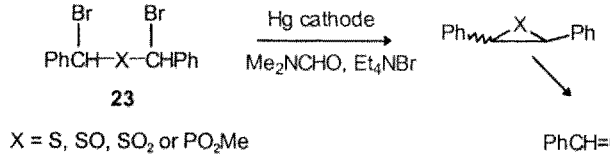
Electrochemical reduction of α,α′-dibromoketones affords the unstable cyclopropanone, which is in equlibrium with the dipolar intermediate **22**. The cyclopropanone hemiacetal is isolated in yields of 40 – 85 % from reaction in acetonitrile and methanol at –20 °C [99]. The dipolar form can be trapped in a cycloaddition process with furan [100]. Reaction with acetic acid leads to the α-acetoxyketone.[101]. Unstable three membered heterocyclic rings are intermediate in the reduction of sulphur and phosphorus linked dibromo compounds **23**. In these reactions, the heteroatom is extruded leaving *cis*- and *trans*-stilbenes as the isolated products [102, 103].

The dimethanesulphonates of 1,3-diols also give cyclopropanes on reduction at a lead cathode in dimethylformamide [104]. The reaction involves reduction of one

substituent to the carbanion level followed by nucleophilic substitution on the re-

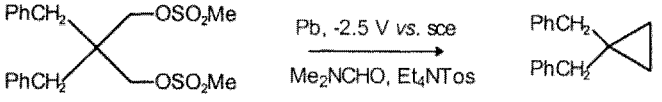


Ref. [100, 101]

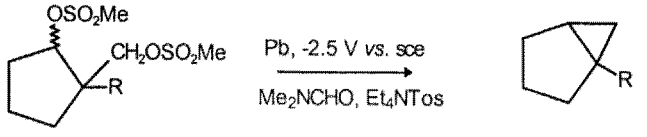


Ref. [102, 103]

maining methanesulphonyl group to form a three-membered ring.



yield 71 %



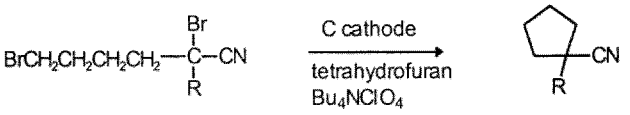
Ref. [104]

yield 55 %

Cyclobutanes and cyclopentanes are formed in low yields by electrochemical reduction of the appropriate α,ω-dibromoalkane in dimethylformamide. 1,4-Dibromobutane affords 29 % cyclobutane along with butane and butene at a vitreous carbon cathode. Addition of 1,1,1,3,3,3-hexafluoropropan-2-ol as a proton

source suppresses the formation of butene and leaves the yield of cyclobutane almost unchanged [105]. Similarly, reduction of 1,5-dibromopentane affords 28 % cyclopentane and the yield is not suppressed on addition of hexafluoroisopropanol as a proton source [106]. 1,6-Dihalohexanes afford less than 5 % of cyclohexane at a vitreous carbon cathode [107]. The cyclization step in these reactions is believed to be an S_N2 displacement of the remaining carbon-bromine bond by a carbanion formed in the initial reductive bond cleavage step. Cyclization must be very fast so as to avoid protonation of the carbanion intermediate.

Reduction of a carbon-bromine bond adjacent to a carbonyl or nitrile function



R = H or Me

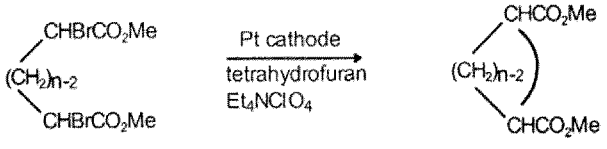
Ref. [108]

generates the resonance-stabilised carbanion in an overall two-electron process. Cyclization of these intermediates by an S_N2 reaction on a second carbon bromine bond gives small to medium sized ring in good yield (Table 4.7) [108, 109]. The ring closure process with stereoisomers of the substrates **24** is not stereospecific.

TABLE 4.7

Formation of cycloalkane-1,2-dicarboxylate esters by reduction of dibromoalkanedicarboxylate esters at a platinum cathode in tetrahydrofuran. Data from ref. [109]

Substrate **24**, n =	Yield of cycloalkane / %
3	60
4	32
5	52
6	60
7	20



24

Alkenes from 1,2-Dibromides and Related Compounds

Reductive elimination from 1,2-dibromides generates the alkene in excellent yields. Conformationally rigid, periplanar *trans*-diaxial, also staggered *trans*-diequatorial, cyclohexane dibromides all afford the alkene at a mercury cathode [110]. In the bicyclo[2,2,2]octane series, the *trans*-2,3-dibromide forms the alkene on dissolving metal reduction [111]. The rigid *cis*-periplanar 1,2 dibromobicyclo[2,2,1]heptane, at a mercury cathode, also gives the strained alkene which can be trapped as a furan adduct [112].

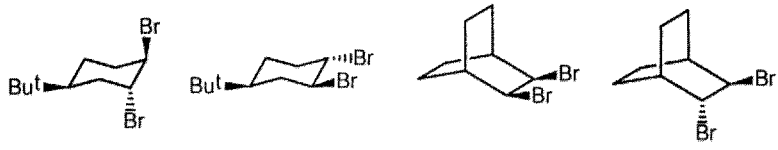
TABLE 4.8

Polarographic half-wave potentials for the reduction of *vic*-dibromides at mercury in dimethylformamide with a tetraalkylammonium salt electrolyte.

Substrate	$E_{½}$ / V *vs.* sce	Ref.
1,2-Dibromoethane	-1.67	[113]
1,2-Dibromopentane	-1.63	[113]
meso-4,5-Dibromooctane	-1.57	[113]
(±)-4,5-Dibromooctane	-1.69	[113]
trans-1,2-Dibromocyclohexane	-1.51	[113]
25	-1.30[a]	[114]
26	-2.11[a]	[114]
27	-1.72[a]	[114]
28	-1.77[a]	[114]

Footnote: (a) Correction to sce of –0.44 V was applied, being the average difference in $E_{½}$ values of substrates common to refs. [113] and [114].

Polarographic half-wave potentials (Table 4.8) for the reduction of 1,2-dibromides are sensitive to the relative stereochemistry of the halide substituents



25 **26** **27** **28**

[113, 114]. Compounds with a *trans*-periplanar arrangement, as in **25**, are reduced at less negative potentials, a *cis*-periplanar arrangement is reduced at slightly more

negative potentials while the staggered arrangement as in compound **26** is reduced only at considerably more negative potentials. Evidence indicates that this elimination reaction involves a stepwise, non-concerted, cleavage of two carbon-bromine bonds. The differences in half-wave potentials are due to an influence of bond orientation on the rate of the first one-electron reaction. The carbon radical formed at this stage is stabilised when in a sp^2 orbital periplanar with the remaining carbon-bromine bond.

In general, *trans*-1,2-dibromocyclohexanes show a single irreversible reduction wave on cyclic voltammetry at room temperature, due to reaction of the diaxial conformer. Equlibration is fast enough to maintain a supply of this conformer at the electrode surface. As the temperature is lowered, a second reduction process at more negative potentials becomes evident in cyclic voltammetry, due to reduction of the diequatorial conformer. Equlibration between the two conformers becomes slower at lower temperatures and some of the diequatorial conformer survives to be reduced at the electrode surface. The cyclohexene is the only product from either conformer. At sufficiently low temperatures, around -80° C, and high scan rates, the relative peak heights no longer change [115]. Under these conditions, the relative peak heights in cyclic voltammetry represent the equlibrium concentrations of the two conformers. The differences in peak potential are due to the kinetics of bond cleavage. Rate constants for the forward and back conformational change can be obtained from digital simulation of the cyclic voltamograms.

Low temperature cyclic voltammetry is also able to demonstrate reduction of the individual rotamers of 2,3-dibromobutane [115]. At room temperature when there is fast bond rotation, reduction proceeds through the conformation with *trans*-periplanar arrangement of carbon-bromine bonds. At -120° C, a second peak at more negative potentials appears in the cyclic voltamogram, due to elimination from the staggered arrangement of carbon-bromine bonds.

Reduction of acyclic 1,2-dibromides gives high yields of the alkene but the reaction is not always stereospecific [113, 116, 117]. When the reaction is carried out using an electron transfer agent it becomes still less stereospecific [113]. Data from reduction of 4,5-dibromooctane are given in Table 4.9. The rotamer with a *trans*-periplanar arrangement of carbon-bromine bonds undergoes a rapid one-electron process to generate a carbon radical and bromide ion. After this event a competition between addition of the second electron followed by elimination of a second bromide ion versus rotation about the carbon-carbon single bond is seen. Very fast addition of the second electron from the electrode surface results in an overall process, which involves *trans*-elimination of periplanar bromine substituents. Slower addition by homogeneous electron transfer allows time for rotation about the carbon-carbon bond and loss of stereochemical integrity in the reaction intermediate.

Addition of the second electron is probably concerted with elimination of bromide ion so that a carbanion intermediate is never formed. Thus, reduction of 1,2-dibromocyclohexanes gives a quantitative yield of the cyclohexene in both aprotic

solvents and in the presence of methanol [110]. Also the elimination of vicinal-dibromides to form alkenes using zinc and acetic acid is well established in the early literature [118].

TABLE 4.9

Stereochemistry of oct-4-ene formed by reduction of 4,5-dibromooctanes to in dimethylformamide containing tetrabutylammonium tetrafluoroborate. Data from ref. [113].

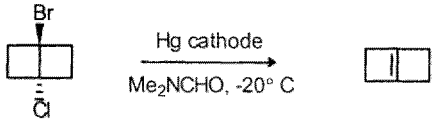
Substrate	Electron source	Product ratio *E* : *Z* oct-4-ene
meso-4,5-Dibromooctane	glassy carbon cathode	100 : 0
	mercury cathode	100 : 0
	homogeneous transfer [a]	87 : 13
(±)-4,5-Dibromooctane	mercury cathode	10 : 90
	homogeneous transfer [a]	38 : 62

Footnote: (a) 1,4-Diacetylbenzene (5.7 mM) used as mediator. *E* : *Z* ratio depends on mediator concentration.

Elimination from 1,2-dibromides under reducing conditions is a useful synthetic procedure for the generation of alkenes. Bromination and cathodic debromination is a means of protecting then deprotecting alkenes. When the cathode potential is controlled near the foot of the polarographic wave, alkene stereochemistry is retained to a high degree [119]. Under these conditions, the *trans*-periplanar arrangement of bromine groups is preferentially reduced.

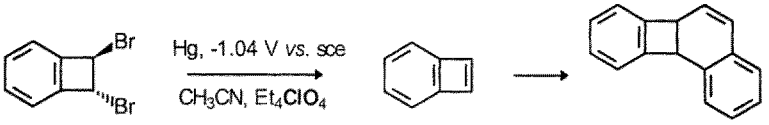
Strained alkenes, including cyclobutenes **29** [120] and benzcyclobutadiene derivatives **30** [121], can be prepared by this route. Particularly advantageous is the wide range of reduction potentials for 1,2-dibromides, which allows some selective reactions. The dibromide **26** can be purified from any of the isomer **25** by reduction at –0.86 V *vs.* sce when the diequatorial bromide remains unchanged and the diaxial compound is converted to the alkene [110]. Bromination of dialkenes followed by selective debromination to recover one alkene leads to protection of the other alkene as the dibromide. Subsequently the second alkene can be recovered by reduction at more negative potentials [122].

Elimination from 1,2-chlorobromo compounds also leads to alkenes. Here, the first electron transfer leads to cleavage of the carbon-bromine bond with formation of a carbon radical. Addition of the second electron leads to elimination of chloride ion with formation of the alkene.



Ref. [120]

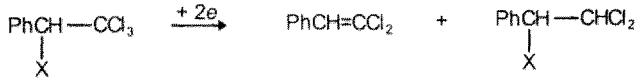
29



Ref. [121]

30

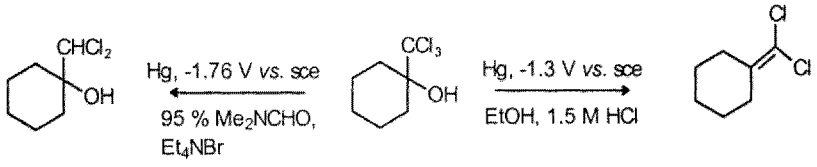
A number of cathodic 1,2-elimination reactions involve one halogen atom and another substituent leaving group. Reduction of the trichloromethyl group in the series of compounds **31** illustrates the range of oxygen based leaving groups. Ei-



31

ther the alkene is formed by elimination or one chlorine atom is replaced by hydrogen [123]. Reaction examples are collected in Table 4.10. Electron withdrawing substituents, X, in **31** favour less cathodic potentials for addition of the first electron and cleavage to form an alkene during addition of the second electron.

In agreement with these observations [124], trichloromethyl carbinols, for example **32**, are reduced in neutral solution to the dichloromethyl carbinol but in acid



32

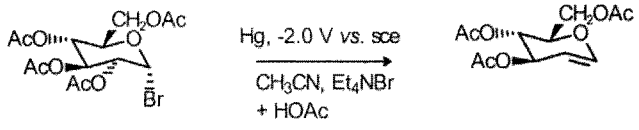
solution elimination of chlorine and the alcohol function occurs to form the alkene. Protonation on the oxygen function allows elimination of water.

TABLE 4.10

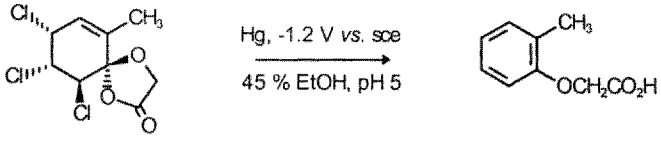
Polarography and reductive elimination reactions of trichloromethyl derivatives in 95 % dimethylformamide, tetraethylammonium bromide. Data from ref. [123].

Substrate $PhCHXCCl_3$, X =	$E_{½}$ / V *vs.*sce	Yield of $PhCH{=}CCl_2$ / %
Cl	-1.21	100
CH_3SO_2O	-1.21	100
p-Me-$C_6H_4SO_2O$	-1.24	100
$C_6H_5CO_2$	-1.31	76
CH_3CO_2	-1.38	70
MeO	-1.54	0
H	-1.52	0

Many examples are available of the elimination of a halogen atom together with a hydroxyl-derived function. Electrochemical reduction of tetra-O-acetyl-α-gluco-

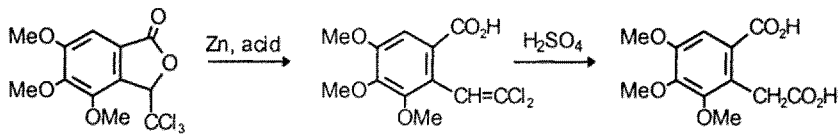


33



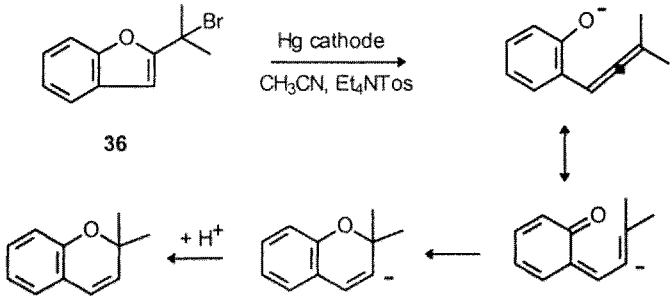
34

pyranosyl bromide **33** under acid conditions affords a quantitative yield of tetra-O-acetylglycal [125]. Compound **34**, which is a byproduct of the chlorination of 2-methylphenoxyacetic acid, is converted to the phenoxyacetic acid at a mercury cathode in acid conditions [126]. Reduction using zinc dust and acid of the trichloromethyl compound **35** affords a dichloromethylene compound [127]. The usefulness of this process is illustrated by the acid catalysed hydrolysis of the dichloromethylene function to carboxylic acid. Electrochemical reduction of side chain



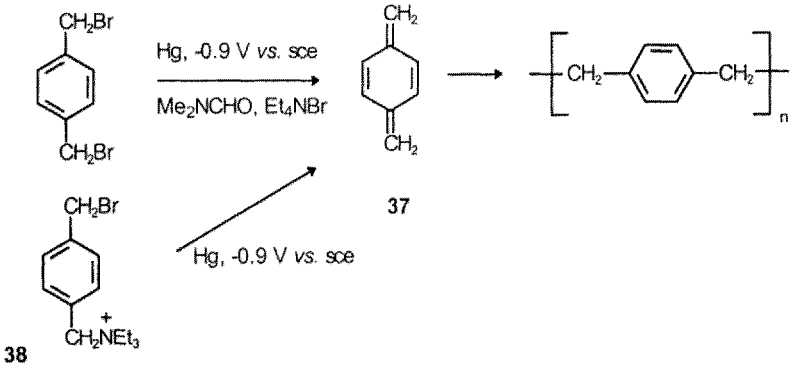
35

brominated benzofurans **36** leads to opening of the furan ring followed by an electrocyclic ring closure process to give the chromene in good yields [128].



36

The dissolving metal reduction of 1,4-di(bromomethyl)benzene has been known for many years to give the insoluble poly(*p*-xylyene) [129]. This process is an analogue of the reduction of 1,2-dihalocompounds. Reduction generates the *p*-quinodimethane **37**, which rapidly polymerises. The same polymer is obtained

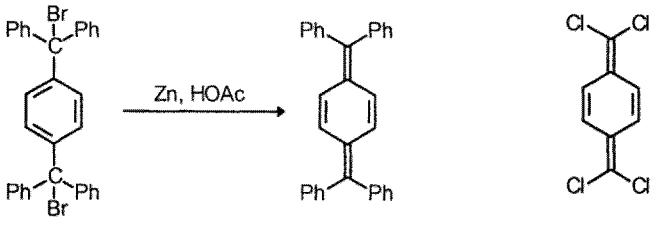


37

38

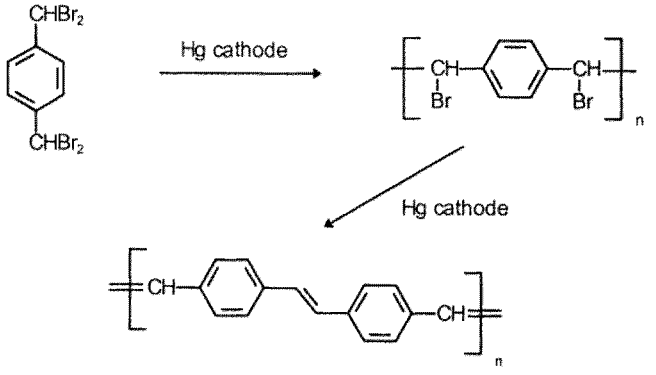
from electrochemical reduction of both the dibromide [130, 131] and the quaternary ammonium salt **38** [130]. Polarography of the dibromide shows a two-electron

wave with $E_{½}$ = -0.80 V *vs.* sce and a second wave of very low height at –1.72 V *vs.* sce which is due to reduction of the intermediate **37** [130]. 1,4-Di(chloromethyl)benzene is reduced at a potential more negative than is compound **37** and yields only 1,4-xylene [132]. Reduction of the dibromide **39** gives a sterically hindered quinodimethane, which is relatively stable [129]. Reduction of 1,4-di(trichloromethyl)benzene under suitable conditions of solvent and temperature yields a crystalline precipitate of the *p*-quinodimethane **40** which quickly polymerises in solution [133].



39 **40**

1,4-Di(dibromomethyl)benzene is reduced at a mercury cathode to yield the poly(*p*-phenylenevinylene) **41**. The reaction proceeds through a brominated poly-

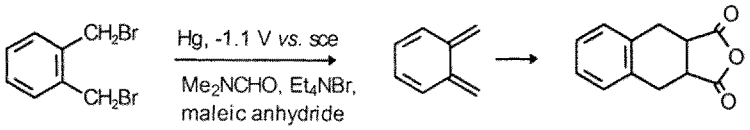


41

(*p*-xylylene) which loses the 1,2 dibromo grouping to introduce a alkene function. The resulting polymer can be made conducting by doping with borontrifluoride or sulphur trioxide and it forms conducting blends with poly(vinyl alcohol) [134].

1,2-di(bromomethyl)benzene **42** shows two polarographic waves with half-wave potentials –0.61 and –1.58 V *vs.* sce in dimethylformamide. Reduction at the potential of the first wave generates the *ortho*-quinonedimethane which quickly po-

lymerises to poly(1,2-xylydene) [130]. The intermediate can be trapped in a Diels-Alder reactions with a number of dienophiles, including maleic anhydride [135, 136]. Reduction of **42** in the presence of maleic anhydride leads to the Diels-Alder



42

product even though maleic anhydride is reduced at a less negative potential than the dibromo compound. Electron transfer mediation by the maleic anhydride radical-anion is involved. In general, the highest yields of Diels-Alder adducts are obtained with those dienophiles which undergo reversible one-electron reduction with a standard potential some 0.5 V less negative than the peak potential for reduction of **42** in cyclic voltammetry [136].

Related to these elimination processes is the reduction of 1,4-dihalides of *trans*-but-2-ene in dimethylformamide to yield butadiene [137].

Reduction of Aryl Halides

Electron addition to aryl halides leads first to the π-delocalised radical-anion. This step is followed by carbon-halogen bond cleavage to give a localised σ-radical, which can accept a second electron either from the electrode or by homogeneous electron transfer from another π-radical-anion. Protonation of the resulting carbanion then leads to overall replacement of the halogen substituent by hydrogen. Reduction of iodobenzenes in acetonitrile containing deuterium oxide, using lithium perchlorate as supporting electrolyte, gives excellent incorporation of a deuterium atom [138]. When the second electron transfer step is slow, the intermediate σ-radical may also abstract a hydrogen atom from good donor solvents.

Since the initial step in this process is the addition of an electron to the lowest unoccupied molecular orbital of the arene, the observed reduction potential is strongly dependent on the energy level of this orbital. In the case of halogen derivatives of more conjugated arenes, bond cleavage occurs at less negative potentials. Bond cleavage from arenes with relatively anodic redox potentials may be so slow (see p. 94) that other reactions intervene. The carbon-chlorine bond is not cleaved when attached to an arene with a standard redox potential anodic of –1.6 V *vs.* sce. The carbon-bromine bond is not cleaved from an arene with a standard redox potential more anodic than –1.2 to 1.6 V *vs.* sce [139]. Since the rate determining step does not involve protons, the polarographic half-wave potentials of aryl halides in protic solvents are not dependent on pH [140]. Both polarographic half-wave potentials and cyclic voltammetry peak-potentials for these substances

do however vary with the electrode material and the supporting electrolyte. Cyclic voltammetry data for the cleavage of carbon-halogen bonds attached to monocyclic arenes are collected in Table 4.11. The polarographic half-wave potentials of substituted iodobenzenes in aqueous ethanol correlate with the substituent Hammett σ-constant [141].

TABLE 4.11

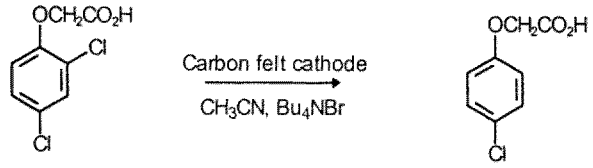
Cyclic voltammetry of aryl halides in dimethyl formamide. Cathodic peak potentials (a) at mercury, scan rate 0.33 V s^{-1}, ref. [29] and (b) at glassy carbon, scan rate 0.1 V s^{-1}, ref. [142].

Substrate	E_p / V *vs.* sce	Substrate	E_p / V *vs.* sce
Chlorobenzene	-2.82 [a]	3-Bromopyridine	-2.27 [a]
Bromobenzene	-2.68 [a]	2-Chlorothiophene	-2.51 [b]
Iodobenzene	-1.93 [a]	3-Chlorothiophene	-2.60 [b]
2-Chloropyridine	-2.32 [a]	2-Bromothiophene	-2.33 [b]
3-Chloropyridine	-2.30 [a]	3-Bromothiophene	-2.52 [b]
2-Bromopyridine	-2.26 [a]	2-Iodothiophene	-1.73 [b]

Some aryl iodides are known to generate the diarylmercury at a mercury cathode. In the case of 4-iodoanisole, reduction at more negative potentials in dimethylformamide leads to the formation of less di(4-methoxyphenyl)mercury. At glassy carbon, anisole is the only reduction product. 4-Bromoanisole gives only anisole at either mercury or carbon [143]. Mercury has been used as cathode material for many preparative experiments with aryl halides but glassy carbon and also stainless steel are very satisfactory alternatives.

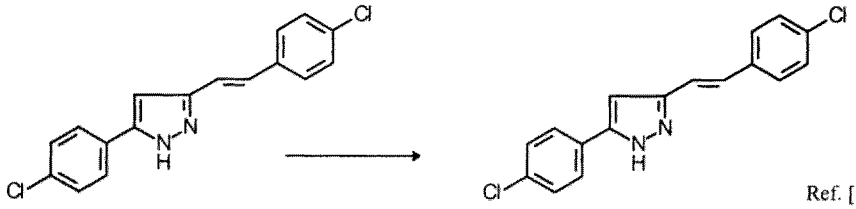
Diphenyliodonium salts give three polarographic waves at a dropping mercury electrode in both water and aprotic solvents [144, 145]. Reduction at the potential of the first wave, $E_{½}$ = -0.5 V *vs.* sce, gives iodobenzene and adsorbed phenylmercury radicals, which rapidly disproportionate to diphenylmercury. At the second wave, $E_{½}$ = -1.7 V *vs.* sce, the iodobenzene, formed at the first wave, undergoes a two-electron reduction to form benzene and iodide ion. The third wave is due to one-electron reduction of the adsorbed phenylmercury radical to benzene and mercury. At the potential of the first wave, electron transfer and carbon-iodine bond cleavage are probably synchronous so that a phenyl radical is generated on the electrode surface and reacts with mercury. During the reduction of iodobenzene, the first formed radical-anion has time to leave the electrode surface before bond cleavage. Further reaction is by single electron transfer to give a phenyl carbanion. Bis(acyloxy)iodobenzenes are reduced to iodobenzene in a single two-electron step with $E_{½}$ = -0.24 V *vs.* sce and acetonitrile as solvent [146].

The influence of electron density distribution in the radical-anion on the rate of carbon-halogen bond cleavage was discussed on page 94. This effect makes possible the selective dehalogenation of polyhalogen aromatic compounds. Examples



Ref. [147]

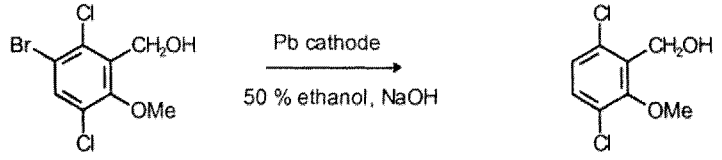
include the selective dechlorination of 2,4-dichlorophenoxyacetic acid [147] and



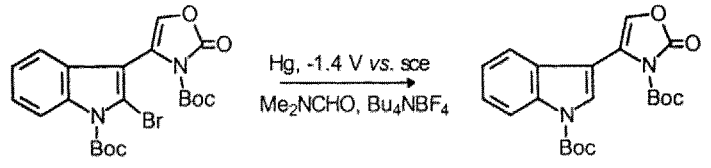
Ref. [148]

43

the pyrazole compound **43** [148]. Bromine has been used as a blocking group to direct the further chlorination of an aromatic ring. Here the carbon-bromine bond is later selectively cleaved by electrochemical reduction [149]. Bromine has also



Ref. [149]



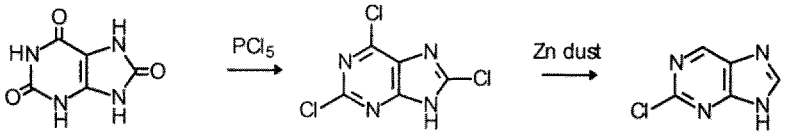
Ref. [150]

44

been used in indole chemistry to block the 2-position and direct substitution into

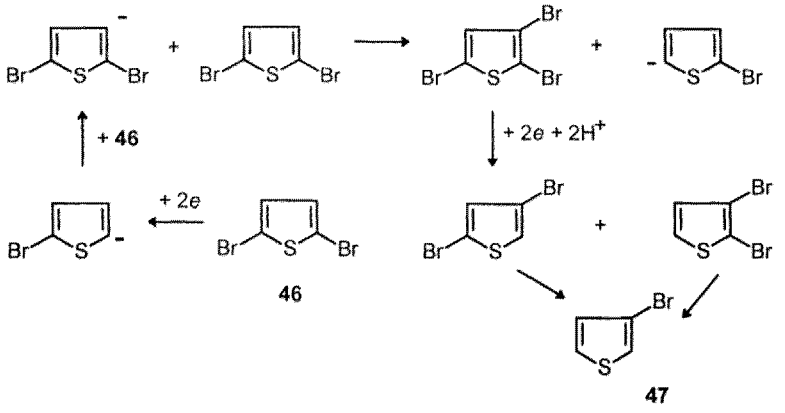
the 3-position during the synthesis of **44** [150]. Reduction of bromothiophenes results in preferential removal of the α-halogen substituents. The conversion of tetrabromothiophene to 3,4-dibromothiophene and then to 3-bromothiophene is easily achieved at a graphite cathode in methanol – dichloromethane, without potential control [151].

Reductive removal of halogen substituents has been of value in the synthesis of pyrimidines and purines since the time of Fisher (1899). Natural purines were deoxygenated in a sequence of reactions involving the replacement of hydroxyl by chlorine through the reaction with phosphorus pentachloride and the reduction using zinc dust and water [152]. 2-Chloropurines **45** are not reduced under these conditions. The 2-iodopurines are however reduced by zinc and water [152]. The elec-



45

trochemical dechlorination 2-amino-4-chloropurine was used in the final stage of a synthesis of 2-aminopurine [153].



46 **47**

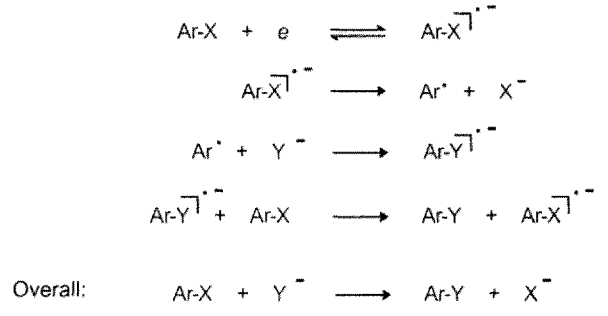
Scheme 4.5 Carbanion assisted halogen exchange during the electrochemical reduction of 2,5-dibromothiophene.

Halogen exchange between an aryl carbanion and a haloarene is well established and occurs by nucleophilic substitution on the halogen substituent [154]. This pro-

cess is observed during electrochemical reduction of aryl halogen compounds in anhydrous aprotic solvents. 2,5-Dibromothiophene **46**, for example, yields some 3-bromothiophene **47** under these conditions by the sequence of reactions shown in Scheme 4.5 [142]. The processes involve transfer of a more acidic hydrogen from one molecule to a thiophene carbanion and also transfer of bromine from one bromothiophene to a thiophene carbanion. Related processes occur during the reduction of benzenes with several bromo substituents [155]. Addition of water to the reaction medium completely suppresses these exchange reactions by rapidly protonating the carbanion intermediates.

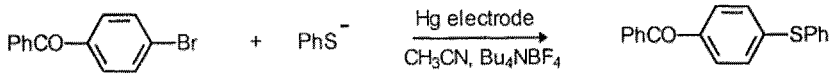
Electrochemically Induced $S_{RN}1$ Reaction

Generation of aryl radicals by reduction of aryl halides in the presence of some nucleophiles, particularly alkyl or aryl sulphide ions and cyanide ions, leads to bond formation with the generation of a new radical-anion. Overall, a reaction between the initial aryl halide and a nucleophile is triggered at the cathode and is an equivalent of the $S_{RN}1$ process. It proceeds in stages according to Scheme 4.6 [156] and requires only a catalytic concentration of radical-anion. The reaction can



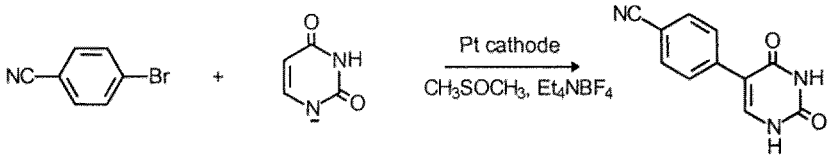
Scheme 4.6. Electrochemically catalysed nucleophilic substitution process.

be illustrated by reaction of 4-bromobenzophenone with thiophenolate ions.



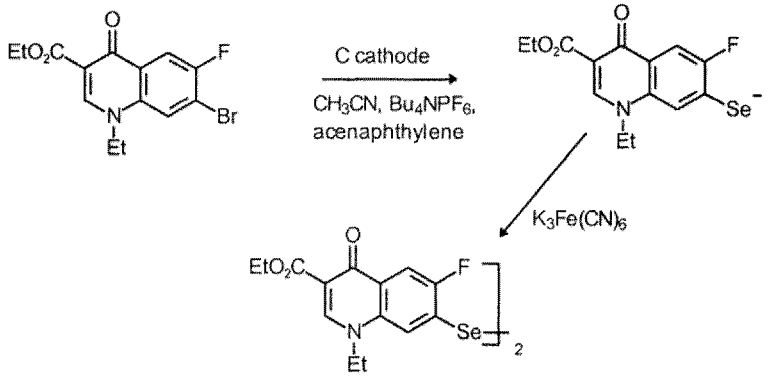
Ref. [156]

When the redox potential of the product is more negative than that of the starting material the reaction should be self-sustaining, catalysed by the injection of a low electron charge. In practice some charge is consumed by competing side reactions. Dimethylsulphoxide as solvent gives better yields of the $S_{RN}1$ product than acetonitrile since the hydrogen abstraction step is slower [157]. Liquid ammonia is a very poor hydrogen atom donor and in this solvent the only reaction to compete with substitution is further reduction of the aryl radical to a carbanion [158]. Much poorer yields of substitution product are obtained with aryl iodides than with aryl bromides because, when using iodo compounds, radicals are generated closer to the electrode and so further reduction can compete more successfully with addition of the nucleophile.



48

5-Aryluracil derivatives **48** have been prepared by this reaction [159]. The $S_{RN}1$



49

reaction is especially useful for the preparation of aryl sulphides, selenides and tellurides [160]. Formation of the diselenide **49** illustrates the method [161]. Reactions are carried out in an undivided cell with a sacrifical magnesium anode. Magnesium ions, however, inactivate the diselenium anions because of complex formation. Addition of tetraethylammonium fluoride to the electrolyte causes

precipitation of magnesium fluoride and prevents the inactivation process. Acenaphthylene is used as an electron transfer agent to avoid direct reduction of the aryl halide at the electrode surface where the radical intermediate is further reduced to the carbanion. Acenaphthylene preferentially forms the radical-anion at the cathode and this species transfers an electron to the aryl halide in solution. Aryl radicals are formed by carbon-bromine bond fission and these rapidly react with the selenium anion.

The sulphur, selenium and tellurium nucleophiles required for these $S_{RN}1$ reactions can be generated in a preliminary step by reduction of a sacrificial cathode of graphite mixed with elemental sulphur, selenium or tellurium [160, 162].

Electrochemically Induced Radical Cyclization Reactions of Aryl Halides

The addition of aryl radicals, generated by chemical reduction of aryldiazonium salts, onto arenes in the Gomberg-Hey reaction is well established [163]. The addition of these radicals to alkenes in the Meerwein reaction is also well known [164]. Aryl σ-radicals generated by electrochemical reduction of aryl halides take part in similar reactions. Good yields of the products are obtained when the intermediate phenyl radical can react in an intramolecular manner. The addition step is then fast and competes successfully with further electron transfer to form the phenyl carbanion, followed by protonation.

Competition between cyclization of the intermediate σ-radical or further reduction is illustrated with the benzanilide substrates **50** [165]. In all, four types of product are formed. Cyclization of the phenyl radical to a six-ring radical intermediate leads to the cyclization product **51**. Cyclization of the phenyl radical to a five-ring radical intermediate leads to the diphenyl **52** after a further electron transfer step. Reduction of the aryl σ-radical before cyclization gives **51**, X = H. Cleavage of the carbonyl-nitrogen bond in the radical-anion affords a trace of the aniline **53**.

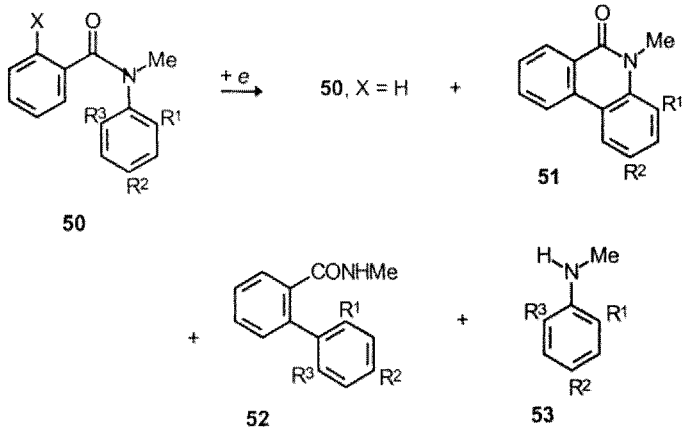
Product yields from reduction of the benzanilides at a mercury cathode in dimethylformamide are listed in Table 4.12. The progression of product yields along a series of related structures where chlorine is replaced by bromine and iodine shows the influence of carbon-halogen bond cleavage rate for the radical-anion. Bond cleavage rate increases in the sequence Cl<Br<I. When the radical-anion has a short life-time, fragmentation generates the σ-radical closer to the electrode and increases the probability of further electron addition to give the phenyl carbanion, before cyclization occurs. Reaction sequences are illustrated for the reduction of 2-chloro-N-methyl benzanilide (Scheme 4.7) [165].

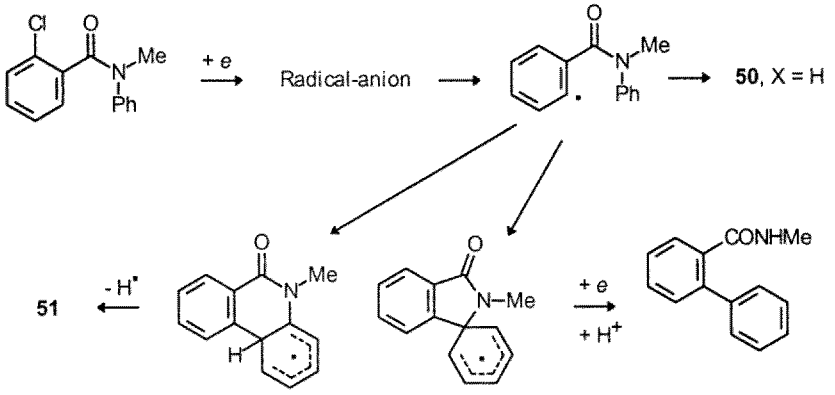
These substrates show restricted rotation about the amide bond. With no *ortho*-substituent present, the *syn*-form predominates with adjacent phenyl rings. *Ortho*-substitution increases the proportion at equlibrium of the rotamer with *anti*-phenyl rings. Reduction of the *anti*-rotamer can lead only to replacement of halogen by hydrogen. For the chlorobenzanilides, the formation of a product with the chlorine

substituent replaced by hydrogen is almost completely due to reduction of the *anti*-rotamer present at equilibrium.

TABLE 4.12
Product yields from reduction of substituted 2-halogeno-N-methyl-benzamides at a mercury cathode in dimethylformamide. Ref. [165].

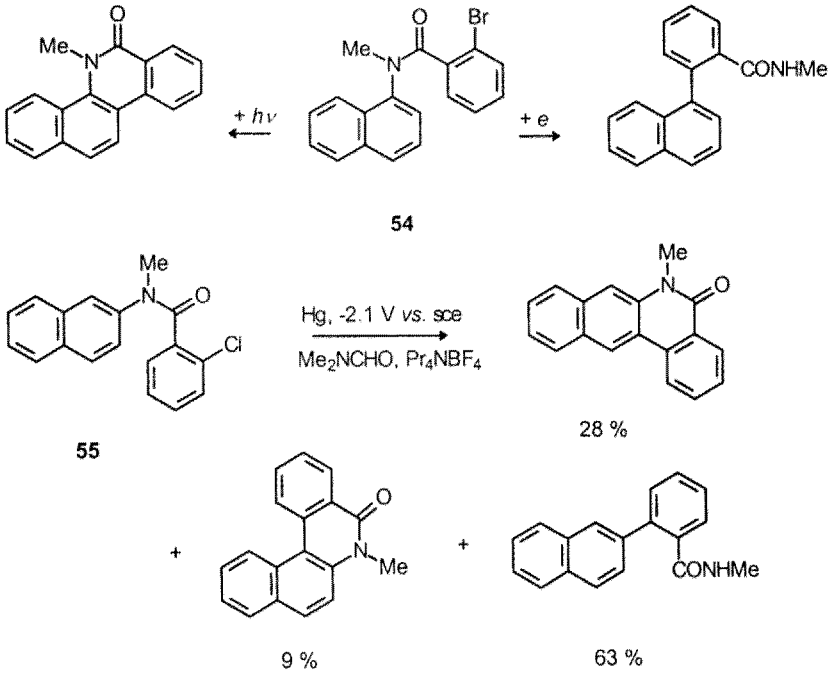
Substrate	$E_{½}$	% Yield of reduction products			
50	/ V *vs.* sce	**50**, X = H	**51**	**52**	**53**
		$R^1 = R^3 = H$ and $R^2 = Me$			
X = Cl	-2.26	13	38	45	4
= Br	-2.16	26	33	38	3
= I	-1.66	45	26	24	5
		$R^1 = R^2 = H$ and $R^3 = Me$			
X = Cl		21	0	76	3
= Br		50	0	49	1
= I		72	0	23	5
		$R^1 = R^3 = Me$ and $R^2 = H$			
X = Cl	-2.28	61	0	39	0
= Br	-2.20	63	0	34	3
= I	-1.67	93	0	7	0





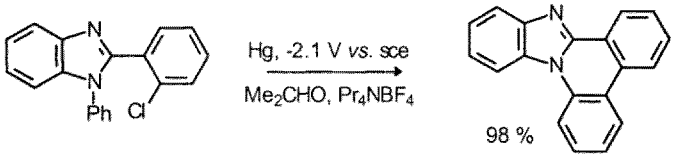
Scheme 4.7. Reaction mechanism for the electrochemical reduction of 2-halo-N-methylbenzanilides, illustrated for 2-chloro-N-methylbenzanilide.

Ortho-substitution in the aniline ring favours the formation of a biphenyl derivative. Thus, in the electrochemical reduction of the 1-naphthylamide **54** the 1-

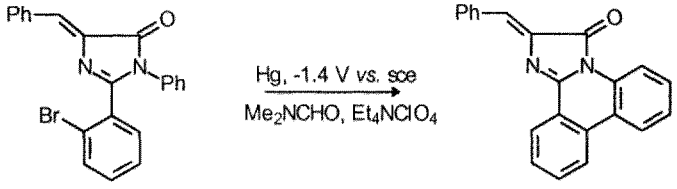


phenylnaphthalene is the sole product [166]. In contrast, the photochemical cyclization of 1-(2-bromobenzoyl)-N-methylnaphthylamines leads to the benzophenanthridone, probably by an electrocyclic intermediate, which loses hydrogen bromide. [167]. Electrochemical reduction of the 2-naphthylamine derivative **55** gives two benzophenanthridones as well as the 2-phenylnaphthalene derivative [166].

Reductive cyclization of the 2-halogenophenyl group onto an adjacent phenyl substituent is a useful reaction for the preparation of condensed ring nitrogen heterocycles. Examples of the process include the formation of aromatic and conjugated π-systems [168, 169]. It has been applied to the synthesis of an aporphine

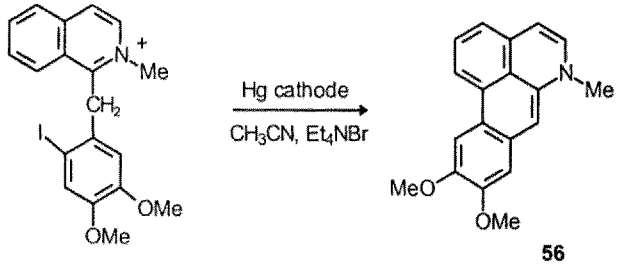


Ref. [168]



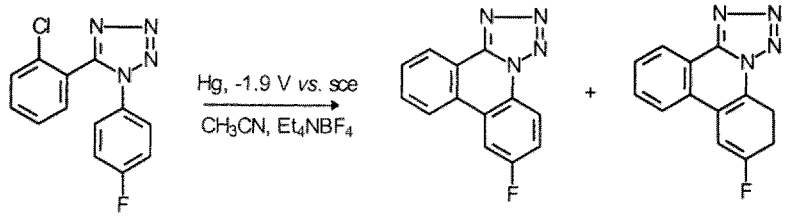
Ref. [168]

derivative **56** [170]. Only products from a six-ring delocalised radical intermediate were found with no products derived from a five-ring intermediate. The latter mode of cyclization appears restricted to the N- methylbenzanilide types. The six-ring radical intermediate in the reaction of the tetrazole derivative **57** is partly trapped by further reduction and a dihydrobenzene can be isolated from the product mixture [171].



56

Reductive cyclization reaction is carried out very efficiently at a stainless steel cathode and a sacrificial magnesium anode in an undivided cell [172]. Under these conditions and at current densities higher than 20 A m^{-2}, the conversion of **57** to **58** gives close to 100 % yield when a low partial pressure of oxygen is introduced during the reaction. Oxygen generates superoxide radical-anion at the cathode and this is an effective dehydrogenating agent for conversion of the dihydrobenzene to

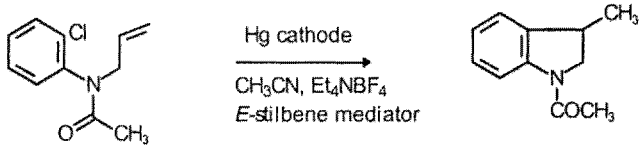


57 **58**, 63 % yield 22 % yield

the benzene level. At lower current densities some of the product with chlorine replaced by hydrogen begins to appear.

Phenyl σ-radicals generated by reduction of aryl halides can also interact with an intramolecular alkene bond. The method has been developed for the formation of dihydroindoles by reductive cyclization of N-allyl-2-chloroacetanilides. The results indicate the importance of a time interval between electron addition to give a radical-anion and the fragmentation of this species to give the active σ-radical. The time interval allows the radical-anion to diffuse away from the electrode surface so that when the σ-radical is formed, it has time to cyclize before it can be reduced at the surface.

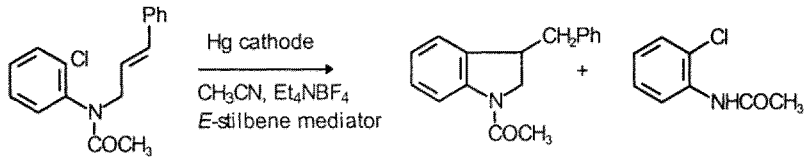
The substrate **59** has an electron donating amide function on the benzene ring. This increases both the energy of the benzene LUMO and the rate of fragmentation of the carbon-chlorine bond relative to the examples where an electron withdrawing heterocyclic ring is present. Carbon-halogen bond cleavage in the radical-anion from **59** is so fast that the σ-radical is generated close to the electrode surface where it is reduced to the carbanion before cyclization occurs. Reduction with no added mediator yields N-allylacetanilide as the sole product. Reductive cyclization of **59** is effected in the presence of *E*-stilbene as mediator. Stilbene is preferentially



59 67 % yield

reduced to the radical-anion at the electrode and stilbene radical-anion then transfers an electron to **59** in solution. Carbon-halogen bond cleavage then occurs and the resulting σ-radical cyclizes before it can be reduced further [173].

The electrochemical cyclization reaction is less successful with the N-(3-phenylallyl)acetanilide **60** which has two potential bond cleavage sites from the radical-anion [173]. Carbon-nitrogen bond cleavage with loss of a 3-phenylallyl radical, leaving an amide nitrogen anion, is favoured over carbon-chlorine bond cleavage.



60

Alternative chemical reactions are available for the generation of phenyl σ-radicals. These include the diazonium salt reactions mentioned earlier and also reaction of aryl bromides and iodides with tributyltinhydride or triphenyltinhydride in the presence of a radical initiator [174]. Electrogeneration of the tin radical by oxidation of triphenyltinhydride at a platinum anode is also used to initiate this process [175]. The carbon-halogen bond cleavage step is due to abstraction of a halogen atom by the trialkyl or triaryltin radical. Cyclization is rapid and is followed by transfer of a hydrogen atom from the tinhydride. The disadvantage of this proces is that it generates spent tin reagents, which may be tedious to separate from the required product.

TABLE 4.13

Yields from addition of phenyl σ-radicals to styrene. Radicals are generated by mediated electrochemical reduction in various solvents. Ref. [176].

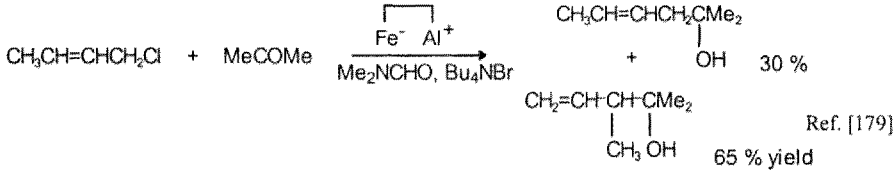
Halogenoarene	Styrene excess	Solvent	Mediator	$ArCH_2CH_2Ph$ % yield
4-Chlorobenzonitrile	5-fold	Me_2SO	1-naphthonitrile	50
4-Chlorobenzonitrile	5-fold	Me_2CHO	1-naphthonitrile	28
4-Chlorobenzonitrile	5-fold	MeCN	1-naphthonitrile	52
Bromobenzene	20-fold	MeCN	methyl benzoate	79
Bromobenzene	9-fold	NH_3(liq.)	4,4′-bipyridyl	90

Phenyl radicals generated electrochemically in dimethylformamide will also add to styrenes in an intermolecular fashion. An electron-transfer mediator is required so that the intermediate phenyl σ-radical will be generated away from the electrode surface [176]. The bimolecular addition to styrene is slower than the intramolecular cyclization process and is in competition with hydrogen abstraction from the solvent. Yields for the addition of phenyl radicals to styrene in various solvents are given in Table 4.13. Acetonitrile, amongst the generally used aprotic solvents, gives the highest yields of addition product. Liquid ammonia is the best solvent for these reactions because it is a poor hydrogen atom donor.

Carbon-Halogen Bond Reactions Catalysed by the Anode Material

The use of sacrificial anodes in an undivided electrochemical cell (p. 8) was originally introduced to dispense with the need for a fragile diaphragm [177]. It was discovered later that ions generated from the sacrificial magnesium, zinc or aluminium can stabilise carbanion intermediates and render them less liable to protonation by traces of water in the aprotic solvent. Proceses involving organic halides and carbonyl compounds, strongly resembling Grignard or Reformatsky reactions, are promoted in these electrochemical cells. Metal ions generated electrochemically by dissolution of the anode are more effective in these processes than ions added to the cathode compartment of a divided cell.

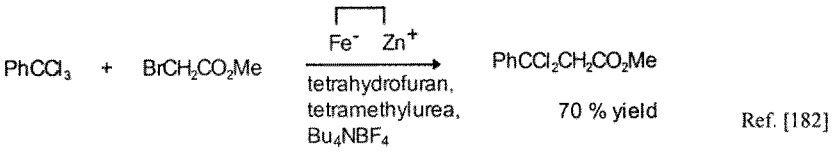
Reduction of a range of allyl and benzyl chlorides at a stainless steel cathode in dimethylformamide in the presence of carbonyl compounds and using a sacrificial anode of aluminium or zinc, leads to a Reformatsky-type reaction in 40-80 % yields. Allyl halide give products by reaction at both the α- and γ-positions. Tetrachloromethane and bromotrifluoromethane take part in similar reactions provided a



zinc anode is used [178]. Aluminium and magnesium are unsuitable because the electrochemically cleaned metal anode will react with these more active halides.

Later work demonstrated that electrochemical Reformatsky-type reactions give the highest yields when carried out in dimethylformamide containing a catalytic amount of zinc bromide, using a zinc cathode and a zinc anode. Activated halides like benzyl bromides [179], allyl bromides [180] and α-bromo esters [181] all react with carbonyl compounds under these conditions. A layer of highly reactive zinc is generated electrochemically on the cathode and this instantly reacts with the

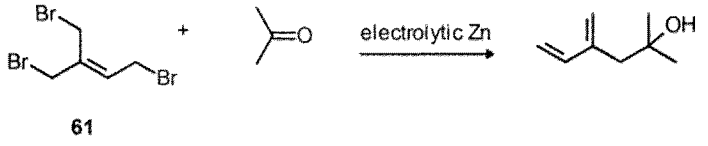
organic halide to give an organozinc species. After a Reformatsky reaction involving the carbonyl compound, zinc ions are recovered and reconverted to active zinc metal. Electrons are consumed in the overall process. The S_N2 reactions between a carbanion, derived from an easily reduced halide such as tetrachloromethane or trichloromethylbenzene, and a reactive alkyl halide are also pro-



Ref. [182]

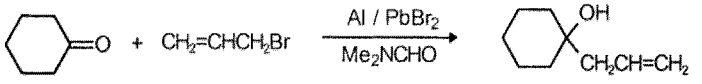
moted under these conditions. The latter cross coupling reaction occurs in 50-70 % yields using a stainless steel cathode and a zinc anode providing zinc ions [182].

A highly active zinc powder can be generated in bulk by electrolysis of a tetraalkylammonium salt in dimethylformamide between a zinc anode and a platinum cathode [183]. This reagent has been used in stoichiometric amounts for Reformatsky-type reactions where the tribromide **61** is used as a precursor for the isoprenyl group [184]. Zinc promoted 1,4-elimination of bromine to give the butadiene system is followed by a Reformatsky reaction of the remaining allylic bromine substituent.



61

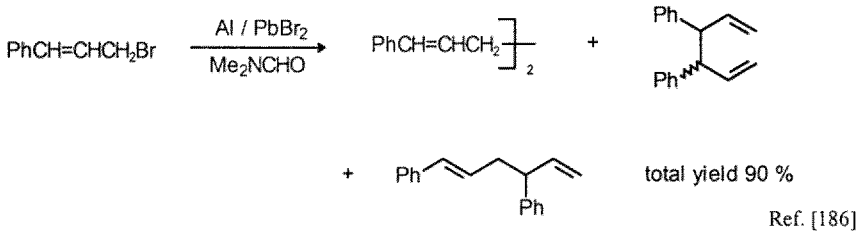
Many of the coupling reactions of benzyl bromides and allyl bromides can also be carried out in dimethylformamide using aluminium foil and a catalytic amount of lead bromide. The process does not require an external voltage supply since dissolving aluminium serves as the electron source. A finely divided lead is probably first formed and this reacts with the organic halide to give an organolead interme-



Ref. [185]

diate. Further reaction steps then afford the organic product and regenerate lead ions, which are recycled. A rapid reaction between aldehydes or ketones and the organolead intermediate generates the Reformatsky-type addition product [185] In the absence of a reactive carbonyl compound, the dimeric benzyl or allyl com-

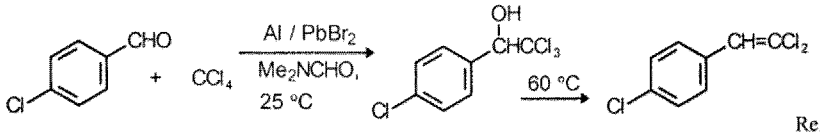
pound is obtained [186]. The allyl coupling process is not regioselective, it leads to



Ref. [186]

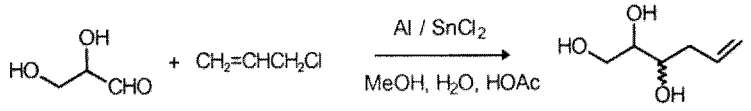
all possible isomeric products. Finely divided lead has been known for some time to convert benzyl chloride to bibenzyl [187].

Coupling between tetrachloromethane and aldehydes to form a trichloromethyl derivative is also effected with this aluminium, lead bromide reagent. At elevated temperatures, the first formed product is reduced further with the elimination of chloride and hydroxyl ions, forming a dichoroalkene [188].



Ref. [188]

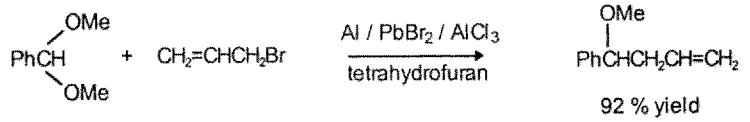
Reformatsky reactions between allyl chloride and carbonyl compounds are also effected in protic solvents using aluminium and a catalytic amount of tin chloride. Finely divided tin is formed and organotin reagents are involved as intermediates. These react with the carbonyl compound releasing tin ions, which are recycled by the dissolving aluminium [189].



Ref. [189]

82 % yield

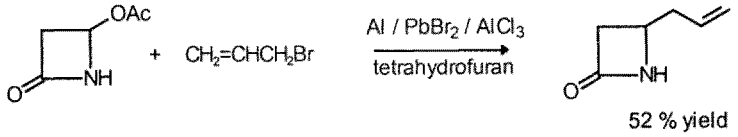
The dissolving aluminium, lead bromide system has been combined with a Lewis acid in tetrahydrofuran to effect the combination of an allyl bromide with an acetal or an α-acetoxyamide. Aluminium chloride is employed as the Lewis acid to



92 % yield

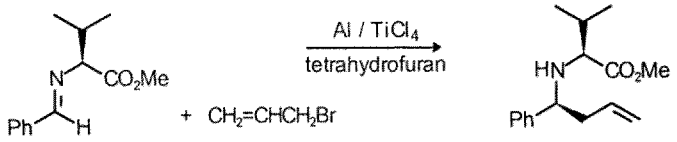
Ref. [190]

activate the acetyl-type function [190].



Ref. [190]

A combination of dissolving aluminium and titanium tetrachloride in tetrahydrofuran promotes the allylation of imines. Here titanium is reduced to titanium(0),



Ref. [191]

which activates the allyl halide. At the same time, aluminium ions act as Lewis acid to activate the imine [191]. The allylation of imines derived from L-valine occurs with 95 % enantioselectivity and the valine residue can be cleaved in an electrochemical oxidative step (p. xxx) to afford the 4-amino-4-phenylbut-1-ene with high optical purity.

Carbon-Halogen Bond Reactions Catalysed by Ni, Co and Pd Complexes

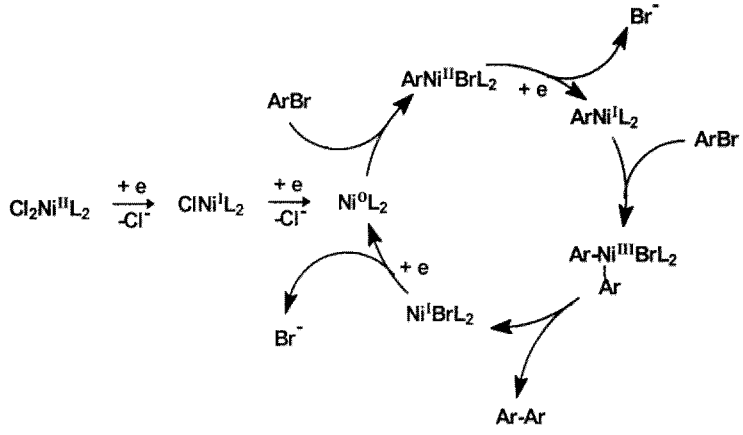
Low oxidation state complexes of nickel, palladium and cobalt undergo oxidative addition reactions with the carbon-halogen bond in aryl and alkyl halides. Some of the resulting aryl metal species are sufficiently stable for isolation and can be prepared electrochemically. Carbon-carbon forming reactions are known which involve a stoichiometric ratio of the resulting alkyl or aryl metal species with an organic halide. In these processes a higher oxidation state of the metal complex is liberated. Electrochemistry offers a conversion of these reactions to a catalytic system by promoting the recycling the transition metal oxidation states [192]. The cathode potential required for these processes is determined by the redox potential for the metal complex system and is less negative than that required for uncatalysed cleavage of the carbon-halogen bond.

Nickel Complexes

Early electrochemical experiments with Ni species used square planar complexes employing a macrocyclic ligand [193]. The use of triphenylphosphine ligands has also been explored [194] but most of the preparative work with Ni com-

plexes has used 2,2′-bipyridine (bipy) as the ligand. Mechanistic studies in this area used 1,2-bis(diphenylphosphino)ethane (dppe) as the ligand [195].

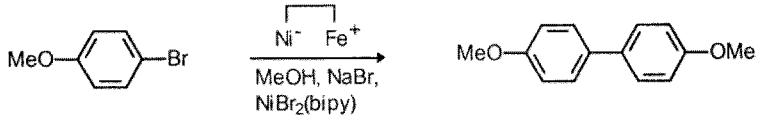
Under controlled potential conditions, formation of biphenyl from bromobenzene in the presence of nickel(II) chloride and dppe occurs only at a potential more



Scheme 4.8. Catalytic cycle for the formation of biphenyl from bromobenzene using nickel complexes where L_2 = 1,2-bis(diphenylphosphino)ethane.

negative than –2.0 V *vs.* sce according to Scheme 4.8. The nickel(II) complex is reduced in two successive one-electron stages, at a less negative potential, to the nickel(o) level. The resulting complex reacts instantly with bromobenzene to give a phenyl nickel(II) species. Reduction at –2.0 V causes formation of phenyl nickel(I) which undergoes oxidative-addition with a second molecule of bromobenzene to form diphenyl nickel(III). This collapses to diphenyl and nickel(I). The last complex is reduced to the nickel(o) level, completing the catalytic cycle.

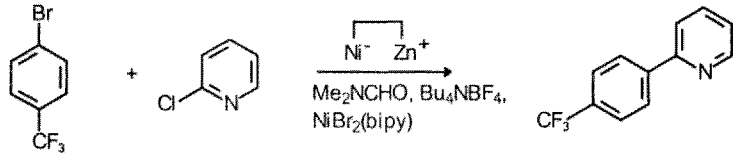
Preparative scale reduction of aryl halides catalysed by nickel(bipy) compounds was originally carried out in N-methylpyrrolidone in the presence of tetrabutylammonium fluoroborate at a gold cathode and a magnesium anode in an undivided cell. The complex $NiBr_2$(bipy) was used as the catalyst source with at least one equivalent of 2,2′-bipyridyl present in solution. A cathode potential of –1.2 V *vs.* sce causes formation of the catalyst Ni(o)$(bipy)_2$ and promotes the overall reaction. Chloro-, bromo- and iodobenzenes having both electron withdrawing and electron donating substituents are converted to the biphenyl [196]. Subsequent work has shown a mixture of ethanol and dimethylformamide to be a suitable solvent with sodium bromide as supporting electrolyte. Both iron and the aluminium alloy, duralumin (Al 94 %; Cu 5 %; Mg 0.5 %; Mn 0.5 %), are suitable as sacrificial an-



Ref. [197]

ode materials [197] and the conversion can be conducted in an undivided cell at constant current. Biphenyls are also obtained from halobenzenes using a sacrificial stainless steel (Fe_{64}/Ni_{36}) anode in dimethylformamide containing tetrabutylammonium fluoroborate and 2,2′-bipyridyl. Catalytic nickel species are formed in this mixture by dissolution of the stainless steel anode [198]. Alternatively, reductive coupling of iodobenzenes with $NiCl_2$(bipy) as catalyst can be carried out using a stoichiometric amount of aluminium metal as the electron source in the presence of lead(II) bromide, which generates cathodic sites of lead on the dissolving aluminium anode. Reaction occurs in methanol containing potassium iodide [199].

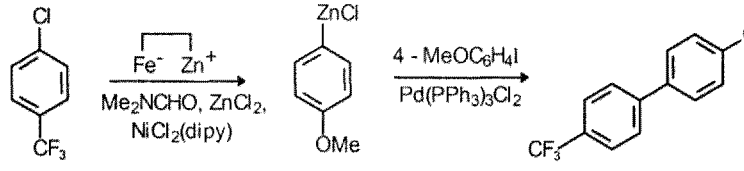
Reduction of a mixture of two aryl halides is not generally a good route to the mixed biaryl. Either a statistical mixture of the three possible biaryls is formed or, if one aryl halide is more reactive, this forms a single biaryl after which, the second aryl halide reacts with itself. The principal exception to this generalisation involves the reduction of a 1:1 mixture of an aryl bromide and 1-chloropyridine. Oxidative-addition to Ni(0) is faster for the carbon-bromine bond. The second oxidative-addition to ArNi(I) is faster for the 2-chloropyridine, possibly due to complexation from the pyridine nitrogen. Overall, the 1-arylpyridine is formed in 55-80 % yields [200].



Ref. [200]

63 % yield

The cross coupling of two aryl halides is achieved by the use of organozinc intermediates. Reduction of one component is carried out in dimethylformamide using a stainless steel cathode and a zinc anode with the nickel catalyst in the pres-

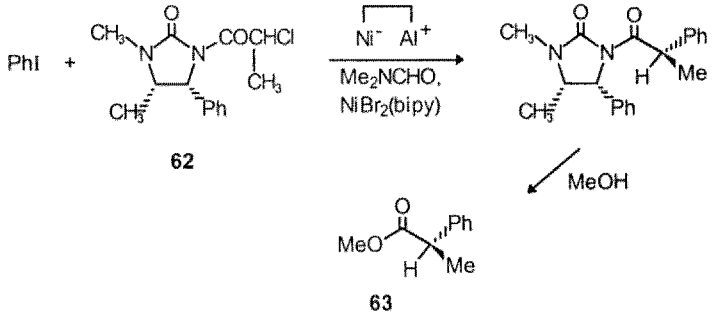


Ref. [201]

83 % yield

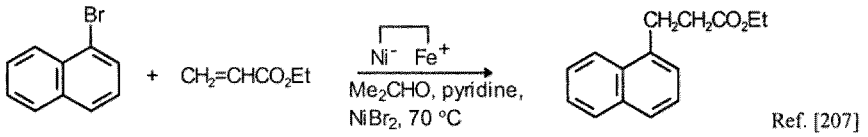
ence of a stoichiometric amount of zinc(II) ions. This system forms the arylnickel species, which then transfers the aryl group to zinc. An arylzinc halide is formed and the nickel species re-enters the catalytic cycle. Addition of the second aryl halide, together with $Pd(PPh_3)_3Cl_2$ as catalyst, affords the mixed diphenyl in good yields. [200, 201]. Electrochemistry here offers the advantage of a simplified procedure for preparation of the necessary organozinc intermediates.

Cross coupling between an aryl halide and an activated alkyl halide, catalysed by the nickel system, is achieved by controlling the rate of addition of the alkyl halide to the reaction mixture. When the aryl halide is present in excess, it reacts preferentially with the Ni(o) intermediate whereas the Ni(I) intermediate reacts more rapidly with an activated alkyl halide. Thus continuous slow addition of the alkyl halide to the electrochemical cell already charged with the aryl halide ensures that the alkyl-aryl coupled compound becomes the major product. Activated alkyl halides include benzyl chloride, α-chloroketones, α-chloroesters and amides, α-chloro-nitriles and vinyl chlorides [202, 203, 204]. Asymmetric induction during the coupling step occurs with over 90 % distereomeric excess from reactions with amides such as **62**, derived from enantiomerically pure (-)-ephedrine, even when **62** is a mixture of diastereoisomers prepared from a racemic α-chloroacid. Methanolysis of the amide product affords the chiral ester **63** and chiral ephedrine is recoverable [205].



Electrodimerization of alkyl halides using the $NiBr_2$(bipy) catalyst is achieved in an undivided cell fitted with a sacrificial magnesium or zinc anode. Ions derived from dissolution of the anode are important in the reaction and the yield of dialkyl drops drastically if a divided cell is used. Benzyl chloride, 1-bromoheptane and α-chloroesters give 50-80 % yields of the dialkyl, contaminated with some product from replacement of halogen by hydrogen [206].

Electrochemical arylation of activate alkenes can be carried out using a nickel catalyst in which the low valency state is stabilised by a pyridine ligand. Under these conditions, the alkene is also involved in coordination to nickel. There is no

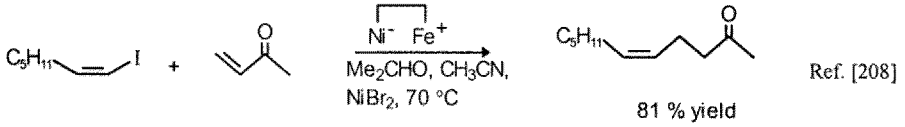


Ref. [207]

50 % yield

coordination of alkene to a Ni(dipy) complex and no coupling to the alkene is observed with this catalyst system. In the nickel-pyridine system, an aryl-nickel-alkene complex is the reactive intermediate, which collapses to give the arylated alkene, regenerating the nickel catalyst. Activated alkenes include α,β-unsaturated esters and nitriles [207].

Addition of a vinyl group, derived from a vinyl halide, to an activated alkene is

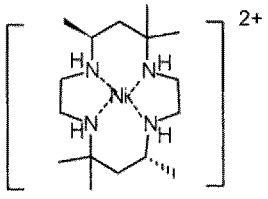


Ref. [208]

81 % yield

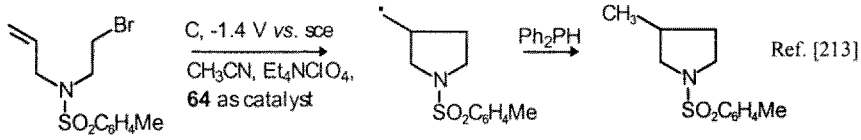
catalysed by Ni(0) species with only acetonitrile as the stabilising ligand. This reaction proceeds with retention of configuration about the vinyl group and is efficient for the preparation of functionalised olefins in one operation [208].

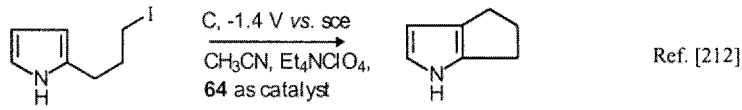
Steric constraints dictate that reactions of organohalides catalysed by square planar nickel complexes cannot involve a *cis*-dialkyl or diaryl Ni(III) intermediate. The mechanistic aspects of these reactions have been studied using a macrocyclic tetraaza-ligand [209] while quantitative studies on primary alkyl halides used Ni(II)(salen) as catalyst source [210]. One-electron reduction affords Ni(I)(salen) which is involved in the catalytic cycle. Nickel(I) interacts with alkyl halides by an outer sphere single electron transfer process to give alkyl radicals and Ni(II). The radicals take part in bimolecular reactions of dimerization and disproportionation, react with added species or react with Ni(I) to form the alkylnickel(II)(salen). Alkanes are also formed by protolysis of the alkylNi(II).



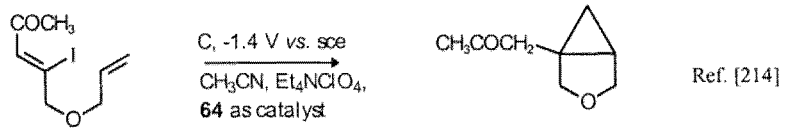
64

The electrochemical generation of alkyl radicals catalysed by square planar nickel complexes has been used to achieve radical-alkene addition reactions. Complex **64** was the catalyst of choice. Intramolecular cyclizations to give five mem-

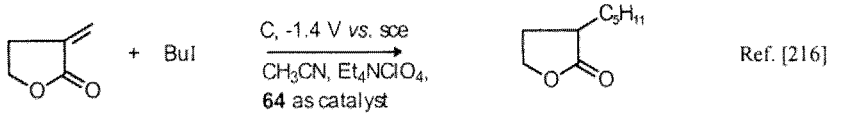




bered rings are promoted [211, 212] and in some reactions diphenylphosphine is added as a hydrogen atom donor to quench the terminal radical species [213]. A cyclopropane ring can be generated by tandem intramolecular trapping as with substrate **65** [214]. Intramolecular cyclization of 2-chlorophenyl allyl ether to give 2-methyl-1,2-dihydrobenzofuran is achieved using a square planar nickel catalyst, whereas using a Ni-bipy system results in cleavage of the allyl-oxygen bond, probably *via* an allyl-nickel complex, along with carbon-chlorine bond cleavage [213, 215]. Related intermolecular radical addition reactions also occur [216].

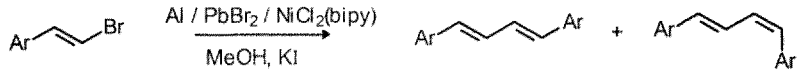


65



The dissolving aluminium - lead bromide system, introduced on p. 135, has been utilised as an electron source for several of the reactions catalysed by

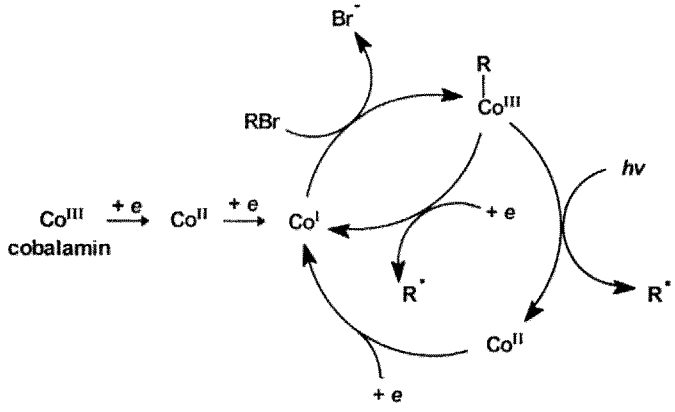
$NiBr_2$(dipy) [217, 218]. These experimental conditions can probably be applied to many other nickel catalysed reactions



Ref. [217]

Cobalt Complexes

Cobalt complexes with square planar tetradentate ligands, including salen, corrin, and porphyrin types, all catalyse the reduction of alkyl bromides and iodides. Most preparative and mechanistic work with these reactions has used cobalamines, including vitamin-B_{12}. A generalised catalytic cycle is depicted in Scheme 4.10 [219]. At potentials around -0.9 V *vs.* sce, the parent ligated Co(III) compound un-

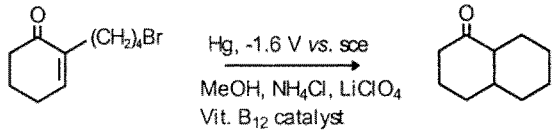


Scheme 4.10. Catalytic cycle for the reduction of alkyl halides by cobalamins. The outer circle represents the combined photo and electrochemical process. The inner shunt is the wholly electrochemical process at more negative potentials. Ligands are omitted for clarity.

dergoes two successive reversible one-electron reduction steps to the Co(I) species which quickly reacts with alkyl halides to yield an alkylCo(III) compound [220, 221]. Reaction with the Co(I) complex can be either an S_N2 displacement process or be induced by single electron transfer. The alkyl radical intermediate formed in a single electron transfer process is detected through competitive reaction with added acrylonitrile before it combines with Co(II) formed in the electron transfer

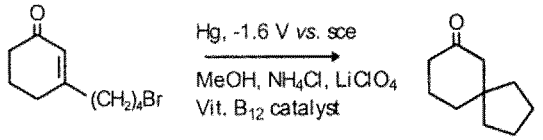
step [222]. Primary alkyl cobalamins are thermally stable but secondary alkyl derivatives are unstable and can serve as sources of alkyl radicals without photochemical assistance. Alkyl cobalamines absorb light in the visible region and the excited state relaxes by homolysis of the carbon-cobalt bond. Alkyl radicals and cobalt(II) species are detected in a glassy matrix [223]. In solution, an added radical scavenger will trap the alkyl radical. At significantly more negative potentials (*ca.* –1.5 V *vs.* sce), alkylcobalamins are reduced in a one-electron step to produce alkyl radicals and ligated Co(I).

Cobalamin catalysed reduction of alkyl halides has found use in organic synthesis because, like square planar Ni(o), it allows formation of alkyl radicals in the bulk of the solution away from the electrode surface. Alkyl radical addition to activated alkenes is achieved in high yields. In the cases of primary alkyl halides,



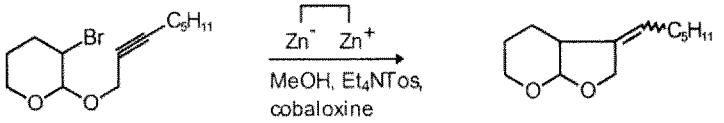
64

photo-assisted electrochemical catalysis allows the formation of the primary radical, which undergoes an intramolecular addition step with substrates such as **64** and **65** to form 5- or 6-membered rings [224].



65

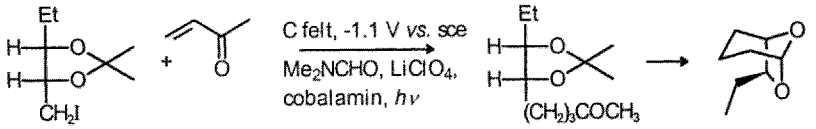
Reductive cyclization onto an unactivated alkene or alkyne is also catalysed by chloro(pyridine)cobaloxine(III). These reactions have been carried out in a divided



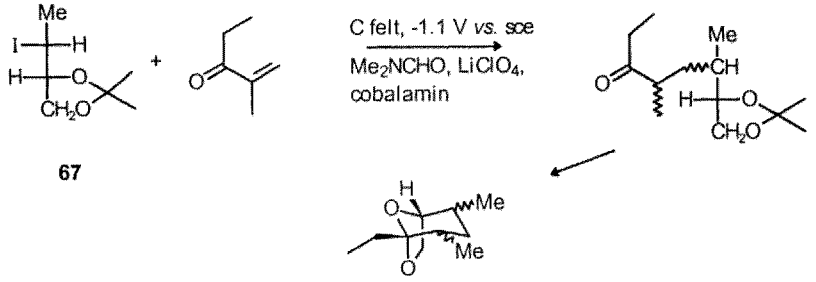
Ref. [226]

cell at a platinum cathode [225] and also in an undivided cell with a zinc cathode and a sacrificial zinc anode [226].

Intermolecular addition of radicals, generated by photo-electrochemical catalysis, to activated alkenes can also be brought about. The reaction of **66** is used as a key step in one synthesis of the insect pheromone, brevicomin [219]. The reaction of a secondary radical from **67** occurs at low cathode potentials and without photochemical assistance [219]. This illustrates the equlibrium between a secondary alkylcobalt(III) species and the radical – cobalt(II) pair. The carbon radical is eventually captured by reaction with the alkene. Further steps in the synthesis lead to four isomers of the pheromone, multistriatin, each of which is a pure enantiomer since



66

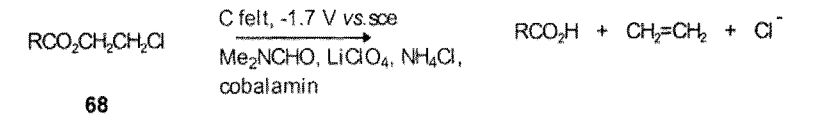


67

one asymmetric centre in the substrate has been retained in the products.

Tandem intra-intermolecular condensation to give **69** has also been reported. Steric effects direct this process to give predominately one stereochemical relationship for the bonds attached to the five-carbon ring [227].

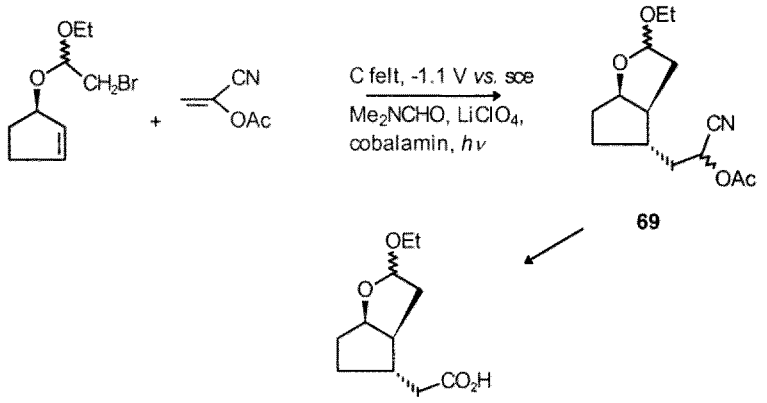
Cobalamin catalysed electrochemical reduction of the 2-chloroethanol ester **68** at negative potentials, without photochemical assistance, leads to a 1,2-elimination process (see p. 115) [228]. This contrasts with the lack of 1,2-elimination during reaction of **66** and **67**. Thus in the purely electrochemical carbon-cobalt bond



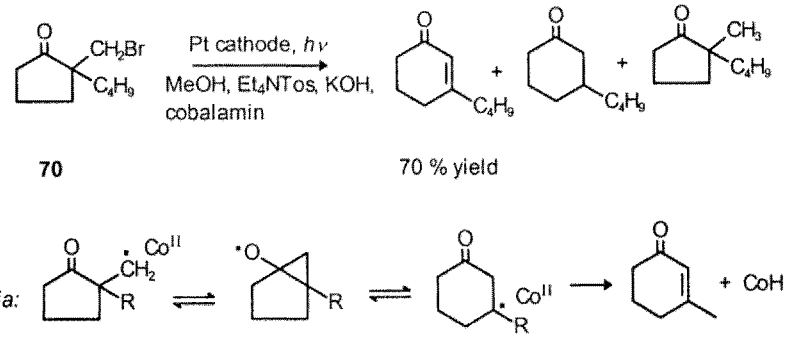
68

cleavage process, the carbon radical is formed at the electrode surface where it is

further reduced to the carbanion and undergoes the 1,2- elimination step. The photochemical or thermal cleavage of carbon-cobalt bonds generates this radical in the bulk of the solution where it is captured by an alkene.



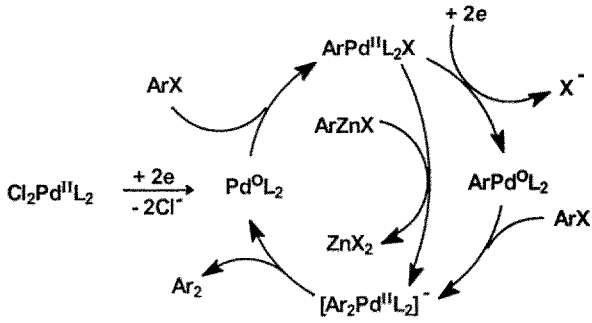
One function of vitamin-B_{12} in nature is to catalyse skeletal rearrangements by involving alkylcobalt intermediates. Skeletal rearrangement *in vitro* starting from a β-bromoketone is able to achieve ring expansion of cycloalkanones [229]. The reaction is illustrated by cobalamin catalysed, photo-assisted reduction of **70**. Steps in the radical rearrangement lead from a primary to a tertiary radical and in the final stage of reaction, a cobalt hydride is eliminated. The reaction mixture has to be maintained alkaline to avoid protolysis of the carbon-cobalt bond.



Palladium Complexes

Palladium(o) triphenylphosphine complexes catalyse the reduction of aryl bromides and iodides in a divided cell to give the diaryl [230]. The catalytic species

can be derived from either $Pd(II)Cl_2(PPh_3)_2$ by reduction or from $Pd(0)(PPh_3)_4$ by loss of two triphenylphosphine ligands and it takes part in a cycle summarised in Scheme 4.11. This cycle differs from the one using nickel(0) complexes because reduction of Pd(II) species involves a two-electron step. The Pd(I) complex cannot be detected as an intermediate and must be readily reduced to Pd(0) [231]. Formation of the biaryl results from colapse of the diarylpalladium(II) intermediate with liberation of a Pd(0) complex which re-enters the catalytic cycle.



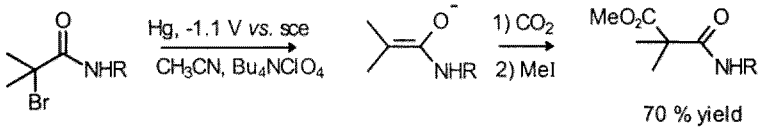
Scheme 4.11. Catalytic cycle for the reduction of aryl halides by palladium complexes. Outer circle represents the electrochemical process, L = Ph_3P and some anionic ligands are omitted for clarity. The inner shunt is the non-electrochemical reaction with arylzinc halides.

Electrochemical reduction of a mixture of aryl halides using this catalyst leads to a statistical distribution of all three possible biaryls. The efficient generation of a mixed biaryl requires the preliminary electrochemical formation of an arylzinc halide, followed by the Pd(0) catalysed reaction between the arylzinc and the second aryl halide. The second stage does not require electrons and the mechanism follows the shunt in Scheme 4.11. Catalysis by nickel(0) species has been used to generate the arylzinc from an aryl halide and zinc(II) ions (see p. 139). In an alternative procedure, reactive aryl halides rapidly give the arylzinc using electrolytically generated, finely divided zinc. Cross coupling with a second aryl halide, by addition of $PdCl_2[(o\text{-}MeC_6H_4)_3]_2$ as catalyst, then affords the biaryl in a one-pot method using a platinum cathode and a zinc anode [232].

Reactions with Carbon Dioxide

The addition of carbanions, generated electrochemically by reduction of the carbon-halogen bond, to carbon dioxide has been examined under a variety of experimental conditions. Direct electrosynthesis of carboxylic acids in a divided cell using an aprotic solvent and a tetraalkylammonium salt as electrolyte is most suc-

cessful with benzyl chloride [233]. Reduction of 4-iodoanisole under these conditions gives at best a 1:1 ratio of anisole and *p*-anisic acid [234]. While the addition of carbanions to carbon dioxide is fast, in these reactions it does not compete successfully with protonation of the carbanion. Electrochemically generated enolate anions are however successfully carboxylated in acetonitrile. Protonation of these anions is slower than for alkyl carbanions and a rate constant of 10^8 M^{-1} s^{-1} is estimated for the carboxylation reaction [235].



Ref. [235]

Yields of the carboxylic acid are greatly improved by working in an undivided cell with a stainless steel cathode and a sacrificial magnesium anode. Electrochemically generated magnesium ions favour the process but spontaneous formation of the Grignard reagent does not occur [236, 237]. Equally good results are obtained [238] using a sacrificial aluminium anode (Table 4.14). Benzyl chloride, vinyl bromides and aryl halides have been used as substrates. Processes using a consumable magnesium anode have been scaled up to pilot plant scale using the electrochemical cell shown in Figure 1.4 [239]. This route has been used for preparation of the anti-inflammatory compounds, fenoprofen and ibuprofen.

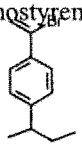
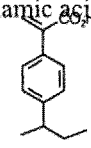
The catalytic cycles for reduction of alkyl and aryl halides using Ni(0), Co(I) or Pd(0) species are interrupted by added carbon dioxide and reaction between the first formed carbon-metal bond and carbon dioxide yields an alkyl or aryl carboxylate. These catalyses reactions have the advantage of occuring at lower cathode potentials than the direct processes summarised in Table 4.14. Mechanisms for the Ni(0) [240] and Pd(0) [241] catalysed processes have been established. Carbon dioxide inserts into the carbon-metal bond in an intermediate. Once the carboxylate-metal species is formed, a further electron transfer step liberates the carboxylate ion reforming the metallic complex catalyst.

Reaction of alkyl and aryl halides, using $NiCl_2(PPh_3)_2$ or $NiCl_2$(bppp) as catalyst source, in a mixture of tetrahydrofuran and hexamethylphosphoric triamide, under carbon dioxide at atmospheric pressure, achieves 40-87 % yields of carboxylic acid using a divided cell with a mercury or carbon cathode [242, 243]. Further refinements of the method use an undivided cell with a carbon cathode and a sacrificial anode of aluminium, copper or zinc [244, 245]. In these reactions, the nickel complex is reduced at less negative potentials than the carbon-halogen bond in the substrate. Thus the process is catalysed by nickel species and reaction yields are not influenced by ions from the dissolving anode.

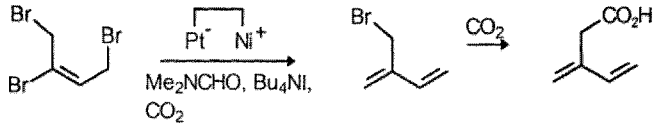
Cobalt(III)(salen) catalyses the carboxylation of benzyl chlorides and allyl chlorides but not of halobenzenes [246]. $PdCl_2(PPh_3)_2$ catalyses the carboxylation of aryl halides, β-bromostyrene and allyl acetates [247].

TABLE 4.14

Formation of carboxylic acids by reduction in dimethylformamide of the carbon-halogen bond in the presence of carbon dioxide and using sacrificial anodes.

Substrate	Anode	Product	Yield / %	Ref.
Benzyl chloride	Mg	Phenylacetic acid	90	[236]
Benzyl chloride	Al	Phenylacetic acid	83	[238]
Chlorobenzene	Mg	Benzoic acid	85	[237]
1,3-Dichlorobenzene	Al	3-Chlorobenzoic acid	70	[238]
4-Chlorofluorobenzene	Mg	4-Fluorobenzoic acid	80	[237]
4-Chloroacetophenone	Mg	4-Acetylbenzoic acid	50	[237]
1-Chloro-2-trifluoromethyl benzene	Mg	2-Trifluoromethylbenzoic acid	80	[237]
3-Bromofuran	Mg	3-Furoic acid	80	[236]
2-Chlorothiophene	Mg	Thiophene-2-carboxylic acid	80	[237]
1-Chloro-1-(4-chlorophenyl)ethane	Al	2-(4-chlorophenyl)-propanoic acid	83	[238]
β-Bromostyrene	Mg	Cinnamic acid	80	[236]
	Mg		93	[248]

Preformed metal complexes are not always essential as catalysts in carboxylation reactions. Reductive carboxylation of the allyl bromide **71** has been demon-



71 57 % yield

strated in an undivided cell with a platinum cathode and a nickel or a manganin

anode in dimethylformamide. Here nickel ions derived from the anode are involved in a catalytic process [249]. The tribromide substrate is useful as a stable precursor for 2-(bromomethyl)butadiene.

References

[1] S. P. Mishra and M. C. R. Symons, *J. Chem. Soc. Perkin Trans. 2*, 1973, 391.
[2] A. Hasegawa and F. Williams, *Chem. Phys. Letters*, 1977, **46**, 66.
[3] C. P. Andrieux, I. Gallardo, J.-M. Savéant and K. B. Su, *J. Am. Chem. Soc.*, 1986, **108**, 638.
[4] J. Grimshaw, J. R. Langan and G. A. Salmon, *J. Chem. Soc. Chem, Commun.*, 1988, 1115.
[5] J. Grimshaw, J. R. Langan and G. A. Salmon, *J. Chem. Soc. Faraday Trans.*, 1994, **90**, 75.
[6] J.-M. Savéant, *J. Am. Chem. Soc.*, 1987, **109**, 6788.
[7] E. D. German and A. M. Kuznetsov, *J. Phys. Chem.*, 1994, **98**, 6120.
[8] V. Pérez, J. M. Lluch and J. Bertrán, *J. Am. Chem. Soc.*, 1994, **116**, 1057.
[9] H. Lund, K. Daasbjerg, T. Lund and S. U. Pedersen, *Acc. Chem. Res.*, 1995, **28**, 313.
[10] M. S. Workentin and R. L. Donkers, *J. Am. Chem. Soc.*, 1998, **120**, 2664.
[11] K. Daasbjerg, S. V. Pedersen and H. Lund, *Acta Chem. Scand.*, 1991, **45**, 424.
[12] E. Hebert, J. P. Mazaleyrat, Z. Welvart, L. Nadjo and J.-M. Savéant, *Nouv. J. Chim.*, 1985, **9**, 75.
[13] C. Amatore and J.-M. Savéant, *J. Electroanal. Chem.*, 1979, **102**, 21.
[14] W. C. Danen, T. T. Kensler, J. G. Lawless, M. F. Marcus and M. D. Hawley, *J. Phys. Chem.*, 1969, **73**, 4389.
[15] J. G. Lawless and M. D. Hawley, *J. Electroanal. Chem.*, 1969, **21**, 365.
[16] K. Alwair and J. Grimshaw, *J. Chem. Soc. Perkin Trans. 2*, 1973, 1150.
[17] R. P. van Duyne and C. N. Reilly, *Analyt. Chem.*, 1972, **44**, 158.
[18] K. Alwair and J. Grimshaw, *J. Chem. Soc. Perkin Trans. 2*, 1973, 1811.
[19] C. P. Andrieux, J.-M. Savéant and D. Zann, *Nouv. J. Chim.*, 1984, **8**, 107.
[20] K. J. Houser, D. E. Bartak and M. D. Hawley, *J. Am. Chem. Soc.*, 1973, **95**, 6033.
[21] B. Aalstad and V. D. Parker, *Acta Chem. Scand. B*, 1982, **36**, 47.
[22] L. Nadjo and J.-M. Savéant, *J. Electroanal. Chem.*, 1971, **30**, 41.
[23] W. C. Danen, T. T. Kensler, J. G. Lawless, M. F. Marcus and M. D. Hawley, *J. Phys. Chem.*, 1969, **73**, 4389.
[24] C. P. Andrieux, A. Le Gorande and J.-M. Savéant, *J. Am. Chem. Soc.*, 1992, **114**, 6892.
[25] P. Maslak, T. M. Vallombroso, W. D. Chapman and J. N. Narvaez, *Angew. Chem. Int. Ed. Engl.*, 1994, **33**, 73.
[26] J. Grimshaw, S. Moore N. Thompson and J. Trocha-Grimshaw, *J. Chem. Soc. Chem. Commun.*, 1983, 783.
[27] G. Farnia, M. G. Severin, G. Capobianco and E. Vianello, *J. Chem. Soc. Perkin Trans. 2*, 1978, 1.

[28] G. Capobianco, G. Farnia, M. G. Severin and E. Vianello, *J. Electroanal. Chem.*, 1984, **165**, 251.
[29] C. P. Andrieux, C. Blocman, J.-M. Dumas-Bouchiat and J.-M. Savéant,*J. Am. Chem. Soc.*, 1979, **101**, 3431.
[30] J. Grimshaw and N. Thompson, *J. Electroanal. Chem.*, 1986, **205**, 35.
[31] C. P. Andrieux and J.-M. Savéant, *J. Electroanal . Chem.*, 1986, **205**, 43.
[32] K. Daasbjerg, H. Jensen, R. Benassi, F. Taddei, S. Antonello, A. Gennaro and F. Maran, *J. Am. Chem. Soc.*, 1999, **121**, 1750.
[33] R. K. Jaworski and R. L. McCreery, *J. Electroanal. Chem.*, 1994, **369**, 175.
[34] D. M. La Perrière, W. F. Carroll, B. C. Willett, E. C. Toop and D. G. Peters, *J. Am. Chem. Soc.*, 1979, **101**, 7561.
[35] W. A. Pritts and D. G. Peters, *J. Electrochem. Soc.*, 1994, **141**, 3319.
[36] C. P. Andrieux, J. Gallardo and J.-M. Savéant, *J. Am. Chem. Soc.*, 1989, **111**, 1620.
[37] M. S. Mbarak and D. G. Peters, *J. Org. Chem.*, 1982, **47**, 3397.
[38] W. F. Carroll and D. G. Peters, *J. Org. Chem.*, 1978, **43**, 4633.
[39] R. S. Abeywickrema and E. W. Della, *J. Org. Chem.*, 1981, **46**, 2352.
[40] D. Occhialini, S. U. Pedersen and H. Lund, *Acta Chem. Scand.*, 1990, **44**, 715.
[41] D. Ochialini, J. S. Kristensen, K. Daasbjerg and H. Lund, *Acta Chem. Scand.*, 1992, **46**, 474.
[42] D. D. M. Wayner, D. J. McPhee and D. Griller, *J. Am. Chem. Soc.*, 1988, **110**, 132.
[43] B. M. Sim, P. H. Milne, D. Griller and D. D. M. Wayner, *J. Am. Chem. Soc.*, 1990, **112**, 6635.
[44] D. D. M. Wayner and D. Griller, *J. Am. Chem. Soc.*, 1985, **107**, 7764.
[45] G. M. McNamee, B. C. Willett, D. M. La Perrière and D. G. Peters, *J. Am. Chem. Soc.*, 1977, **99**, 1831.
[46] R. L. Shao and D. G. Peters, *J. Org. Chem.*, 1987, **52**, 652.
[47] M. W. Baldwin, R. E. Wyant and L. F. Vaaler, *US* 4253921 (1981); *Chem. Abs.*, 1981, **95**, 6493.
[48] A. P. Tomilov, Yu. D. Smirnov and S, L. Varshavskii, *J. Gen. Chem. USSR*, 1965, **35**, 390.
[49] S. Daolio, G. Mengoli and D. Pletcher, *Ann. Chim. (Rome)*, 1982, **72**, 263.
[50] K. Vieira and D. G. Peters, *J. Org. Chem.*, 1986, **51**, 1231.
[51] B. C. Willet, W. M. More, A. Salajegheh and D. G. Peters, *J. Am. Chem. Soc.*, 1979, **101**, 1162.
[52] W. M. Moore, A. Salajegeh and D. G. Peters, *J. Am. Chem. Soc.*, 1975, **97**, 4954.
[53] L. Eberson, *Acta Chem. Scand.*, 1968, **22**, 3045.
[54] T. Shono, N. Kise, N. Uematsu, S. Morimoto and E. Okazaki, *J. Org. Chem.*, 1990, **55**, 5037.
[55] A. J. Bard and A. Merz, *J. Am. Chem. Soc.*, 1979, **101**, 2959.
[56] M. M. Baizer, *US* 3876541 (1975); *Chem. Abs.*, 1975, **83**, 9162.
[57] S. Torii, H. Tanaka, T. Ohshima and M. Sasaoka, *Bull. Chem. Soc. Japan*, 1986, **59**, 3975.
[58] O. R. Brown, H. R. Thirsk and B. Thornton, *Electrochim. Acta*, 1971, **16**, 495.
[59] R. B. Yamaski, M. Tarle and J. Casanova, *J. Org. Chem.*, 1979, **44**, 4519.
[60] J. Grimshaw and J. S. Ramsey,*J. Chem. Soc. B*, 1968, 61
[61] C. Deluca, A. Inesi, L. Rampazzo, *J. Chem. Sco. Perkin Trans. 2*, 1985, 209.
[62] D. A. Koch, B. J. Henne and D. E. Bartak, *J. Electroanal. Chem.*, 1987, **134**, 3062.
[63] F. M. Triebe, K. J. Borhani and M. D. Hawley, *J. Am. Chem. Soc.*, 1979, **101**, 4637.

[64] E. d'Incan, S. Sibille and J. Périchon, *Tetrahedron Letters*, 1986, **27**, 4175.
[65] S. Sibille, E. d'Incan, L. Leport and J. Périchon, *Tetrahedron Letters*, 1986, **27**, 3129.
[66] T. Nonala, T. Ota and K. Odo, *Bull. Chem. Soc. Japan*, 1977, **50**, 419.
[67] J. L. Webb, C. K. Mann and H. M. Walborsky, *J. Am. Chem. Soc.*, 1970, **92**, 2042.
[68] H. M. Walborsky and C. Hamdouchi, *J. Am. Chem. Soc.*, 1993, **115**, 6406.
[69] S. Jaouannet, R. Hazard and A. Tallec, *J. Electroanal. Chem.*, 1980, **111**, 397.
[70] A. J. Fry and R. H. Moore, *J. Org. Chem.*, 1968, **33**, 1283.
[71] T. Iwasaki, Y. Urabe, Y. Ozaki, M. Miyoshi and K. Matsumoto, *J. Chem. Soc. Perkin Trans. 1*, 1976, 1019.
[72] S. Tsuboi, Y. Ishiguro and A. Takeda, *Bull. Chem. Soc. Japan*, 1987, **60**, 830.
[73] Heisel, *Ger. Pat.* 848807 (1956); *Chem. Abs.*, 1956, **50**, 6229.
[74] F. Karrenbrock and H.-J. Schäref, *Tetrahedron Letters*, 1978, 1521.
[75] T. Shono, N. Kise, M. Masuda and T. Suzumoto, *J. Org. Chem.*, 1985, **50**, 2527.
[76] T. Shono, N. Kise and T. Suzumoto, *J. Am. Chem. Soc.*, 1984, **106**, 259.
[77] M. Steiniger and H. J. Schäfer, *Bull. Chem. Soc. Japan*, 1988, **61**, 125.
[78] H. Claus and H. J. Schäfer, *Tetrahedron Letters*, 1985, **26**, 4899.
[79] H. P. Fritz and W. Kornrumpf, *Liebigs Ann. Chem.*, 1978, 1416.
[80] H. P. Fritz and W. Kornrumpf, *J. Electroanal. Chem.*, 1979, **100**, 217.
[81] A. Merz and G. Thumm, *Liebigs Ann. Chem.*, 1978, 1526.
[82] K. Brand and M. Matsui, *Ber.*, 1913, **46**, 2942.
[83] K. Brand, O. Horn and W. Bausch, *J. prakt. Chem. [2]*, 1930, **127**, 240.
[84] F. Karrenbrock, H. J. Schäfer and I. Langer, *Tetrahedron Letters*, 1979, 2915.
[85] W. J. M. van Tilborg and C. J. Smit, *Rec. Trav. chim. Pays-Bas*, 1980, **99**, 202.
[86] M. Devaud, F. Azzouzi and B. T. Bi, *J. Chem. Research (M)*, 1991, 1052.
[87] P. Jubault, C. Feasson and N. Collignon, *Bull. Soc. chim. France*, 1994, **131**, 1001.
[88] R. Willstätter and J. Bruce, *Ber.*, 1907, **40**, 4456.
[89] M. R. Rifi, *J. Am. Chem. Soc.*, 1967, **89**, 4442.
[90] M. R. Rifi, *Tetrahedron Letters*, 1969, 1043.
[91] W. A. Pritts and D. G. Peters, *J. Electrochem. Soc.*, 1994, **141**, 990.
[92] A. J. Fry and W. E. Britton, *J. Org. Chem.*, 1973, **38**, 4016.
[93] J. Hoffmann and J. Voss, *Chem. Ber.*, 1992, **125**, 1415.
[94] Azizullah and J. Grimshaw, *J. Chem. Soc. Perkin Trans. 1*, 1973, 425.
[95] T. Adachi, T. Iwasaki, M. Muneji and I. Inoue, *J. Chem. Soc. Chem. Commun.*, 1977, 248.
[96] P. G. Gassman and G. S. Proehl, *J. Am. Chem. Soc.*, 1980, **102**, 6862.
[97] W. F. Carroll and D. G. Peters, *J. Am. Chem. Soc.*, 1980, **102**, 4127.
[98] K. B. Wiberg, G. A. Epling and M. Jason, *J. Am. Chem. Soc.*, 1974, **96**, 912.
[99] W. J. M. van Tilborg, R. Plump, R. de Ruiter and C. J. Smit, *Rec. Trav. chim. Pays-Bas*, 1980, **99**, 206.
[100] J. P. Dirlem, L. Eberson and J. Casanova, *J. Am. Chem. Soc.*, 1972, **94**, 240.
[101] A. J. Fry and J. J. O'Dea, *J. Org. Chem.*, 1975, **40**, 3625.
[102] A. J. Fry and L.-L. Chung, *Tetrahedron Letters*, 1976, 645.
[103] A. J. Fry, K. Ankner and V. Handa, *Tetrahedron Letters*, 1981, **22**, 1791.
[104] T. Shono, Y. Matsumura, K. Tsubata and Y. Sugihara, *J. Org. Chem.*, 1982, **47**, 3090.
[105] W. A. Pritts and D. G. Peters, *J. Electroanal. Chem.*, 1995, **380**, 147.
[106] W. A. Pritts and D. G. Peters, *J. Electrochem. Soc.*, 1994, **141**, 3319.
[107] M. S. Mubarak and D. G. Peters, *J. Org. Chem.*, 1995, **60**, 681.

[108] S. Satoh, M. Itoh and M. Tokuda, *J. Chem. Soc. Chem. Commun.*, 1978, 481.
[109] M. Mitani, H. Takeuchi and K. Koyama, *Chem. Letters*, 1986, 2125.
[110] J. Casanova and H. R. Rogers, *J. Org. Chem.*, 1974, **39**, 2408.
[111] N. A. Lerkel, J. E. Huber and L. H. Zalkow, *J. Am. Chem. Soc.*, 1962, **84**, 2226.
[112] E. Stamm, L. Walder and R. Keese, *Helv. Chim. Acta*, 1978, **61**, 1545.
[113] D. Lexa, J.-M. Savéant, H. J. Schäfer, K. B. Su. B. Vering and D. L. Wang, *J. Am. Chem. Soc.*, 1990, **112**, 6162.
[114] J. Zavoda, J. Krupicka and J. Sicher, *Coll. Czech. Chem. Commun.*, 1963, **28**, 1664.
[115] K. M. O'Connell and D. H. Evans, *J. Am. Chem. Soc.*, 1983, **105**, 1473.
[116] T. Lund, S. U. Pedersen, H. Lund, K. M. Cheung and J. H. P. Utley, *Acta Chem. Scand. B*, 1987, **41**, 285.
[117] P. Fawell, J. Avraamides and G. Hefter, *Aust. J. Chem.*, 1991, **44**, 791.
[118] A. Windaus, *Ber.*, 1906, **39**, 518.
[119] U. Husstedt and H. J. Schäfer, *Tetrahedron Letters*, 1981, **22**, 623.
[120] K. B. Wiberg, W. F. Bailey and M. E. Jason, *J. Org. Chem.*, 1974, **39**, 3803.
[121] R. D. Rieke and P. M. Hudnall, *J. Am. Chem. Soc.*, 1973, **95**, 2646.
[122] U. Husstedt and H.-J. Schäfer, *Synthesis*, 1979, 964.
[123] A. Merz, *Electrochim. Acta*, 1977, **22**, 1271.
[124] A. Merz, *Angew. Chem. Int. Ed. Engl.*, 1977, **16**, 57.
[125] F. Maran, E. Vianello, G. Catelani and F. Dangeli, *Electrochim. Acta*, 1989, **34**, 587.
[126] H. Lund, *Acta Chem. Scand.*, 1963, **17**, 2139.
[127] A. N. Meldrum and P. H. Parikh, *Proc. Indian Acad. Sci. A*, 1934-5, **1**, 430; *Chem. Abstr.*, 1935, **29**, 3323.
[128] M. Tsukayama, H. Utsumi, A. Kunugi and H. Nozaki, *Heterocycles*, 1997, **45**, 1131.
[129] J. Thiele and H. Balhorn, *Ber.*, 1904, **37**, 1463.
[130] F. H. Covitz, *J. Am. Chem. Soc.*, 1967, **89**, 5403.
[131] J. H. P. Utley, Y. P. Gao, J. Gruber and R. Lines, *J. Mater. Chem.*, 1995, **5**, 1297.
[132] C. Amatore, F. Gaubert, A. Jutand and J. H. P. Utley, *J. Chem. Soc. Perkin Trans. 2*, 1996, 2447.
[133] H. G. Gilch, *J. Polymer Sci. Pt. A*, 1964, **4**, 1351.
[134] J. H. P. Utley, Y. Gao, J. Gruber, Y. Zhang and A. Munoz-Escalona, *J. Mater. Chem.*, 1995, **5**, 1837.
[135] E. Eru, G. E. Hawkes, J. H. P. Utley and P. B. Wyatt, *Tetrahedron*, 1995, **51**, 3033.
[136] E. Oguntoye, S. Szunerits, J. H. P. Utley and P. B. Wyatt, *Tetrahedron*, 1996, **52**, 7771.
[137] E. Brillas and J. M. Costa, *J. Electroanal. Chem.*, 1976, **69**, 435.
[138] J. R. Cockrell and R. W. Murry, *J. Electrochem. Soc.*, 1972, **119**, 849.
[139] K. Alwair and J. Grimshaw, *J. Chem. Soc. Perkin Trans. 2*, 1973, 1811.
[140] E. Gergely and T. Iredale, *J. Chem. Soc.*, 1951, 13.
[141] W. H. Hussey and A. J. Diefenderfer, *J. Am. Chem. Soc.*, 1967, **89**, 5359.
[142] M. S. Mubarak and D. G. Peters, *J. Org. Chem.*, 1996, **61**, 8074.
[143] M. S. Mubarak, L. L. Karras, N. S. Murcia, J. C. Bart, J. Z. Stemple and D. G. Peters, *J. Org. Chem.*, 1990, **55**, 1065.
[144] M. S. Mbarak and D. G. Peters, *J. Electroanal. chem.*, 1983, **152**, 183.
[145] M. S. Mubarak and D. G. Peters, *J. Org. Chem.*, 1985, **50**, 673.
[146] G. Kokkinidis, M. Papadopoulou and A. Varvoglis, *Electrochim. Acta*, 1989, **34**, 133.

[147] A. Tsyganok, K. Otsuka, I. Yamanaka, V. Plekhanov and S. Kulikov, *Chem. Letters*, 1996, 261.
[148] J. Grimshaw and J. Trocha-Grimshaw, *J. Chem. Soc. Perkin Trans. 1*, 1973, 1275.
[149] H. M. Becker and S. Sehring, *Ger. Offen*, 2331711 (1975); *Chem. Abstr.*, 1975, **82**, 139622.
[150] A. M. Marte, G. Mousset, M. Prudhomme and E. Rodriguespereira, *Electrochim. Acta*, 1995, **40**, 1805.
[151] S. Dapperheld, M. Feldhues, H. Litterer, F. Sistig and P. Wegener, *Synthesis*, 1990, 403.
[152] E. Fisher, *Ber.*, 1899, **31**, 2550.
[153] T. Kusmierek, B. Czochralska, N. G. Johansson and D. S. Shugar, *Acta Chem. Scand. B*, 1987, **41**, 701.
[154] M. G. Reinecke, *Tetrahedron*, 1982, **38**, 8074.
[155] M. S. Mubarak and D. G. Peters, *J. Electroanal. Chem.*, 1997, **435**, 47.
[156] J. Pinson and J.-M. Savéant, *J. Am. Chem. Soc.*, 1978, **100**, 1506.
[157] C. Amatore, J. Pinson J.-M. Savéant and A. Thiebault, *J. Am. Chem. Soc.*, 1982, **104**, 817.
[158] C. Amatore, J. Chaussard, J. Pinson, J.-M. Savéant, and A. Thiebault, *J. Am. Chem. Soc.*, 1979, **101**, 6012.
[159] M. Médebielle, M. A. Oturan, J. Pinson and J.-M. Savéant, *Tetrahedron Letters*, 1993, **34**, 3409.
[160] M. Genesty, C. Thobie, A. Gautier and C. Degrand, *J. Appl. Electrochem.*, 1993, **23**, 1125.
[161] C. Thobiegautier, C. Degrand,M. Nour and P. L. Compagnon, *J. Electroanal. Chem.*, 1993, **344**, 383.
[162] M. Genesty and C. Degrand, *New J. Chem.*, 1998, **22**, 349.
[163] D. H. Hey, *Quart. Rev.*, 1971, **25**, 586.
[164] C. S. Rondestvedt, *Org. Reactions*, 1976, **24**, 225.
[165] J. Grimshaw, R. J. Haslett and J. Trocha-Grimshaw, *J. Chem. Soc. Perkin Trans. 1*, 1977, 2448.
[166] J. Grimshaw and R. J. Haslett, *J. Chem. Soc. Perkin Trans. 1*, 1980, 657.
[167] W. J. Begley and J. Grimshaw, *J. Chem. Soc. Perkin Trans. 1*, 1977, 2324.
[168] J. Grimshaw, R. Hamilton and J. Trocha-Grimshaw, *J. Chem. Soc. Perkin Trans. 1*, 1982, 229.
[169] J. Grimshaw and S. A. Hewitt, *Proc. Royal Irish Acad. B*, 1983, **83**, 93.
[170] R. Gottlieb and J. L. Neumeyer, *J. Am. Chem. Soc.*, 1976, **98**, 7108.
[171] S. Donnelly, J. Grimshaw and J. Trocha-Grimshaw, *J. Chem. Soc. Perkin Trans. 1*, 1993, 1557.
[172] S. Donnelly, J. Grimshaw and J. Trocha-Grimshaw, *Electrochim. Acta*, 1996, **41**, 489.
[173] M. Dias, M. Gibson, J. Grimshaw, I. Hill, J. Trocha-Grimshaw and O. Hammerich, *Acta Chem. Scand.*, 1998, **52**, 549.
[174] K. Jones and J. M. D. Storey, *Tetrahedron*, 1993, **49**, 490.
[175] H. Tanaka, H. Ogawa, H. Suga, S, Torii, A. Jutand, S. Aziz, A. G. Suarez and C. Amatore, *J. Org. Chem.*, 1996, **61**, 9402.
[176] Z. Chami, M. Gareil, J. Pinson, J.-M. Savéant and A. Thiebault, *J. Org. Chem.*, 1991, **56**, 586.

[177] J. Chaussard, J.-C. Folest, J.-Y. Nédélec, J. Périchon, S. Sibile and M. Troupel, *Synthesis*, 1990, 369.
[178] S. Sibile, E. d'Incan, L. Leport and J. Périchon, *Tetrahedron Letters*, 1986, **27**, 3129.
[179] C. Gosmini, Y. Rollin, C. Gebehenne, E. Lojou, V. Ratovelomanana and J. Périchon, *Tetrahedron Letters*, 1994, **35**, 5637.
[180] Y. Rollin, S. Derien, E. Dunach, C. Gebchenne and J. Périchon, *Tetrahedron*, 1993, **49**, 7723.
[181] Y. Rollin, C. Gebchenne, S. Derien, E. Dunach and J. Périchon, *J. Organometal. Chem.*, 1993, **461**, 9.
[182] J.-Y. Nédélec, H. A. H. Mouloud, J. C. Folest and J. Périchon, *J. Org. Chem.*, 1988, **53**, 4720.
[183] M. Tokuda, N. Kurono and N. Mimura, *Chem. Letters*, 1996, 1091.
[184] M. Tokudo, N. Mimura, K. Yohioka, T. Karasowa, H. Fujita and H. Suginome, *Synthesis*, 1993, 1086.
[185] H. Tanaka, S. Yamashita, T. Hamatani, Y. Ikemoto and S. Torii, *Synth. Commun.* 1987, **17**, 789.
[186] H. Tanaka, S. Yamashita and S. Torii, *Bull. Chem. Soc. Japan.*, 1987, **60**, 1951.
[187] J. A. Azoo and J. Grimshaw, *J. Chem. Soc. C*, 1968, 2403.
[188] H. Tanaka, S. Yamashita, M. Yamanoue and S. Torii, *J. Org. Chem.*, 1989, **54**, 444.
[189] K. Uneyama, N. Kamaki, A. Moriya and S. Torii, *J. Org. Chem.*, 1985, **50**, 5396
[190] H. Tanaka, S. Yamashita, Y. Ikemoto and S. Torii, *Tetrahedron Letters*, 1988, **29**, 1721.
[191] H. Tanaka, K. Inoue, U. Pokorski, M. Taniguchi and S. Torii, *Tetrahedron Letters*, 1990, **31**, 3023.
[192] J.-Y. Nédélec, J. Périchon and M. Troupel, *Topics in Current Chemistry*, 1997, **185**, 141.
[193] C. Gosden, K. P. Healey and D. Pletcher, *J. Chem. Soc. Dalton Trans.*, 1978, 972.
[194] G. Shiavon, G. Bontempelli and B. Corain, *J. Chem. Soc. Dalton Trans.*, 1981, 1074.
[195] C. Amatore, A. Jutand and L. Mottier, *J. Electroanal. Chem.*, 1991, **306**, 125.
[196] Y. Rollin, M. Troupel, D. G. Tuck and J. Périchon, *J. Organomet. Chem.*, 1986, **303**, 131.
[197] V. Courtois, R. Barhdadi, M. Troupel and J. Périchon, *Tetrahedron*, 1997, **53**, 11569.
[198] M. Oçafrain, M. Devaud, M. Troupel and J. Périchon, *J. Chem. Soc. Chem. Commun.*, 1995, 2331.
[199] H. Tanaka, S. Sumida, N. Kobayashi, N. Komatsu and S. Torii, *Inorg. Chim. Acta*, 1994, **222**, 323.
[200] C. Gosmini, S. Lasry, J.-Y. Nédélec and J. Périchon, *Tetrahedron*, 1998, **54**, 1289.
[201] S. Sibille, V. Ratovelomanana, J.-Y. Nédélec and J. Périchon, *Synlett.*, 1993, 425.
[202] M. Durandetti, S. Sibille, J.-Y. Nédélec and J. Périchon, *Synthetic Commun.*, 1994, **24**, 145.
[203] M. Durandetti, J.-Y. Nédélec and J. Périchon, *J. Org. Chem.*, 1996, **61**, 1748.
[204] M. Durandetti, J. Périchon and J.-Y. Nédélec, *Tetrahedron Letters*, 1997, **38**, 8683.
[205] M. Durandetti, J. Périchon and J.-Y. Nédélec, *J. Org. Chem.*, 1997, **62**, 7914.
[206] J. C. Folest, J.-Y. Nédélec and J. Périchon, *J. Chem. Res. S*, 1989, 394.
[207] S. Condon-Guegnot, E. Léonel, J.-Y. Nédélec and J. Périchon, *J. Org. Chem.*, 1995, **60**, 7684.
[208] S. Condon-Guegnot, D. Dupré, J.-Y. Nédélec and J. Périchon, *Synthesis*, 1997, 1457.
[209] A. Bakac and J. H. Espenson, *J. Am. Chem. Soc.*, 1986, **108**, 713.

[210] M. S. Murbank and D. G. Peters, *J. Electroanal. Chem.*, 1995, **388**, 195.
[211] S. Ozaki, H. Matsushita and H. Ohmori, *J. Chem. Soc. Perkin Trans.*, 1993, 2339.
[212] S. Ozaki, S. Mitoh and H. Ohmori, *Chem. Pharm. Bull.*, 1996, **44**, 2020.
[213] S. Ozaki, I. Horiguchi, H. Matsushita and H. Ohmori, *Tetrahedron Letters*, 1994, **35**, 725.
[214] S. Ozaki, E. Matsui, J. Waku and H. Ohmori, *Tetrahedron Letters*, 1997, **38**, 2705.
[215] S. Olivera and E. Dunach, *Synlett.*, 1994, 531.
[216] S. Ozaki, E. Matsui and H. Ohmori, *Chem. Pharm. Bull.*, 1997, **45**, 198.
[217] H. Tanaka, A. Kosaka, Y. Yamashita, K. Morisaki and S. Torii, *Tetrahedron Letters*, 1989, **30**, 1261.
[218] H. Tanaka, S. Sumida, K. Sorajo, Y. Kameyama and S. Torii, *J. Chem. Soc. Perkin Trans. 1*, 1997, 637.
[219] R. Scheffold, S. Abrecht, R. Orlinski, H.-R. Ruf, P. Stamouli, O. Tinembart, L. Walder and C. Weymuth, *Pure Appl. Chem.*, 1987, **59**, 363.
[220] D. Lexa and J.-M. Savéant, *Acc. Chem. Res.*, 1983, **16**, 235.
[221] D.-L. Zhou, J. Gao and J. F. Rusling, *J. Am. Chem. Soc.*, 1995, **117**, 1127
[222] D.-L. Zhou, P. Walder, R. Scheffold and L. Walder, *Helv. Chim. Acta*, 1992, **75**, 995.
[223] D. N. Ramakrishna and M. C. R. Symons, *J. Chem. Soc. Perkin Trans. 2*, 1983, 187.
[224] R. Scheffold, M. Dike, S. Dike, T. Herold and L. Walder, *J. Am. Chem. Soc.*, 1980, **102**, 3642.
[225] S. Torii, T. Inokuchi and Y. Yukawa, *J. Org. Chem*, 1985, **50**, 5875.
[226] T. Inokuchi, H. Kawafuchi, K. Aoki, A. Yoshida and S. Torii, *Bull. Chem. Soc. Japan.*, 1994, **67**, 595.
[227] S. Busato and R. Scheffold, *Helv. Chim. Acta*, 1994, **77**, 92.
[228] R. Scheffold and E. Amble, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 629.
[229] T. Inokuchi, M. Tsuji, H. Kawafuchi and S. Torii, *J. Org. Chem.*, 1991, **56**, 5945.
[230] S. Torii, H. Tanaka and K. Morisaki, *Tetrahedron Letters*, 1985, **26**, 1655.
[231] C. Amatore, E. Carré, A. Jutand, H. Tanaka, Q. Ren and S. Torii, *Chem. Eur. J.*, 1996, **2**, 957.
[232] N. Kurono, K. Sugita, S. Takasugi and M. Tokuda, *Tetrahedron*, 1997, **55**, 6097.
[233] M. M. Baizer and J. H. Wagenknecht, *U. S. Pat.*, 3764492 (1973); *Chem. Abstr.*, 1973, **79**, 142364.
[234] N. S. Murein and D. G. Peters, *J. Electroanal. Chem.*, 1992, **326**, 69.
[235] F. Maran, M. Fabrizio, F. D'Angeli and E. Vianello, *Tetrahedron*, 1988, **44**, 2351.
[236] O. Sock, M. Troupel and J. Périchon, *Tetrahedron Letters*, 1985, **26**, 1509.
[237] M. Heintz, O. Sock, C. Saboureau, J. Périchon and M. Troupel, *Tetrahedron*, 1988, **44**, 1631.
[238] G. Silvestri, S. Gambino, G. Gulotta, *Angew. Chem. Int. Ed. Eng.*, 1984, **23**, 979.
[239] J. Chaussard, M. Troupel, Y. Robin, G. Jacob and J. P. Juhasz, *J. Appl. Electrochem.*, 1989. **19**, 345.
[240] C. Amatore and A. Jutand, *J. Am. Chem. Soc.*, 1991, **113**, 2819.
[241] C. Amatore, A. Jutand, F. Khalil and M. F. Nielsen, *J. Am. Chem. Soc.*, 1992, **114**, 7076.
[242] M. Troupel, Y. Rollin, J. Périchon and J.-F. Fauvarque, *Nouv. J. Chim.*, 1981, **5**, 621.
[243] J.-F. Fauvarque, A. Jutand and M. François, *New J. Chem.*, 1986, **10**, 119.
[244] J.-F. Fauvarque, A. Jutand, M. François and M. Petit, *J. Appl. Electrochem.*, 1988, **18**, 109.

[245] J.-F. Fauvarque, J. Jacquelin, A. Jutand and Y. Zelicourt, *Fr. Demande* FR 2597510 (1987); *Chem. Abstr.*, 1988, **108**, 175956.
[246] J. C. Folest, J. M. Duprilot, J. Périchon, Y. Robin and J. Devynck, *Tetrahedron Letters*, 1985, **26**, 2633.
[247] S. Torii, H. Tanaka, H. Hamatani, K. Morisaki, A. Jutand, F. Pflüger and J.-F. Fauvarque, *Chem. Letters*, 1986, 169.
[248] H. Kamekawa, H. Senboku and M. Tokuda, *Electrochim. Acta,* 1997, **42**, 2117.
[249] M. Tokuda, A. Yoshikawa, H. Suginome and H. Senboku, *Synthesis*, 1997, 1143.

CHAPTER 5

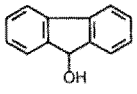
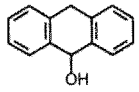
REDUCTIVE BOND CLEAVAGE PROCESSES - II

Introduction

The carbon-heteroatom bonds in saturated alkyl alcohols, ethers, sulphides and amines cannot be cleaved by electrochemical reduction. This situation is modified substantially by the presence of an adjacent unsaturated group. Reaction can be initiated by addition of an electron to the π-antibonding orbital leading to an overall two-electron cleavage of the carbon-heteroatom bond. In the previous chapter (p. 95) rate constant data for the cleavage of benzyl sulphides and benzylpyridinium salts were used to illustrate the influence of both π-system reduction potential and nature of the leaving group on the cleavage of carbon-heteroatom bonds.

TABLE 5.1

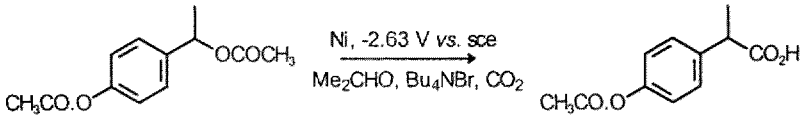
Potentials for the reduction of benzyl-heteroatom bonds in dimethylformamide. Cyclic voltammetry at a gold electrode.

Polarography, ref. [1]		Cyclic voltammetry, ref. [2]	
Substrate	$E_{½}$ / V *vs.* sce	Substrate	E_p / V *vs.* sce
$PhCH_2OH$	(a)	$PhCH_2Cl$	-2.37
Ph_3COH	-2.81	$PhCH_2OCOCH_3$	-2.65
$PhCH{=}CHCH_2OH$	-2.57	$PhCH_2OCOPh$	-2.10
	-2.45	$PhCH_2OPh$	-2.87
		$PhCH_2SPh$	-2.68
		$PhCH_2SO_2CH_2Ph$	-2.51
		$[PhCH_2NMe_3]^+$	-2.22
	-2.05	$[PhCH_2PPh_3]^+$	-1.78

Footnote: (a) No reduction wave seen.

Further data from the polarography and cyclic voltammetry in dimethylformamide are given in Table 5.1 for a series of overall two-electron processes leading to cleavage of a benzyl-heteroatom bond. The first electron transfer step is of the dissociative electron transfer type leading to a benzyl radical. This radical is reduced further, at the working potential, to the benzyl carbanion. The carbanion from benzyl chlorides, esters, ethers, sulphides, sulphones and quaternary ammonium salts can be trapped by carbon dioxide to form phenylacetic acid [2]. Reac-

tion affords good yields in an undivided cell with a sacrificial magnesium anode and complements the carboxylation of benzyl bromides (p. 148). The intermediate benzyl carbanion can also be trapped with acetic anhydride to form a benzyl



94 % Ref. [2]

methyl ketone [3].

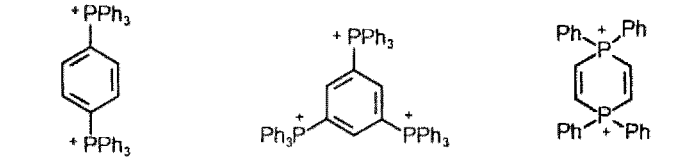
TABLE 5.2

Polarographic half-wave potentials for onium salts in aqueous solution

Substrate	$E_{½}$ / V *vs.* sce	Group cleaved	Ref.
$PhN^{+}Me_3$	(a)		[4]
$PhCH_2N^{+}Me_2$	-1.51	$PhCH_2$	[4]
$MeP^{+}Ph_3$	-1.91	Ph, Me (trace)	[5]
$PhCH_2P^{+}Ph_3$	-1.60	$PhCH_2$	[5]
$CH_2{=}CHCH_2P^{+}Ph_3$	-1.67	$CH_2{=}CHCH_2$	[5]
$MeAs^{+}Ph_3$	-1.54	Ph	[5]
$PhCH_2As^{+}Ph_3$	-1.26	$PhCH_2$	[5]
$CH_2{=}CHCH_2As^{+}Ph_3$	-1.20	$CH_2{=}CHCH_2$	[6]

Footnote: (a) Wave merged with background.

Tetrasubstituted onium salts are cleaved by reduction and lose the substituent which gives the most stable radical. Polarographic half-wave potentials for some of



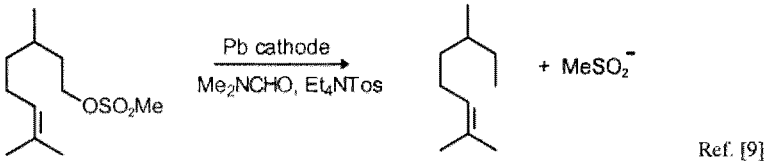
-1.212 V *vs.* sce -0.994 V *vs.* sce -0.000 V *vs.* sce

Scheme 5.1. Half-wave potentials for some phosphonium salts forming characterised radical-ions after one-electron addition.

these salts are given in Table 5.2. Some phosphonium salts add one electron to form a stable radical-ion (Scheme 5.1). Esr-spectroscopy indicates that the unpaired electron in these radical-ions is delocalised due to dπ-pπ conjugative interaction between the phosphorus atom and the centre of unsaturation [7]. The term ylid-radical has been used to describe these species [8].

Carbon-Oxygen Bond Cleavage

Aliphatic alcohols are not reducible under electrochemical conditions. Conversion to a suitable anionic leaving group however does allow carbon-oxygen bond cleavage. Thus, methanesulphonates are reduced at a lead electrode under constant current conditions and this affords an overall two step process for the conversion of alcohols to alkanes [9].Deoxygenation of alcohols by this route has been applied successfully in the presence of other functional groups which are difficult to reduce such as alkene, epoxide, ester and nitrile. Cyclopropanes are formed in 50-97 %

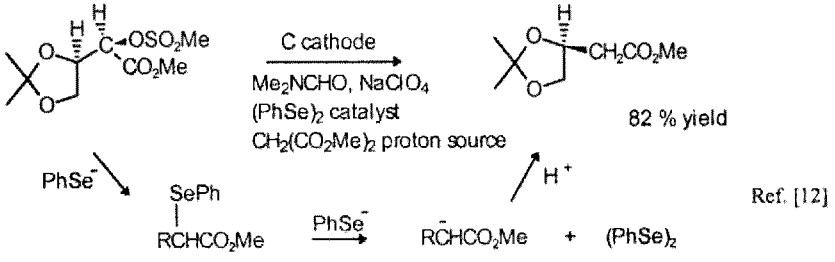


81 % yield

Ref. [9]

yields by reduction of the methane sulphonates of 1,3-diols [10] (see p. 113). Toluene-4-sulphonates react in a different manner on electrochemical reduction, leading to cleavage of the sulphur-oxygen bond with formation of the original alcohol and toluene-4-sulphinic acid [11].

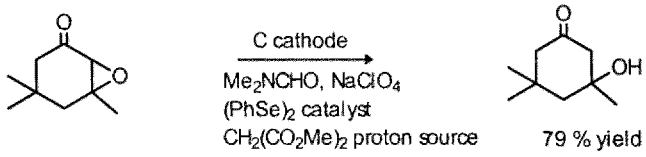
Deoxygenation of α-hydroxy esters is achieved under milder conditions by reaction of the methanesulphonate with electrochemically generated phenylselenium



Ref. [12]

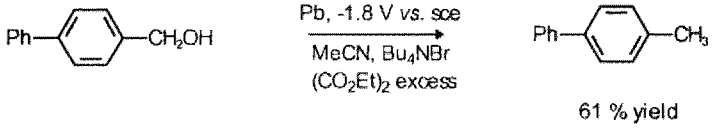
catalyst. The catalyst is recycled in an electrochemical step but the deoxygenation

process proceeds through a series of nucleophilic displacement reactions [12]. The same recyclable catalyst can effect the ring opening of α,β-epoxycarbonyl compounds [13]. Direct reduction of these substrates also leads to fission of the carbon-oxygen bond adjacent to the carbonyl function but the desired product then undergoes further reduction of the carbonyl group to alcohol [14].



Ref. [13]

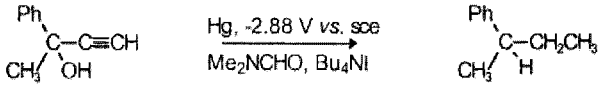
A further route for the deoxygenation of alcohols is based on the reduction of oxalate esters. Diethyl oxalate undergoes a reversible one-electron addition to give the radical-anion detectable by esr-spectroscopy. This and related radical-anions decompose rapidly by cleavage of the oxygen-alkyl bond to form the alkyl radical and oxalate half ester [15]. Further reduction of the radical at the working potential, followed by protonation, then yields the alkane. The direct reduction of oxalate esters fails on a preparative scale because the esters are easily hydrolysed by bases generated at the cathode, but the process has been adapted for deoxygenation of benzyl alcohols [16]. Benzyl alcohols undergo rapid transesterification with ethyl oxalate in dimethylformamide or acetonitrile in the presence of electrogener-



Ref. [16]

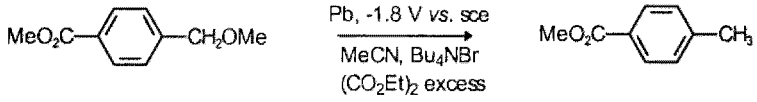
ated base. The benzyl oxalate, which is formed, undergoes reductive carbon-oxygen bond fission to yield the corresponding toluene in 30-70 % yields. Allyl alcohols are deoxygenated in a corresponding reaction.

Carbon-oxygen bonds adjacent to an aromatic ring or an alkene function can be cleaved by reduction at very negative potentials [1]. The process is often followed by reduction of the activating group as in **1**. In these processes, the reduction potential of the activating group controls the electrode potential required. Thus an

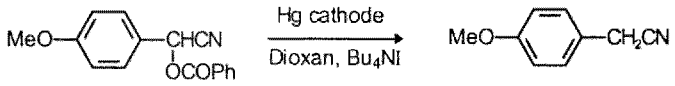


1 90 % yield

electron withdrawing group on the benzene ring, as in **2**, leads to a less negative

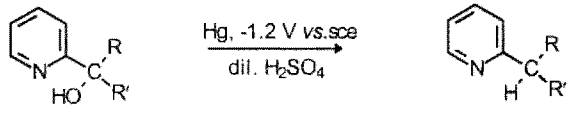


2 61 % yield

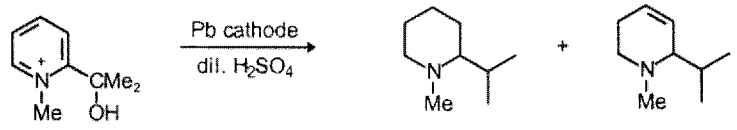


3

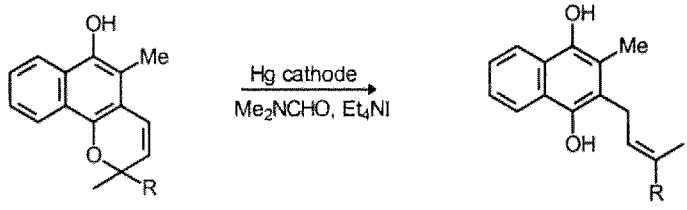
reduction potential for the benzyl-oxygen bond cleavage step [17]. Benzaldehyde cyanhydrin benzoates **3** are also readily deoxygenated at a lead cathode [18]. 1-Pyridinyl ethanols can be deoxygenated at more accessible potentials because the protonated pyridine ring is a good electron acceptor. Controlled potential reduction of 2- and 4-substituted pyridines such as **4** gives the alkyl pyridine [19]. Related quaternary pyridinium salts are reduced to alkylpiperidines [20]. Ene and polyene



4



Ref. [20]

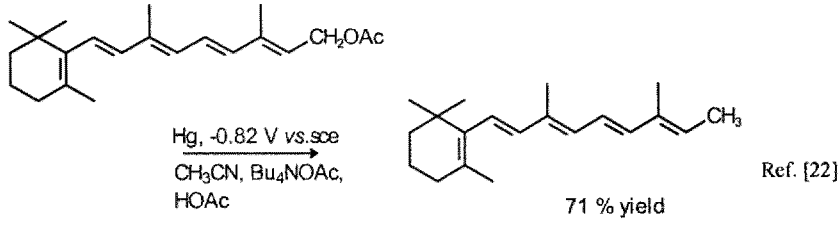


Ref. [21]

functions can also function as activating groups [21, 22].

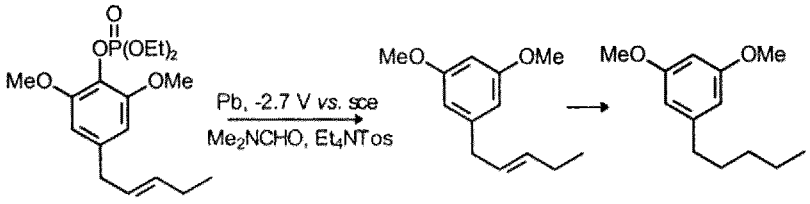
The deoxygenation of phenyl esters and ethers can be achieved by electrochemical reduction provided the function is converted into a good leaving group.

Some success has been achieved with phosphate ester and with tetrazolium ether leaving groups.



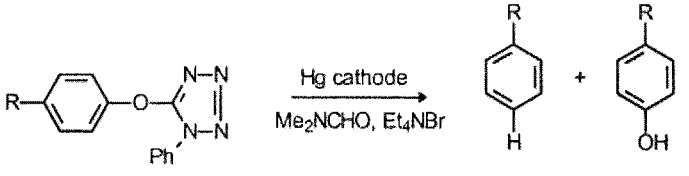
Ref. [22]

In the electrochemical reduction of aryl diethyl phosphates, the initial one-electron addition is to the aryl ring and this is concerted with expulsion of the diethyl phosphate anion leaving an aryl radical. Further electron addition and protonation leads to the reaction product in 43-73 % yields. Examples of this electro-



5

chemical reaction all use a phenol with at least one *ortho*-substituent [23]. An important function of the *ortho*-substituent in these and related reactions of halobenzenes is to increase the rate of bond cleavage in the radical-anion intermediate. In the case of substrate **5**, the vigorous reaction conditions result in migration of the alkene bond into conjugation with the benzene ring when it is reduced the the



6

R = Me	30 %	30 %
R = CN	53 %	nil

dihydro stage. Phenyl diethyl phosphate is reduced by potassium in liquid ammonia releasing a phenyl radical which has been trapped by reaction with acetone enol in the same solvent [24].

Deoxygenation of a phenol by reduction of the aryl tetrazolyl ether **6** is only successful when the aryl ring has an electron withdrawing substituent. One-electron addition then occurs on that ring and is followed by the required carbon-oxygen bond cleavage [25]. When the aryl ring has an electron donating substituent, electron addition occurs on the tetrazole ring to be followed by bond cleavage with regeneration of the phenol.

Simple diphenyl ethers require too negative an electrode potential for cleavage of the carbon-oxygen bond by electrochemical reduction in dimethylformamide or acetonitrile. Bond cleavage can be achieved under more drastic conditions by reduction with sodium in liquid ammonia in a process initiated by addition of a solvated electron to the benzene π^* -orbital [26, 27, 28]. Where there is a large difference in electron affinity between the two benzene rings, a preference is shown for cleavage of the carbon-oxygen bond to the ring with the less negative reduction potential. There is also preferential cleavage of the bond with an adjacent *ortho*-substituent. In other circumstances, cleavage of diphenyl ethers by this method gives a mixture of the two possible products.

TABLE 5.3

. Cleavage of substituted diphenyl ethers with sodium in liquid ammonia. Ref. [26].

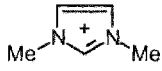
Substrate R-O-R′		Phenolic cleavage products / mole %	
R	R′	ROH	R′OH
Phenyl	2-Methylphenyl	Phenol 46 %	2-Cresol 54 %
Phenyl	4-Methylphenyl	Phenol 39 %	4-Cresol 61 %
Phenyl	4-Methoxyphenyl	Phenol 19 %	4-Methoxyphenol 81 %
2-Methoxyphenyl	4-Methoxyphenyl	Guaiacol 1 %	4-Methoxyphenol 99 %
Phenyl	4-Aminophenyl	none	4-Aminophenol 100 %
Phenyl	4-Carboxyphenyl	Phenol 100 %	none

Quaternary Ammonium Salts

Tetraalkylammonium salts are frequently used as the inert electrolyte in electrochemical reactions. These salts are however reductively decomposed in dimethylformamide at potentials around –2.96 V *vs.* sce. At a glassy carbon cathode, tetra-

ethylammonium ions form triethylamine and the ethyl radical. At the working potential, the radical is further reduced to the carbanion. Protonation by extraneous water then affords ethane and hydroxide ion. The base formed in this way promotes Hofmann elimination to form ethene [29].

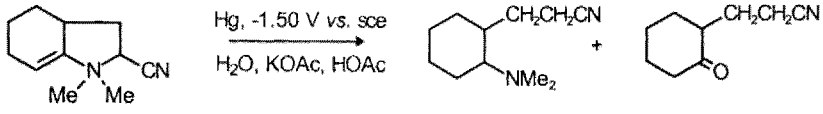
At very negative potentials, using a mercury cathode, tetraalkylammonium ions are deposited as a crystalline tetraalkylammonium amalgam. Tetramethylammonium amalgam slowly decomposes at 0 °C to give trimethylamine and a methyl radical [30, 31]. The amalgam formed by reduction of dimethylpyrrolidinium cation **7** is more stable and characterisation of this class of materials has centred on



7

the pyrrolidinium species [32]. Amalgam formation occurs around –2.6 V *vs.* sce from dimethylformamide and the quaternary ion reforms at potentials less negative than –2.6 V *vs.* sce. Electrolysis leads to a solid film on the surface of the electrode with a stoichiometry $R_4N(Hg)_5$ and having a half-life of 6.3 h at 5 °C [33]. Related solid films are also formed at cathodes of lead, bismuth and tin [34]. Crystalline graphite forms tetraalkylammonium-graphite lamellar compounds [35].

Quaternary ammonium salts with bulky substituents are less prone to form amalgams and a carbon-nitrogen bond can be cleaved by electrochemical reduction in aqueous solution using a divided cell and a cathode of mercury [36] aluminium [37], or lead [36, 38]. A one-electron transfer process results in the formation of a tertiary amine and the most stable radical. Allyl and benzyl groups, for example, are readily cleaved. The phenyl group can also be cleaved from the phenyltrimethylammonium ion to give benzene and trimethylamine [36]. Enamine quaternary salts **8** are cleaved to give an enamine and carbon radical stabilised by the adjacent nitrile group. Further reduction at the working potential leads to saturation of the



8 60 % 14 %

enamine function giving a mixture of *cis* and *trans* isomers of the aminonitrile. Some enamine is hydrolysed before it can be reduced [39].

A pulse radiolysis study of the reaction between aqueous solvated electrons and benzyltrimethylammonium ions shows that dissociative electron transfer occurs to generate the benzyl radical, identified by uv-spectroscopy. No detectable intermediate is formed [40].

Preparative scale reduction of benzyltrimethylammonium salts in water at aluminium affords trimethylamine, bibenzyl and toluene, although the polarographic wave in water merges with the background current. Bibenzyl is formed by dimerization of the benzyl radical while a further one-electron reduction of the radical leads to toluene [41]. Similarly, allyltriethylammonium salts give biallyl and propene together with triethylamine [42]. The dimeric products, *meso* and (±)-2,3-diphenylbutane, obtained by reduction of (-)-1-phenylethyltrimethylammonium salts are completely racemised as expected when the 1-phenylethyl radical is a reaction intermediate [43].

Sodium amalgam [44] and lead-sodium alloy [45] have both been used for the reductive cleavage of quaternary ammonium salts in aqueous solution. Such reactions are electron transfer in nature and the ease of cleavage of groups follows the rules previously discussed. Cinnamanyltrimethylammonium ion affords 1-phenylpropene while benzyltrimethylammonium ion yields toluene on reaction with sodium amalgam [46]. Both of these reducing agents also react with water to form hydroxide ions and hydrogen so that the Hofmann elimination from the quaternary ammonium salt may be an important side reaction.

Quaternary Phosphonium and Arsonium Salts

TABLE 5.4

Polarographic half-wave potentials for tetraphenyl and triphenyl onium salts in water. Ref.[47].

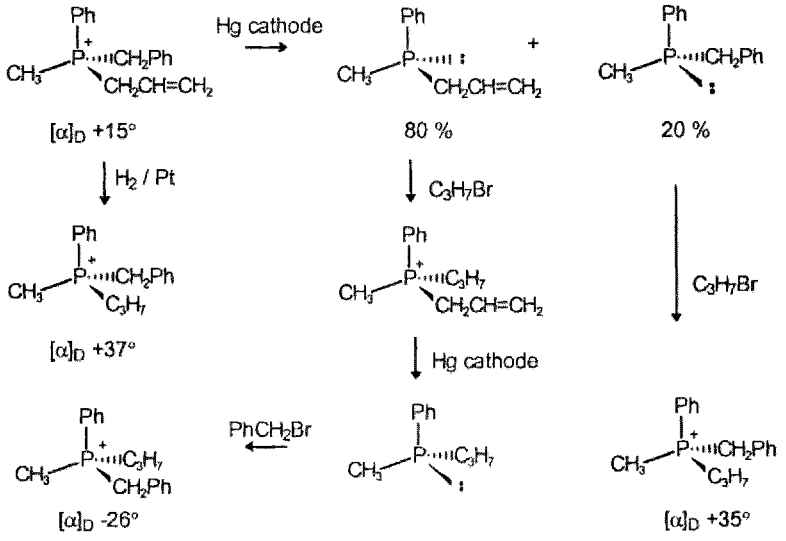
Substrate	$E_{½}$ V *vs.* sce	Substrate	$E_{½}$ V *vs.* sce
Ph_4P^+	-1.79 [a]	Ph_3S^+	-1.15 [b]
Ph_4As^+	-1.42 [a]	Ph_3Se^+	-0.98 [b]
Ph_4Sb^+	-0.74 [b]	Ph_3Te^+	-0.77 [b]

Footnotes: (a) Two-electron wave.
(b) One-electron wave, with a second one-electron wave at more negative potentials.

Phosphonium and arsonium salts with at least one phenyl substituent undergo reductive cleavage of one carbon-heteroatom bond to give a carbon radical and leaving the trisubstituted heteroatom [6]. Some half-wave potentials are given in Table 5.2. Benzyl and allyl substituents are cleaved in preference. Alkyltriphenyl onium salts show competition in the cleavage reaction to give both phenyl and alkyl radicals. The proportion of alkyl cleavage is small for methyl and increases for

ethyl isopropyl and *tert.*-butyl substituents. Alkyl radicals generated in this way will add to the alkene bond in styrene [48].

Cleavage reactions are best carried out in aqueous solution. In aprotic solvents, electrogenerated bases lead to the conversion of onium salts to the ylids which are not reducible [49]. The sequence of reactions shown in Scheme 5.2 shows that the bond cleavage process for phosphonium salts proceeds with retention of configuration around the phosphorus atom [50]. Retention of configuration at arsenic is also observed [51]. This electrochemical process is a route to asymmetric trisubstituted phosphorus and arsenic centres.



Scheme 5.2. Demonstration of retention of configuration during electrochemical cleavage of the carbon-phosphorus bond, Ref. [49].

Polarographic half-wave potentials for tetraphenyl onium salts become progressively less negative on moving down the periodic table (Table 5.4) due to the decreasing strength of the carbon-heteroatom bond. Phosphorus and arsenic compounds show one two-electron wave due to cleavage of one phenyl group followed at this potential by one-electron reduction of the phenyl radical. The stibonium compound shows two one-electron waves. The first wave is due to cleavage of the phenyl-antimony bond to give triphenylstibine and a phenyl radical, which is adsorbed onto the mercury surface as PhHg$^{\cdot}$ radical and yields diphenylmercury. The

second wave at –1.3 to –1.4 V *vs.* sce is due to reduction of this phenyl radical to form benzene [52].

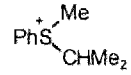
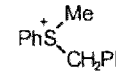
Carbon-Sulphur and related Bond Cleavage

Sulphides, Sulphonium salts and related Compounds

Triphenyl sulphur, selenium and telurium cations are reductively cleaved at less negative potentials, moving down the periodic table (Table 5.4). At the first polarographic wave, a one-electron process results in the formation of phenyl radicals, probably adsorbed on the mercury surface. Only the reaction of triphenylsulphonium ions has been studied in detail and the products are diphenylsulphide and diphenylmercury. A second polarographic wave has $E_{½}$ = -1.33 to –1.39 V *vs.* sce over the range of pH 5 to 12 and reduction at the plateau of this wave gives diphenylsulphide and benzene [53].

TABLE 5.5

Reduction of sulphonium salts: polarographic half-wave potentials, $E_{½}$ ref. [54], in water; cyclic voltammetry peak potentials, E_p ref. [55], in acetonitrile at glassy carbon, scan rate 50 mV s^{-1}.

Substrate	$E_{½}$ V *vs.* sce	Substrate	E_p V *vs.* sce
$Et_3\overset{+}{S}$	(a)		-1.73
$CH_2{=}CHCH_2\overset{+}{S}Me_2$	-1.46		-1.63
$PhCH_2\overset{+}{S}Me_2$	-1.30		-1.31

Footnote: (a) Wave merges with background.

One-electron cleavage of the carbon-sulphur bond has provided examples of both dissociative electron transfer and electron addition followed by fast bond cleavage already discussed on p. 95. Phenyldialkylsulphonium ions are cleaved in a one-electron process at a glassy carbon electrode and release the most stable alkyl radical [55]. Polarographic data is given in Table 5.5. Results from the cyclic voltammetry of these ions, substituted on the phenyl ring by an electron withdrawing group, have provided further demonstrations of the change from dissociative electron transfer to electron addition followed by fast bond cleavage [56]. The

choice between these two reaction pathways depends on the energy of the LUMO, which accepts an electron, and the strength of the bond to be cleaved. The dichotomy in reaction pathways has also been demonstrated using diarylalkylsulphonium salts as substrates [57].

The reductive cleavage of sulphonium salts in aprotic solvents leads to the generation of radical and then carbanions in a further electron transfer step. Protonation of the carbanion by extraneous water leaves a hydroxide ion. Basic species formed in this way can abstract a proton from sulphonium ion to give the ylid, which is not reducible. A good example is the reduction of **9** in dimethylsulphoxide, which consumes only one Faraday and follows the course shown [58].

$$\underset{\mathbf{9}}{Me_2\overset{+}{S}CH_2CN} + e \longrightarrow Me_2S + \dot{C}H_2CN$$

$$\dot{C}H_2CN + e \longrightarrow \bar{C}H_2CN$$

$$Me_2\overset{+}{S}CH_2CN + \bar{C}H_2CN \longrightarrow Me_2\overset{+}{S}\bar{C}HCN + CH_3CN$$

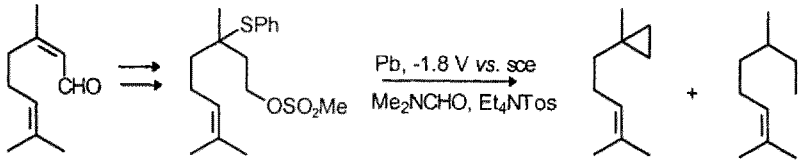
In a second type of side reaction, the carbanion formed can be alkylated by reaction with the sulphonium ion to yield unexpected products [59]. This reaction sequence is followed for the reduction of ethoxysulphonium salts **10**. Cleavage of the sulphur-oxygen bond, which is the weakest bond in the species, leads to an alkoxyl radical. This is reduced further to the alkoxide, which attacks an ethoxysulphonium ion to form diethyl ether [60].

$$\underset{\mathbf{10}}{(PhCH_2)_2\overset{+}{S}-OEt} + e \longrightarrow (PhCH_2)_2S + \dot{O}Et$$

$$\dot{O}Et + e \longrightarrow \bar{O}Et$$

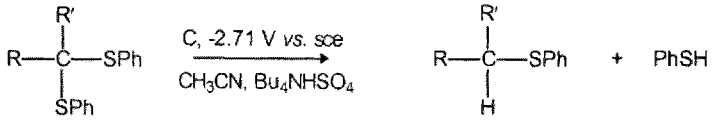
$$(PhCH_2)_2\overset{+}{S}-OEt + \bar{O}Et \longrightarrow (PhCH_2)_2SO + Et_2O$$

Generation of carbanions by the reductive cleavage of the carbon-sulphur bond has been utilised in the synthesis of cyclopropanes from α,β-unsaturated carbonyl compounds. The starting material is first transformed into the phenyl alkyl sulphide such as **11**. Reductive cleavage of the sulphide group affords the alkyl carbanion, which then displaces the methanesulphonate function to form a cyclopropane [61]. Reaction is performed in dry dimethylformamide to minimise interference by protonation of the carbanion, with subsequent reductive cleavage of the carbon-oxygen bond in the methanesulphonate group. Cyclopropane formation is always



11 69 % 12 %

accompanied by a low yield of the open chain hydrocarbon, generated by this alternative reaction.



76 - 91 % Ref. [62]

One carbon-sulphur bond in dithioacetals can be preferentially cleaved because of stabilization of the intermediate carbon radical by an adjacent sulphur substituent [62].

Sulphoxides

Since their discovery in 1866, it has been known that sulphoxides are reducible by zinc and acid to the corresponding sulphide [63]. The equivalent electrochemical process cannot be characterised because sulphoxides also decrease the hydrogen overpotential [64]. Dialkyl sulphoxides are not reduced in absence of protons and dimethyl sulphoxide is used as a solvent for electrochemical reduction. Phenyl methyl sulphoxide gives a single two-electron wave on polarography in both ethanol ($E_{½}$ = -2.17 V *vs.* sce) and dimethylformamide ($E_{½}$ = -2.32 V *vs.* sce), forming phenyl methyl sulphide [65].

Sulphones

Dialkyl sulphones are not reducible at a mercury cathode. Aryl alkyl and diaryl sulphones are however reduced with cleavage of a carbon-sulphur bond. Polarographic half-wave potentials for this process are given in Table 5.6. One-electron addition in aprotic media to phenyl methyl sulphone [66] and to diphenyl sulphone [67] leads in both cases to a delocalised radical-anion in which the sulphone group can be described as contributing a vacant symmetrical dπ-orbital to the conjugated system. Phenyl methyl sulphone radical-anion is prepared and characterised in liq-

uid ammonia. Diphenyl sulphone radical-anion is stable at –70 °C but decomposes rapidly at room temperature.

Electrochemical reduction of aryl sulphones in methanol leads to cleavage of one carbon-sulphur bond in a two-electron process. Alkyl aryl sulphones with an electron donating substituent in the aryl ring give the arenesulphinic acid and an alkane [68, 69]. Methyl phenyl sulphone and alkyl aryl sulphones with an electron withdrawing substituent in the aryl ring are cleaved to the substituted arene and the alkylsulphinic acid [70], see Scheme 5.2. In addition, a bulky *ortho*-substituent such as *tert.*-butyl favours cleavage to the arene and alkanesulphinic acid [71].

TABLE 5.6

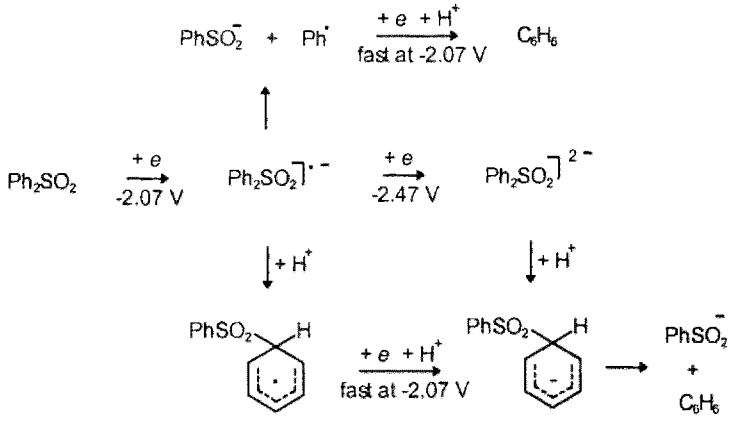
Polarographic half-wave potentials ($E_{½}$ / V *vs.* sce) and number of electrons involved (n) for reduction of one molecule of sulphoxides in methanol and in dimethylformamide.

Substrate	Solvent					
	Methanol			Dimethylformamide		
	$E_{½}$	n	Ref.	$E_{½}$	n	Ref.
$PhSO_2Me$	-2.17	2	[72]	-2.05	2	[73]
$PhSO_2CH_2Ph$	-2.07	2	[72]	–		
$PhSO_2CH{=}CHPh$	–			-1.47	1	[74]
$PhSO_2Ph$	-2.06	2	[72]	-2.05	1	[75]
$PhSO_2$–  –CN	1.59	2	[72]	-1.63	1	[76]
α-Naphthyl-SO_2Me	–			-1.89	1	[77]

Cleavage of methyl phenyl sulphone yields trace of ethane along with methane while ethyl phenyl sulphone affords traces of ethene along with ethane. It is probable therefore that bond cleavage occurs at the radical-anion stage to give alkyl radicals which are either reduced further and protonated to the alkane or undergo dimerization and disproportionation [68]. Electron withdrawing groups on the phenyl ring polarise charge density distribution in the radical-anion so that protonation occurs on the carbon bearing the sulphonyl group. Further reduction of the radical is followed by elimination of alkanesulphinate ion [70, 78].

Alkyl naphthyl sulphones are reduced at lower potentials than their phenyl analogues and give two one-electron waves on cyclic voltammetry in dimethyl-

formamide. The first wave for methyl naphthyl sulphone is reversible at fast sweep rates. Reduction at this potential leads to naphthalene and methanesulphinic acid. Benzyl naphthyl sulphones also show two one-electron waves on cyclic voltammetry in dimethylformamide. The first wave is now no longer reversible at the sweep rates used. Carbon-sulphur bond cleavage is rapid giving the stabilised benzyl radical and naphthalenesulphinic acid [77].

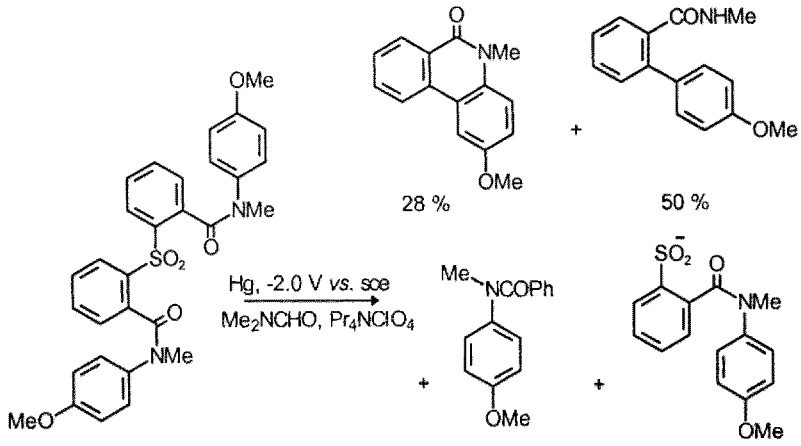


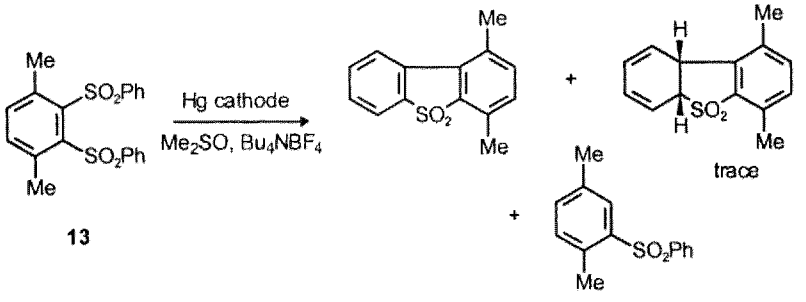
Scheme 5.2. Pathways proposed for the reduction of diphenyl sulphone in dimethylsulphoxide containing variable amounts of water. Potentials measured *vs.* sce.

Diphenyl sulphone gives two one-electron waves in dimethylformamide and the addition of up to 3 % water causes the first wave height to increase and the second wave to diminish to zero. Total wave height remains the same. The first wave is due to formation of the radical-anion and is reversible at medium sweep rates. Cleavage of the carbon-sulphur bond in the presence of water occurs through protonation of the radical-anion followed by fast one-electron addition, and in aprotic solvents from the dianion level [75], as indicated in Scheme 5.2. In the cases of unsymmetrically substituted diphenyl sulphones, carbon-sulphur bond cleavage occurs preferentially at the aryl ring with either none or electron withdrawing substituents because of preferential addition of the electron to this ring. Additionally, and irrespective of type, an *ortho*-substituent favours cleavage of the adjacent carbon-sulphur bond [72, 76].

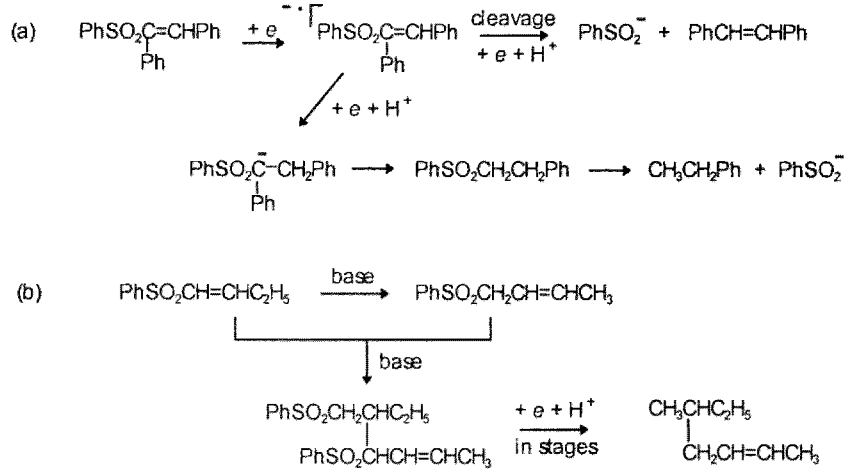
Cleavage of the radical-anion to give a phenyl σ-radical also occurs in aprotic solvents and can be demonstrated using substrates where the phenyl radical is trapped in an intramolecular addition process. Substrate **12** gives products analogus to those from reduction of the 2-halogeno-N-methylbenzanilides (p. 129) at a mercury cathode in aprotic solvents [79]. Similarly **13** undergoes a related cyclization of the σ-radical intermediate [80].

Reaction of both methyl phenyl sulphone and diphenyl sulphone with potasium in liquid ammonia [24] leads to the formation of a dianion, which cleaves to give $C_6H_5^-$, isolated as benzene. The initial electron transfer cannot be dissociative, as was the case for diethyl phenyl phosphate (p. 163), since the phenyl σ-radical is not detected. The radical-anions from these sulphones have sufficiently long lifetime in liquid ammonia to allow reaction with a further electron.





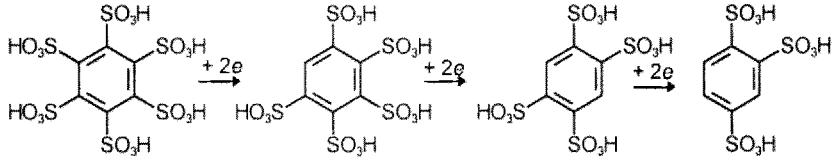
Reduction of phenyl vinyl sulphones in dimethylformamide containing phenol as proton donor causes loss of phenylsulphinate ion. The reaction probably involves a series of electron and proton addition steps [74]. In absence of a proton source, phenyl vinyl sulphone radical-anion undergoes a dimerization reaction discussed on p. 57. Reactions of alkyl substituted vinyl sulphones are complicated by alkene migration in the presence of electrogenerated bases. Dimers are formed and further reduction leads to loss of phenylsulphinate ion [81] (Scheme 5.3).



Scheme 5.3. Reduction of pyenyl vinyl sulphones: (a) in dimethylformamide containing phenol as a proton donor; (b) in absence of a proton donor.

Arenesulphonic Acids

Benzene mono- di- and tri-sulphonic acids are stable towards electrochemical reduction. More highly sulphonated compounds undergo a two-electron cleavage of a carbon-sulphur bond with elimination of sulphurous acid [82]. Thus benzene-hexa-sulphonic acid **14**, in aqueous solution at pH 8, shows three two-electron polarographic waves with half-wave potentials –1.00, -1.45 and 1.65 V *vs.* sce, due to the sequential loss of substituents. The half-wave potentials are independent of pH.

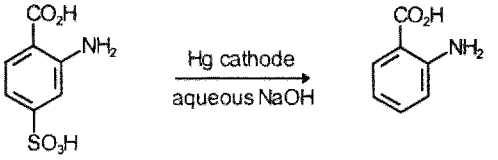


14

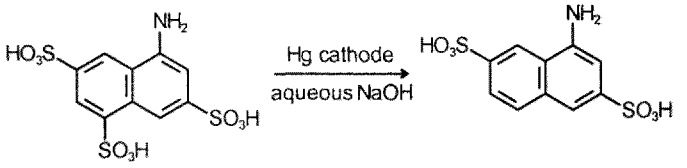
Some benzenesulphonic acids with an electron withdrawing carboxyl group in the ring will also undergo carbon-sulphur bond cleavage [83].

Reductive desulphonation of naphthalenesulphonic acids is also observed [84]. The 1-sulphonic acid substituent in a wide range of sulphonated naphthylamines is removed by reduction at mercury in aqueous sodium hydroxide [85]. Reductive

desulphonation of 5-chloroanthraquinone-1-sulphonic acid is another related process [86]. The advantage of electrochemical desulphonation is that in many cases the process yields a different product to the desulphonation process using aqueous acid at elevated temperatures.



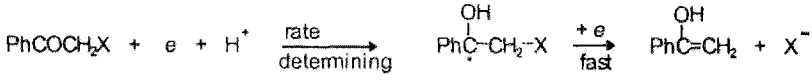
Ref. [83]



Ref. [85]

Cleavage Assisted by an adjacent Carbonyl Function

Carbon-heteroatom bonds of α-substituents to a carbonyl function are cleaved at less cathodic potentials than those required in the absence of the carbonyl group. The polarographic reduction of these systems has been extensively studies in aqueous media. The half-wave potentials are also less negative than those of the non-substituted carbonyl compounds. Electron addition involves an interaction between the π*-orbital of the carbonyl group and the σ-orbital of the departing group.

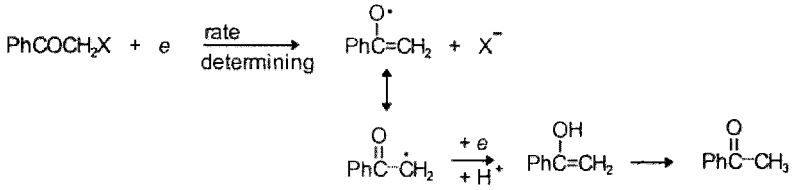


Scheme 5.4. Proton assisted cleavage of bonds adjacent to a carbonyl function

In acid solution the half-wave potentials for these processes are pH dependent. The overall reaction involves two electrons and is irreversible. Bond cleavage is believed to lead to the enol as shown in Scheme 5.4. Where, as with acetophenone, the ketone product is electroactive at more negative potentials, the wave height for ketone reduction is less than expected and is limited by the rate of enol to ketone tautomerism. This is because the enol is not electroactive.

For most substituents, in the region of neutrality and at higher pH values, the half-wave potential becomes independent of pH. In this region, electron transfer is synchronous with bond cleavage and loss of the leaving group creates a carbon

radical as in Scheme 5.5. Fast follow-up reduction of this radical leads to the ketone. Some half-wave potential values in this pH independent region are give in Table 5.7 and illustrate the combined influence of carbonyl group and leaving group on the rate of this electron transfer process. Figure 5.1 illustrates typical half-wave potential – pH profiles.



Scheme 5.5. Cleavage of bonds adjacent to a carbonyl function at high pH, protons are no longer involved in the rate determining step.

TABLE 5.7

Polarographic half-wave potentials ($E_{½}$), in the pH independent region, for the cleavage of bonds adjacent to a carbonyl function; pH values at the onset of ylid formation.

Substrate	$E_{½}$ /V *vs.* sce	pK_a ylid	Ref.
$PhCOCH_2F$	-1.05		[87]
$PhCOCH_2Cl$	-0.55		[88]
$PhCOCH_2Br$	-0.24		[88]
$PhCOCH_2OAc$	-1.32		[89]
$PhCOCH_2\overset{+}{N}R_3$	-0.98		[90]
$PhCOCH_2\overset{+}{N}R_2Ph$	-0.67	12.5	[91]
$PhCOCH_2\overset{+}{S}Et_2$	-0.61	7.0	[91]
$PhCOCH_2\overset{+}{S}MePh$	-0.40	6.5	[91]
$CH_3COCH_2\overset{+}{N}R_3$	-1.28		[90]
$CH_3COCH_2\overset{+}{P}Ph_3$	-1.33	7.0	[92]

Substrates with protons that are ionisable in alkaline solution have a second pH dependent region of the half-wave potential. Included here are amine substituents,

protonated in acid but losing the proton in alkali, and onium salts forming the ylid at high pH. In acid solution these substrates and ylids are protonated the behaviour follows Scheme 5.5 or 5.6. In the pH range where the substrate loses this proton, half-wave potential becomes pH dependent because kinetic protonation on the carbon centre is required to assist bond cleavage.

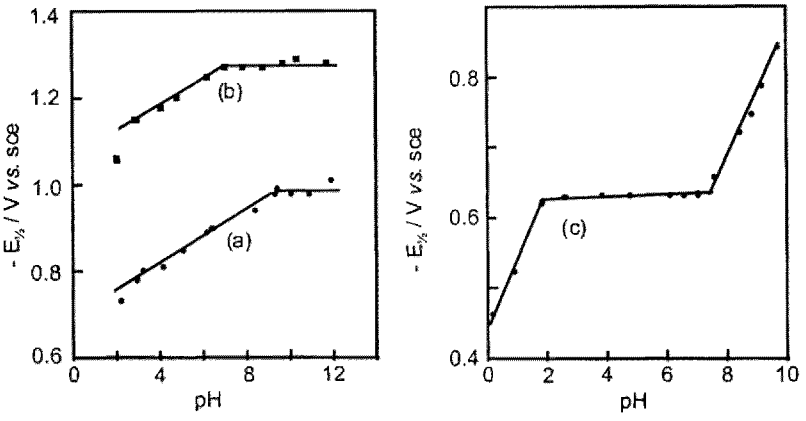
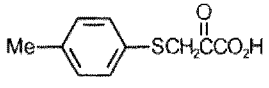
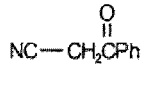


Figure 5.1. Variation of half-wave potential ($E_{½}$) with pH for α-substituted ketones: (a) N-methyl-N-phenacylpiperidinium cation, (b) N-methyl-N-(2-oxopropyl)piperidinium cation, (c) diethyl-(phenacyl)-sulphonium cation. Data from refs. [90] and [91].

In strongly alkaline solutions, the carbonyl group in some substrates forms a true enolate ion. Enolate ions undergo protonation on oxygen under kinetic control and are not reducible. Consequently the polarographic wave due to reductive cleavage and involving participation of the carbonyl function, falls to zero height. This phenomenon is observed in alkaline solution for carbon-sulphur bond cleav-



15

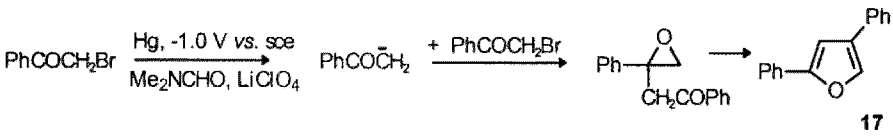


16

age in **15** [93] and carbon-nitrile bond cleavage in **16** [89].

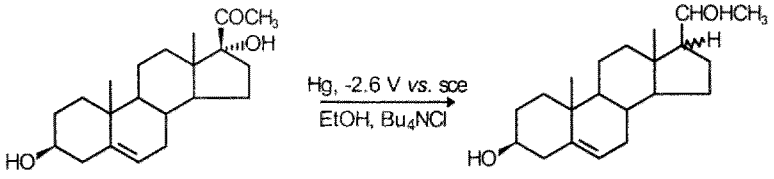
Reduction of ω-bromoacetophenone in aprotic solvents leads to acetophenone enolate. This is trapped by reaction with a second molecule of substrate to yield

2,4-diphenylfuran **17** in good yield [94, 95]. ω-Bromoacetophenone semicarba-



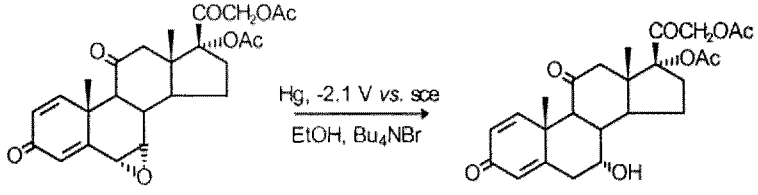
17

zones are reduced in aprotic solvents to the carbon radical with cleavage of the carbon-bromine bond. Radical dimerization gives a quantitative yield of 1,2-dibenzoylethane semicarbazone [96].



18

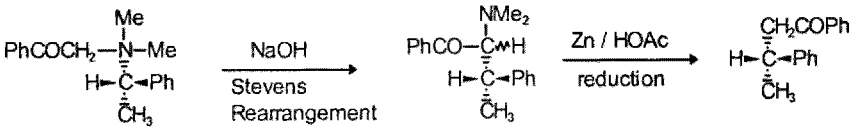
Use has been made of the bond cleavage processes initiated by an adjacent carbonyl function for the modification of steroidial ketols such as **18** [97]. Reduction in ethanol eliminates the hydroxyl function and in the same reaction, the carbonyl function is reduced to a secondary alcohol. In compound **19** where there are several groups to act as electrophores, carbon-oxygen bond cleavage is initiated from the most easily reduced dienone function [98]. Cleavage of the carbon-oxygen bond in an α-acetoxycarbonyl function is achievable in good yields from multifunctional compounds such as the sesquiterpene taxol [99].



19 36 % yield

Cleavage of α-aminoketones and their quaternary ammonium salts by sodium amalgam or zinc dust and acid has been used in synthetic procedures. This process was a key step in determining the stereochemistry of the Stevens rearrangement for

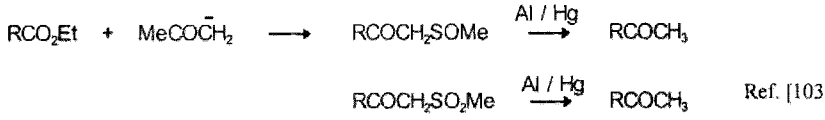
compound **20** [100]. An early attempt to apply the sodium amalgam reduction to dialkyl benzyl phenacyl ammonium salts led to the original discovery of the Stevens rearrangement [101]. Reduction of α-aminoketone ammonium salts in aprotic



20

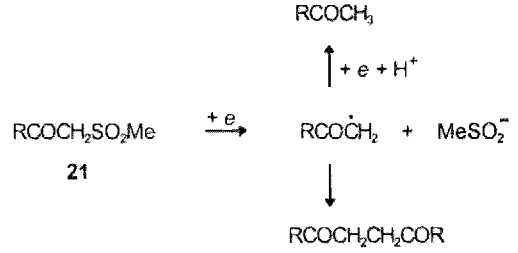
solvents leads to some carbon-nitrogen bond cleavage but electrogenerated base also causes the Stevens rearrangement of some of the substrate [102].

One synthetic route to methyl ketones involves the cleavage of carbon-sulphur bonds in either sulphoxides or sulphones using aluminium amalgam as the electron



Ref. [103]

source [103]. The reduction step in this sequence may also be carried out in an electrochemical cell. Thus, β-ketosulphoxides are cleaved in aqueous dimethyformamide at a mercury cathode in a divided cell. Overall four Faradays are required as the first formed RSO^- ion is further reduced to the mercaptan [104]. However the pH of the solution must be kept below 12.5 to avoid side reactions catalysed by electrogenerated base [105]. Electrochemical reduction of β-



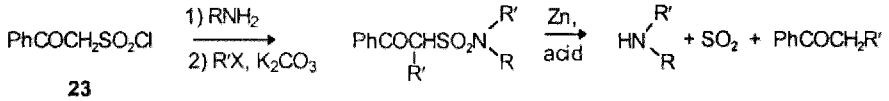
21

22

ketosulphones does not always follow a single reaction pathway. The methyl sulphones **21** where R is an alkyl group undergo a two-electron cleavage reaction to yield a ketone and methylsulphinic acid. The optimum pH for this process is 7.8. Acid solution favours the further reduction of the ketone product while basic solution causes condensation reactions to occur [106]. However, when R is an aryl

group substantial yields of the diketone **22**, which is a one-electron product, are generated [107, 108]. Reduction of the related phenyl sulphones always gives the ketone and benzenesulphinic acid [106].

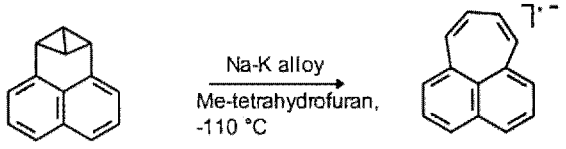
The sulphonyl chloride **23** is proposed as a protecting group for the Gabriel synthesis of secondary amines from primary amines. At the deprotecting stage, carbon-sulphur bond cleavage is achieved using zinc and acid as the electron source [109].



23

Carbon-Carbon Bond Cleavage

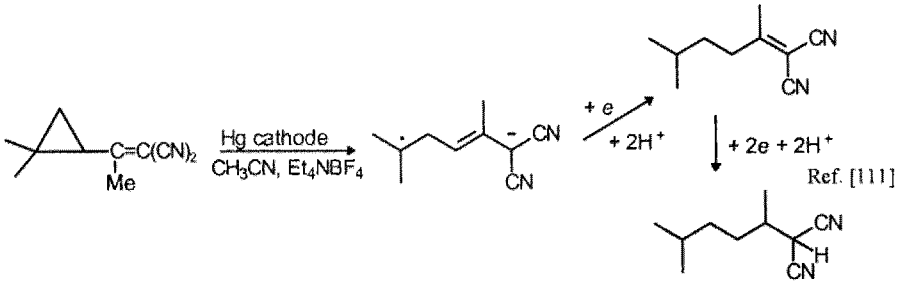
Cyclopropane rings adjacent to an electrochemically-generated radical-anion undergo carbon-carbon bond cleavage with ring opening. Several such reactions have been demonstrated by esr spectroscopic detection of the radical-anion product. The radical-anion of **24** is unstable even at low temperatures and only the ring



24

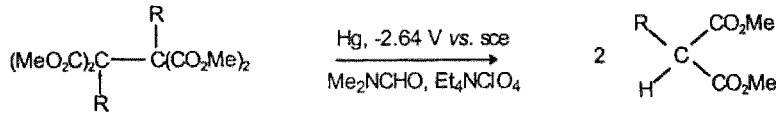
opened product can be detected [110].

Ring opening is observed during the preparative scale reduction of 1-cyclopropylethyidenemalononitriles where the carbon-carbon bond cleavage occurs with preferential formation of the most substituted carbon radical intermediate [111]. Cleavage of the carbon-carbon bond is also activated by four carbomethoxy sub-



Ref. [111]

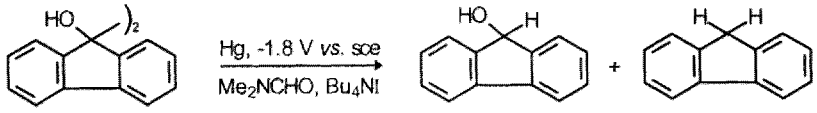
stituents. Ethane-tetracarboxylate esters undergo bond cleavage by reduction in dimethylformamide at a mercury cathode, best at 60 °C [112]. Pinacols with electron accepting hydrocarbon substituents undergo carbon-carbon bond cleavage in dimethylformamide around the potentials necessary for the hydrocarbon to form



89 % yield

Ref. [112]

the radical-anion [113]. These compounds also undergo carbon-oxygen bond cleavage.



Ref. [113]

The carbon-nitrile bond in cyanoalkanes is cleaved by reduction at very negative potentials. This is the route for decomposition of acetonitrile at the limit for its use as an aprotic solvent in electrochemistry [114, 115]. Preparative scale reduction of cyanoalkanes is best carried out in anhydrous ethylamine containing lithium chloride as supporting electrolyte and gives 60-80 % yields of the alkane plus cyanide ion.

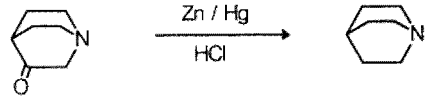
1,2- and 1,4-Benzonitriles show two one-electron waves in polarography. The first wave is reversible and results in the formation of a stable radical-anion. The second wave is irreversible and leads to the formation of benzonitrile and cyanide ion [116].

The Abnormal Clemmensen Reaction

Cleavage of carbon-nitrogen bonds adjacent to the carbonyl function can occur during the Clemmensen reaction. In most cases these reactions passed unnoticed until the products were re-examined by N. J. Leonard [117]. The processes were termed abnormal Clemmensen reactions. Prior to this work, the only unusual Clemmensen reduction processes noted were of ω-butoxy-2,4-dihydroxyacetophenone which gives 1-ethyl-2,4-dihydroxybenzene [118] and of ω-dimethylaminoacetophenone which gives ethylbenzene and dimethylamine [119].

Clemmensen reduction can be effected either using amalgamated zinc or cadmium and hydrochloric acid, or in the equivalent electrochemical reaction at cathodes of cadmium or lead in 30 % sulphuric acid (see p. 344). Where the amino function is associated with a ring system, Clemmensen reduction of α-aminoketones gives rise to three types of product:

(a) The normal Clemmensen product is found for only a very few examples where the carbon-nitrogen bond is held rigidly in the plane of the carbonyl function.



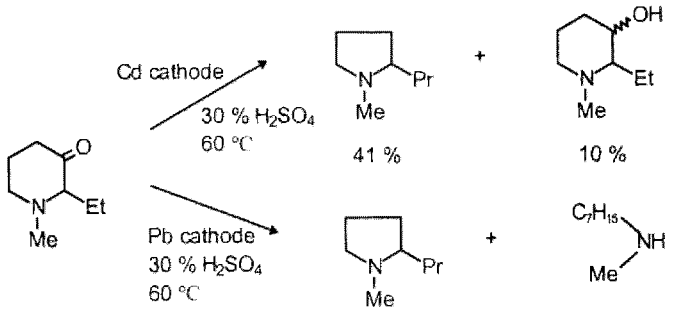
25

Thus 2-ketoquinuclidine **25** gives quinuclidine in good yields [120]. There is no overlap between the σ-bond and the carbonyl π*-orbital to assist simultaneous electron transfer and bond cleavage.

(b) For most substrates there is sufficient overlap for carbon-nitrogen bond cleavage to be the first stage of reaction. The amine group may then interact with the carbonyl group to give an imine, which reduces to the dihydro compound.

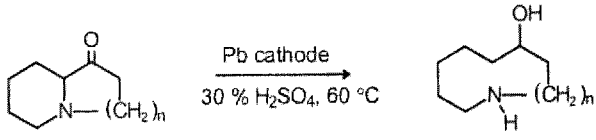
(c) Where imine formation does not occur, the carbonyl group is reduced either to methylene or to the secondary alcohol [121].

The relative importance of pathways (b) and (c) depends on temperature and the cathode material.



Ref. [126]

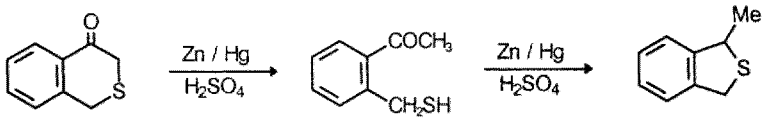
Electrochemical reduction of bicyclic-α-aminoketones **25** is a route to medium



25, n = 1 to 4

ring azacycloalkanols [122]. Pathway (b) is not important during the reactions of these substrates.

A related abnormal Clemmensen reduction is found with ketone α-thioethers, as



26

for compound **26**. Reaction leads to cleavage of the carbon-sulphur bond and subsequent formation of a thioketal, which is reduced to the dialkyl sulphide [119].

References

[1] H. Lund, H. Doupeaux, M. A. Michel, G. Mousset and J. Simonet, *Electrochim. Acta*, 1974, **19**, 629.
[2] J. Gal, J. C. Folest, M. Troupel, M. O. Moingeon and J. Chaussard, *New J. Chem.*, 1995, **19**, 401.
[3] J. Gal, J. C. Folest, M. Troupel, P. Guitton and Y. Robin, *New J. Chem.*, 1996, **20**, 375.
[4] J. S. Mayell and A. J. Bard, *J. Am. Chem. Soc.*, 1963, **85**, 421.
[5] L. Horner and J. Haufe, *J. Electroanal. Chem.*, 1969, **20**, 245.
[6] L. Horner, F. Röttger and H. Fuchs, *Chem. Ber.*, 1963, **96**, 3141.
[7] R. D. Rieke, R. A. Copenhafer, C. K. White, A. Aguiar, J. C. Williams and M. S. Chattha, *J. Am. Chem. Soc.*, 1977, **99**, 6656.
[8] H. J. Cristou, B. Chabaud, L. Labaudinière and H. Christol, *Electrochim. Acta*, 1984, **29**, 381.
[9] T. Shono, Y. Matsumura, K. Tsubata and Y. Sugihara, *Tetrahedron Letters*, 1979, 2157.
[10] T. Shono, Y. Matsumura, K. Tsubata and Y. Sugihara, *J. Org. Chem.*, 1982, **47**, 3090.
[11] L. Horner and H. Neumann, *Chem. Ber.*, 1965, **98**, 3462.
[12] T. Inokuchi, T. sugimoto, M. Kusumoto and S. Torii, *Bull. Chem. Soc. Japan*, 1992, **65**, 3200.
[13] T. Inokuchi, M. Kusumoto and S. Torii, *J. Org. Chem.*, 1990, **55**, 1548.
[14] K. Boujlel and J. Simonet, *Electrochim. Acta*, 1979, **24**, 481.
[15] J. Voss, K. Thimm and L. Kistenbrügger, *Tetrahedron*, 1977, **33**, 259.
[16] Nazar-ul-Islam, D. W. Sopher and J. H. P. Utley, *Tetrahedron*, 1987, **43**, 2741.

[17] J. C. Coleman, Nasar-ud-din, H. G. Gilde J. H. P. Utley B. C. L. Weedon and L. Eberson, *J. chem. Soc. Perkin Trans. 2*, 1973, 1903.
[18] S. Wawzonek and J. D. Fredrickson, *J. Electrochem. Soc.*, 1959, **106**, 325.
[19] T. Nonaka, T. Ota and T. Fuchigami, *Bull. Chem. Soc. Japan*, 1977, **50**, 2965.
[20] M. Ferles, O. Kocian, M. Lebl, J. Lovy, S. Radl, A. Silhankova and P. Stern, *Coll. Czech. Chem. Commun.*, 1976, **41**, 598.
[21] V. G. Mairanovskii, O. I. Volkova, E. A. Obol'nikova and G. I. Samokhvalov, *Dokl. Akad. Nauk. S. S. S. R.*, 1971, **199**, 829.
[22] J. G. Gourcy, M. Hodler, B. Terem and J. H. P. Utley, *J. Chem. Soc. Chem. Commun.*, 1976, 779.
[23] T. Shono, Y. Matsumura, K. Tsubata and Y. Sugihara, *J. Org. Chem.*, 1979, **44**, 4508.
[24] R. A. Rossi and J. F. Bunnett, *J. Am. Chem. Soc.*, 1974, **96**, 112.
[25] U. Akbulut, L. Toppare and J. H. P. Utley, *J. Chem. Soc. Perkin Trans. 2*, 1982, 391.
[26] P. A. Sartoretto and F. J. Sowa, *J. Am. Chem. Soc.*, 1937, **59**, 603.
[27] A. L. Kranzfelder, J. J. Verbane and F. J. Sowa, *J. Am. Chem. Soc.* 1937, **59**, 1488.
[28] F. C. Weber and J. J. Sowa, *J. Am. Chem. Soc.*, 1938, **60**, 94.
[29] C. E. Dahm and D. G. Peters, *J. Electroanal. Chem.*, 1996, **402**, 91.
[30] H. N. McCoy and W. C. Moore, *J. Am. Chem. Soc.*, 1911, **33**, 273.
[31] G. B. Porter, *J. Chem. Soc.*, 1954, 760.
[32] E. Kariv-Miller, C. Nanjundiah, J. Eaton and K. E. Swenson, *J. Electroanal. chem.*, 1984, **167**, 141.
[33] E. Kariv-Miller and V. Svetlicic, *J. Electroanal. Chem.*, 1985, **205**, 319.
[34] V. Svetlicic, P. B. Lawin and E. Kariv-Miller, *J. Electroanal.Chem.*, 1990, **284**, 185.
[35] J. Berthelot, M. Jubault and J. Simonet, *J. Chem. Soc. Chem. Commun.*, 1982, 759.
[36] L. Horner and A. Mentrup, *Liebigs Ann. Chem.*, 1961, **646**, 49.
[37] M. Finkelstein, R. C. Peterson and S. D. Ross, *J. Am. Chem. Soc.*, 1959, **81**, 2361.
[38] B. Emmert, *Ber.*, 1909, **42**, 1507.
[39] P. E. Iversen and J. O. Madsen, *Tetrahedron*, 1975, **30**, 3477.
[40] K. Bobrowski, *J. Phys. Chem.*, 1981, **85**, 382.
[41] S. D. Ross, M. Finkelstein and R. C. Peterson, *J. Am. Chem. Soc.*, 1970, **92**, 6003.
[42] R. N. Gedge, Y. N. Sadam and R. Eng, *J. Org. Chem.*, 1980, **45**, 3721.
[43] S. D. Ross, M. Finkelstein and R. C. Peterson, *J. Am. Chem. Soc.*, 1960, **82**, 1582.
[44] H. Emde, *Ber.*, 1909, **42**, 2950.
[45] F. Fichter and H. Stenzl, *Helv. Chim. Acta*, 1933, **16**, 571.
[46] P. Groenewoud and R. Robinson, *J. Chem. Soc.*, 1934, 1692.
[47] H. Matsuo, *J. Sci. Hiroshima Univ. Ser. A*, 1958, **22**, 281; *Chem. Abstr.*, 1960, **54**, 4206.
[48] J. H. Wagenknecht and M. M. Baizer, *J. Org. Chem.*, 1966, **31**, 3885.
[49] V. L. Pardini, L. Roullier, J. H. P. Utley and A. Webber, *J. Chem. Soc. Perkin Trans. 2*, 1981, 1520.
[50] L. Horner, H. Fuchs, H. Winkler and A. Rapp, *Tetrahedron Letters*, 1963, 965.
[51] L. Horner and H. Fuchs, *Tetrahedron Letters*, 1963, 1573.
[52] M. D. Morris, P. S. McKinney and E. C. Woodbury, *J. Electroanal. Chem.*, 1965, **10**, 85.
[53] P. S. McKinney and S. Rosenthal, *J. Electroanal. Chem.*, 1968, **16**, 261.
[54] A. Lütteringhaus and H. Machatzke, *Liebigs Ann. Chem.*, 1964, **621**, 165.
[55] F. D. Saeva and B. P. Morgan, *J. Am. Chem. Soc.*, 1984, **106**, 4121.

[56] C. P. Andrieux, M. Robert, F. D. Saeva and J.-M. Savéant, *J. Am. Chem. Soc.*, 1994, **116**, 7864.
[57] A. Ghanimi and J. Simonet, *New J. Chem.*, 1997, **21**, 257.
[58] J. Wagenknecht and M. M. Baizer, *J. Electrochem. Soc.*, 1967, **114**, 1095.
[59] P. Beak and T. A. Sullivan, *J. Am. Chem. Soc.*, 1982, **104**, 4450.
[60] J. Q. Chambers, P. H. Maugin and C.-S. Liao, *J. Electroanal. Chem.*, 1978, **87**, 239.
[61] T. Shono, Y. Matsumura, S. Kashimura and H. Kyutotu, *Tetrahedron Letters*, 1978, 1205.
[62] N. Schultzvonitter and E. Steckhan, *Tetrahedron*, 1987, **43**, 2475.
[63] A. Saytzeff, *Liebigs Ann. Chem.*, 1866, **139**, 354.
[64] G. B. Gavioli, G. Davolio and E. S. Guidetti, *J. Electroanal. Chem.*, 1970, **27**, 135.
[65] G. Grandi, L. Benedatti, R. Andreoli and G. B. Gavioli, *J. Electroanal. Chem.*, 1974, **54**, 221.
[66] E. Keller and R. G. Hayes, *J. Phys. Chem.*, 1969, **73**, 3901.
[67] R. Gerdil and E. A. C. Lucken, *Mol. Phys.*, 1965, **9**, 529.
[68] L. Horner and H. Neumann, *Chem. Ber.*, 1965, **98**, 1715.
[69] J. Simonet and G. Jeminet, *Bull. Soc. chim. France*, 1971, 2754.
[70] O. Manoušek, O. Exner and P. Zuman, *Coll. Czech. Chem. Commun.*, 1968, **33**, 3988.
[71] B. Lamm and K. Ankner, *Acta Chem. Scand. B*, 1977, **31**, 375.
[72] L. Horner and E. Meyer, *Liebigs Ann. Chem.*, 1975, 2953.
[73] B. Lamm and J. Simonet, *Acta Chem. Scand. B*, 1974, **28**, 147.
[74] K. Ankner, B. Lamm and J. Simonet, *Acta Chem. Scand. B*, 1977, **31**, 742.
[75] J. A. Cox and L. Ozment, *J. Electroanal. Chem.*, 1974, **51**, 75.
[76] L. Horner and E. Meyer, *Ber. Bunsenges. phys. Chem.*, 1975, **79**, 136.
[77] B. Lamm and K. Ankner, *Acta Chem. Scand. B*, 1978, **32**, 264.
[78] R. Gerdil, *Helv. Chim. Acta*, 1973, **56**, 197.
[79] J. Grimshaw and J. Trocha-Grimshaw, *J. Chem. Soc. Perkin Trans. 1*, 1979, 779.
[80] M. Nari, C. Dellerba, G. Garbarino, G. Scaponi and G. Capodaglio, *J. Chem. Soc. Perkin Trans. 2*, 1984, 951.
[81] J. Delaunay, A. Orliac-Le Moing and J. Simonet, *New J. Chem.*, 1993, **17**, 393.
[82] E. Yu. Khmel'nitskaya, G. A. Mezentseva and N. S. Dokunikhin, *Soviet Electrochem.*, 1980, **16**, 940.
[83] Kalle and Co., *DRP* 146716 (1902); *Chem. Zent.*, 1903, II, 1226.
[84] E. S. Levin and N. A. Osipova, *J. Gen. Chem. U.S.S.R.*, 1962, **32**, 2060.
[85] Bayer and Co., *DRP* 248527 (1911); *Chem. Zent.*, 1913, I 478..
[86] British Dyestuffs Corporation Ltd., *US* 1724928 (1929); *Chem. Abstr.*, 1929, **23**, 4627.
[87] P. J. Elving and J. T. Leone, *J. Am. Chem. Soc.*, 1957, **75**, 1546.
[88] P. J. Elving and J. T. Leone, *J. Am. Chem. Soc.*, 1960, **82**, 5076.
[89] H. Lund, *Acta Chem. Scand.*, 1960, **14**, 1927.
[90] P. Zuman and V. Horak, *Coll. Czech. Chem. Commun.*, 1961, **26**, 176.
[91] J.-M. Savéant, *Bull. Soc. chim. France*, 1967, 481.
[92] H. Matschiner and K, Issleib, *Z. anorg. allgem. Chem.*, 1967, **354**, 60.
[93] M. B. Fleury and J. Moiroux, *Bull. Soc. chim. France*, 1971, 4637.
[94] F. Barba, M. D. Velasco and A. Guiardo, *Synthesis*, 1981, 625.
[95] F. Barba, M. D. Velasco and A. Guiardo, *Electrochim. Acta*, 1983, **28**, 259.
[96] F. Barba, M. D. Velasco, A. Guirado and N. Moreno, *Synthetic Commun.*, 1985, **15**, 939.

[97] P. Kabasakalian, J. McGlotten, A. Basch and M. Y. Yudis, *J. Org. Chem.*, 1961, **26**, 1738.
[98] E. L. Shapiro, M. J. Gentles, P. Kabasakalian and A. Magetti, *J. Org. Chem.*, 1981, **46**, 5017.
[99] J. P. Pulicani, J. D. Bourzat, H. Bouchard and A. Commerçon, *Tetrahedron Letters*, 1994, **35**, 4999.
[100] J. H. Brewster and M. W. Kline, *J. Am. Chem. Soc.*, 1952, **74**, 5179.
[101] T. S. Stevens, E. M. Creighton, A. B. Gordon and M. MacNicol, *J. Chem. Soc.*, 1928, **130**, 3193.
[102] P. E. Iversen, *Tetrahedron Letters*, 1971, 55.
[103] E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1345.
[104] B. Lamm and B. Samuelsson, *Acta Chem. Scand.*, 1969, **23**, 691.
[105] B. Samuelsson and B. Lamm, *J. Chem. Soc. Perkin Trans. 1*, 1972, 652.
[106] B. Lamm and B. Samuelsson, *Acta Chem. Scand.*, 1970, **24**, 561.
[107] B. Samuelsson and B. Lamm, *Acta Chem. Scand.*, 1970, **24**, 3070.
[108] B. Lamm and B. Samuelsson, *J. Chem. Soc. Chem. Commun.*, 1970, 1010.
[109] J. B. Hendrickson, R. Berberon and D. D. Sternbach, *Tetrahedron*, 1975, **31**, 2517.
[110] R. Rieke, M. Ogliaruso, R. McClurg and S. Winstein, *J. Am. Chem. Soc.*, 1966, **88**, 4729.
[111] A. J. Bellamy and J. B. Kerr, *Acta Chem. Scand. B*, 1979, **96**, 7846.
[112] D. A. White and J. H. Wagenknecht, *J. Electrochem. Soc.*, 1981, **128**, 1470.
[113] M. A. Michel, G. Mousset, J. Simonet and H. Lund, *Electrochim. Acta*, 1975, **20**, 143.
[114] M. Fleischmann, G. Mengoli and D. Pletcher, *J. Electroanal. Chem.*, 1973, **43**, 308.
[115] B. F. Becker and H. P. Fritz, *Liebigs Ann. Chem.*, 1976, 1015.
[116] A. Gennaro, F. Maran, A. Maye and E. Vianello, *J. Electroanal. Chem.*, 1985, **185**, 353.
[117] N. J. Leonard and W. C. Wildman, *J. Am. Chem. Soc.*, 1949, **71**, 3089.
[118] C. D. Hurd and G. W. Fowler, *J. Am. Chem. Soc.*, 1939, **61**, 249.
[119] J. v. Braun and K. Weissbach, *Ber.*, 1929, **62**, 2416.
[120] G. R. Clemo and T. P. Metcalfe, *J. Chem. Soc.*, 1937, 1989.
[121] N. J. Leonard, S. Swann and H. L. Dryden, *J. Am. Chem. Soc.*, 1952, **74**, 2871.
[122] N. J. Leonard, S. Swann and G. Fuller, *J. Am. Chem. Soc.*, 1954, **76**, 3193.

CHAPTER 6

OXIDATION OF AROMATIC RINGS

Radical-Cations

Aromatic hydrocarbons are oxidised through loss of an electron from the highest occupied π-molecular orbital. This process generates a π-delocalised radical-cation. The electron transfer process is generally irreversible in acetonitrile under normal conditions because the radical-anion reacts rapidly with extraneous nucleophiles, including residual water. A second irreversible oxidation wave is seen at more positive potentials due to the formation of a transitory dication. Solutions of 9,10-diphenylanthracene radical-cation however can be prepared in acetonitrile using an electrochemical flow cell system and the reaction with water followed by uv-spectroscopy [1]. For some substrates, in carefully purified acetonitrile containing suspended aluminium oxide to absorb residual water, both electron transfer process becomes reversible on the time scale of cyclic voltammetry [2]. Dichloromethane [3], and mixtures of dichloromethane with fluorosulphonic acid [4] or trifluoroacetic acid [5, 6] are better solvents in which to demostrate the reversible one-electron oxidation of aromatic species. The anions present, as well as the solvents themselves, are poor nucleophiles while any water is protonated by the acid and not available for nucleophilic attack.

Table 6.1. Half-wave potentials for the oxidation of aromatic substrates in acetonitrile at a platinum rotating disc electrode.

Substrate	$E_{½}$ / V *vs.* sce	Ref.
1,3-Dimethylbenzene	2.15	[7]
1,3,5-Trimethylbenzene	2.18	[7]
1,2,4,5-Tetramethylbenzene	1.71	[7]
Hexamethylbenzene	1.66	[7]
Naphthalene	1.76	[8]
1-Methoxynaphthalene	1.38	[9]
1,4-Dimethoxynaphthalene	1.10	[9]
Anthracene	1.35	[8]
9,10-Diphenylanthracene	1.18	[1]
9,10-Di(4-methoxyphenyl)anthracene	1.12	[2]
4,4′-Dimethoxybiphenyl	1.25	[2]

Radical-cations were first prepared in solution and characterised by esr spectroscopy using chemical methods for the oxidation of aromatic hydrocarbons. Concentrated sulphuric acid [10] or antimony pentachloride in dichloromethane [11, 12] have been used as solvents. Oxidation using lead dioxide in fluorosulphonic acid at -75 °C proves to be a satisfactory chemical route for substrates having an electron withdrawing substituent [13]. Characterization by esr spectroscopy of electrochemically generated radical-cations can be frustrated by the high reactivity of these species in the solvents used. Thus hexaethylbenzene shows a reversible one-electron wave with $E^\circ = 1.72$ V *vs.* sce in trifluoroacetic acid and the radical-cation can be characterised by esr spectroscopy but hexamethylbenzene radical-cation is too reactive for detection [14]. Electrochemically generated 9,10-diphenylanthracene radical-cation has been characterised in acetonitrile [1].

Radical-cations from unsubstituted aromatic hydrocarbons show a strong tendency to form a sandwich π-complex with a molecule of the neutral compound. Dimeric species are detectable from esr measurements in solution. The crystalline naphthalene complex $(C_{10}H_8)_2PF_6$ can be prepared electrochemically and X-ray diffraction data indicates a sandwich arrangement of the two naphthalene rings with their symmetry axes orthogonal [15]. Dimeric species have also been prepared from both pyrene [16] and perylene [17]. Anthracene radical-cation dimer is characterised in solution [2, 3]. Dark green coloured, solid dimeric cations were prepared in 1931 by the action of antimony pentachloride on hydrocarbons in chloroform solution but their structure was unrecognised [18, 19]. Radical-cations with bulky substituents however do not in general form a complex with the substrate. Thus 2,3,6,7-Tetra-methoxybiphenylene radical-cation is obtained as the non-associated crystalline perchlorate from acetonitrile [20].

This tendency for association is demonstrated during the formation of radical-cations by γ-irradiation of the hydrocarbon in a soft glass from chlorobutane-isopentane mixtures [21]. Radiolysis produces oxidising species, which generate the radical-cation, and also solvated electrons. The latter are scavenged by the chlorobutane to generate butyl radicals and chloride ions. In a glass of suitable viscosity, benzene gives the monomer radical-cation which slowly transforms to the dimer $(C_6H_6)_2^+$ and naphthalene shows similar behaviour. These processes are followed by uv spectroscopy. In this glass, benzene and naphthalene monomer have λ_{max} 556 nm and 709 nm respectively while the corresponding dimers have λ_{max} 926 nm and 1030 nm [21].

Aromatic radical-cations are generated by pulse-radiolysis of benzene derivatives in aqueous solution. Radiolysis generates solvated electrons, protons and hydroxyl radicals. The electrons are converted by reaction with peroxydisulphate ion to form sulphate radical-anion, which is an oxidising species, and sulphate. In another proceedure, electrons and protons react with dissolved nitrous oxide to form hydroxyl radicals and water, Hydroxyl radicals are then made to react with either thallium(I) or silver(I) to generate thallium(II) or silver(II) which are powerfully

oxidising species. Reaction of the aromatic substrate with one of these oxidising agents generates the radical-cation, the whole process occurring within microseconds from the initiating pulse of radiation.

Radical-cations generated in this way are characterised by their uv spectra (Table 6.2) and their esr spectra. The oxygen lone-pairs in methoxybenzene radical-cations participate in delocalization of the positive charge so that, on the esr time-scale, phenomena due to hindered rotation about the benzene-oxygen bond appear. The two *ortho*-hydrogens in anisole radical-cation have different esr coupling constants. 1,4-Dimethoxybenzene radical-cation is found as a mixture of *cis*- and *trans*-isomers due to this hindered rotation [22].

Table 6.2. Long wavelength uv absorption bands of benzene radical-cations in water, determined by pulse-radiolysis techniques.

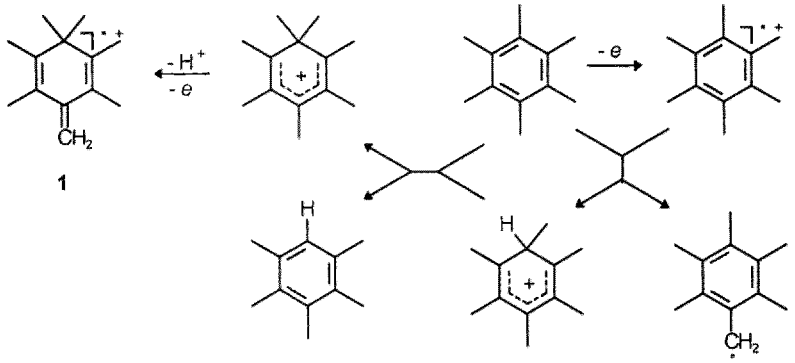
Substrate	λ_{max} / nm	ε / M^{-1} cm^{-1}	Ref.
Toluene	430		[23]
1,4-Dimethylbenzene	435	2050	[23]
Mesitylene	475	2250	[23]
Anisole	430	3800	[22]
1,4-Dimethoxybenzene	460	9540	[22]
1,2,3-Trimethoxybenzene	420	2800	[22]

Pulse-radiolysis experiments allow an examination of the first steps in the decay of radical-cations. Solutions of the radical-cation in the region of 10^{-5} M are generated. Bimolecular reactions between species at this level of concentration proceed relatively slowly and this simplifies interpretation of the experimental data. Particularly, electron transfer between radical-cations and radical species derived from them is not observed during the experiment.

Methylbenzenes lose a proton from a methyl group to form a benzyl radical. In aqueous M-perchloric acid this reaction is fast with a rate constant in the range 10^4 – 10^7 s^{-1} and the process is not reversible [24]. The process becomes slower as the number of methyl substituents increases. Hexaethylbenzene radical cation is relatively stable. When the benzyl radical is formed, further reactions lead to the development of a complex esr spectrum. Anodic oxidation of hexamethylbenzene in trifluoroacetic acid at concentrations greater than 10^{-4} M yields the radical-cation **1** by the process shown in Scheme 6.1 [14]. Preparative scale, anodic oxidation of methylbenzenes leads to the benzyl carbonium ion by oxidation of the benzyl radicals formed from the substrate radical-cation. Products isolated result from further reactions of this carbonium ion.

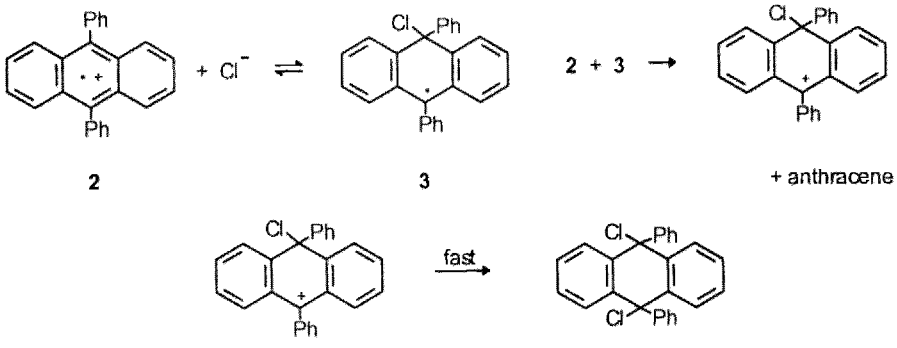
The second important reaction of radical-cations is attachment of a nucleophile to one of the ring carbon atoms. In solutions at pH > 4 radical-cations generated by

pulse-radiolysis react principally with water as a nucleophile. This process is reversible [22, 23]. The radical species in this equilibrium can be prepared independently by the addition of hydroxyl radicals to the benzene precursor. In acid solution it is converted to the radical cation with loss of water in a bimolecular process with rate constant in the region of 10^9 M^{-1} s^{-1}.



Scheme 6.1. Methyl group transfer during the anodic oxidation of hexamethylbenzene in trifluoroacetic acid.

Electrochemically generated solutions of radical-cations will react with nucleophiles in an inert solvent to generate a radical intermediate. Under these conditions the intermediate is oxidised to the carbonium ion by a further radical-cation. Generally, an aromatic system is then reformed by loss of a proton. Reactions of 9,10-diphenylanthracene radical-cation nucleophiles in acetonitrile are conveniently followed either by stop flow techniques or by spectroelectrochemistry. Reaction with chloride ion follows the course shown in Scheme 6.2, where the termination



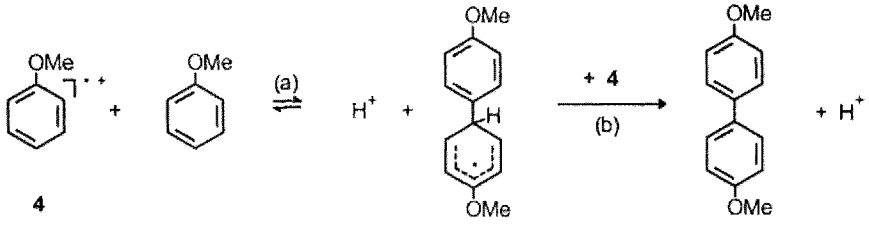
Scheme 6.2. Reaction of 9,10-diphenylanthracene radical-cation with chloride ion.

stage is now addition of chloride ion to the carbonium ion. The process involves a pre-equlibrium between the radical-cation and the nucleophile followed by a rate-determining electron transfer step [25]. Equation 6.1 is the overall rate-equation. In

$$\text{Rate} = k_{app.}[DPA^{\cdot+}]^2[Cl^-] \qquad \text{Eq. 6.1}$$

contrast, reactions of the radical-cation with water [1, 26] and with pyridine [25] are first order in both radical-cation and nucleophile concentrations. Here the first addition of the nucleophile to the radical-anion is rate determining.

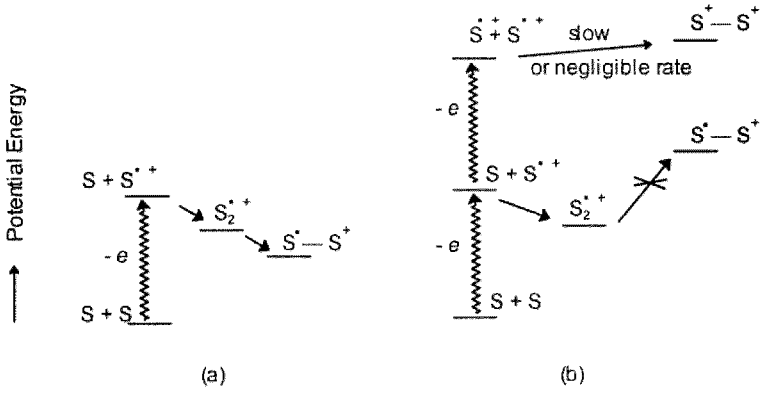
A third important reaction of aromatic radical-cations is carbon-carbon bond formation with a further aromatic substrate. This reaction is limited to the oxidation in acetonitrile of substrates with electrondonating substituents. Radical-cations from benzene, naphthalene and anthracene form π-complexes but do not form a σ-bonded reaction intermediate. The dimerization reaction has been investigated both by pulse-radiolysis [22] in water and by electrochemical methods [27] in acetoni-



Scheme 6.3. Dehydrodimerization reaction for anisole. (a) Rate-determining step at low concentrations of anisole. (b) Rate-determining at high concentrations of anisole.

trile. It follows the course shown in Scheme 6.3 illustrate by the reaction of anisole. Overall the reaction is a dehydrodimerization. The radical-cation and a molecule of substrate form a σ-bonded complex in a reversible pre-equlibrium. This complex is oxidised irreversibly by a second radical-cation. At low substrate concentrations, the rate-determining stage is formation of the σ-complex and the overall reaction is first order in both radical-cation and substrate. At substrate concentrations around 15 mM, formation of the σ-complex becomes a pre-equlibrium, which is rapidly established and the rate-determining stage is further oxidation of this comlex by the radical-cation. The overall rate is then second order in radical-cation concentration. Under pulse-radiolysis conditions where the radical-cation concentration is very low, reaction is first order and the σ-complex can be characterised by its uv-spectrum.

The dehydrodimerization reaction involving aromatic radical-cations is fast only when electron donating substituents are present in the benzene ring. These substituents stabilise the σ-intermediate. Benzene, naphthalene and anthracene radical-cations form a π-sandwich complex with the substrate but lack the ability to stabilise the σ-intermediate so that radical-cation substrate reactions are not observed. The energy level diagram of Scheme 6.4 illustrates the influence of electron donating substituents in stabilising the Wheland type σ-intermediate.



Scheme 6.4. Energy level diagrams for reactions of aromatic radical-cations with their substrate S: (a) Substrates having electron donating methoxy substituents. (b) No electron donating substituents present. The wavy lines indicate a single electron transfer process.

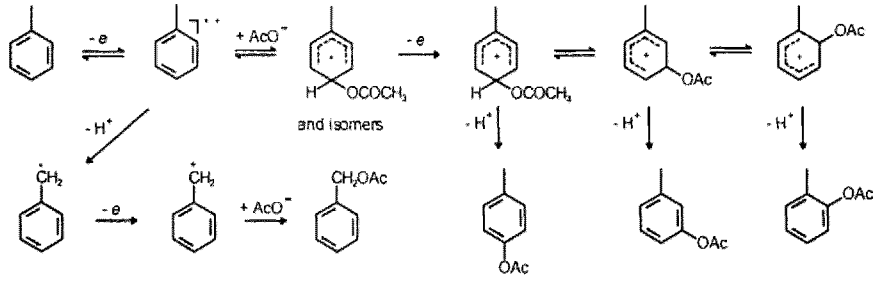
Cross coupling reactions, for example between 9-phenylanthracene radical-cation and anisole or toluene are known. 9-Phenylanthracene is more easily oxidised than anisole or toluene and carbon-carbon bond formation takes place by reaction between 9-phenylanthracene radical-cation and the substituted benzene. These reactions follow a kinetic scheme related to that of Scheme 6.3(b) in which a second electron transfer step is rate determining, although an inverse dependence of the rate on the concentration of 9-phenylanthracene can be detected [28].

Oxidative Substitution Reactions

Anodic substitution reactions of aromatic hydrocarbons have been known since around 1900 [29, 30]. The course of these processes was established primarily by a study of the reaction between naphthalene and acetate ions. Oxidation of naphthalene in the presence of acetate gives 1-acetoxynaphthalene and this was at first taken to indicate trapping of the acetyl radical formed during Kolbe electrolysis of

acetate ion [31]. Later workers showed that acetoxylation reactions of other aromatic hydrocarbons take place at anode potentials characteristic of the hydrocarbon and not at the one potential to be expected if the initial step is oxidation of acetate. In general these reactions take place at potentials much less anodic than those required for the Kolbe reaction. Reaction of naphthalene under vigorous conditions at high anode potentials gives 1-methylnaphthalene as a side product, the yield of which falls substantially at lower anode potentials [32]. This and all subsequent work confirms that the aromatic radical-cation is the reaction intermediate in anodic substitution process. Nucleophiles mostly react to form a σ-bond but for some examples, such as halide ions, [33] the nucleophile is oxidised by electron transfer and bond formation does not take place. Methylnaphthalene arises from reaction of methyl radicals generated when the anodic potential is sufficient to initiate the Kolbe process. Pyridine oxidises at more anodic potentials than either benzene or naphthalene. Electrolysis of sodium acetate in pyridine leads to 2- and 4-methylpyridines [34] since acetate is now preferentially oxidised at the anode, generating methyl radicals, which react with pyridine. Anodic substitution reactions involving methoxide ions [35] or cyanide ions [36] were first assumed to involve methoxy radicals and cyanide radicals respectively. The reactive species is now recognised to be the aromatic radical-cation, which couples with the nucleophilic anion.

Aromatic compounds undergo acetoxylation during electrochemical oxidation in acetic acid containing sodium acetate [37]. The radical-cation is first formed and reacts with acetate ion in an equlibrium step which is driven forward by further oxidation of the radical product. Alkyl substituted benzene radical-cations may also lose a proton from the benzylic position in an irreversible step after which further reaction leads to side chain acetoxylation. Scheme 6.5 illustrates these processes with toluene as substrate. Loss of the benzylic proton is energetically favoured due to overlap between the aromatic ring and the forming benzylic radical accommodated in a *p*-orbital. In triptycene, which shows only nuclear acetoxylation and no α-acetoxylation [38], the equivalent benzyl orbital is sp^3 hybridised and held orthogonal to the benzene rings. In the general case, benzylic and nuclear



Scheme 6.5. Steps in the anodic oxidation of toluene in acetic acid, sodium acetate.

substitution processes compete. Benzene derivatives with four or more methyl substituents give mostly benzyl acetates.

Nuclear substitution will occur at the point of highest positive charge density in the radical-cation. Further oxidation gives the delocalised carbonium ion and at this stage the acetyl group can migrate by a 1,2-bridging process. The isomeric ratio for nuclear substitution is therefore controlled by the relative energy of the isomeric carbonium ion intermediates and not by the direction of the initial substitution step. Table 6.3 gives the observed product ratios at a platinum anode.

Table 6.3. Isomer distribution from acetoxylation of aromatic compounds at a platinum anode in acetic acid, sodium acetate. Ref. [37]

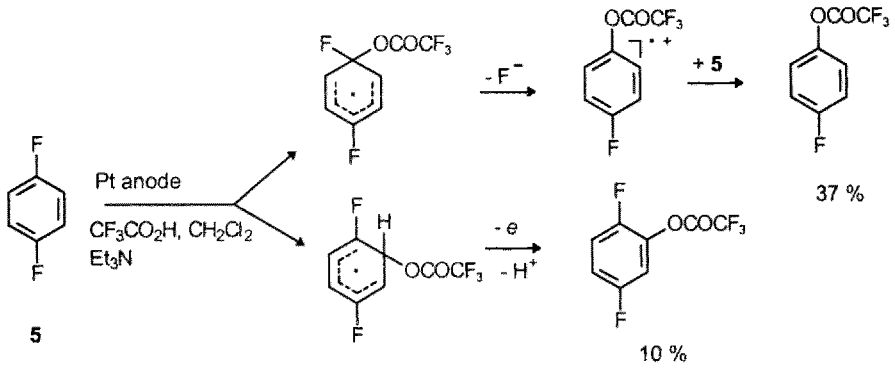
Substrate	Acetoxylation Products			
	Side chain / %	Nuclear isomer distribution		
		ortho / %	*meta* / %	*para* / %
Toluene	28.6	43	11	46
Ethylbenzene	50.5	44	10	46
Isopropylbenzene	46.7	44	16	40
tert.Butylbenzene		35	22	43
Fluorobenzene		34	8	58
Chlorobenzene		37	5	58
Anisole		67	4	29
Biphenyl		31	1	68
Naphthalene		96 [a]	4 [b]	

Footnotes: (a) 1-acetoxynaphthalene; (b) 2-acetoxynaphthalene.

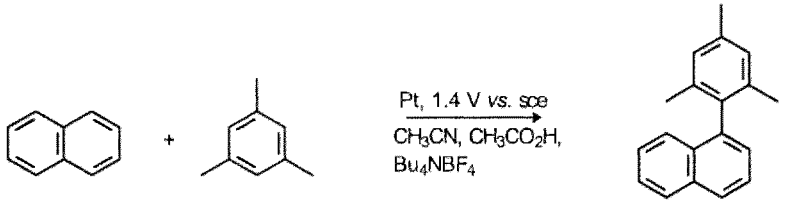
The isomer distribution obtained from the oxidation of mesitylene in acetic acid, sodium acetate depends on the anode material. Graphite strongly favours nuclear substitution to side chain substitution in the ratio 23:1 while at platinum this ratio is 4:1. Oxidation of methyl benzenes in acetic acid containing tetrabutylammonium fluoroborate and no acetate ion gives benzyl acetate as the major product since loss of a proton from the radical-cation is now faster than nuclear substitution by acetic acid as the only nucleophile present [39].

Ipso-substitution is rarely observed during anodic acetoxylation reactions. However, 1,4-difluorobenzene **5** in trifluoroacetic acid gives both the normal product and the product of replacement of fluorine by trifluoroacetoxy [40]. Oxidation of 2- and 4-fluoroanisoles in acetic acid leads to replacement of the fluorine by acetoxy [41], while reaction of hexafluorobenzene leads to tetrafluoro-1,4-benzoquin-

one [42]. These reactions probably proceed as indicated for compound **5**. Methoxylation and cyanation reactions of methoxybenzenes afford many examples of *ipso*-substitutions, which are introduced on p. 199. In the hydrocarbon series, anodic oxidation of *para*-xylene in methanol containing sodium methoxide gives a low yield of the two isomeric 1,4-dimethoxy-1,4-dimethylcyclohexa-2,5-dienes [43].



In the absence of strongly nucleophilic anions, naphthalene radical-cation will react with nucleophilic aromatic hydrocarbons. Oxidation of naphthalene in dichloromethane or acetonitrile with Bu_4NBF_4 as electrolyte gives 1,1-binaphthyl in the first stage of reaction and a polymer after prolonged reaction [44]. Naphthalene is more readily oxidised than methylbenzenes and oxidation of a mixture with naphthalene gives rise to coupling products from mesitylene [44], isodurene and pentamethylbenzene [45]. Oxidation of methylbenzenes alone in dichloromethane

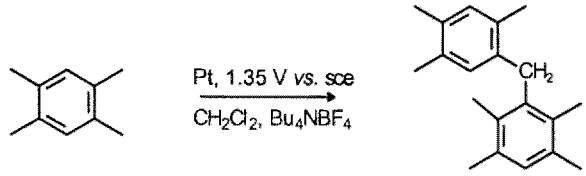


Ref. [44]

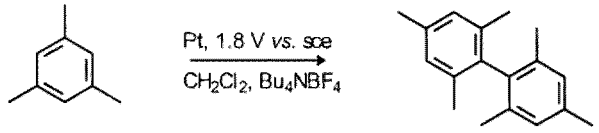
gives rise to two types of product, one by electrophilic attack of the radical-cation on the substrate, the other by electrophilic attack of a benzyl carbonium ion on the substrate [46, 47]. Reaction between radical-cations or benzyl carbonium ions and acetonitrile as the nucleophile has been observed in some cases and this leads to an acetamide after addition of water [48, 49].

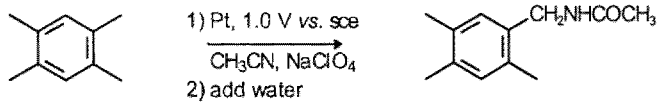
Electrochemical oxidation affords a simple route for the conversion of benzene derivatives to the corresponding phenol *via* the phenyl acetate. In practice however high yields are difficult to achieve because the product readily undergoes further

oxidation. Reaction has to be carried out to low conversion after which the product



Ref. [44]

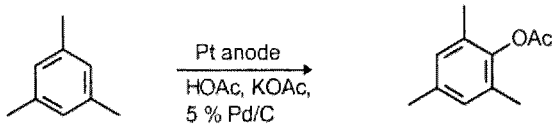




Ref. [49]

is isolated and the reactant recirculated. Techniques have been developed for reaction in an emulsion of dichloromethane and aqueous acetate, which allow relatively easy product isolation from the dichloromethane layer [50]. A further refinement employs trifluoroacetic acid in place of acetic acid when trifluoroacetates are formed. These are less easily oxidised because of the electron withdrawing effect of the trifluoroacetate group so the reaction can be carried out to higher conversion with less risk of further oxidation [40].

The α-substitution product from oxidation of methylbenzenes in acetic acid can be eliminated by electrochemical hydrogenolysis at the cathode. An undivided cell is used and a palladium on carbon catalyst is suspended in the medium. The necessary hydrogen is generated by reduction of protons at the cathode. In this way, the



Ref. [51]

79 %

α-substitution product is both eliminated and the recovered substrate is re-circulated. The major isolated products result from nuclear substitution [51].

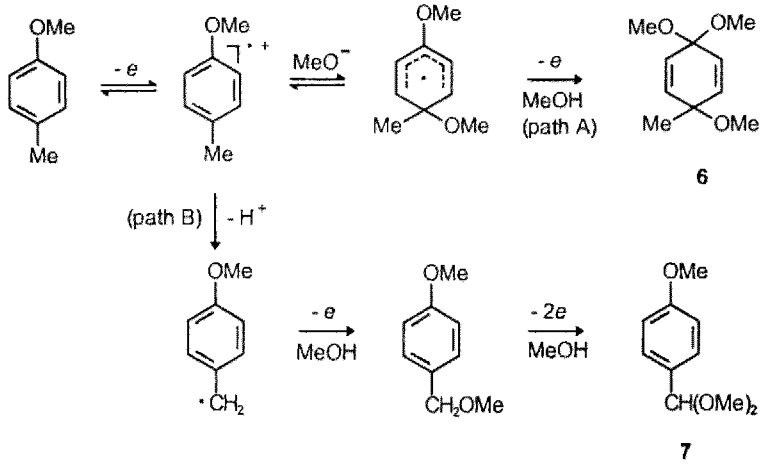
Benzene, naphthalene and anthracene afford quinones by oxidation in aqueous based media and these processes are technically important. Electrochemical oxida-

tion of benzene emulsified with dilute sulphuric acid has been known since 1880 to yield quinone [52]. Yields of quinone up to 81 % of the benzene consumed were achieved [53]. Later (1923) anodic formation of quinone in a divided cell was combined with circulation of the reaction mixture through the cathode chamber to yield hydroquinone by reduction of any quinone present [54]. This process forms the basis of hydroquinone manufacture to the present day. The electrolyte is an emulsion of benzene in dilute sulphuric acid and reaction is conducted at 70 °C. Hydroquinone passes into the aqueous layer, which is separated and cooled when the product crystallises. Benzene and sulphuric acid are re-circulated [55].

Benzene radical-cation is formed at the anode and reacts with water as a nucleophile to form phenol as an intermediate. Phenol is more readily oxidised than benzene and is converted to 1,4-dihydroxybenzene. Further oxidation of this in the anode chamber leads to quinone.

Naphthalene and anthracene are oxidised as a suspension in aqueous acid with a transition metal ion as electron carrier. The transition metal ion is converted to a high valency state at the anode and then reacts with the aromatic hydrocarbon. This indirect oxidation process gives higher yields than direct oxidation of naphthalene or anthracene [56]. Manganese(III), cerium(IV) and chromium(VI) have all been used as electron carriers. Cerium(IV) methanesulphonate in methanesulphonic acid is generally favoured. It is used either in catalytic ammounts together with the hydrocarbon in the electrochemical cell [57] or is generated in stoichiometric amounts in the cell and then reacted with hydrocarbon outside the cell [58]. The transition metal solution is re-circulated under controlled conditions so as to diminish the problems of electrode fouling and deactivation [59].

Side chain oxidation of methylbenzenes has been developed into a route for the

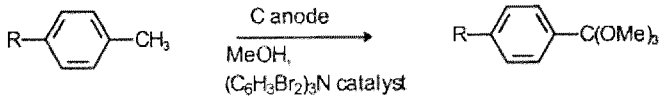


Scheme 6.6. Oxidation of 4-methylanisole in methanol, sodium methoxide.

preparation of some benzaldehydes on a technical scale. Reactions are carried out in either methanol and sodium methoxide or in methanol and acid and lead to isolation of the aldehyde dimethylacetal. The conversion of toluene to benzaldehyde and 4-*tert*.butyltoluene to 4-*tert*.butylbenzaldehyde is carried out in methanol, sulphuric acid at a graphite anode [60, 61]. The same conversions are effected using cerium(IV) methanesulphonate in methane sulphonic acid [62] or ceric ammonium nitrate in methanol [63], coupled with re-oxidation of cerium at the anode.

A general reaction scheme is illustrated in Scheme 6.6 for the oxidation of 4-methylanisole in alkaline solution. *Ipso*-substitution is characteristic for reaction of methoxybenzene radical-cations with many nucleophiles including methoxide and cyanide ions. At a platinum anode some *ipso*-substitution occurs and compound **6** can be isolated along with the benzaldehyde acetal **7**. *Ipso*-substitution involves reaction of the nucleophile at a point on the radical-cation of high positive charge density. The methoxy group is not able to bridge adjacent carbon atoms of the ring, as is acetoxy, and so does not migrate. However the nucleophilic addition step is in general reversible. Rapid oxidation of the radical intermediate leads to irreversible *ipso*-substitution by path A. At a carbon anode this second electron transfer step is relatively slow. Because the nucleophilic addition is reversible in acid solution, the radical-cation now becomes available for rapid irreversible loss of a proton to give the benzyl radical by path B. This reaction is known to be fast even in acid solution [24]. Subsequent steps now involve formation of the benzyl carbonium ion, reaction with methanol to form the benzyl methyl ether and further anodic oxidation to the acetal [64]. Oxidation of methylbenzenes in methanol containing sulphuric acid leads to the dimethyl acetal in good yield with negligible nuclear substitution.

Indirect electrochemical oxidation of substituted toluenes in methanol affords good yields of side chain substitution products. Tris(2,4-dibromophenyl)amine is



	Yield
R = Bu^t	71 %
Me	76 %
Br	72 %
Cl	83 %
H	95 %

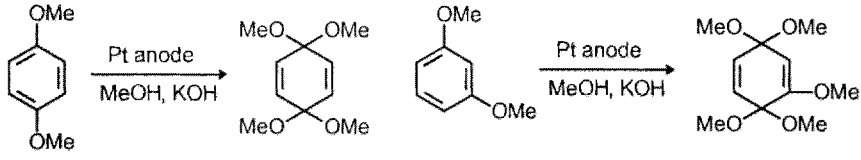
Ref. [65]

used as electron transfer agent. The amine is oxidised at the anode to a radical-cation and this transfers an electron from the aromatic hydrocarbon in solution. Further oxidation requires a second electron acceptor and before this encounter is achieved, the hydrocarbon radical-cation loses a proton. Further reaction follows

path B in Scheme 6.6 and side chain oxidation steps continue so that the final product is a benzoic acid ortho-ester [65].

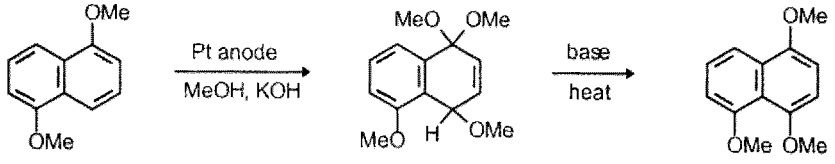
Conversion of toluenes to the benzoic acid is also accomplished by anodic oxidation in acetic acid containing some nitric acid. It is not clear if this reaction involves the aromatic radical-cation or if the oxidising agents are nitrogen oxide radicals generated by electron transfer from nitrate ions [66, 67]. Oxidation of 4-fluorotoluene at a lead dioxide anode in dilute sulphuric acid gives 4-fluorobenzoic acid in a reaction which involves loss of a proton from the aromatic radical-cation and them in further oxidation of the benzyl radical formed [68].

Anodic nuclear substitution by methoxide or cyanide ions gives acceptable yields only for methoxybenzenes and methoxynaphthalenes. The nucleophile is attached to the point of highest positive charge density in the radical-cation and for many examples this leads to *ipso*-substitution. Oxidation of 1,4-dimethoxybenzene in methanol containing potassium hydroxide leads to the quinone diketal **8** [69]. The reaction is a general one for 1,4-dimethoxybenzenes [70, 71] and 1,4-



8 **9**

dimethoxy-naphthalenes [72, 73]. Further nuclear methoxylation is observed with some substrates such as in the formation of **9** [69] Quinone ketals cannot easily be prepared by any other route. They effectively protect the quinone function during further operations and can easily be hydrolysed under acid conditions. The anodic



10 85 %

oxidation of benzene or chlorobenzene in methanol containing tetramethylphosphonium fluoride as supporting electrolyte also gives quinone diketals [74]. Methoxylation of 1,5-dimethoxy-naphthalene **10** gives the *ipso*-substitution product, which can easily be transformed to 1,4,5-trimethoxynaphthalene [75].

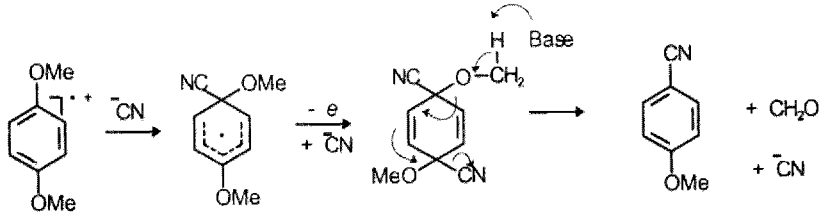
Reactions between aromatic hydrocarbon radical-cations and cyanide ions, with few exceptions, give low yields of nuclear substitution products [76]. In some cases, better results have been obtained by anodic oxidation of the aromatic compound in an emulsion of aqueous sodium cyanide and dichloromethane with tetrabutylammonium hydrogen sulphate as a phase transfer agent [77, 78]. Methoxybenzenes give exceptionally good yields from reactions in acetonitrile containing tetraethylammonium cyanide, sometimes with displacement of methoxide [79, 80]

Table 6.4. Products from reactions between aromatic radical-cations and cyanide ions

Substrate	Route	Product	Yield / %	Ref.
Naphthalene	b	1-Cyanonaphthalene	69	[77]
Anisole	b	4-methyoxbenzonitrile	57	[77]
1,2-Dimethoxybenzene	a	2-Methoxybenzonitrile	94	[79, 80]
1,3-Dimethoxybenzene	b	2,4-Dimethoxybenzonitrile	58	[80]
1,3-Dimethoxybenzene	a	2,4-Dimethoxybenzonitrile	12	[79]
1,4-Dimethoxybenzene	a	4-Methoxybenzonitrile	95	[79]
1,2,3-Trimethoxybenzene	a	2,6-Diemthoxybenzonitrile	86	[79, 80]
1,2,4-Trimethoxybenzene	b	2,4-Dimethoxybenzonitrile	38	[80]
1,3,5-Trimethoxybenzene	b	2,4,6-Trimethoxybenzonitrile	56	[80]
4,4'-Dimethoxybiphenyl	b	4-Cyano-4'-methoxybiphenyl	78	[78]

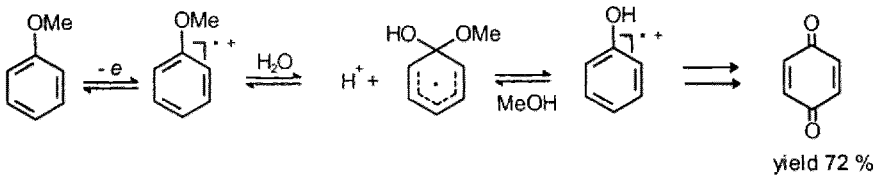
Footnotes: Route a, acetonitrile and tetraethylammoniun cyanide;
Route b, aqueous sodium cyanide and dichloromethane emulsion.

The mechanism for replacement of a methoxyl group by cyanide in these reactions follows Scheme 6.7. The radical-cation reacts with cyanide ion at the point of highest positive charge density. Oxidation of the radical so formed to the carbonium ion is followed by elimination of proton and formaldehyde [79]. The elimination step is analogous to the conversion of cyanhydrins to the carbonyl compound and cyanide ion in basic solution.



Scheme 6.7. Oxidation of 1,4-dimethoxybenzene in the presence of cyanide ions.

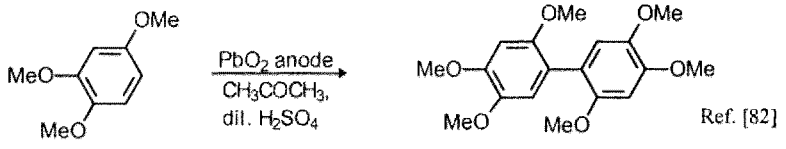
Anodic oxidation of methoxybenzenes in aqueous sulphuric acid also leads to loss of the methoxy substituent, this time through *ipso*-substitution on the radical-cation by water. Anisole and 4-methoxyphenol are both converted to quinone [81]. The elimination of methanol is catalysed by protons by the mechanism illustrated in Scheme 6.8. Diphenyl derivatives have also been isolated from oxidation of some methoxybenzenes. They arise through the competitive reaction involving a



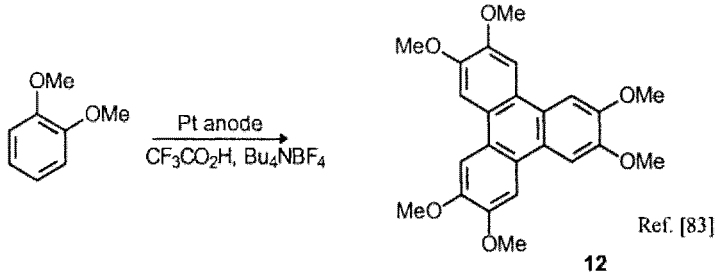
Scheme 6.8. Oxidation of anisole to quinone at a lead dioxide anode in dilute sulphuric acid.

radical-cation and a molecule of the substrate. This reaction can be observed under pulse-radiolysis conditions with very dilute solutions of the radical-cation (p. 191). Because in the low concentrations used there, further oxidation steps are negligibly slow.

Anodic oxidation of 1,2,3-trimethoxybenzene in acetone containing dilute sulphuric acid gives 2,6-dimethoxybenzoquinone but in contrast 1,2,4-trimethoxybenzene affords the dehydrodimer **11** in good yield [82]. Dehydrodimerization becomes an important process in the oxidation of methoxybenzenes in dichlo-



11 Yield 85 %

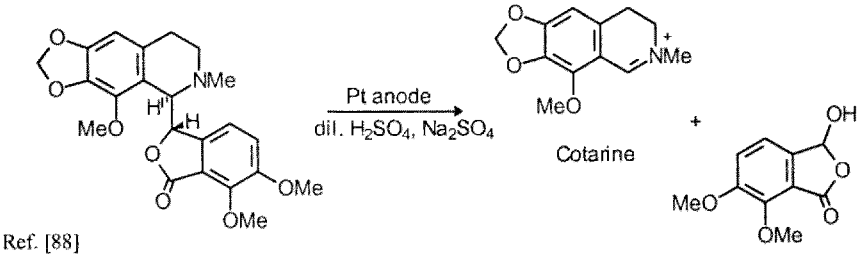


12

romethane – trifluoroacetic acid. Preparation of the dimer can be achieved provided the reaction is carried to low conversion so as to avoid over oxidation of the product [83]. 1,2-Dimethoxybenzene gives a good yield of the triphenylene **12** from anodic oxidation in trifluoroacetic acid [84].

Cleavage of a benzylic carbon-carbon bond is observed from aromatic radical-cations in cases where the resulting fragments are stabilised by substituents. Bond cleavage occurs, for example, with dialkylphenylcarbinols involving loss of the more stable alkyl radical and leaving a phenyl alkyl ketone [85, 86].

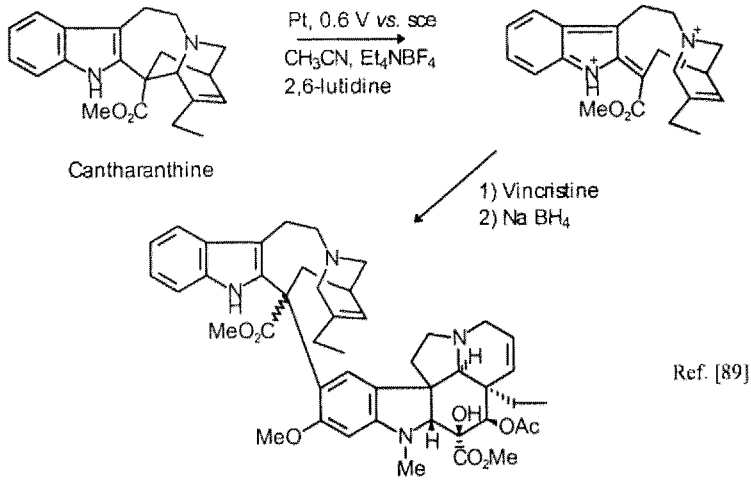
The oxidative cleavage of narcotine to cotarine and opianic acid is an example of this reactivity. This reaction has been known since 1844, using manganese di-



Ref. [88]

Narcotine

oxide and sulphuric acid as the oxidising agent [87]. It can also be carried out electrochemically [88]. A related oxidative carbon-carbon bond cleavage process is used to generate from cantharanthine an intermediate cation which when con-



Ref. [89]

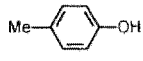
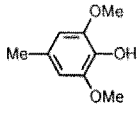
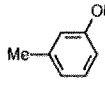
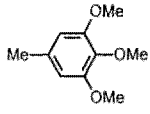
densed with vindoline leads to a synthesis of the important alkaloid anhydrovinblastine [89]. This bond cleavage process can be looked upon as initiated by a radical-cation generated either from the indole residue, or generated from oxidation of the tertiary amine lone pair.

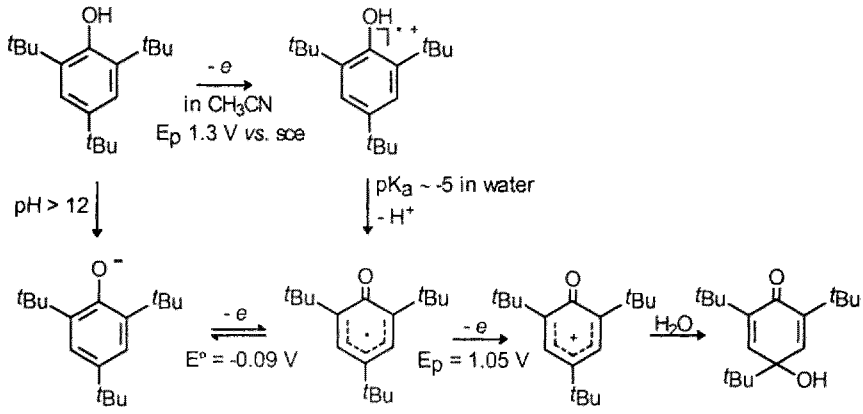
Cleavage of the carbon-oxygen bond in benzyl ethers occurs on oxidation in aqueous acetonitrile. Loss of a benzylic proton from the radical-cation, formation of a hemiacetal and then hydrolysis, initiate the process [90]. Cleavage of the carbon-oxygen bond is not a direct electrochemical step. The 4-methoxybenzyl ether is recommended as a protecting group for alcohols. It can be removed by anodic oxidation to reform the alcohol together with anisaldehyde. Removal of the aldehyde as its bisulphite complex leaves the alcohol in 69-88 % yields [91]. 4-Methoxybenzylcarbonyl chloride is used as an amine-protecting group in peptide synthesis. The group can be removed by anodic oxidation [92]

Oxidation of Phenols

Phenols show a two-electron oxidation wave on cyclic voltammetry in acetonitrile at a less positive potential than for the corresponding methyl ether (Table 6.5) or a related hydrocarbon. Phenol radical-cation is a strong acid with pK_a *ca.* –5 in water [93], so the two-electron oxidation wave for phenols is due to formation of a phenoxonium ion such as **13**, where the complete oxidation process is illustrated for 2,4,6-tri-*tert*-butylphenol. Phenoxide ions are oxidised at considerably less positive potentials than the corresponding phenol. They give rise to a one-electron wave on cyclic voltammetry in aqueous acetonitrile or in aqueous ethanol containing potassium hydroxide. 2,4,6-Tri-*tert*-butylphenoxide ion is reversibly oxidised to the radical in a one-electron process with E° = -0.09 V *vs.* sce. The radical undergoes a further irreversible one-electron oxidation with E_p = 1.05 V *vs.* sce on cyclic voltammetry forming the phenoxonium ion which reacts with water [94].

Table 6.5. Half-peak potentials from cyclic voltammetry of phenols and methoxybenzenes in acetonitrile, $LiClO_4$, scan rate 100 mV s^{-1}. Ref. [95]

Substrate	$Ep_{½}$ / V *vs.* sce	Substrate	$Ep_{½}$ / V *vs.* sce
	1.27		0.85
	1.54		1.11

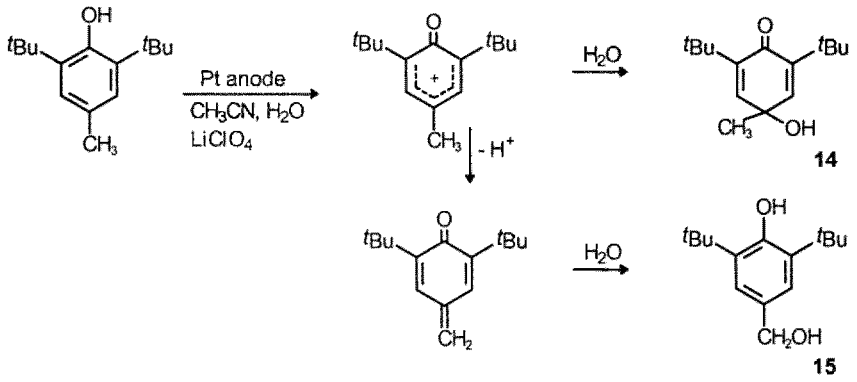


13

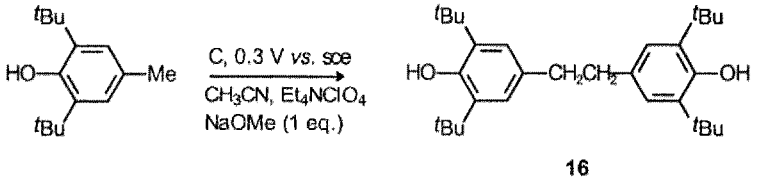
In general, the oxidation of a phenol in a solution at high pH will generate the phenoxy radical in a reversible process. The anode potential for this process becomes more positive as the pH falls due to the equlibrium between phenol and phenoxide. Oxidation of this phenoxy radical occurs at more positive potentials and eventually these two processes will merge to a single two-electron wave. The rate of these processes is limited by the rate of ionisation of the phenol. Finally at low pH values the direct oxidation of the phenol, initially forming the radical-cation, will become the dominant process [96]. The conditions for electrochemical oxidation of phenols can be adjusted to generate either the phenoxy radical or the phenoxonium ion intermediate. Oxidation of phenols is also carried out using a chemical oxidant, an iron(III) – iron(II) couple being frequently used. The iron system has $E^\circ \sim 0.5$ V *vs.* sce in dilute hydrochloric acid while ferricyanide – ferrocyanide has $E^\circ \sim 0.2$ V *vs.* sce in water, so these oxidising agents will generate the phenoxy radical.

Isolable products related to the radical or the phenoxonium ion are obtained by oxidation of phenols heavily substituted by electron donating substituents. 2,4,6-Triphenylphenol is taken as an example. In acetonitrile containing tetramethylammonium hydroxide, oxidation of the phenolate ion at a rotating graphite electrode shows a reversible one-electron process with $E_{½} = 0.166$ V *vs.* sce. The radical is formed and undergoes rapid and reversible dimerization. In acetic acid containing sodium acetate, the phenol shows a reversible two-electron process with $E_{½} = 0.741$ V *vs.* sce in which the phenoxonium ion is generated. The cation rapidly and reversibly reacts with acetate ion to form a covalent ester [97]. The phenoxonium hexachloroantimonate is generated as a crystalline solid from reaction between this ester and antimony pentachloride [98].

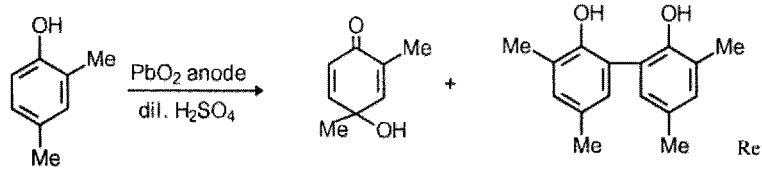
Reactions of the phenoxonium ion with nucleopiles are illustrated by the oxidation of 2,6-di-*tert*-butyl-4-methylphenol [99, 100]. At high water concentrations in



acetonitrile, the dienone **14** is the major product whereas at low water concentrations more of the benzyl alcohol **15** is formed. Hydroxylation always occurs *para* to the original phenolic substituent. The dimer **16** is obtained on oxidation of the phenoxide in acetonitrile [101]. Under these conditions, the phenoxy radical is formed and abstracts a benzylic hydrogen atom from another molecule of phenol. Dimerization of the resulting benzyl radicals generates **16**.



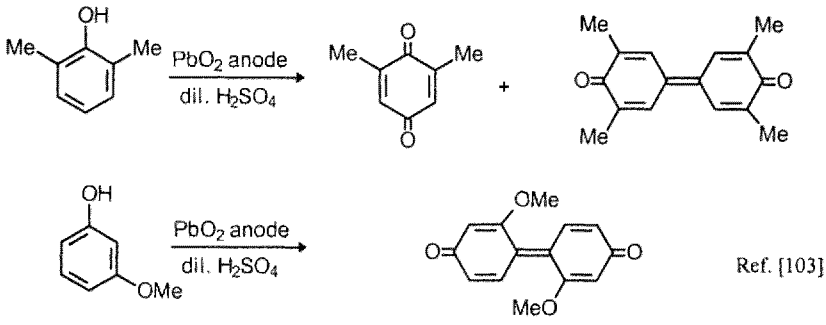
Reactions of phenols are frequently carried out at a lead dioxide anode in dilute aqueous sulphuric acid. A phenoxonium ion is the reactive intermediate. In dilute solution, the major reaction is *para*-hydroxylation of the phenol [100]. Phenols



Ref. [100]

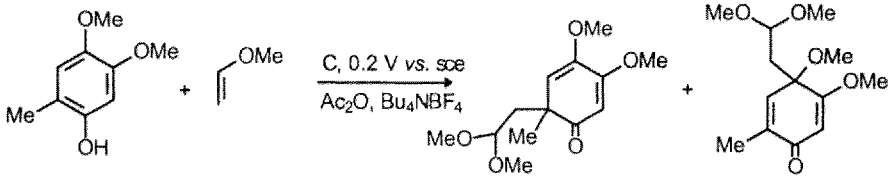
with only hydrogen in the 4-position are converted to the 1,4-quinone. The reaction

is used for the manufacture of some quinones and hydroquinones [102]. A competing reaction in a concentrated solution of the phenol is attack of the phenoxonium ion on a molecule of the phenol, leading to the phenol dehydrodimer or to a diphenoquinone where the starting phenol has no *para*-substituent [100, 103]. Diphenoquinones are the usual products in a less nucleophilic solvent mixture [104].



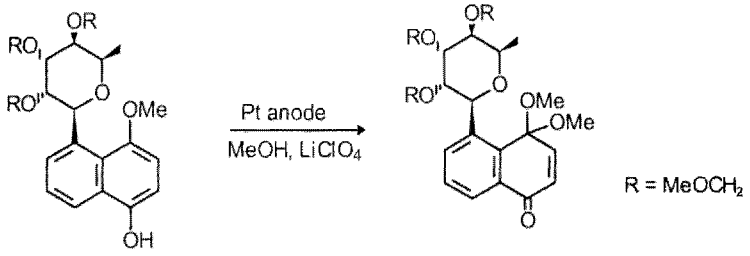
Ref. [103]

The phenoxonium ion derived from **17** is substituted in both *ortho*- and *para*-positions by electron rich alkenes [105] and also by furan



17

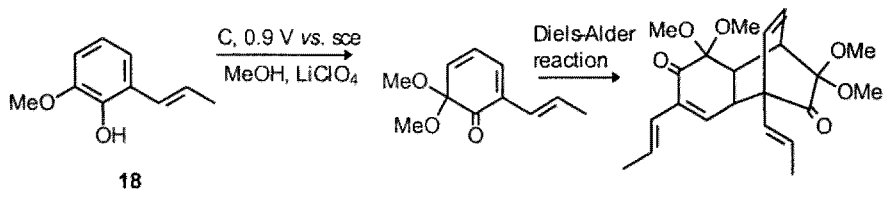
Oxidation of 4-methoxyphenols in methanol is a route to 4,4-dimethoxycyclohexa-2,5-dienones [106]. An example of this process is given for a naphthalene derivative [107]. A similar reaction of 2-methoxyphenols in methanol gives the



R = $MeOCH_2$

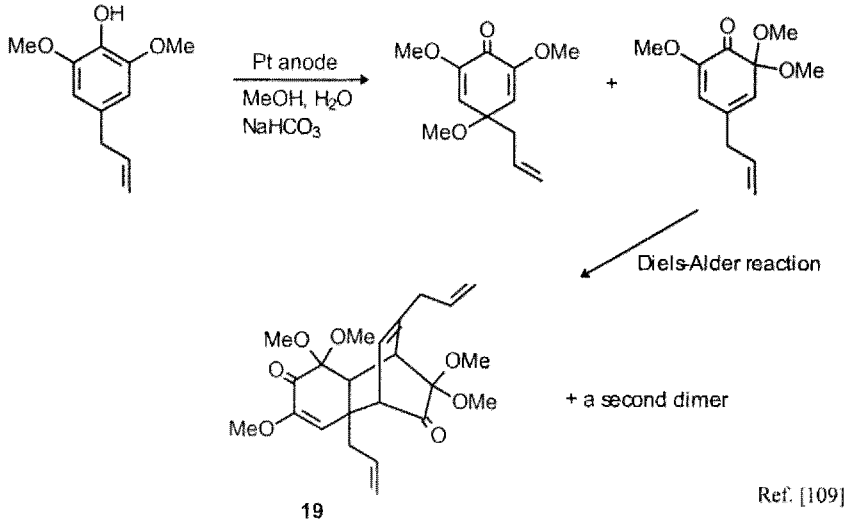
Ref. [107]

2,2-dimethoxycyclohexa-3,5-dienone. These dienes readily undergo the Diels-Alder reaction with a second molecule as illustrated by the oxidation of **18** [108].



18

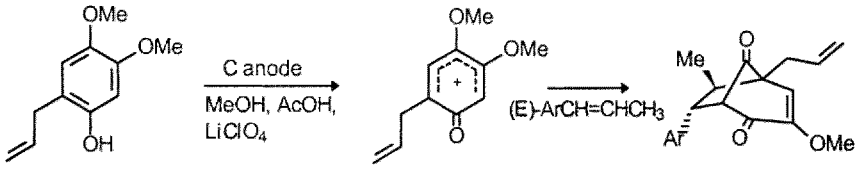
Electrochemical oxidation of 2,6-dimethoxy-4-allylphenol in aqueous methanol buffered with sodium hydrogen carbonate gives similar amounts of 2- and 4-methoxy substitution products. The 2-methoxylated product readily undergoes a Diels-Alder reaction with itself. The dimer **19**, the natural product asatone, is found in some 1 % yield and most of the 2-methoxylated product is lost by addition of the allyl alkene bond across the diene system of a second molecule [109].



19

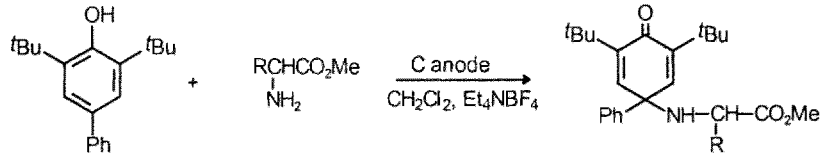
Ref. [109]

The anodic oxidation of 4-methoxyphenols in acetic acid effectively stabilises the phenoxonium ion, in an equlibrium with the acetoxylation product. This allows an intermolecular [5 + 2] 6π-cycloaddition processes with some alkenes [110]. The cycloaddition process has been used very successfully in the synthesis of a number of natural products [111]. The rate of cycloaddition is sensitive to substituents on the alkene bond and in unfavourable cases other reactions of the phenoxonium ion predominate.

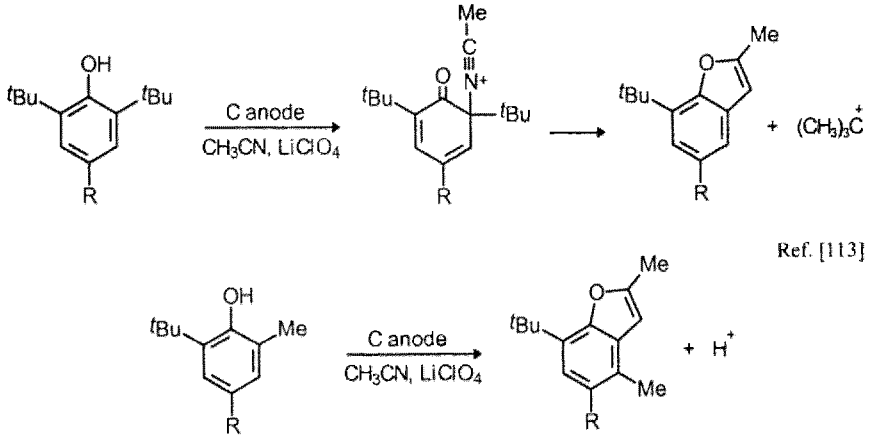


Ref. [110] Ar = 3,4-methylenedioxyphenyl 81 %

Oxidation of 2,6-di-*tert*-butyl-4-phenylphenol **20** in the presence of an amino acid ester as the nucleophile leads to the formation of amine protected amino acid derivatives. The protecting group is stable towards bases and can be removed ei-

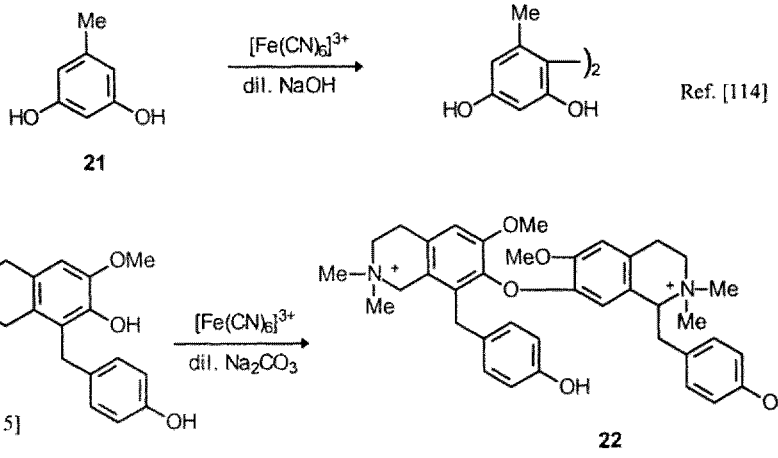


ther by acid catalysis or hydrogenolysis [112]. Racemization of the amino acid is not encountered during the overall process. In the absence of any other nucleophile the phenoxonium ion will react with acetonitrile solvent. Addition of the nucleophile is reversible and most likely occurs at both 2- and 4-positions. These reactions with acetonitrile lead finally to the irreversible expulsion or rearrangement of one *ortho*-alkyl group [113].

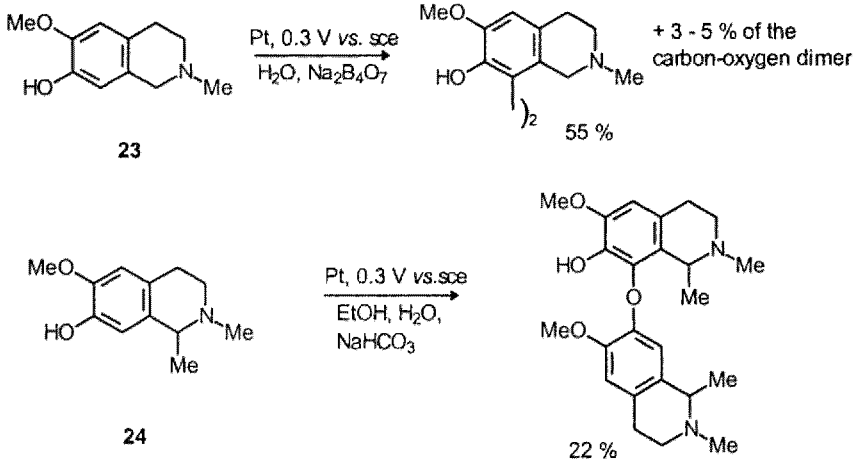


Ref. [113]

The intermolecular coupling of phenols is used extensively in what are believed to be biomimetic alkaloid syntheses. Aqueous solutions of iron(III) salts are most frequently used as the oxidising agent and the dimerization process must involve phenoxy radicals. Examples are the dimerization of orcinol **21** [114] and the formation of bis-benzyltetrahydroisoquinolines **22** [115].

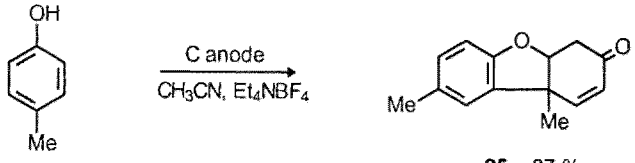


The electrochemical route also achieves intermolecular coupling of phenolic tetrahydroquinolines. For the relatively unhindered substrate **23**, coupling occurs by



carbon-carbon bond formation, but even moderate steric hindrance as in **24** leads to carbon-oxygen bond formation [116, 117]. These processes involve phenoxy radical intermediates. Electrochemical oxidation of **24** in strongly alkaline solution, using methanolic sodium methoxide, gives only the carbon-carbon dimer [118].

Parallel oxidations either electrochemically [117] or with iron(III) salts [119] in water have also been made using 1-alkyl-7-hydroxy-6-methoxytetrahydroisoquinoline salts as substrates. 4-Methylphenol is oxidised at a carbon anode in alkaline solution to give Pummerer's ketone **25** by the *ortho-para* coupling of two phenoxy radicals [120].



25, 37 %

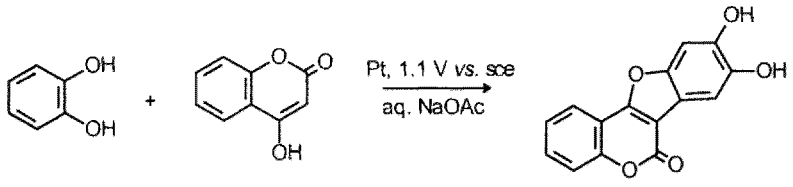
1,2-Benzoquinones are conveniently prepared in solution by the anodic oxidation of catechols. 1,2-Quinones are unstable in solution but they have a sufficient lifetime for the redox process to be reversible at a rotating disc electrode. Reaction involves two electrons and two protons and the half-wave potential varies with pH at 25 °C according to Equation 6.1. Some redox potentials for catechols and hydroquinones are given in Table 6.6.

$$E_{½} = E° - 0.059pH \qquad \text{Eq 6.1}$$

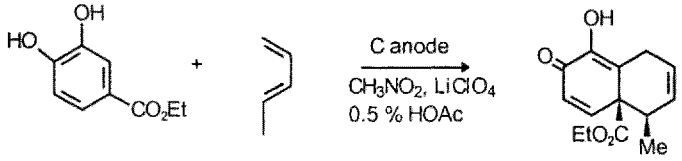
Table 6.6. Reversible potentials for hydroquinone – quinone systems in aqueous solution

Substrate	$E_{½}$ / V *vs.* sce		Ref.
	pH 6.27	pH 0	
Catechol	0.167	0.551	[121]
4-Methylcatechol	0.135	0.509	[121]
3-Methylcatechol	0.120	0.504	[121]
3,4-Dihydroxy benzoic acid	0.205	0.589	[121]
Hydroquinone	0.078	0.474	[122]
Methylhydroquinone	0.022	0.418	[122]
2,5-Dimethylhydroquinone	-0.068	0.365	[122]
2,6-Dimethylhydroquinone	-0.064	0.361	[122]

Anodic oxidation of catechols enables the unstable quinones to be prepared and reacted *in situ*. Reaction of the 1,2-quinone with a 1,3-dicarbonyl compound gives a high yield of a benzofuran [123, 124]. Both 1,2- and 1,4-quinones, prepared electrochemically in nitromethane, are efficiently trapped in Diels-Alder reactions with butadienes [125].



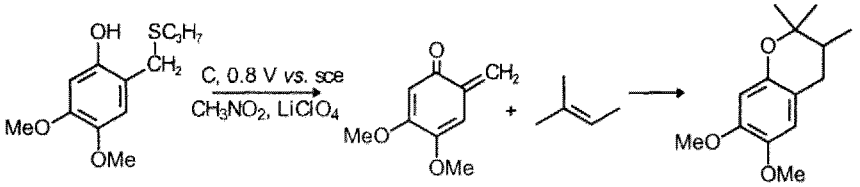
95 % Ref. [123]



Ref. [125]

92 %

ortho-Quinone methides are formed by the anodic oxidation of 2-hydroxybenzylsulphides. These unstable intermediates can be trapped by cycloaddition to an alkene [126]. The methide arises by loss of both a proton and a sulphide radical from the substrate radical-cation as indicated for compound **26**.



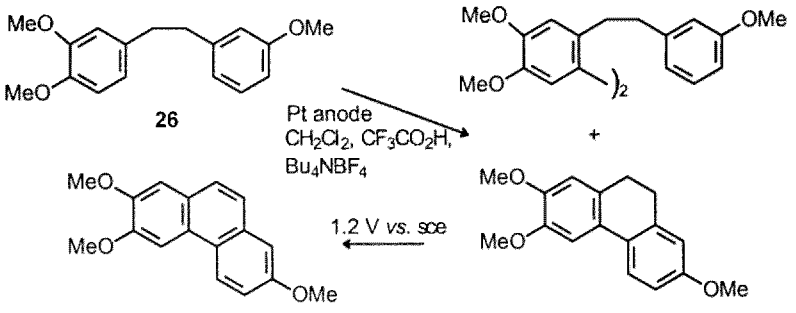
26

Intramolecular Cyclization Processes

Intramolecular oxidative coupling between two aromatic rings bearing electron-donating substituents is an important ring closure process. The intermolecular version, in which the carbon-carbon bond-forming step involves a radical-cation and an arene, has already been discussed (p. 191). When the two arene rings are equivalent as in **27**, the mechanism of the coupling step is not so clear because first one and then the second arene ring can be converted to the radical-cation at nearly the same electrode potential. Coupling can be of either the radical-cation substrate or the radical-cation radical-cation type depending on factors, which alter the rates of already fast reactions [127]. For simplicity, most of the intramolecular reactions

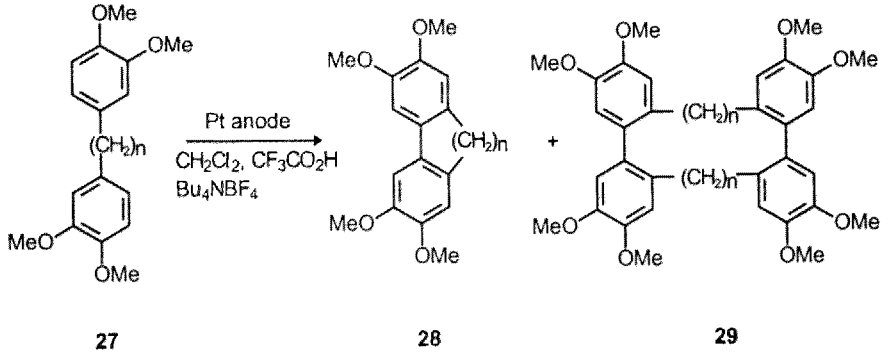
are treated here as involving a radical-cation, arene carbon-carbon bond-forming step.

The existence of two competing bond-forming processes is however well illustrated by the reactions of **26**. This substrate undergoes two consecutive one-electron oxidation steps at 1.21 and 1.62 V *vs.* sce, because of the differing substi-



tution patterns in the two benzene rings. Oxidation at the potential of the first step gives mainly the dehydrodimer while production of the cyclization product is favoured by more positive oxidation potentials. An intermolecular radical-cation arene process is preferred whereas at potentials giving a radical-cation from both aromatic rings, cyclization by a radical-cation radical-cation reaction occurs [128]. The dihydrophenanthrene is itself dehydrogenated at 1.21 V *vs.* sce to form the trimethoxyphenanthrene.

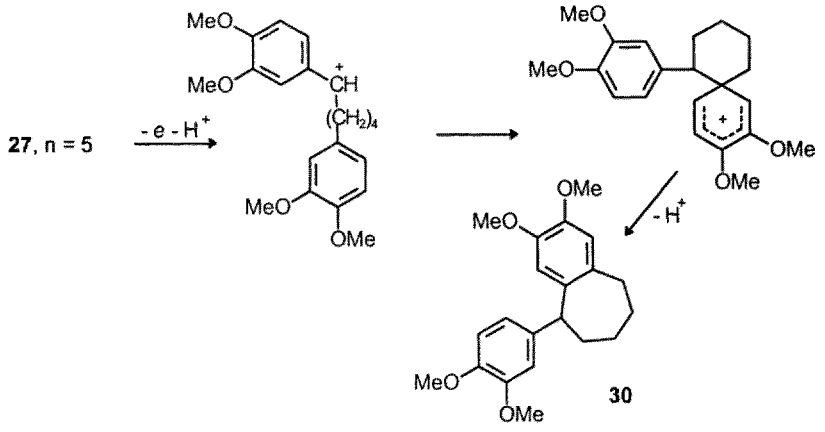
Oxidation of the series of α,ω-diarylalkanes **27** gives both the cyclised product **28** and a dehydrodimer type product **29** depending on the length of the alkane



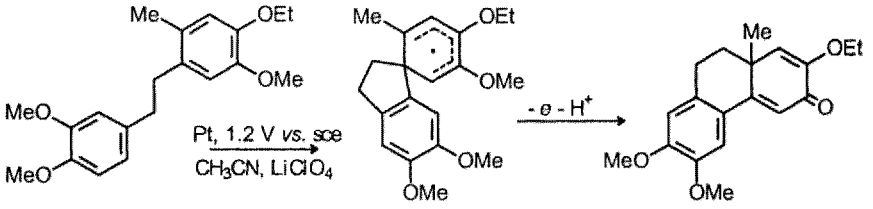
27 **28** **29**

chain [128, 129]. Good yields of cyclized product are obtained for n = 1 to 4. Where n = 2, the initially formed product is further oxidised to the phenanthrene level. These, and other results, indicate that initial cyclization to a 5- or 6-member-

ed intermediate is most favoured and so the conversion of **27**, n = 5 to **30** probably proceeds through a spiro 6-ring intermediate, followed by rearrangement. Com-



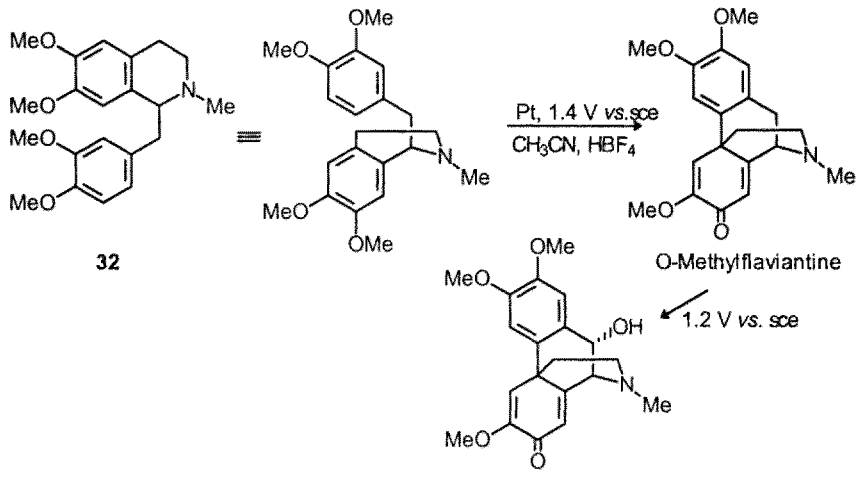
pound **31** shows reaction through a 5-membered carbocyclic intermediate. The final product is obtained by oxidation of the intermediate to a delocalised carbonium ion, followed by a skeletal rearrangement [130].



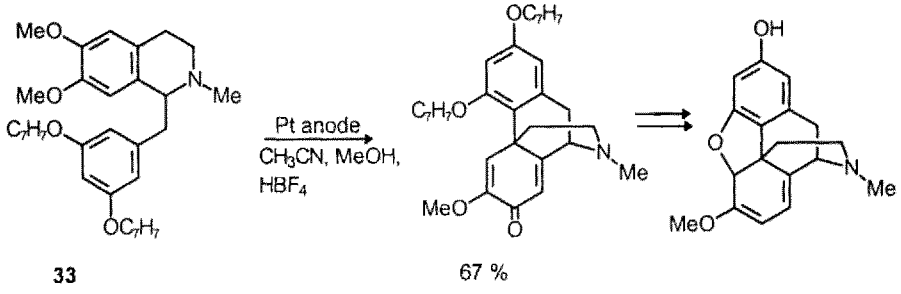
31

Oxidative cyclization has been applied very successfully to the benzyltetrahydroisoquinoline group of alkaloids. Laudanosine **32** affords O-methylflavinantine on anodic oxidation by carbon-carbon bond formation at the radical-cation level as indicated on the laudanosine structure [131, 132]. Reaction under acid conditions give the best yields because the amine function is protonated and so protected from oxidation [132, 133]. In many cases the nitrogen is protonated at the pH of a sodium hydrogen carbonate buffer used as electrolyte [120]. Further oxidation of O-methyl-flavinantine leads to hydroxylation at the benzylic position [133]. Non-protonated laudanosine is oxidised at lower potentials with loss of one electron from the nitrogen lone-pair. In concentrated solutions the amine radical-cation accepts an electron from the aromatic ring of a second laudanosine molecule and the

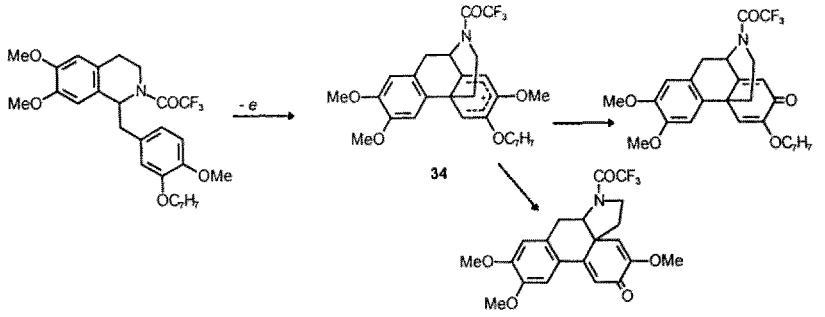
overall product is again O-methylflavinanthine. In dilute solutions, the amine radical-cation fragments a carbon-carbon bond (see p. 202) to give the dimethoxybenzyl radical and a 3,4-dihydroisoquinolinium ion [134].



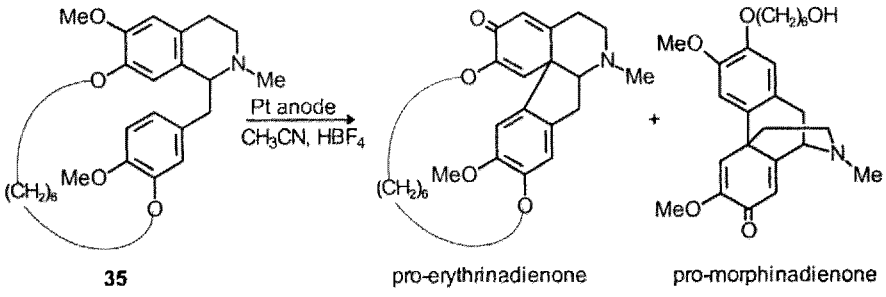
A number of alkaloids with the morphinadienone skeleton have been synthesised by this route starting with the appropriately substituted benzyltetrahydroisoquinoline [135]. The substitution pattern in morphine however precludes a synthesis by this route. A close approach to the morphine skeleton begins with substrate **33** [136].



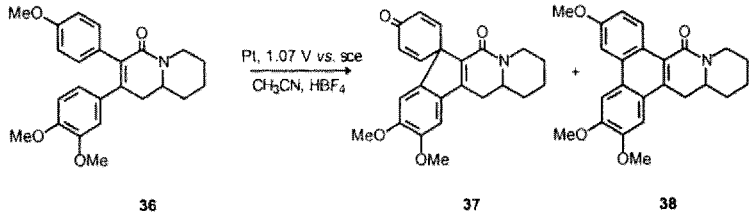
The use of N-trifluoroacetyl in place of the protonated N-methyl function in these oxidative cyclization reactions has been explored. Generally these substrates lead to products of the O-methylflavinanthine type. In one instance, the delocalised carbonium ion intermediate **34** was found to undergo a competitive rearrangement when lack of a nucleophile in solution led to a slow demethylation step [137].



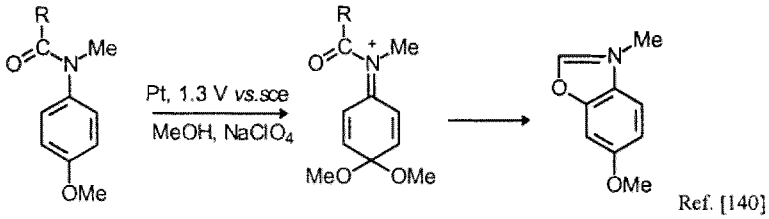
Oxidative carbon-carbon bond formation from laudanosine derivatives generally favours a 6-membered ring. Severe steric constraints result in exceptions to this rule. Oxidation of the bridged ether derivative **34** results in carbon-carbon bond formation to form a 5-membered ring product and this process has been used for one stage in the synthesis of erythrina alkaloids [138]. Some of the morphinadienone system is also formed, in spite of the steric constraint imposed by the ether-bridge.



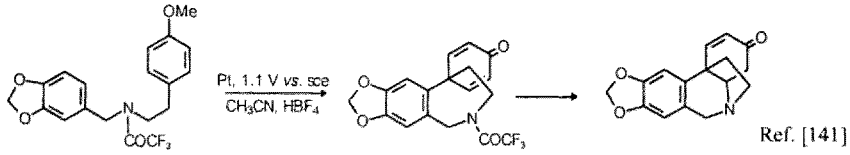
A new 5-membered ring product **37** is formed by anodic oxidation of **36** together with the 6-ring compound **38**. It is likely that **38** is formed by rearrangement of a 5-ring intermediate, in competition with loss of the methyl group to give **37**. A related rearrangement of **37** to a demethylated **38** occurs by the action of protons [139].



Cyclization to a 5-membered ring is observed during the oxidation of 4-methoxyanilides in methanol. In these cases the *gem*-dimethoxy compounds are intermediates [140]. Anodic oxidation of the more flexible structure **39** leads to a 7-membered ring structure and further steps afford (±)-oxocrinine [141]. Further examples of this 7-membered ring generation use tetramethoxy analogues of **39** [142].



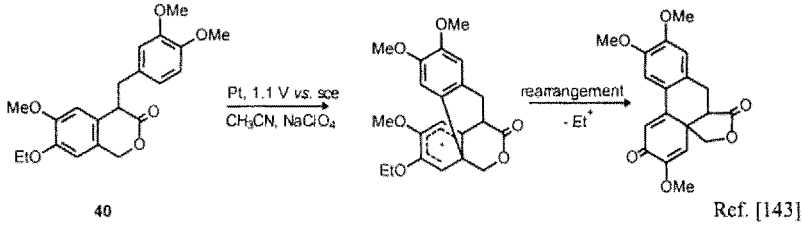
Ref. [140]



39 (±)-oxocrinine

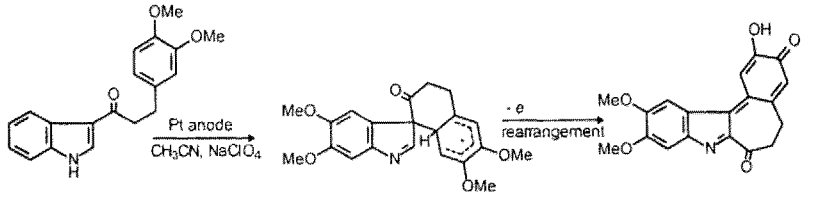
Ref. [141]

Oxidative ring closure of other heterocyclic analogues of laudanosine generally favours 6-membered ring formation [143, 144]. Rearrangement of carbonium ion intermediates to a structure with less steric strain, as in the reaction of **40**, is sometimes observed. Formation of a conjugated system as in the reaction of **41** is also a driving force for rearrangement [145].



40

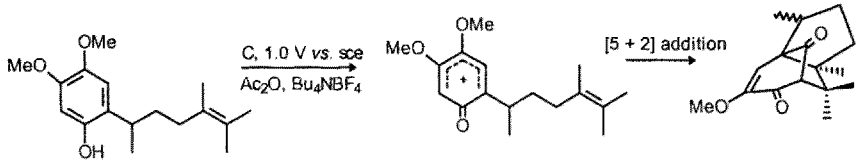
Ref. [143]



41

Ref. [145]

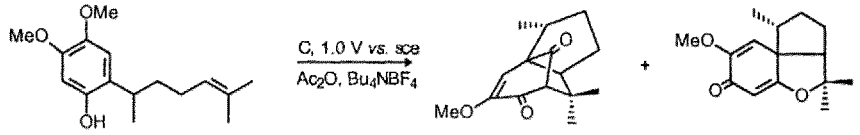
The delocalised carbonium ion formed by the anodic oxidation of 3,4-dimethoxyphenol will take part in intramolecular [5 + 2] cycloaddition with an attached alkene [146, 147]. This step has been used in the synthesis of a number of complex diterpenes. Acetic anhydride, containing acetic acid, is the best solvent for these



41

Ref. [148]

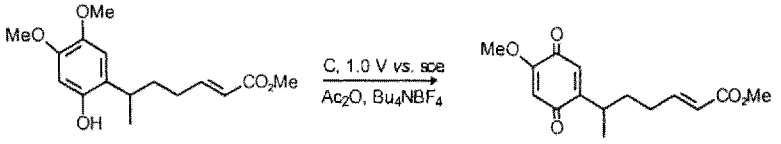
processes. The phenyl acetate is the species undergoing oxidation and an acylonium ion is lost from the initially formed radical-cation, leaving a delocalised radical which is further oxidised to the carbonium ion. The cycloaddition step is favoured by the presence of electron donating substituents on the alkene **41**. Electron donation substituents as in **42** can however also promote electrophilic addition of



42 [5 + 2] addition electrophilic addition

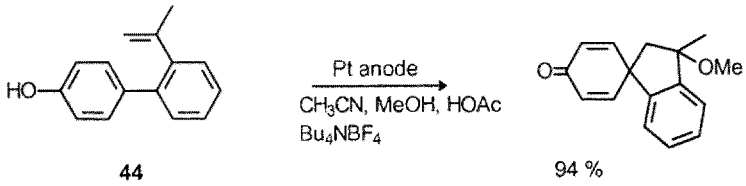
Ref. [148]

the carbonium ion onto the alkene group and where the alkene is an enol ether function, electrophilic addition becomes the major reaction [146, 148]. Electron withdrawing substituents as in **43** strongly disfavour these addition processes and oxidation of this substrate yields the corresponding 1,4-quinone [149].

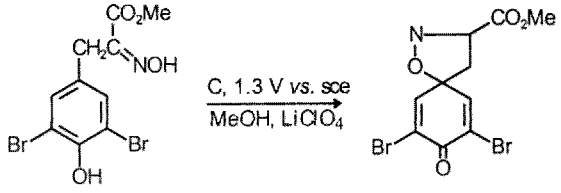


43

Electrophilic addition to the alkene with the formation of a 5-membered ring occurs on anodic oxidation of **44** [150]. Reaction of the intermediate delocalised carbonium ion with the adjacent hydroxyl function in **45** also results in the formation of a 5-membered ring [151].



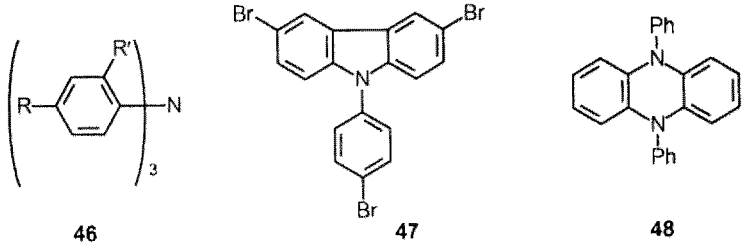
44 94 %



45 100 %

Oxidation of Anilines

One-electron oxidation of aniline derivatives gives a radical-cation in which the unpaired electron is distributed over both the nitrogen atom and the aromatic system. The further reactions of these intermediates more resemble those of aromatic compounds than of aliphatic amines. Some of the radical-cations are very stable in solution: Wurster's blue, prepared by oxidation of tetramethyl-1,4-phenylenediamine [152], and Wurster's red from N,N-dimethyl-1,4-phenylenediamine [153] have been known since 1879. They were recognised as radical-cations by Michaelis [154].



46 **47** **48**

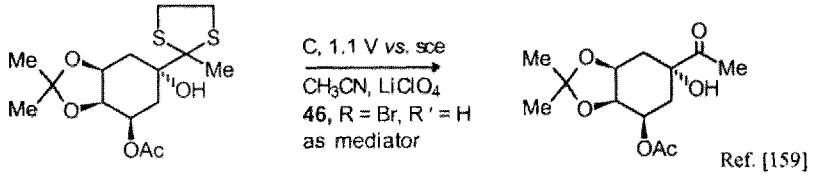
Anodic oxidation of triphenylamine gives the radical-cation which is rapidly converted to the dehydrodimer, tetraphenylbenzidine. A *para*-substituent prevents this dimerization and gives radical-cations very stable in acetonitrile solution against nucleophiles [155]. This class of compound was first prepared as the per-

chlorate. Usually now, the hexachloroantimonate salts are prepared by the action of antimony pentachloride [156, 157]. Oxidation potentials for some triphenylamines and related compounds are given in Table 6.7.

Table 6.7. Reversible potentials for amine radical-cation systems in acetonitrile

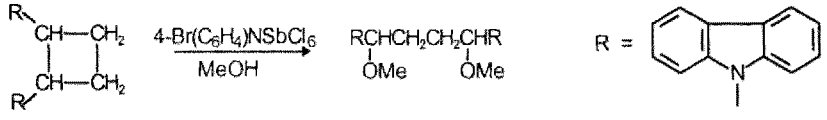
Substrate	E° / V *vs.* sce	Ref.
46, R = OMe, R′ = H	0.52	[157]
46, R = Br, R′ = H	1.06	[157]
46, R = R′ = Br	1.50	[157]
47	1.48	[157]
48	-0.11	[158]

Triarylamines are used as electron transfer agents in mediated oxidation processes. They promote oxidations at a lower anode potential and prevent fouling of the electrode surface, which can occur when the substrate is oxidised directly. Removal of the dithioacetal protecting group is achieved using tris(4-bromophenyl)amine as electron transfer agent in acetonitrile. Application to the deprotection of **49** illustrates how the reaction can tolerate a number of other functional groups [159]. Mediated oxidation of methylbenzenes in methanol causes



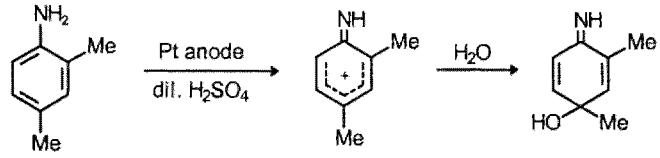
49 90 % Ref. [159]

side chain methoxylation and the process yields the benzoic acid *ortho*-ester [65]. Ring opening of the cyclobutane ring in **50** occurs by electron transfer to tris(4-bromophenyl)amine radical-cation [160].



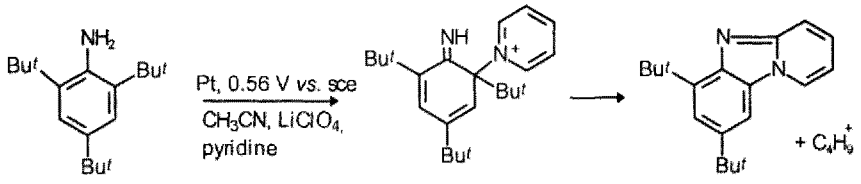
50

Anodic oxidation of phenylamines is irreversible and involves the loss of two electrons and a proton to give a delocalised carbonium ion, which reacts further. Oxidation of 2,4-dimethyl-aniline to give **51** illustrates the process [161]. Interac-



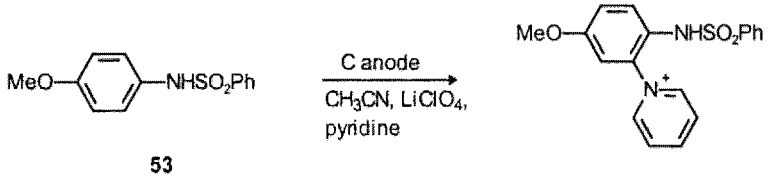
51

tion between the carbonium ion and pyridine is illustrated by the reaction of 2,4,6-tri(*tert*-butyl)aniline The intermediate is trapped and subsequent loss of a *tert*-butyl carbonium ion followed by cyclization leads to **52** [162]. Excess of the aniline can



52

also react with the carbonium ion, so oxidation of benzenesulphonanilides is likely to give a cleaner reaction between the delocalised carbonium ion and an added nucleophile. This process is illustrated by the pyridination of **53** [163].

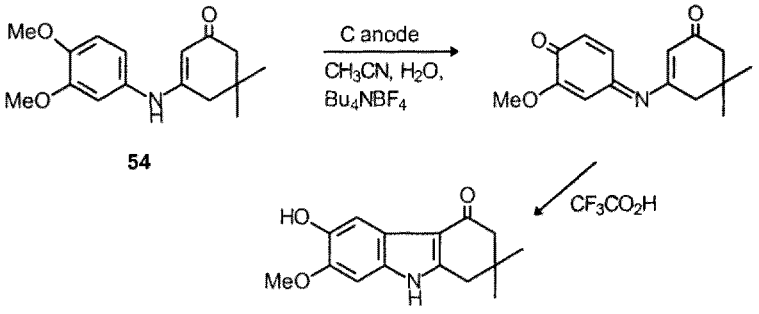


53

In the presence of water, oxidation of 4-methoxyaniline gives the quinone imine. The example **54** is converted by oxidation and ring closure to the tetrahydrocarbazole [164].

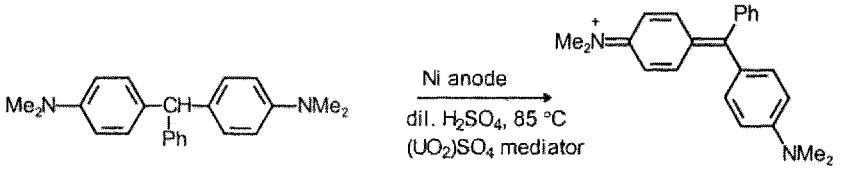
Aniline itself undergoes intramolecular coupling and further oxidation to give aniline black. Poly(aniline) can be deposited as a thin coherent film on the anode by continuously cycling the potential between –0.2 and 0.8 V *vs.* sce [165]. Oxidation of aniline using manganese(II) - manganese(III) as mediator in dilute sulphuric

acid is an old process for the formation of 1,4-benzoquinone [166]. Here the 1,4-linked polymer is oxidised to a poly(imine) and then hydrolysed to the quinone.



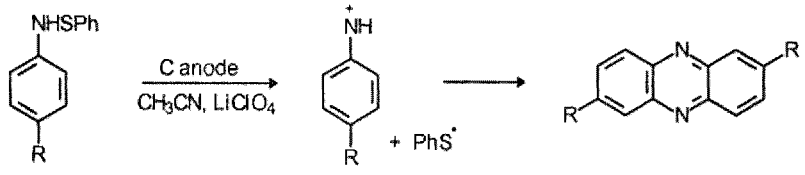
54

Derivatives of N,N-dimethyl-4-methylaniline afford the iminomethine on anodic oxidation. This reaction allows the conversion of leucocompounds to the triphenylmethane dye, such as Malachite Green **55** [167].



55

Anodic oxidation of benzenesulphenanilides **56** leads to cleavage of the nitrogen-sulphur bond in the radical-cation with the formation of a nitrenium ion, which deprotonates to the nitrene. The intermediate dimerises to a phenazine [168].



56

Oxidation of Aromatic Heterocycles

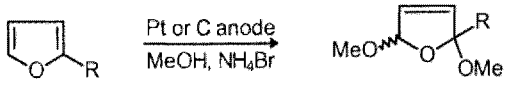
Five-Membered Rings

Table 6.8. Half-wave potentials for the oxidation of 5-membered heterocyclic rings at a rotating platinum anode in acetic acid, sodium acetate

Substrate	$E_{½}$ / V *vs.* sce	Ref.
Thiophene	1.91	[32]
Furan	1.70	[32]
2,5-Dimethylfuran	1.20	[32]
Pyrrole	1.2[a]	[169]

Footnote: (a) E_{pa} on cyclic voltammetry in acetonitrile containing tetraethylammonium fluoroborate.

The electrochemical oxidation of furans has been exploited since 1952 [170]. The usual electrolyte is ammonium bromide in methanol, at – 5 °C, using an undivided cell with either platinum or graphite as anode and a nickel or stainless steel cathode. Reaction involves the anodic generation of bromine, which oxidises the furan to a carbonium ion intermediate that is quenched with methanol. The final reaction product is a 2,5-dihydro-2,5-dimethoxyfuran, found as a 1:1 mixture of stereoisomers. This electrochemical method gives as good or better yields than the direct oxidation of furan by bromine in methanol. It has been applied to a wide range of 2-substituted furans **57** [170, 171, 172]. The process is carried out on a

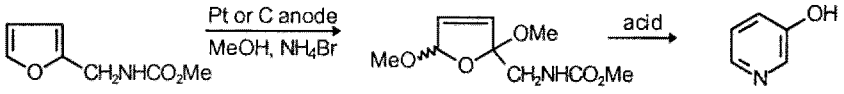


57 R = H, CH_3, CH_2OH, CHO, or CO_2 Me

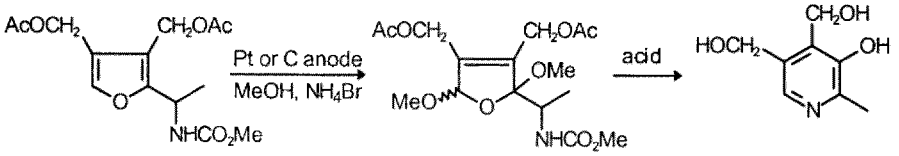
technical scale with furan using a graphite anode in a flow-through cell [173]. The laboratory scale flow-through cell described on p. 284 has also been used for this oxidation. A platinum anode encased in an ion-exchange membrane containing the electrolyte ions can be used for the oxidationof furan in methanol with no added electrolyte [174]. Methoxylation of furans in methanol containing sodium methoxide also occurs but generally lower yields are obtained under these conditions [175].

Furans with bulky α-substituents such as 2-*tert*-butylfuran [176] and 2-acetoxyfuran dimethyl acetal [177] show no effect of steric hindrance and are readily converted to the dihydro-dimethoxy product. 3,4-Substituted furans are also converted to dihydrodimethoxy derivatives [178, 179].

Oxidation of N-acyl-2-aminomethylfurans leads to an intermediate that can be converted by treatment with acid to a 3-hydroxypyridine [180, 181]. Such a transformation is used as one stage in a synthesis of pyridoxine [181, 182].



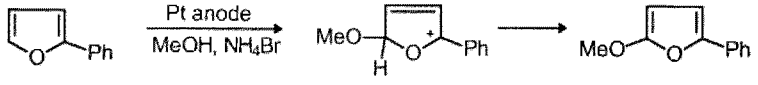
Ref. [180]



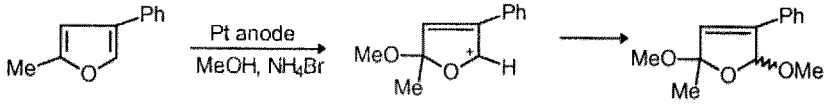
pyridoxine

Ref. [182]

Some furans with conjugating 2- or 3-substituents show abnormal behaviour during oxidation in methanol. Only one methoxy group is introduced after which loss of a proton restores the furan to substituent conjugation. This behaviour is shown by 2- and 3-phenylfurans and by 2-(then-2-yl)furan. 2-Methyl-4-phenyl-



Ref. [176]

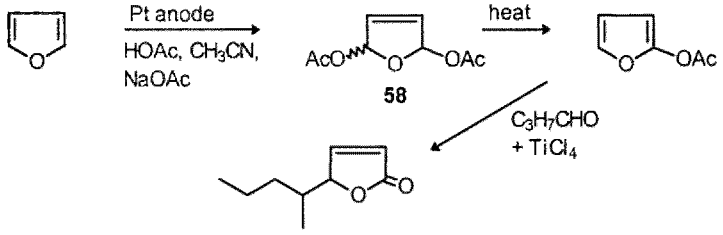


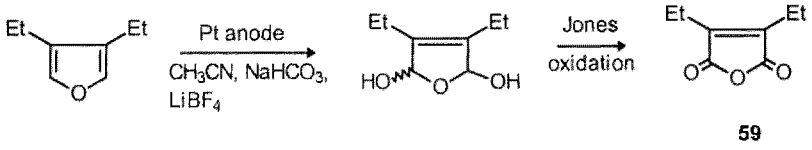
Ref. [183]

furan shows normal behaviour however because proton loss from the intermediate carbonium ion is now blocked [176, 183].

2,5-Dimethylfuran is also oxidised in methanol containing sodium cyanide to a mixture of the stereoisomers of 2-cyano-2,5-dihydro-5-methoxy-2,5-dimethylfuran in low overall yields [184].

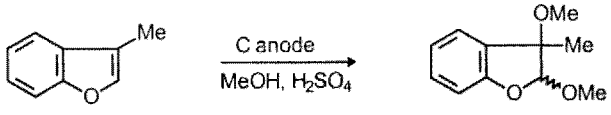
Anodic oxidation of furans in acetic acid leads to the 2,5-diacetoxy-2,5-dihydrofuran **58** [185, 186]which is readily converted to 2-acetoxyfuran. This has proved a valuable intermediate for the synthesis of butenolides [187]. Reactions in moist acetonitrile yield the 2,5-dihydro-2,5-dihydroxyfurans which can be oxidised to the maleic anhydride **59** [188]. Oxidation of furan-2-carboxylic acid in methanol and sulphuric acid is a route to the ester of α-ketoglutaric acid [189].





59

Benzofurans are oxidised at a carbon anode in methanol at – 10 °C to the 2,3-dihydro-2,3-dimethoxybenzofuran [190].



Ref. [190]

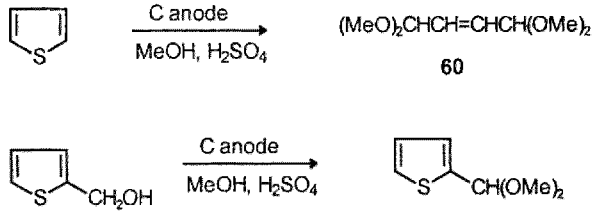
Technically important electrochemical reactions of pyrrole and thiophene involve oxidation in non-nucleophilic solvents when the radical-cation intermediates react with the neutral molecule causing polymer growth [169, 191]. Under controlled conditions polymer films can be grown on the anode surface from acetonitrile. These films exhibit redox properties and in the oxidised, or cation doped state, are electrically conducting. They can form the positive pole of a rechargeable battery system. Pyrroles with N-substituents are also polymerizable to form coherent films [192]. Films have been constructed to support electroactive transition metal centres adjacent to the electrode surface forming a modified electrode.

Pentaphenyl- and 2,3,4,5-tetraphenyl-pyrrole show reversible one-electron oxidation to the radical-cation in acetonitrile with E° = 0.86 and 1.008 V *vs.* sce re-

spectively. The radical-ion species have been characterised by uv- and esr-spectroscopy [193, 194].

In methanol, the radical-cation intermediates from oxidation of thiophenes and N-methylpyrroles can be trapped to give low molecular weight products. Reactivity resembles that of furan but with additional consequences because of the properties of thioethers and amines.

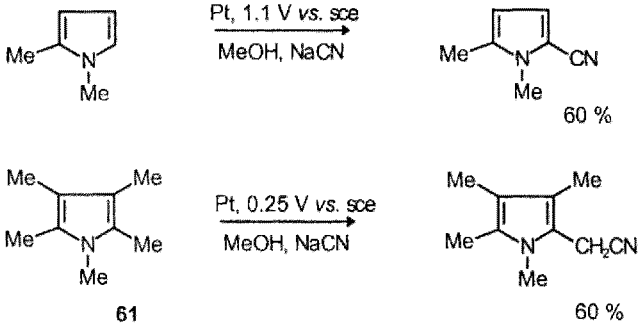
Thiophenes are oxidised in methanol containing sulphuric acid, using an undivided cell, to give acetals with loss of the sulphur as sulphur dioxide. Thiophene itself affords the diacetal **60** [195] and related reactions are found for 2-, 3- and 2,5-substituted thiophenes [196, 197]. Reaction of 2-hydroxymethylthiophene does



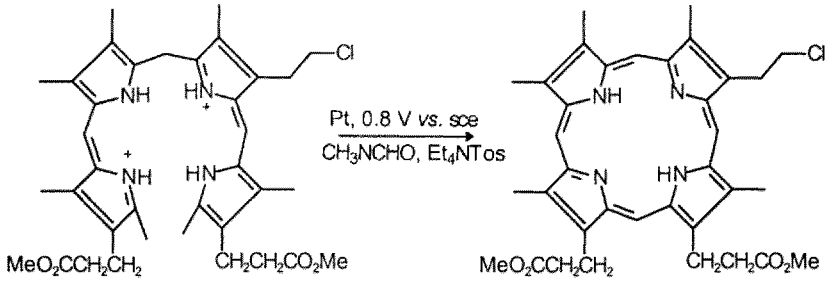
not follow this rule. Here, reaction involves loss of a proton from the radical-cation to give the benzylic-type radical, which is further converted to 2-thiophenealdehyde dimethyl acetal [198].

Benzothiophenes retain the sulphur atom during anodic oxidation and give 2,3-dihydro-2,3-dimethoxy products [199] analogous to the oxidation of benzofuran.

Formation of low molecular weight products from oxidation of N-methylpyrrole is most successfully achieved with methanol and sodium cyanide as electrolyte. The radical-cation is captured by cyanide ion and 2-cyanopyrroles are formed in good yields when a 2-position in the substrate is vacant. In this reaction, a carbon-carbon bond is formed at the site of highest charge density. When both 2- and 5-positions are blocked by a methyl group, the intermediate radical-cation loses a proton to give the benzylic-type radical. Further reaction leads to cyanation on the 2-methyl group as in **61** [200].

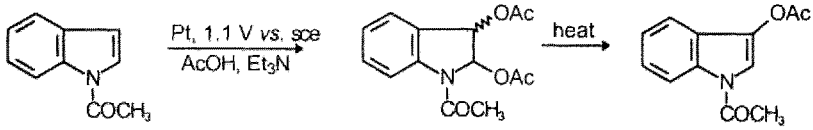


Cyclization of the tetrapyrrole **62** to a porphyrin, with expulsion of one methyl group, is achieved in moderate yields by electrochemical oxidation in a divided cell [201].



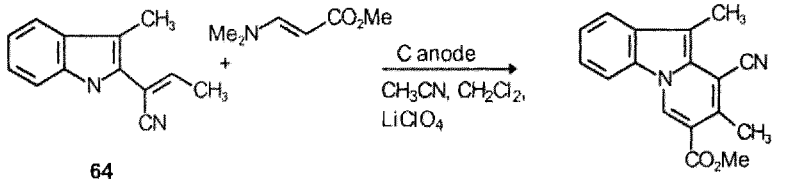
62 40 %

Electrochemical oxidation of indole [202] and N-methylindole [203] in acetonitrile gives rise to dimers and trimers. These are oxidised further to polymers. Oxidation of N-acetylindoles in acetic acid results in acetoxylation of the heterocyclic ring. Indole yields **63** as a mixture of stereoisomers. Pyrolysis affords the 1,3-diacetylindole from which indigo can be obtained by the action of alkali and air [204].



63, 76-82 %

2-Vinylindole radical-cations, for example that derived from **64**, take part in a Diels-Alder reaction with alkenes. Subsequent oxidation of the initial product with loss of two protons and dimethylamine gives the pyrido[1,2a]indole. Reaction is achieved either by direct electrochemical oxidation or by photochemical electron



64

transfer to 2,4,6-triphenylpyrillium [205]. A 3-substituted indole is required to block the oligomerization of the indole cation-radical. The photochemical radical-

cation Diels-Alder reaction has also been applied to a reaction between indoles and [206] dienes and to the self-condensation of electron rich cyclohexadienes [207].

Six-Membered Rings

Pyridine, quinoline and acridine show more positive oxidation potentials than the corresponding aromatic hydrocarbons. The oxidation potentials in Table 6.9 should be compared with data in Table 6.1.

Table 6.9. Half-wave potentials for the oxidation of aromatic 6-membered nitrogen heterocycles at a rotating platinum anode acetonitrile, tetraethylammonium perchlorate [208].

Substrate	$E_{½}$ / V *vs.* sce
Pyridine	[a]
Quinoline	1.97
Isoquinoline	1.84
Acridine	1.58
Phenazine	1.91

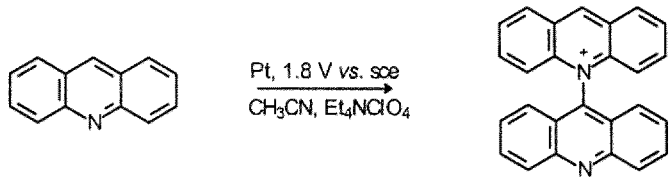
Footnote: (a) No wave observable

Radical-cations can be generated from these nitrogen heterocycles by γ-irradiation in a glass composed of CCl_3F + CF_2BrCF_2Br. Irradiation generates electrons, which are immobilised by dissociative attachment to the solvent, and positive charges which migrate through the glass and are captured by the solute. Two types of radical-cation are formed:

(a) A σ-type formed by loss of one electron from the nitrogen lone pair and where the unpaired electron is located on the nitrogen atom. This type is formed by the nitrogen analogues of benzene, pyridine [209], pyridazine, pyrimidine and pyrazine [210].
(b) A π-type where the unpaired electron is delocalised over the aromatic π-system. This type is easily distinguished because their uv-spectra resemble those of the corresponding aromatic hydrocarbon. Quinoline, isoquinoline, acridine and phenazine form this type of radical-cation [210].

Oxidation of acridine in anhydrous acetonitrile leads to a dimer **65** formed by reaction of the nitrogen in one molecule of the substrate with the point of highest positive charge density in a radical-cation [208]. Anodic oxidation of neat pyridine

gives 2-pyridylpyridinium by radical substitution of the N-pyridyl radical onto the



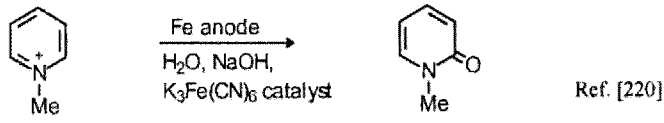
65

2-position of pyridine, and then further oxidation steps [211]. The N-pyridyl radical is also formed from oxidation of pyridine with persulphate ion [212].

Oxidation of methylpyridines in 60-80 % sulphuric acid at a lead dioxide anode leads to the pyridinecarboxylic acid [213]. The sulphuric acid concentration is critical and little of the product is formed in dilute sulphuric acid [214]. In these reactions, electron loss from the π-system is driven by concerted cleavage of a carbon-hydrogen bond in the methyl substituent. This leaves a pyridylmethyl radical, which is then further oxidised to the acid. The procedure is run on a technical scale in a divided cell to give the pyridinecarboxylic acid in 80 % yields [215]. Oxidationof quinoline under the same conditions leads to pyridine-2,3-dicarboxylic acid [214, 216]. 3-Haloquinolines afford the 5-halopyridine-2,3-dicarboxylic acid [217]. Quinoxaline is converted to pyrazine-2,3-dicarboxylic acid by oxidation at a copper anode in aqueous sodium hydroxide containing potassium permanganate [218].

The electrochemical reduction of oxygen in dimethylformamide generates oxygen radical-anion. This will abstract a hydrogen atom from the methyl group in a methylpyridine, the process finally leading to the pyridinecarboxylic acid [219].

N-Methylpyridinium and N-methylquinolinium ions are oxidised in water to the pyridone and quinolone respectively. A two-compartment cell with an iron anode is used with a catalytic amount of ferricyanide present. The electrolyte is main-



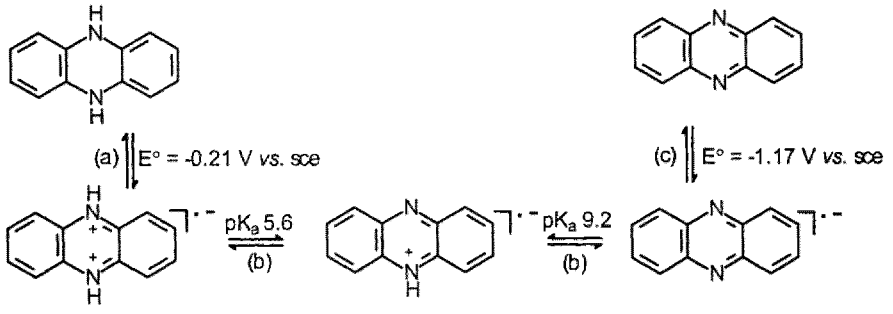
Ref. [220]

95 %

tained alkaline by the addition of sodium hydroxide solution [220, 221]. Ferricyanide is probably the active oxidising agent in homogeneous solution and it is regenerated electrochemically.

The system dihydrophenazine-phenazine shows a combination of redox and proton dissociation equlibria in aqueous solution summarised in Scheme 6.8. Phe-

nazine is the stable form under ambient conditions and in aprotic solvents shows two one-electron reduction waves with $E_{½}$ = -1.17 and –1.84 *vs.* sce [222]. The phenazyl radical **66** is extensively delocalised over the whole molecule and is best represented as phenazine with the odd electron accommodated in the lowest unoc-

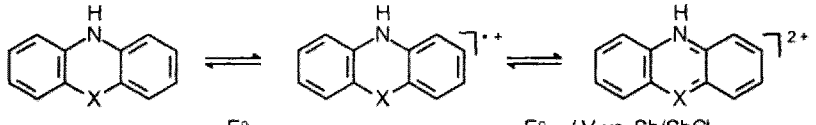


66

Scheme 6.8. Redox and acid dissociation properties of dihydrophenazine, solvents: (a) 30 % perchloric acid ; (b) aqueous buffers; (c) dimethylformamide.

cupied molecular orbital [223]. The two values for pK_a are determined by changes in the uv-spectrum with pH after phenazine is reacted with solvated electrons, generated by pulse-radiolysis, in buffered solution [224]. The fully protonated form is obtained by two-electron reduction of phenazine in aqueous perchloric acid [222].

For the related compounds, phenothiazine and phenoxazine, the reduced form is stable under ambient conditions and oxidation occurs in two one-electron steps. A comparison between the redox behaviour of the two compounds is best made in an antimony trichloride medium where both the radical-cation and the dication levels are stable (Scheme 6.9) [225]. In perchloric acid, phenothiazine shows reversible

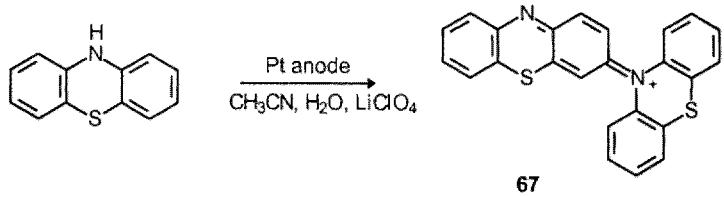


	E°	E° / V *vs.* $Sb/SbCl_3$
X = S phenothiazine	0.122	0.196
X = O phenoxazine	0.155	1.12

Scheme 6.9. Redox behaviour of phenothiazine and phenoxazine in antimony trichloride containing butylpyridinium tetrachloroaluminate.

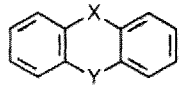
oxidation to the radical-cation with $E_{½}$ = 0.52 and is further oxidised with $E_{½}$ = 1.00 V *vs.* sce to phenazothionium with loss of a proton [226]. The radical-cation

has pK_a 4-5 in water [227]. Salts of phenothiazine radical-cation are described in the early literature but they were not recognised as unpaired electron species [228]. From crystal structure data [229], phenothiazine radical-cation has a shortened carbon-sulphur bond due to partial double bond character and has the two benzene rings each planar but inclined with a dihedral angle of 172 °. Phenoxazine radical-cation is planar.



67

Preparative scale electrochemical oxidation of phenothiazine in aqueous acetonitrile, with no added acid, leads to the radical formed by proton loss from the radical-cation. The radical dimerizes and further oxidation leads to the green quinonoid cation **67** [230].



68

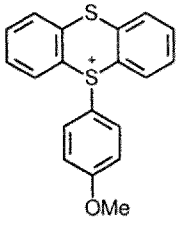
Table 6.10. Half-wave potentials for the oxidation of heterocycles **68** at a rotating platinum anode in acetonitrile, lithium perchlorate [231].]

X	Y	$E_{½}$ / V *vs.* sce		X	Y	$E_{½}$ / V *vs.* sce	
O	O	0.991		O	Te	0.366	
O	S	0.825	1.32	S	S	0.865	1.19
O	Se	0.751	1.31	Se	Se	0.832	

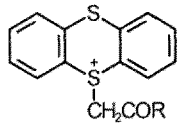
The heterocycles **68** can all be oxidised in acetonitrile to radical-cations at the potentials indicated in Table 6.10. A number also undergo a second one-electron oxidation to the dication.

Thianthrene, **68** X = Y = S, radical-cation is obtained by oxidation in trifluoroacetic acid containing perchloric acid and the evaporation of the solvent [232]. It shows electrophilic behaviour on the sulphur atom. When the electrochemical oxidation of thianthrene is carried out in aqueous acetic acid, the monoxide is obtained

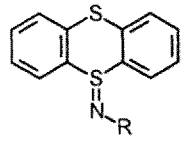
in quantitative yield [233]. Electron transfer to form the sulphoxide follows the reaction between the radical-cation and water to give a radical intermediate. Related reactions occur between the radical-cation and anisole to give **69** [234], methyl ketones to give **70** [235] and primary amines to give the sulphimine derivative **71** [236].



69

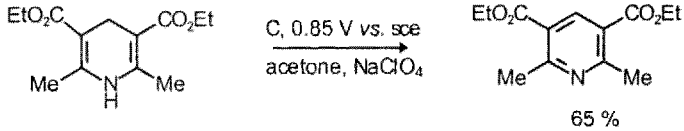


70

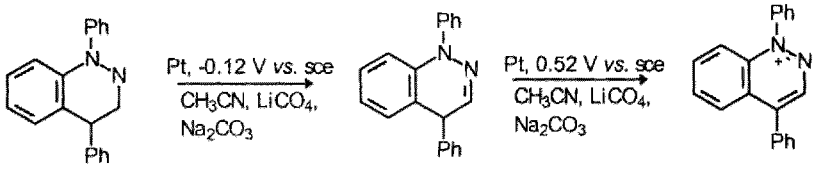


71

Phenoxanthin, **68** X = S Y = O, is prepared by the electrochemical oxidation of diphenyl ether in dichloromethane and trichloroacetic acid containing tetraethylammonium perchlorate at a composite anode of carbon and sulphur. The anode generates sulphur cations, which carry out electrophilic substitution on the benzene ring [237]. Phenoxathiin radical-cation, formed at the potential of the first oxidation wave, has been characertised by esr spectroscopy [238].



Ref. [239]



Ref. [241]

1,4-Dihydropyridines are oxidised to the pyridine at a graphite anode [239, 240]. Similarly, 1,2,3,4-tetrahydrocinnolines can be oxidised at the potential of the first wave to give the 1,4-dihydrocinnoline and at the potential of the second wave to give the cinnoline [241].

References

[1] R. E. Sioda, *J. Phys. Chem.*, 1968, **72**, 2322.
[2] O. Hammerich and V. D. Parker, *Electrochim. Acta*, 1973, **18**, 537.
[3] J. Phelps, K. S. V. Santhanam and A. J. Bard, *J. Am. Chem. Soc.*, 1967, **89**, 1752.
[4] O. Hammerich, V. D. Parker and A. Ronlán, *Acta Chem. Scand. B*, 1976, **30**, 89.
[5] O. Hammerich, N. S. Moe and V. D. Parker, *J. Chem. Soc. Chem. Commun.*, 1972, 156.
[6] B. Fabre, K. Mochelet, N. Simonet and J. Simonet, *J. Electroanal. Chem.*, 1977, **425**, 67.
[7] T. Sato and M. Kamada, *J. Chem. Soc. Perkin Trans. II*, 1977, 384.
[8] H. O. House, D. Koepsell and W. Jaeger, *J. Org. Chem.*, 1973, **38**, 1167.
[9] A. Zwieg, A. H. Maurer and B. G. Roberts, *J. Org. Chem.*, 1967, **32**, 1321.
[10] S. I. Weissman, E. DeBoer and J. J. Conradi, *J. Chem. Phys.*, 1957, **26**, 963.
[11] I. C. Lewis and L. S. Singer, *J. Chem. Phys.*, 1965, **43**, 2712.
[12] O. W. Howarth and G. K. Fraenkel, *J. Am. Chem. Soc.*, 1966, **88**, 4514.
[13] A. P. Rudenko, *Russian J. Org. Chem..*, 1994, **30**, 1946.
[14] H. P. Fritz and R. O. Artes, *Electrochim. Acta*, 1981, **26**, 417.
[15] H. P. Fritz, H. Gebauer, P. Freidrich, P. Echer, R. Artes and U. Schubert, *Z. Naturforsch. B*, 1978, **33**, 498.
[16] T. C. Chiang, A. H. Reddoch and D. F. Williams, *J. Chem. Phys.*, 1971, **54**, 2051.
[17] L. Alcacer and A. H. Maki, *J. Phys. Chem.*, 1974, **78**, 215.
[18] K. Brass and E. Tengler, *Ber.*, 1931, **64**, 1650.
[19] K. Brass and U. Fanta, *Ber.*, 1936, **69**, 1.
[20] A. Ronlan and V. D. Parker, *J. Chem. Soc. Chem. Commun.*, 1974, 33.
[21] B. Badger and B. Brocklehurst, *Trans. Faraday Soc.*, 1969, **65**, 2582.
[22] P. O'Neill, S. Steenken and D. Schulte-Frohlinde, *J. Phys. Chem.*, 1975, **79**, 2773.
[23] K. Sehested, J. Holcman and E. J. Hart, *J. Phys. Chem.*, 1977, **81**, 1363.
[24] K. Sehested and J. Holeman, *J. Phys. Chem.*, 1978, **82**, 651.
[25] J. F. Evans and H. N. Blount, *J. Org. Chem.*, 1976, **41**, 516.
[26] H. N. Blount and T. Kuwana, *J. Electroanal. Chem.*, 1970, **27**, 464.
[27] C. Amatore and J.-M. Savéant, *J. Electroanal. Chem.*, 1983, **144**, 59.
[28] U. Svanholm and V. D. Parker, *J. Am. Chem. Soc.*, 1976, **98**, 2942.
[29] H. D. Law and F. M. Perkin, *Trans. Faraday Soc.*, 1904, **1**, 31.
[30] H. D. Law and F. M. Perkin, *Chem. News*, 1905, **52**, 66.
[31] R. P. Linstead, J. C. Bunt, B. C. L. Weedon and B. R. Shephard, *J. Chem. Soc.*, 1952, 3624.
[32] L. Eberson and K. Nyberg, *J. Am. Chem. Soc.*, 1966, **88**, 1686.
[33] L. Eberson and K. Nyberg, *Acta Chem. Scand. B*, 1978, **32**, 235.
[34] S. Goldschmidt and M. Missinger, *Chem. Ber.*, 1954, **87**, 956.
[35] T. Inoue, K. Koyama and S. Tsusumi, *Bull. Chem. Soc. Japan*, 1964, **37**, 1597.
[36] K. Koyama, T. Susuki and S. Tsutsumi, *Tetrahedron Letters*, 1965, 627.
[37] L. Eberson, *J. Am. Chem. Soc.*, 1967, **89**, 4669.
[38] Z. Blum, L. Cedheim and L. Eberson, *Acta Chem. Scand. B*, 1977, **31**, 662.
[39] L. Eberson and K. Nyberg, *Acta Chem. Scand. B*, 1975, **29**, 168.
[40] K. Fujimoto, Y. Tokuda, H. Mackawa, Y. Matsubara, T. Mizuno and I. Nishiguchi, *Tetrahedron*, 1996, **52**, 3889.
[41] K. Nyberg and L. G. Wistrand, *J. Chem. Soc. Chem. Commun.*, 1976, 899.
[42] Z. Blum and K. Nyberg, *Acta Chem. Scand. B*, 1979, **33**, 73.

[43] F. Barba, A. Guirado and I. Barba, *J. Org. Chem.*, 1984, **49**, 3022.
[44] K. Nyberg, *Acta Chem. Scand.*, 1971, **25**, 3770.
[45] K. Nyberg, *Acta Chem. Scand.*, 1973, **27**, 502.
[46] K. Nyberg, *Acta Chem. Scand.*, 1970, **24**, 1609.
[47] K. Nyberg, *Acta Chem. Scand.*, 1971, **25**, 2499.
[48] O. Hammerich and V. D. Parker, *J. Chem. Soc. Chem. Commun.*, 1974, 245.
[49] L. Eberson and K. Nyberg, *Tetrahedron Letters*, 1966, 2389.
[50] L. Eberson and B. Helgée, *Acta Chem. Scand. B*, 1978, **32**, 157.
[51] L. Eberson and E. Oberrauch, *Acta Chem. Scand. B*, 1981, **35**, 193.
[52] M. A. Renard, *Compt. rend.*, 1880, **91**, 715. L. Gattermann and F. Friedrichs, *Ber.*, 1894, **27**, 1942.
[53] R. Kempf, *Friedländer's Fortschritte der Teerfarbenfabrikation*, Vol. 6, p.109. H. Inoue and M. Shikata, *J. Chem. Ind. (Japan)*, 1921, **24**, 567; *Chem. Abstr.*, 1922, **16**, 1046.
[54] A. Seyewetz and G. Miodon, *Bull. Soc. chim. France [4]*, 1923, **33**, 449.
[55] M, Fremery, H. Hoever and G. Schwarzlose, *Chem. Ing. Tech.*, 1974, **46**, 635.
[56] A. Fontana and F. M. Perkin, *Z. Elektrochem.*, 1904, **11**, 99.
[57] R. P. Koch and R. M. Spotnitz, *US* 4639298 (1987); *Chem. Abstr.*, 1987, **106**, 127956.
[58] R. P. Koch, *US* 4794172 (1988); *Chem. Abstr.*, 1989, **110**, 231107.
[59] T. Tzedakis and A. Savall, *J. Appl. Electrochem.*, 1997, **27**, 589.
[60] D. Degner, H. Hannebaum, H. Siegel and W, Gramlich, *DE* 3322399 (1983); *Chem. Abstr.*, 1985, **102**, 139818.
[61] D. Degner, H. Ross and H. Hannebaum, *DE* 3172726 (1983); *Chem. Abstr.*, 1983, **98**, 169382.
[62] R. P. Koch and R. M. Spotnitz, *US* 4639298 (1987); *Chem. Abstr.*, 1987, **106**, 127956.
[63] S. Torii, H. Tanaka, T. Inokuchi, S. Nakane, M. Akada, N. Saito and T. Sirakawa, *J. Org. Chem.*, 1982, **47**, 1647.
[64] A. Nilsson, U. Palmquist, T. Petterson and A. Ronlan, *J. Chem. Soc. Perkin Trans. 1*, 1978, 708. The reaction scheme has been amended.
[65] K. H. Grosse Brinkhaus, E. Steckhan and D. Degner, *Tetrahedron*, 1986, **42**, 553.
[66] R. F. Dunbrook and A. Lowry, *Trans. Am. Electrochem. Soc.*, 1924, **45**, 89.
[67] J. F. Conn and A. Lowry, *Trans. Am. Electrochem. Soc.*, 1926, **50**, 334.
[68] F. Fichter and J. Rosenweig, *Helv. Chim. Acta*, 1933, **26**, 1154.
[69] B. Belleau and N. L. Weinberg, *J. Am. Chem. Soc.*, 1963, **85**, 2525.
[70] M. J. Manning, P. W. Raynolds and J. S. Swenton, *J. Am. Chem. Soc.*, 1976, **98**, 5008.
[71] D. R. Henton, R. L. McCreery and J. S. Swenton, *J. Org. Chem.*, 1980, **45**, 3422.
[72] P. W. Raynolds, M. J. Manning and J. S. Swenton, *J. Chem. Soc. Chem. Commun.*, 1977, 499.
[73] M. J. Manning, D. R. Henton and J. S. Swenton, *Tetrahedron Letters*, 1977, 1679.
[74] R. Pistorius, *Ger. Offen.*, 2547463 (1977); *Chem. Abstr.*, 1977, **87**, 134621.
[75] M. G. Dobson and J. S. Swenton, *J. Am. Chem. Soc.*, 1981, **103**, 2361.
[76] K. Koyama, T. Susuki and S. Tsutsumi, *Bull. Chem. Soc. Japan*, 1968, **41**, 2663 (or 2667).
[77] L. Eberson and B. Helgée, *Chem. Scr.*, 1974, **5**, 47; *Chem. Abstr.*, 1974, **80**, 82473.
[78] L. Eberson and B. Helgée, *Acta Chem. Scand. B*, 1977, **31**, 813.
[79] S. Andreas and E. W. Zahnow, *J. Am. Chem. Soc.*, 1969, **91**, 4181.
[80] L. Eberson and B. Helgée, *Acta Chem. Scand. B*, 1975, **29**, 451.
[81] F. Fichter and W. Dietrich, *Helv. Chim. Acta*, 1924, **7**, 131.

[82] H. G. H. Erdtman, *Proc. Roy. Soc. Series A*, 1933, **143**, 191.
[83] A. Ronlan, K. Bechgaard and V. D. Parker, *Acta Chem. Scand.*, 1973, **27**, 2375.
[84] Bechgaard and V. D. Parker, *J. Am. Chem. Soc.*, 1972, **94**, 4749.
[85] E. A. Mayeda, *J. Am. Chem. Soc.*, 1975, **97**, 4012.
[86] M. H. Khalifa and A. Rieker, *J. Chem. Res. (S)*, 1977, 316.
[87] F. Wöhler, *Liebigs Annalen Chem.*, 1844, **50**, 1.
[88] M. Zh. Zhurinov and B. A. Serikbaev, *Khim. Tekhnol. Silikaty*, 1974, 334; *Chem. Abstr.*, 1975, **83**, 17642.
[89] I. Tabakovic, E. Gunic and I. Juranic, *J. Org. Chem.*, 1997, **62**, 947.
[90] E. A. Mayeda, L. L. Miller and J. F. Wolf, *J. Am. Chem. Soc.*, 1972, **94**, 6812.
[91] S. M. Weinreb G. A. Epling, R. Comi and M. Reitano, *J. Org. Chem.*, 1975, **40**, 1356.
[92] F. Weygand and K. Hunger, *Chem. Ber.*, 1962, **95**, 1.
[93] E. J. Land, G. Porter and E. Strachan, *Trans. Faraday Soc.*, 1961, **57**, 1885.
[94] J. A. Richards, P. E. Whitson and D. H. Evans, *J. Electroanal. Chem.*, 1975, **63**, 311.
[95] U. Palmquist, A. Nilsson, V. D. Palker and A. Ronlán, *J. Am. Chem. Soc.*, 1976, **98**, 2517.
[96] The argument follows an inverse analogy with the reduction of enones, p. 70. A complete experimentally determined pH profile for oxidation of a phenol is not available.
[97] F. W. Steuber and K. Dimroth, *Chem. Ber.*, 1966, **99**, 258.
[98] K. Dimroth, U. Umbach and H. Thoma, *Chem. Ber.*, 1967, **100**, 132.
[99] A. Ronlan and V. D. Parker, *J. Chem. Soc. (C)*, 1971, 3214.
[100] A. Nilsson, A. Ronlan and V. D. Parker, *J. Chem. Soc. Perkin Trans. 1*, 1973, 2337.
[101] R. C. Halleher, *Ger. Offen*, 2700152 (1977); *Chem. Abstr.*, 1977, **87**, 108551.
[102] G. C. Jones and R. H. Meen, *US* 4935253 (1977); *Chem. Abstr.*, 1977, **87**, 75732. Y. Watanabe and N. Nojiri, *Japan Kokai*, 78 40728 (1978); *Chem. Abstr.*, 1978, **89**, 33323.
[103] F. Fichter and W. Dietrich, *Helv. Chim. Acta*, 1924, **7**, 132.
[104] S. Torii, A. L. Dhimane, Y. Araki and T. Inokuchi, *Tetrahedron Letters*, 1989, **30**, 2105.
[105] Y. Shizuri, K. Nakamura and S. Yamamura, *J. Chem. Soc. Chem. Commun.*, 1985, 530.
[106] C.-P. Chen and J. S. Swenton, *J. Chem. Soc. Chem. Commun.*, 1985, 1291.
[107] D. J. Hart, G. H. Merriman and D. G. J. Young, *Tetrahedron*, 1996, **52**, 14437.
[108] M. Iguchi, A. Nishiyama, H. Eto and S. Yamamura, *Chem. Letters*, 1981, 939.
[109] M. Iguchi, A. Nishijama, Y. Teada and S. Yamamura, *Tetrahedron Letters*, 1977, 4511.
[110] Y. Shizuri and S. Yamamura, *Tetrahedron Letters*, 1983, **24**, 3797.
[111] H. Takakura and S. Yamamura, *Tetrahedron Letters*, 1999, **40**, 299.
[112] M. H. Khalifa, G. Jung and A. Rieker, *Liebigs Ann. Chem.*, 1982, 1068.
[113] E. L. Dreher, J. Bracht, M. El-Mobayed, P. Hütter, W. Winter and A. Rieker, *Chem. Ber.*, 1982, **115**, 288.
[114] R. K. Haynes, H. Hess and H. Musso, *Chem. Ber.*, 1974, **107**, 3723.
[115] B. Franck and G. Schlingloff, *Leibigs Ann. Chem.*, 1963, **668**, 145.
[116] J. M. Bobbitt, K. H. Weisgraber, A. S. Steinfeld and S. G. Weiss, *J. Org. Chem.*, 1971, **35**, 2884.
[117] J. M. Bobbitt, H. Yagi, S. Shibuya and J. T. Stock, *J. Org. Chem.*, 1971, **36**, 3006.
[118] J. M. Bobbitt, I. Noguchi, H. Yagi and K. H. Weisgraber, *J. Org. Chem.*, 1976, **41**, 845.

[119] B. Franck, G. Blaschke and K. Lewejohann, *Liebigs Ann. Chem.*, 1965, **685**, 207.
[120] L. L. Miller, R. F. Stewart, J. D. Gillespie, V. Ramchandran, Y. H. So and F. R. Stermitz, *J. Org. Chem.*, 1978, **43**, 1580.
[121] L. Horner and E. Geyer, *Chem. Ber.*, 1965, **98**, 2016.
[122] O. Ryba, J. Petranek and J. Pospisil, *Coll. Czech. Chem.Commun.*,1965, **30**, 843.
[123] Z. Gruioc, I. Tabakovic and M. Trkovnik, *Tetrahedron Letters*, 1976, 4823.
[124] S. M. Golabi and D. Nematollah, *J. Electroanal. Chem.*, 1997, **420**, 127.
[125] K. Chiba and M. Tada, *J. Chem. Soc. Chem. Commun.*, 1994, 2485.
[126] K. Chiba, J. Sonoyama and M. Tada, *J. Chem. Soc. Perkin Trans 1*, 1996, 1435.
[127] J. B. Kerr, T. C. Jempty and L. L. Miller, *J. Am. Chem. Soc.*, 1979, **101**, 7338.
[128] A. Ronlan, O. Hammerich and V. D. Parker, *J. Am. Chem. Soc.*, 1973, **95**, 7132.
[129] A. Ronlan and V. D. Parker, *J. Org. Chem.*, 1974, **39**, 1014.
[130] J. R. Falck, L. L. Miller and F. R. Stermitz, *J. Am. Chem. Soc.*, 1974, **96**, 2981.
[131] L. L. Miller F. R. Stermitz and J. R. Falch, *J. Am. Chem. Soc.*, 1971, **93**, 5941.
[132] T. Kametani, K. Shishido and S. Takano, *J. Heterocyclic Chem.*, 1975, **12**, 305.
[133] L. Christensen and L. L. Miller, *J. Org. Chem.*, 1981, **46**, 4876.
[134] M. Hutchins, M. Sainsbury and D. I. C. Scopes, *J. Chem. Soc. Perkin Trans. 1*, 1983, 2059.
[135] E. Kotani and S. Tobinaga, *Tetrahedron Letters*, 1973, 4759.
[136] H. J. Schäfer, G. Burgbacher, C. Schlegel and H. Class, *Ber. Bunsen-Ges. Phys. Chem.*, 1988, **92**, 1231.
[137] H. Klünenberg, C. Schäffer and H. J. Schäfer, *Tetrahedron Letters*, 1982, **23**, 4581.
[138] M. Murase and S. Tobinaga, *Heterocycles*, 1981, **15**, 1219.
[139] E. Kotani, M. Kitazawa and S. Tobinaga, *Tetrahedron*, 1974, **30**, 3027.
[140] H. Omori, C. Ueda, Y. Nobusue, N. Saitou, T. Yokota and M. Masui, *J. Chem. Soc. Perkin Trans. 2*, 1981, 1599.
[141] E. Kotani, N. Takeuchi and S. Tobinaga, *J. Chem. Soc. Chem. Commun.*, 1973, 550.
[142] M. Sainsbury and J. Wyatt, *J. Chem. Soc, Perkin Trans.1*, 1976, 661.
[143] A. J. Majeed, M. Sainsbury and S. A. Hall, *J. Chem. Soc, Perkin Trans.1*, 1984, 833.
[144] P. Bird, G. G. Black, H. Lloyd, M. Sainsbury and D. I. C. Scopes, *J. Chem. Soc. Perkin Trans. 1*, 1986, 1197.
[145] M. Sainsbury, *Heterocycles*, 1978, **9**, 1349.
[146] S. Maki, T. Suzuki, S. Kosemura, Y. Shizuri and S. Yamamura, *Tetrahedron Letters*, 1991, **32**, 4973.
[147] S. Yamamura, Y. Shizuri, H. Shigemori, Y. Okuno and M. Ohkubo, *Tetrahedron*, 1991, **47**, 635.
[148] Y. Shizuri, M. Ohkubo and S. Yamamura, *Chem. Letters*, 1989, 113.
[149] S. Maki, S. Kosemura, S. Yamamura and S. Ohba, *Tetrahedron Letters*, 1993, **34**, 6083.
[150] G. W. Morrow, Y. Chen and J. S. Swenton, *Tetrahedron*, 1991, **47**, 655.
[151] H. Noda, M. Niwa and S. Yamamura, *Tetrahedron Letters*, 1981, **22**, 3247.
[152] C. Wurster and E. Schobig, *Ber.*, 1879, **12**, 1808.
[153] C. Wurster and R. Sendtner, *Ber.*, 1879, **12**, 1803.
[154] L. Michaelis and E. J. Hill, *J. Am. Chem. Soc.*, 1933, **55**, 1481.
[155] E. T. Seo, R. F. Nelson, J. M. Fritsch, L. S. Marcoux, D. W. Leedy and R. N. Adams, *J. Am. chem. Soc.*, 1966, **88**, 3498.
[156] F. A. Bell, A. Ledwith and D. C. Sherrington, *J. Chem. Soc. C*, 1969, 2719.
[157] W. Schmidt and E. Steckhan, *Chem. Ber.*, 1980, **113**, 577.

[158] G. Cauquis, H. Delhomme and D. Sevre, *Tetrahedron Letters*, 1971, 4113.
[159] M. Platen and E. Steckhan, *Chem. Ber.*, 1984, **117**, 1679.
[160] P. Beresford, M. C. Lambert and A. Ledwith, *J. Chem. Soc. C*, 1970, 2508.
[161] F. Fichter and P. Müller, *Helv. Chim. Acta*, 1925, **8**, 290.
[162] G. Cauquis, J.-L. Cros and M. Geniès, *Bull Soc. chim. France*, 1971, 3760.
[163] H. Sayo and A. Ueda, *Chem. Pharm. Bull.*, 1977, **25**, 640.
[164] H.-J. Schäfer and W. Eilenberg, *Heterocycles*, 1989, **28**, 979.
[165] A. F. Diaz and J. A. Lagan, *J. Electroanal. Chem.*, 1980, **111**, 111.
[166] C. F. Boehringer and Sohn, *DRP* 117129 (1899); *Chem. Zentralblatt*, 1901, I, 285.
[167] A. Lowry and E. H. Haux, *Trans. Am. Electrochem. Soc.*, 1921, **40**, 123.
[168] H. Sayo, K. Mori, A. Ueda and T. Michida, *Chem. Pharm. Bull.*, 1978, **26**, 1682.
[169] A. F. Diaz, J. Crowley, J. Bargon, G. P. Gardini and J. B. Torrence, *J. Electroanal. Chem.*, 1981, **121**, 355.
[170] N. Clauson-Kass, F. Limborg and K. Glens, *Acta Chem. Scand.*, 1952, **6**, 531.
[171] N. Clauson-Kass, F. Limborg and P. Dietrich, *Acta Chem. Scand.*, 1952, **6**, 545.
[172] For a summary of earlier work see: F. Limborg and N. Clauson-Kass, *Acta Chem. Scand.*, 1953, **7**, 234.
[173] D. Degner, H. Nohe and H. Hammebaum (BASF A.-G.), *Ger.* 2710420(1978); *Chem. Abstr.*, 1979, **90**, 94451.
[174] E. Raoult, J. Sarrazin and A. Tallec, *J. Applied Electrochem.*, 1985, **15**, 85.
[175] S. M. Ross and M. Finkelstein, *J. Org. Chem.*, 1969, **34**, 1018.
[176] I. Stibor, J. Srogl and M. Janda, *J. Chem. Soc. Chem. Commun.*, 1975, 397.
[177] J. T. Nielsen, N. Elming and N. Clauson-Kass, *Acta Chem. Scand.*, 1955, **9**, 9.
[178] N. Elming, *Acta Chem. Scand.*, 1952, **6**, 572.
[179] N. Elming and N. Clauson-Kass, *Acta Chem. Scand.*, 1955, **9**, 23.
[180] N. Clauson-Kass, N. Elming and Z. Tyle, *Acta Chem. Scand.*, 1955, **9**, 1.
[181] N. Elming and N. Clauson-Kass, *Acta Chem. Scand.*, 1955, **9**, 23.
[182] T. Shono, Y. Matsumura, K. Tsubata and J. Takato, *Chem. Letters*, 1981, 1121.
[183] M. Janda, J. Srogl, H. Bvorakova, D. Dvorak and I. Stillov, *Coll. Czech. Chem. Commun.*, 1981, **46**, 906.
[184] K. Yoshida and T. Fueno, *Bull. Chem. Soc. Japan*, 1969, **42**, 2411.
[185] N. Clauson-Kass, A. Lie and N. Elming, *Acta Chem. Scand.*, 1950, **4**, 1233.
[186] D. Degner and C. Rentzen (BASF A.-G.), *Ger. Offen*, 2601543 (1977); *Chem. Abstr.*, 1977, **87**, 92656.
[187] T. Shono, Y. Matsumura and S. Yamane, *Tetrahedron Letters*, 1981, **22**, 3269.
[188] J. M. Froborg and T. S. Goran, *J. Org. Chem.*, 1975, **40**, 122.
[189] C. J. V. Scanio, *US* 3871977 (1975); *Chem. Abstr.*, 1975, **83**, 68078.
[190] J. Srogl, M. Janda, I. Stilbor and R. Rozinek, *Synthesis*, 1975, 717.
[191] S. Tanaka, M. Sato and K. Kacriyama, *Makromol. Chem.*, 184, **185**, 1295.
[192] D. Curran, J. Grimshaw and S. D. Perera, *Chem. Soc. Rev.*, 1991, **20**, 391.
[193] G. Cauquis and M. Genies, *Bull. Soc. chim. France*, 1967, 3220.
[194] P. J. Grossi, L. Marchetti, R. Ramasseul, A. Rassat and D. Serve, *J. Electroanal. Chem.*, 1978, **87**, 353.
[195] M. Janda, *Coll. Czech. Chem. Commun.*, 1963, **28**, 2524.
[196] M. Janda and L. Paviensky, *Coll. Czech. Chem. Commun.*, 1967, **32**, 2675.
[197] M. Janda, J. Srogl, M. Nemec and A. Janousova, *Coll. Czech. Chem. Commun.*, 1973, **38**, 1221.
[198] M. Janda, J. Srogl and M. Synackova, *Coll. czech. Chem. Commun.*, 1972, **37**, 2584.

[199] J. Strogl, M. Janda, I. Stilbor, J. Kos and V. Vyskocil, *Coll. Czech. Chem. Commun.* 1977, **43**, 2015.
[200] Y. Kunihiso, *J. Am. Chem. Soc.*, 1979, **101**, 2116.
[201] K. L. Swanson, K. M. Snow, D. Jeyakumar and K. M. Smith, *Tetrahedron*, 1991, **47**, 685.
[202] P. Jennings, A. C. Jones, A. R. Mount and A. D. Thomson, *J. Chem. Soc. Faraday Trans.*, 1997, **93**, 3791.
[203] A. Berlin, A. Canavesi, G. Schiavon, S. Zecchin and G. Zotti, *Tetrahedron*, 1996, **52**, 7947.
[204] S. Torii, T. Yamanaka and H. Tanaka, *J. Org. Chem.*, 1978, **43**, 2882.
[205] C. F. Gurtler, S. Blechart and E. Steckhan, *Synletters*, 1994, 141.
[206] A. Gieseler, E. Steckhan, O. Wiest and F. Knoch, *J. Org. Chem.*, 1991, **56**, 1405.
[207] J. Mlcoch and E. Steckhan, *Tetrahedron Letters*, 1987, **28**, 1081.
[208] L. Marcoux and R. N. Adams, *J. Electroanal.Chem.*, 1974, **49**, 111.
[209] T. Shida and T. Kato, *Chem. Phys. Letters*, 1979, **68**, 106.
[210] T. Kato and T. Shida, *J. Am. Chem. Soc.*, 1979, **101**, 6869.
[211] W. R. Turner and P. J. Elving, *Anal. Chem.*, 1965, **37**, 467.
[212] P. Baumgarten, *Ber.*, 1936, **69**, 1938.
[213] M. Yokoyama, *Bull. Chem.Soc. Japan*, 1932, **7**, 69.
[214] M. Kulka, *J. Am. Chem. Soc.*, 1946, **68**, 2472.
[215] J. E. Toomey (Reilly Tar and Chemical Corp.) *US* 4482439 (1984); *Chem. Abstr.*, 1985, **102**, 102453.
[216] P. N. Gupta and G. M. Rather, *Asian J. Chem.*, 1989, **1**, 52.
[217] J. C. Cochran and W. F. Little, *J. Org. Chem.*, 1961, **26**, 808.
[218] T. Kimura, S. Yamada, K. Yoshizue and T. Nagoya, *Yakugaku Zasshi*, 1957, **77**, 891; *Chem. Abstr.*, 1958, **52**, 1181.
[219] H. Sagae, M . Fujihara, H. Lund and T. Osa, *Heterocycles*, 1979, **13**, 321.
[220] K. Neundlinger and M. Chur, *J. prakt. Chem [2]*, 1914, **89**, 466.
[221] O. Fischer and M. Chur, *J. prakt. Chem. [2]*, 1916, **93**, 363.
[222] K. Alwair and J. Grimshaw, *J. Chem. Soc. Perkin Trans. 2*, 1973, 1811.
[223] V. P. Chacko, C. A. McDowell and B. C. Singh, *Mol. Phys.*, 1979, **38**, 321.
[224] P. S. Rao and E. Hayon, *Anal. Chem.*, 1976, **48**, 564.
[225] D. M. Chapman, A. C. Buchanan, G. P. Smith and G. Mamantov, *J. Am. Chem. Soc.*, 1986, **108**, 654.
[226] J. P. Billon, *Bull. Soc. chim. France*, 1961, 1923.
[227] F. G. Bordwell and M. J. Bausch, *J. Am. Chem. Soc.*, 1986, **108**, 2473.
[228] F. Kermann and L. Diserens, *Ber.*, 1915, **48**, 318.
[229] A. Singhabhandu, P. D. Robinson, J. H. Fang and W. E. Geijer, *Inorg. Chem.*, 1975, **14**, 318.
[230] P. Hanson and R. O. C. Norman, *J. Chem. Soc. Perkin Trans. 2*, 1973, 264.
[231] C. Barry, G. Cauquis and M. Maurey, *Bull. Soc. chim. France*, 1966, 2510.
[232] O. Hammerich, N. S. Moe and V. D. Parker, *J. Chem. Soc. Chem. Commun.*, 1972, 156.
[233] K. Uneyama and S. Torii, *Tetrahedron Letters*, 1971, 329.
[234] U. Svanholm, O. Hammerich and V. D. Parker, *J. Am. Chem. Soc.*, 1975, **97**, 101.
[235] K. Kim and H. J. Shine, *Tetrahedron Letters*, 1974, 4431.
[236] K. Kim and H. J. Shine, *J. Org. Chem.*, 1974, **39**, 2537.

[237] D. Elothmani, Q. Tho Do, J. Simonet and G. LeGuillanton, *Bull. Soc. chim. France*, 1994, **131**, 779.
[238] G. Barry, G. Cauquis and M. Maurey, *Bull. Soc. chim. France*, 1966, 2510.
[239] H. Berge, P. Jeroschewski and K. Tellert, *Ger. (East)*, 106376 (1974); *Chem. Abstr.*, 1972, **82**, 23757.
[240] J. Stradins, J. Beilis, J. Uldrikjis, G.Duburs, A. E. Sausins and B. Cekavicius, *Khim. Geterotsikl. Soedin.*, 1975, 1525; *Chem. Abstr.*, 1974, **84**, 81644.
[241] G. Cauquis, B. Chabaud and M. Genies, *Bull. Soc. chim. France*, 1975, 583.

CHAPTER 7

REDUCTION OF AROMATIC RINGS

Aromatic Compounds - Radical-Anions

With stringent precautions to avoid the presence of water, polycyclic aromatic hydrocarbons show two one-electron reversible waves on cyclic voltammetry in dimethylformamide (Table 7.1). These are due to sequential one-electron additions to the lowest unoccupied molecular π–orbital [1]. Hydrocarbons with a single benzene ring are reduced at very negative potentials outside the accessible range in this solvent. Radical-anions of polycyclic aromatic hydrocarbons [2] and also alkyl benzenes [3] were first obtained by the action of alkali metals on a solution of the hydrocarbon in tetrahydrofuran. They have been well characterised by esr spectroscopy. The radical-anions form coloured solutions with absorption bands at longer wavelength than the parent hydrocarbon [4,5].

TABLE 7.1

Reduction potentials for polycyclic aromatic hydrocarbons in rigorously dried dimethylformamide, tetrabutylammonium bromide, determined by cyclic voltammetry. Ref. [1].

Substrate	First electron addition E° / V *vs.* sce	Second electron addition E° / V *vs.* sce
Anthracene	-1.915	-2.655
9,10-Diphenylanthracene	-1.830	-2.505
Chrysene	-2.225	-2.730
Coronene	-2.030	-2.255
Perylene	-1.640	-2.255

Protonation by residual water in the solvent is the rate-determining step in the decay of most aromatic anion-radicals. Hydrogen ions and also general acids are effective protonating agents. In only a very few cases has dimerization of the radical-anion been found to be faster than protonation. The dimerization step has been followed by electrochemical techniques for 1,3-dicyanobenzene radical-anion where the rate constant is 2.4×10^5 M^{-1} s^{-1} [6]. Methyl anthracene-9-carboxylate radical-anion reversibly dimerises through the 10-position [7]. Preparative scale

reduction of naphthalenes, discussed later, affords some minor products resulting from hydrodimerization.

Rate constants for the protonation of radical-anions in dimethylformamide by added phenol can be determined by electrochemical techniques [8]. Pulse radiolysis methods have been used to measure the rate constants in an alcohol solvent. This technique generates the radical-anion on a very short time scale and uv-spectroscopy is then be used to follow the protonation of this species to give the neutral radical with different uv-absorption characteristics [9]. In the case of anthracene, the protonation rate is 5×10^3 M^{-1} s^{-1} with phenol in dimethylformamide and 5×10^4 s^{-1} in neat isopropanol. Protonation by hydrogen ions approaches the diffusion-controlled limit with a rate constant of 10^{10} M^{-1} s^{-1} in ethanol [9].

The delocalised radical formed by protonation of the radical-anion is more easily reduced than the starting arene. For some polycyclic aromatic hydrocarbons, the redox potential for this radical species can be determined using a cyclic voltammetry technique [10]. Reduction in dimethylformamide is carried out to the potential for formation of the dianion. The dianion undergoes rapid monoprotonation and on the reverse sweep at a fast scan rate, oxidation of the monoanion to the radical can be observed. The radical intermediate from pyrene has E° = -1.15 V *vs.* sce in dimethylformamide compared to E° = -2.13 V *vs.* sce for pyrene.

TABLE 7.2

Polarography of nitrogen containing aromatic compounds, values of the half-wave potential for the first reduction wave in dimethylformamide, tetraethylammonium iodide.

Substrate	$E_{½}$ / V *vs.* sce	Ref.	Substrate	$E_{½}$ / V *vs.* sce	Ref.
			Naphthalene	-2.51[a]	[11]
Pyridine	-2.68[a]	[11]	Quinoline	-2.12	[12]
Pyrimidine	-2.31[a]	[11]	Isoquinoline	-2.15[a]	[11]
Pyridazine	-2.14[a]	[11]	Quinoxaline	-1.62	[12]
Pyrazine	-1.57[a]	[11]	Quinoxaline-$2H^+$	-0.06[b]	[12]
1,3,5-Triazine	-2.00[a]	[11]	Phenazine	-1.17	[12]
1,2,4,5-Tetrazine	-0.82[a]	[11]	Phenazine-$2H^+$	+0.15[b]	[12]

Footnotes: (a): Data scaled taking $E_{½}$ for quinoline as -2.12 V *vs.* sce.
(b): Solvent was 30 % perchloric acid.

Decay of arene hydrocarbon radical-anions formed during preparative scale electrochemical reduction in the presence of general acids involves protonation as

the rate-determining step, then reduction of the so formed radical by an unprotonated radical-anion, and finally protonation of the carbanion to give a dihydro derivative of the original arene. When protonation of the radical-anion approaches the diffusion-controlled limit, the radical is generated at the electrode surface and direct electron transfer occurs to give the carbanion.

Nitrogen containing aromatic ring systems are reduced at less negative potentials than the corresponding aromatic hydrocarbon and show a polarographic wave in aprotic solvents. Half-wave potentials for the first one-electron addition step are given in Table 7.2. Excellent correlation is found between these potentials and the energy level of the lowest unoccupied molecular orbital. Pyridine and pyridazine radical-anions have been generated electrochemically in liquid ammonia at -70° C using tetramethylammonium iodide as supporting electrolyte, and characterised by esr spectroscopy [13]. The radical-anions from nitrogen arenes generally have shorter lifetimes compared to those of the corresponding hydrocarbon, and their decomposition rate is dependent on both the solvent and the counter-ion. In aqueous solution under any conditions, protonation of pyridine radical-anion is so fast that only the protonated form can be detected in pulse radiolysis, and for this species pK_a is greater than 13 [14]. The protonated species decomposes by a second order process.

The equilibrium between radical-anion and dimer for pyridine and quinoline has been examined in a number of aprotic solvents. Radical-anions of pyridine dimerise rapidly in liquid ammonia in the presence of alkali metal ions [15] In hexamethylphosphoramide with alkali metal counter ions, the monomer is detectable in an equlibrium concentration [16]. The monomeric species can be stabilised by substituents and 2- or 4-cyanopyridines give radical-anions which persist in liquid ammonia while 3-cyanopyridine radical-anion dimerises with a rate constant of 2×10^6 [17]. Quinoline radical-anion is stable in hexamethylphosphoramide [16] but in liquid ammonia it dimerises irreversibly [18].

Protonation of aromatic hydrocarbon radical-anions requires a change of carbon atom hybridization from the sp^2 to the sp^3 state. This is found to be an irreversible process, which proceeds at a fast but measurable rate. Protonation of the radical-anion from nitrogen ring systems, however, involves the nitrogen lone pair and does not require a change in hybridization. The nitrogen centre in the parent compound is also hydrogen bonded to any proton donors in solution. As a consequence, protonation of nitrogen ring radical-anions by available donors is often synchronous with electron transfer to the parent molecule.

Electrochemical reduction of 1-alkylpyridinium salts **1** leads to the addition of one electron with the formation of a π-delocalised radical-zwitterion. This is a formally neutral species. Both this species and the N-protonated pyridine radical-anion are essentially π–delocalised radicals. The radical-zwitterion from 1-methylpyridinium shows a long wavelength absorption band in water with λ_{max} 750 nm [19]. The nitrogen ring radical-zwitterions take up further electrons at more

negative potentials (Table 7.3). Whereas the first polarographic wave for 1-alkylpyridinium salts in aqueous solution is a one-electron, pH independent process, the waves at more negative potentials involve more than one electron and may be pH dependent. Radical-zwitterions decay by a rapid dimerization process in both water and aprotic solvents [20]. Dimerization of the radical-zwitterion from 1-methylpyridinium proceeds with a rate constant greater than 10^7 M^{-1} s^{-1} and involves reaction at the 4-position of the pyridine ring [21].

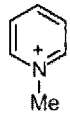
TABLE 7.3

Polarography of 1-methylpyridinium derivatives in aqueous buffers.

Pyridine substrate	$E_{½}$ / V *vs.* sce		Ref.
	1st wave	2nd wave	
1-Methylpyridinium **1**	-1.32		[21]
2-Cyano-1-methyl	-0.77,[b]	-1.21 at pH 5.0	[22]
3-Cyano-1-methyl	-0.87	-1.60 at pH 11.5	[23]
4-Cyano-1-methyl	a, b		[24]
3-Carboxamide-1-methyl	-0.79	-1.72, pH independent	[25]

Footnotes: (a): Reaction is complicated by the loss of cyanide ion.
(b): Below pH 5 the nitrile is protonated and reduced to CH_2NH_2

Delocalised radical-zwitterions are formed also from other aromatic π–systems bearing a positive charge. Tropylium salts **2** show a one-electron reduction wave on polarography in acetonitrile with $E_{½}$ = -0.17 V *vs.* sce [26]. The zwitterion is more stable in 6 M sulphuric acid where a second one-electron wave is seen at



1

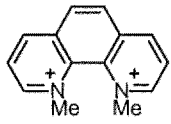
2

3

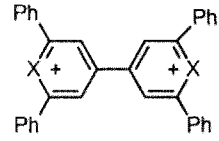
more negative potentials [27]. The zwitterion from heptaphenyltropylium is stable on a time-scale of seconds in acetonitrile [28]. Pyrylium salts **3** also show a one-electron reduction wave on polarography in acetonitrile and the radical-zwitterion from 2,4,6-triphenylpyrylium is stable in acetonitrile [29].

Aromatic π-systems bearing two positive charges can accept one electron to form a delocalised radical-cation, which is isoelectronic with the radical-anion from the corresponding aromatic hydrocarbon. The phenanthrene analogue **4** is one such example [30]. Pyrazine is bis-protonated and reduced in acid solution to the

deep violet radical-anion [31]. Bipyridinium salts **5**, X = NMe also belong to this class. They are reduced in a reversible step to the violet coloured and relatively stable radical-ion [32,33]. The N,N-dimethyl derivative of 4,4'-bipyridyl finds ex-



4

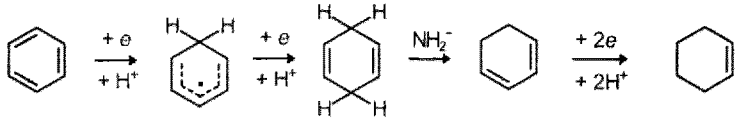


5

tensive use as a herbicide. It interferes with the electron transport mechanism in living cells. Pyrilium salts **5**, X = O and thiapyrilium analogues **5**, X = S also undergo a one-electron reduction step to the coloured radical-ion.

Aromatic Hydrocarbons

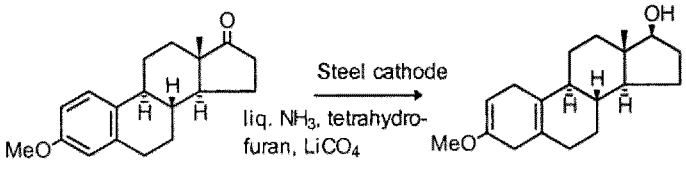
Reduction of benzenoid hydrocarbons with solvated electrons generated by the solution of an alkali metal in liquid ammonia, the Birch reaction [34], involves homogeneous electron addition to the lowest unoccupied π-molecular orbital. Protonation of the radical-anion leads to a radical intermediate, which accepts a further electron. Protonation of the delocalised carbanion then occurs at the point of highest charge density and a non-conjugated cyclohexadiene **6** is formed by reduction of the benzene ring. An alcohol is usually added to the reaction mixture and acts as a proton source. The non-conjugated cyclohexadiene is stable in the presence of



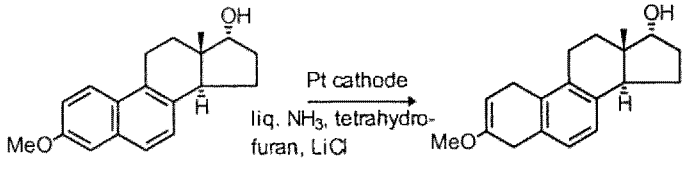
6 **7** **8**

alkoxide ions. When no alcohol is present, ammonia acts as a proton source and the reaction generates amide ions. This base is able to catalyse the conversion of the non-conjugated diene to the more thermodynamically favoured conjugated cyclohexadiene **7**. Solvated electrons are able to reduce conjugated dienes to give the cyclohexene **8**. Choice of the appropriate reaction conditions leads to one compound from **6**, **7** and **8** as the product from the Birch reduction of benzene. Solvated electrons, in the presence of alcohol as a proton source, reduce naphthalene to 1,4-dihydro-naphthalene.

Benzene is reduced at such negative potentials that the radical-anion cannot be identified in the usual electrochemical solvents. However benzene derivatives can undergo an electrochemical equivalent of the Birch reaction when protons are present to trap the low concentration of radical-anion formed at very negative potentials. Electrochemical reductions have been achieved in liquid ammonia. Benzene itself is converted in this solvent to cyclohexa-1,4-diene at an aluminium cathode in an undivided cell with sodium chloride as electrolyte and methanol as proton source [35]. The reaction has been applied to reduction of estrone methyl ether **9** where both the benzene ring and the carbonyl group react [36]. The naphthalene ring system in equilenin methyl ether **10** is also reduced to the dihydro stage [37]. Electron donating properties of methoxy and alkyl ring substituents govern the position of protonation for ionic intermediates in these reductions. Positions of highest charge density in the corresponding radical-anions are now found on atoms without electron donating substituents and protonation at these positions leads to the cyclohexadienes shown.



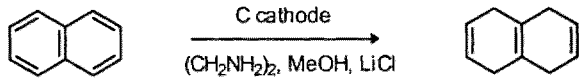
9



10

Most effort over the electrochemical reduction of benzene hydrocarbons has centred on finding a reaction medium, which is also a better solvent for the substrate than liquid ammonia. Aliphatic amines have proved useful solvents and they may be used in an undivided electrochemical cell. Base is generated at the cathode while an equivalent of acid is generated in the anode reaction so that mixing of the cell contents maintains a neutral solution. An alcohol is usually added as a proton donor to prevent the build-up of a localised highly basic environment. The simultaneous anode reaction is oxidation of the amine. Electrodes of platinum, aluminium or graphite have been used. Under these conditions, benzene [38] is converted

to cyclohexa-1,4-diene in methylamine containing lithium chloride as electrolyte. Estrone methyl ether **9**, with the carbonyl function protected as the ketal, is converted to the 1,4-dihydroderivative in ethylenediamine containing lithium chloride [39]. Naphthalene is reduced in both six membered rings to give the tetrahydro derivative **11** [40]. Selective reduction of the benzene ring to the dihydro level can

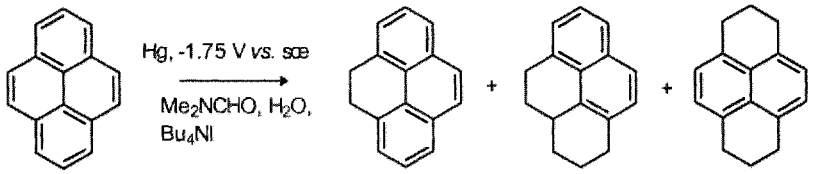


11

be achieved in the presence of a nonconjugated alkene group [41]

Hexamethylphosphoramide, which is a liquid under ambient conditions, is able to solvate electrons. Mixtures of this solvent with up to 21 % ethanol are effective for the electrochemical Birch type reactions. The strong hydrogen bonding between the two solvents suppresses hydrogen evolution at the cathode [42]. Benzene is reduced at constant current in this solvent to a mixture of hydrocarbons, cyclohexane being formed early in the process [43, 44].

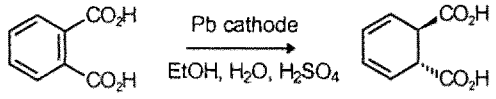
Aprotic solvents can be used for the reduction of aromatic hydrocarbons, particularly the condensed ring systems. Solvents used for the conversion of benzene to cyclohexa-1,4-diene at a mercury cathode under constant current conditions include dimethoxyethane [45] and N-methylpyrrolidone [46]. Each solvent contained water as a proton source and tetraethylammonium bromide as supporting electro-



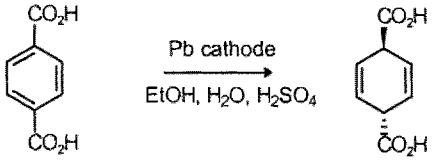
12 Yield: 29 % 57 % 7 %

lyte. The more easily reducible naphthalene is converted to 1,4-dihydronaphthalene at a mercury cathode, potential -2.4 V *vs.* sce, in acetonitrile containing water with tetraethylammonium 4-toluenesulphonate as electrolyte [47]. Pyrene **12** is reducible at –1.75 V *vs.* sce in dimethylformamide. Initially, 4,5- and 1,12-dihydropyrenes are formed. The latter undergoes isomerisation and further reduction to give two hexahydropyrenes [48].

Benzene and naphthalene rings having an electron withdrawing carboxylic acid or ester substituent are more easily reduced by an electron transfer process than the parent hydrocarbons themselves. Phthalic acid **13** and terephthalic acid **14** are converted to the dihydro derivatives at a lead cathode in sulphuric acid [49, 50]. These



13

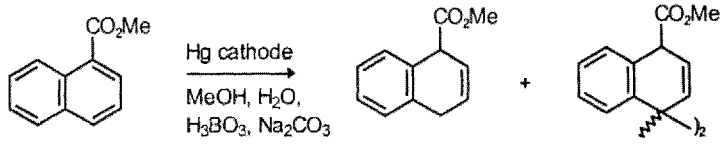


14

reactions have been developed to pilot scale production [51]. The aromatic ring in benzoic acid is not reducible electrochemically in acid solution. Instead, the carboxylic acid function is reduced to the primary alcohol (p. 353).

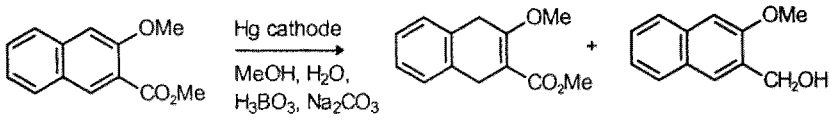
Reduction of the aromatic rings in phthalic acid [52] and in terephthalic acid [53] using sodium and alcohol was first noted by Beyer in 1888. The delocalised anionic reaction intermediates have the highest charge density on the carbonyl oxygen atom. Protonation occurs on oxygen to give an enol and this isomerises to the thermodynamically stable carbonyl form, thus placing hydrogens on the ring atoms bearing the carboxyl groups. During reduction of phthalic acid in alkaline solution, the initial product isomerises to the conjugated enecarboxylate which is then further reduced to cyclohexen-2,3-dicarboxylic acid [54].

Naphthalene monocarboxylic acids are reducible at a mercury cathode in aqueous alkaline solution. Naphthalene-1-carboxylic acid gives the 1,4-dihydro com-



15 Yield: 42 % 20 %

pound and naphthalene-2-carboxylic acid gives the 1,2-dihydro compound in good yields [55]. Reduction of methyl naphthalene-1-carboxylate **15** also affords some hydrodimer, probably by a radical-anion, radical-anion coupling process [56]. For some methyl naphthalene-2-carboxylates, such as **16**, reduction of the ester function is also seen [57].



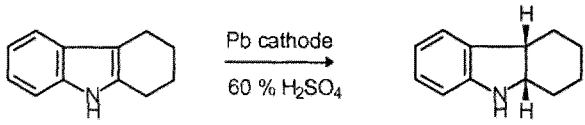
16 Yield: 20 % 20 %

Reduction at a mercury cathode of benzene rings having an electron donating substituent can be achieved in aqueous solution when a tetraalkylammonium hydroxide is used as electrolyte. A reaction temperature of 60 - 80° C is necessary [58]. Tetraalkylammonium salts are known to displace the layer of adsorbed water molecules at the mercury interface, which allows more negative potentials to be reached before the onset of hydrogen evolution. A tetraalkylammonium amalgam is thought to be formed at the mercury surface at negative potentials and this transfers an electron to the substrate [59]. Reduction is more current efficient with tetrahydrofuran as co-solvent. Under these conditions, methoxybenzene, in which the methoxy group is electron donating, is converted to 1-methoxycyclohexa-1,4-diene in 70 % yield and estrone methyl ether **9** affords 92 % yield of the reduction product [60].

Thiophene, Pyrrole and Indole Derivatives

Pyrrole polymerises under reducing conditions. Thiophene-2-carboxylic acid is reduced in alkaline solution at –2.3 V *vs.* sce, on a mercury cathode, to the 2,5-dihydro compound [61]. Under these same conditions, furan-2-carboxylic acid is also reduced to the 2,5-dihydro compound [62].

N-, 2- and 2,3- alkylsubstituted indoles are reduced in acid solution to give good yields of the dihydroindole [63]. Indole itself is polymerised under the acid conditions. Reaction was originally carried out in a medium of 60 % sulphuric acid at a lead cathode with no attempt made to find the optimum acid concentration. More recently, 20 % sulphuric acid has been proposed as the solvent in these reactions [64]. Reduction of tetrahydrocarbazole **17** gives predominately *cis*-hexahydrocarbazole, the thermodynamically favoured isomer, along with 1 –2 % of the *trans*-isomer [65]. 2,3-Dimethyl-indole yields a mixture of the *cis*- and *trans*-dihydroindole isomers [63,66].

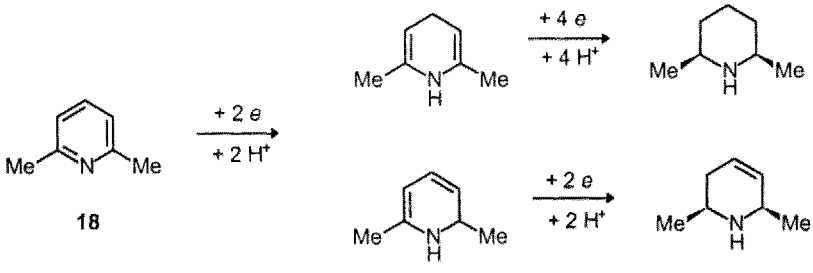


17

Pyridine, Quinoline and Isoquinoline Derivatives

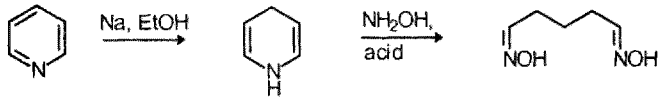
Electron transfer reduction of the pyridine ring was achieved by Ladenberg during his classical synthesis of the piperidine alkaloid, coniine [67]. Sodium in refluxing alcohol, under vigorous conditions, was the reagent used. Electrochemical reduction of alkyl pyridines to the corresponding piperidine is achieved at a lead cathode in 10 % sulphuric acid. Reduction under both acid and alkaline conditions yields mixtures of the piperidine with up to 20 % of the 1,2,3,5,6-tetrahydropyridine [68], the presence of which was not recognised by the early workers. The conversion of 2-propylpyridine to (±)-coniine is now carried out by catalytic hydrogenation over Adams's catalyst [69]

Electron transfer reduction of pyridines in both acid and alkaline solution generates the protonated radical-anion. This rapidly accepts a further electron and a proton to give a mixture of dihydropyridines. Enamine structures in these dihydropyridines can tautomerise to the imine, which is more readily reduced than the original pyridine molecule. Further reaction of the 1,4-dihydropyridine leads to piperidine while reduction of the 1,2-dihydropyridine leads to a tetrahydropyridine in which the alkene group cannot tautomerise to the imine and which is not therefore reduced to the piperidine stage. The reaction sequence is illustrated for 2,6-dimethyl-pyridine **18** which yields the thermodynamically favoured *cis*-2,6-dimethylpiperidine in which the two alkyl substituents occupy *equatorial* conformations.

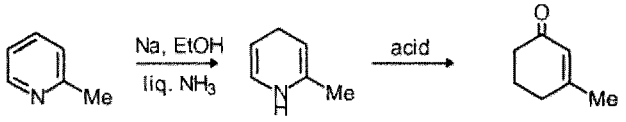


18

Dimerization of the radical-zwitterion intermediate in the electrochemical reduction of pyridines in acid solution occurs to only a minor extent. Some 2 – 3 % of a mixture of reduced 4,4′- and 2,2′-dipyridyls has been found among the reduction products from pyridine [70]. Higher yields of reduced dipyridyls are formed in aqueous alkali at a cadmium cathode [71]. Pentafluoropyridine is reducible in aprotic solvents at –1.8 V *vs.* sce yielding octafluoro-4,4′-dipyridyl through dimerization of the radical-anion and then loss of fluoride ion [72]. Reduction of pyridine by sodium in liquid ammonia in absence of any other proton source leads to products formed by dimerization of the radical-anion [73]. Reduction with one equivalent of sodium and alcohol [74] under less vigorous conditions than originally used by Ladenberg, or in liquid ammonia as co-solvent [75], leads to a mixture of dihydropyridines from which derivatives of the 1,4-dihydropyridine can be



Ref. [74]



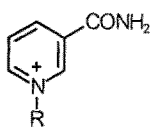
Ref. [75]

readily isolated. Hydrolysis of this intermediate leads to a 1,5-dicarbonyl compound, either isolated as the oxime, or converted by acid treatment into a cyclohexenone.

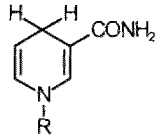
N-Alkylpyridinium salts give mainly N,N′-dialkyltetrahydro-4,4′-dipyridyl derivatives on reduction in neutral and slightly alkaline aqueous solution [76]. These products can be oxidised to the N,N′-dialkyl-4,4′-dipyridyl. The radical-zwitterion derived from 4-cyano-1-methylpyridine couples and then loses cyanide ion to form N,N′-dimethyl-4,4′-dipyridyl in 39 % yield [77].

The pyridinium salt NAD **19a** and its reduced form NADH **20a** are important co-factors for many enzymes. The reduced form is involved in enzyme mediated reductions where it is converted to NAD. In natural systems, NAD is converted back to NADH by another enzyme-controlled process. Attempts to effect the direct electrochemical conversion of NAD to NADH are not very successful. Reduction on a mercury cathode at –1.1 V *vs.* sce on the first one-electron reduction wave leads to the radical-zwitterion, which reacts further to give dimers. Three stereoisomers of the 4,4′-dimer account for 90 % of the mixture and three 4,6′-dimers form the remainder [78]. Reduction at –1.8 V on the second reduction wave produces only 50 % of enzymatically active 1,4-NADH. The NAD analogue **19b** shows related behaviour and one-electron reduction affords two diastereoisomers

of the 4,4'-dimer [79]. A change in the cathode material from mercury to platinum alters the profile of products from the reduction of NAD analogues. Thus, reduction of 1-benzyl-3,5-di(carbamoyl)pyridinium at –1.1 V *vs.* sce in aqueous medium at pH 7 yields dimers at mercury but the NADH type product is obtained in 100 % yield at a platinum cathode [80]. The change in mechanism at platinum is due to

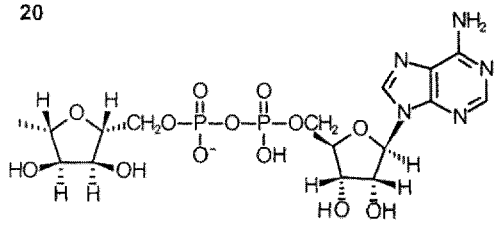


19



20

a, R =

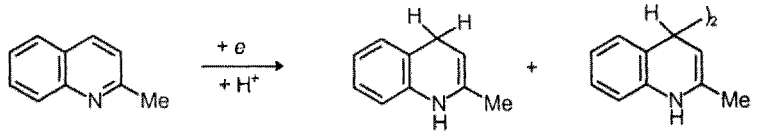


b, R = CH_2Ph

interaction between the radical-zwitterion and chemisorbed hydrogen atoms.

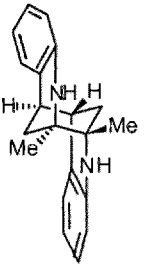
Conversion of NAD to NADH can be achieved in high yield by reduction with a Rh(I)bipyridyl complex bound to polyethyleneglycol [81] and used in a flow through membrane reactor. The auxiliary reagent is converted to the Rh(III) complex which can be cycled to the Rh(I) state either at a carbon cathode or by the action of formate. The membrane discriminates against high molecular weight compounds and retains the rhodium polyethyleneglycol complex within the electrochemical cell whilst allowing NADH to pass into a second reactor.

Reduction of quinolines in acid solution at a lead cathode or by dissolving zinc leads to attack on the heterocyclic ring with the formation of 4,4-coupled products, together with the tetrahydroquinoline [82,83]. In the case of 2- and 4-methyl substituted quinolines, dimeric products are obtained in 10 – 90 % yields. In these processes, dimerization of the one-electron addition product is in competition with further reduction to give the 1,4-dihydroquinoline. The latter is an enamine and it

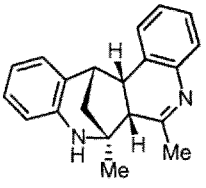


21

isomerises in acid solution to the imine, which is then reduced to the tetrahydroquinoline. 4,4′-Hydrodimers of quinoline have two enamine functions and these are isomerised to the imine. One-electron reduction of each imine now results in intramolecular carbon-carbon bond formation because of the close proximity of the two groups. By this mechanism, reduction of 2-methylquinoline **21** in acid solution leads to a dimer of structure **22** [84] arising from the further reactions of a *meso*-4,4-hydrodimer. Related compounds are obtained from other methyl and dimeth-



22



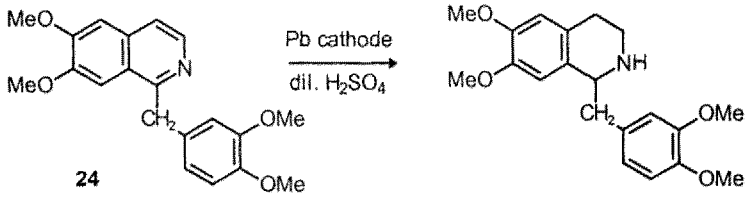
23

ylquinolines. Some (±)-4,4′-hydrodimer is probably also formed but steric considerations do not allow this to be reduced further with intramolecular carbon-carbon bond formation. Polymeric reduction products are also reported in these reduction processes, formed by the intermolecular coupling during reduction of imine functions.

Quinolines are reduced in alkaline solution at a lead cathode or by sodium and alcohol to another class of dimeric product [85,86]. The *meso*-4,4′-hydrodimer is again an intermediate in the process. It undergoes slower conversion to the imine tautomer under alkaline conditions and the intramolecular aldol condensation between one imine function and the remaining enamine function leads to the product **23** [86].

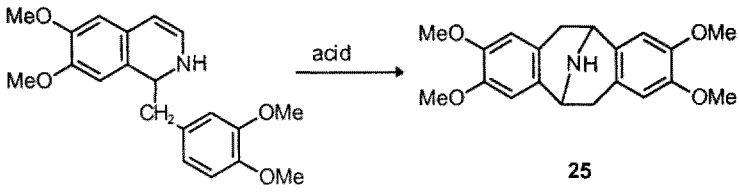
1,4-Dihydro-1-methylquinoline can be prepared by brief treatment of 1-methylquinolinium salts with sodium amalgam in water under alkaline conditions [87]. Reduction of quinolinium salts in acid solution gives dimeric compounds with structures analogous to **22**, but with N-alkyl substituents [83].

Reduction of isoquinolines in acid solution leads to saturation of the heterocy-



24

clic ring and, before the advent of catalytic hydrogenation, this was an important reaction in the isoquinoline alkaloid field. Berberine [88] and papaverine **24** [89] are both converted to the tetrahydro derivative at a lead cathode in dilute sulphuric

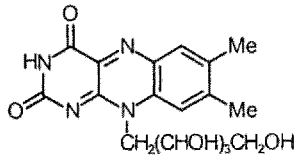


25

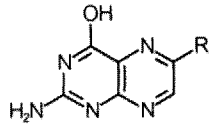
acid. The 1,2-dihydro compound must be an intermediate in the latter process because, under appropriate conditions, it is partly trapped in an intramolecular acid catalysed reaction to form pavine **25** [90,91]. Reduction of isoquinoline with zinc in acetic anhydride affords a 1,1-hydrodimer as the N,N-diacetyl derivative [92].

Other Nitrogen Heterocycles

A number of nitrogen heterocyclic, aromatic compounds, riboflavin **26**, folic acid **27a** and biopterin **27b**, isolated from natural sources, are related in structure to natural redox enzyme cofactors. The electrochemistry of these and related compounds has been studied extensively.



26



27

a: R = CH_2NH—C$_6$H$_4$—$CONHCHCO_2H$ ($CH_2CH_2CO_2H$)

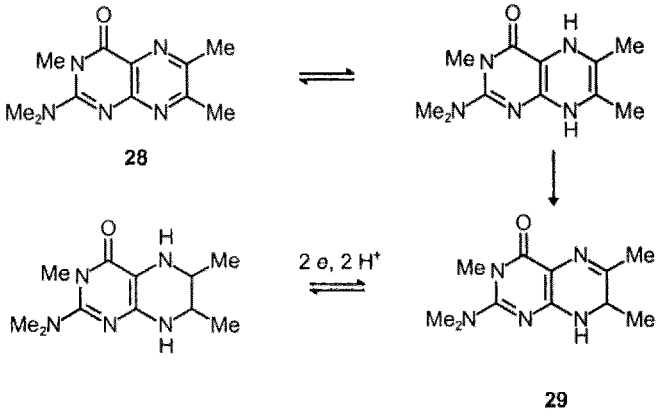
b: R = $CHOHCHOHCH_3$

Riboflavin undergoes a reversible and overall two-electron reduction process, in two overlapping one-electron steps. Both the final product and the one-electron reduction intermediate show acid base equlibria in the pH range 6-7. Thus a number of species take part in the redox process. Experimental investigation aimed at deriving the related equlibrium constants involves generation of the dihydro-

derivative in a buffer solution and subjecting this to redox titration with ferricyanide solution [93]. A graph of potential *versus* electrons transferred is obtained. At pH 6.9, the redox reaction occurs in two one-electron steps separated by 55.1 mV and the semiquinone formation constant is 0.117. In the natural enzymes, this prosthetic group is surrounded by protein and semiquinone formation can be more favoured. Polarography of riboflavin in aqueous buffers indicates two overlapping one-electron reduction waves with a middle potential of –0.460 V *vs.* sce at pH 7.38 [94].

Riboflavin is the redox component of flavin adenine dinucleotide FAD. It is derived from FAD by hydrolysis of a phosphate ester link. The fully oxidised form of FAD is involved in many dehydrogenaze reactions during which it is converted to the fully reduced form. The fully oxidised state is restored either by another redox enzyme or by interaction with oxygen and hydrogen peroxide is liberated. The one-electron reduced, semiquinone form of FAD, is involved in some electron transfer steps.

The biologically active relatives of folic acid and biopterin are the tetrahydro compounds with a reduced pyrazine ring. Reduction to this level occurs rapidly *in vivo*. The corresponding electrochemical process is well illustrated by reduction of the N-methylated analogue **28** [95]. Reduction to the 5,8-dihydro stage is a reversible two-electron and two-proton process. The product rapidly tautomerises to the



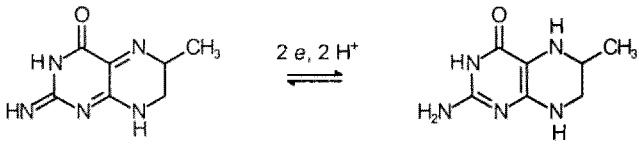
28 **29**

imine form **29**, which is reduced in a second two-electron step at more negative potentials. Pyrazine itself [96] as well as fused ring heterocycles with one pyrazine moiety [97] show related redox steps.

Electrochemical reduction of folic acid is a convenient route to tetrahydrofolic acid. Reaction is performed in an aqueous buffer of triethylamine bicarbonate [98]. Water and buffer salts can then be removed by freeze-drying. The process generates a new asymmetric centre on the tetrahydropyridazine ring and only one of the

diasteriomers is biologically active. An excess of the required isomer is generated by reduction in the presence of a catalytic ammount of strychnine [99] according to the process described on p. 80. The coenzyme derived from folic acid is involved in the synthesis of purines during which process it interacts with formate to provide a one-carbon source.

Tetrahydrobiopterin is involved in the enzymic reaction between phenylalanine and oxygen to give tyrosine and water. Investigation of the process *in vitro* has

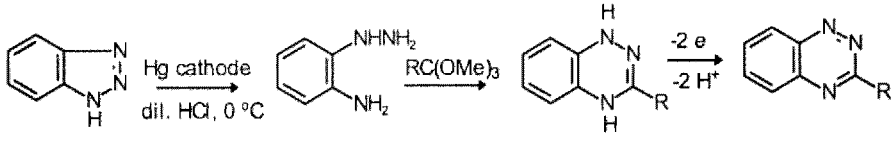


30

used a synthetic analogue of biopterin, **27** with R = Me [100]. During the reaction, the tetrahydro compound is converted to the oxidised form **30**, and this is reduced enzymatically back to the tetrahydro stage. The dihydro form **30** is unstable and rapidly isomerises to the 7,8-dihydropteridine, analogue of **29** [101]. The latter can also be reduced enzymatically to the tetrahydro stage.

Nitrogen-Nitrogen Bond Cleavage

A characteristic reaction of 1,2,3-triazoles is cleavage of one nitrogen-nitrogen

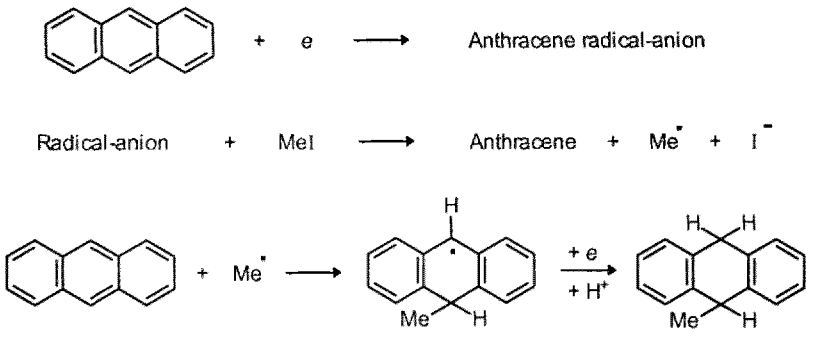


31

bond during electrochemical reduction. This gives a convenient preparation of 2-aminophenylhydrazine **31** from benzotriazole [102]. The process strongly resembles the nitrogen-nitrogen bond cleavage reaction of phenylhydrazones (p. 363). Condensation of the aminohydrazine with an *ortho*-ester gives the dihydrobenzotriazine which can be oxidised to the benzotriazine either electrochemically or using ferricyanide.

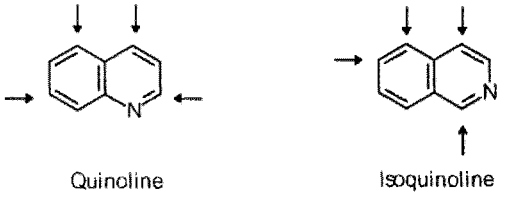
Reductive Alkylation and Carboxylation

Aromatic radical-anions react as nucleophiles towards alkyl halides and carbon dioxide. With alkyl halides, the rate-determining step is an outer sphere one-electron transfer to generate the alkyl radical and halide ion. The radical then adds



Scheme 7.1. Reductive alkylation of anthracene by iodomethane

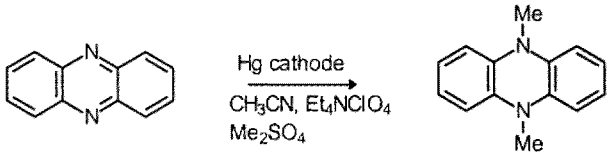
to the aromatic species in a reaction cage process to generate a delocalised radical. The later is relatively easily reduced to the carbanion which protonates. Reaction between anthracene and methyl chloride (Scheme 7.1) gives the 9-alkylated derivative while reaction with *tert*-butyl chloride gives a mixture of 1- and 2-alkylation products [103]. Compared with the Friedel-Crafts reaction, these processes generate a different spectrum of alkylation products. For many examples, complex mixtures of products result. Reaction between pyrene and *tert*-butyl chloride however gives the otherwise difficulty accessible 1-*tert*-butylpyrene in 50 %



Scheme 7.2. Centres of attack during reductive alkylation of quinoline and isoquinoline

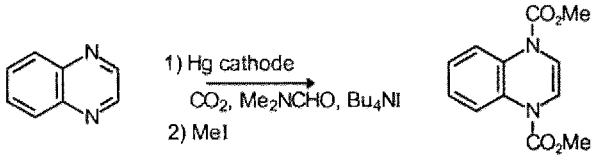
yield [104]. Reaction between quinoline or isoquinoline and *tert*-butyl chloride [105] or 1-bromoadamantane [106] occurs at a number of sites as indicated in Scheme 7.2. In contrast, the radical-anion from phenazine **32** has charge density concentrated on nitrogen and behaves towards alkyl halides as an inner sphere nucleophile. It is alkylated on nitrogen [107].

Aromatic radical-anions will react with carbon dioxide. The redox process for carbon dioxide has E° = -2.2 V *vs.* sce [108], so the high yield reactions with the



32

more easily reduced pyrazine [109] and quinoxaline **33** [110] involve nucleophilic addition by the negatively charged nitrogen atoms and not single electron transfer



33

to carbon dioxide. Naphthalene, which is reduced at a more negative potential than carbon dioxide, affords 1,4-dihydronaphthalene-1,4-dicarboxylic acid in 43 % yield [111]. In this case, reaction is likely to be initiated by single electron transfer from the naphthalene radical-anion to carbon dioxide, followed by radical attack on the naphthalene ring.

Electrocatalytic Hydrogenation

Cathodes of finely divided platinium metals [112], nickel and nickel boride (Ni_2B) [113] generate a surface layer of adsorbed hydrogen atoms from aqueous solutions. The systems have potential for catalytic hydrogenation of aromatic compounds where the required hydrogen is obtained by the cathodic discharge of protons. The only metals effective for electrocatalytic hydrogenation, are those which operate in ordinary catalytic hydrogenation. Reduction of hydrocarbons on nickel surfaces achieves current efficiencies of up to 47 %. The remaining current is accounted for by the evolution of hydrogen gas. Higher current efficiencies can be

obtained by the periodic application of potential with short rest periods during which the surface layer of hydrogen atoms can react with the substrate [114].
The best conditions for hydrogenation of hydrocarbons employ ethylene glycol as solvent because this is less easily adsorbed on nickel, with reaction temperatures around 80 °C [115]. Evolution of oxygen at the anode generates protons to replace those discharged at the cathode. Naphthalene dissolved in ethylene glycol gives tetrahydronaphthalene with 42 % current efficiency at nickel boride, while phenanthrene and anthracene yield mixtures of hydrogenation products [115]. Rhodium black plated onto carbon is effective for the reduction of phenols to cyclohexanols in dilute sulphuric acid [112].

References

[1] B. S. Jensen and V. D. Parker, *J. Am. Chem. Soc.*, 1975, **97**, 5211.
[2] A. Carrington, F. Dravnierkes and M. C. R. Symons, *J. Chem. Soc.*, 1959, 947.
[3] J. R. Bolton and A Carrington, *Mol. Phys.*, 1961, **4**, 497.
[4] G. J. Hoijtink and W. P. Weijland, *Rec. Trav. Chim. Pays-Bas*, 1957, **76**, 836.
[5] S. Hayano and M. Fujihira, *Bull. Chem. Soc. Japan*, 1971, **74**, 1496.
[6] A. Gennaro, A. M. Romanin, M. G. Severin and E. Vianello, *J. Electroanal. Chem.*, 1984, **169**, 279.
[7] C. Z. Smith and J. H. P. Utley, *J. chem. Research S*, 1982, 18.
[8] C. Amatore and J.-M. Savéant, *J. Electroanal. Chem.*, 1980, **147**, 1.
[9] S. Arai and L. M. Dorfman, *J. Chem. Phys.*, 1964, **41**, 2190.
[10] R. Dietz and M. E. Peover, *Trans. Faraday Soc.*, 1966, **62**, 3535.
[11] K. B. Wiberg and T. P. Lewis, *J. Am. Chem. Soc.*, 1970, **92**, 7154.
[12] K. Alwair and J. Grimshaw, *J. Chem. Soc. Perkin 2*, 1973, 1811.
[13] C. L. Talcott and R. J. Myers, *Molecular Phys.*, 1967, **12**, 549.
[14] P. Neta, *Radiation Res.*, 1972, **52**, 471.
[15] O. R. Brown R. J. Butterfield and J. P. Millington, *Electrochim. Acta*, 1982, **27**, 1663.
[16] J. Chaudhuri, S. Kume, J. Jager-Grodzinski and M. Szwarc, *J. Am. Chem. Soc.*, 1968, **90**, 6421.
[17] O. R. Brown and R. J. Butterfield, *Electrochim. Acta*, 1982, **27**, 1647.
[18] O. R. Brown and R. J. Butterfield, *Electrochim. Acta*, 1982, **27**, 1663.
[19] E. M. Kosower, E. J. Land and A. J. Swallow, *J. Am. Chem. Soc.*, 1972, **94**, 986.
[20] D. Talmor, J. Hermolin and E. Kirowa-Eisner, *J. Electroanal. Chem.*, 1982, **139**, 81.
[21] J. G. Gaudiello, D. Larkin, J. D. Raun, J. J. Sosnowski, E. E. Bancroft and H. N. Blount, *J. Electroanal. Chem.*, 1982, **131**, 203.
[22] I. Carelli, M. E. Cardinali and A. Casini, *J. Electroanal. Chem.*, 1979, **105**, 205.
[23] I. Carelli, M. E. Cardinali, A. Casini and A. Arone, *J. Org. Chem.*, 1976, **41**, 3967.
[24] J. Volke and A. M. Kardos, *Coll. Czech. Chem. Commun.*, 1967, **33**, 2560.
[25] I. Carelli, M. E. Cardinali and F. Micheletti-Moracci, *J. Electroanal. Chem.*, 1980, **107**, 391.
[26] H. Volz and W. Lotsch, *Tetrahedron Letters*, 1969, 2275.

[27] M. R. Feldman and W. C. Flythe, *J. Org. Chem.*, 1978, **43**, 2596.
[28] J. M. Leal, T. Tcharani and A. J. Bard, *J. Electroanal. Chem.*, 1978, **91**, 275.
[29] F. Pragst, R. Ziebig, U. Seydewitz and C. Driesel, *Electrochim. Acta*, 1980, **25**, 341.
[30] S. Hünig, J. Gross and W. Schenk, *Liebigs Ann. Chem.*, 1973, 324.
[31] E. D. Moorhead, D. Britton, *Anal. Letters*, 1968, **1**, 541.
[32] J. Volke and V. Volkova, *Coll. Czech. Chem. Commun.*, 1969, **34**, 2037.
[33] S. Hünig and G. Ruider, *Liebigs Ann. Chem.*, 1974, 1415.
[34] A. J. Birch and G. S. Rao, *Advances in Organic Chemistry*, 1972, **8**, 1.
[35] E. C. French, *US* 3488266 (1970); *Chem. Abstr.*, 1970, **72**, 62291.
[36] K. Junghans, *Ger. Offen.*, 2337155 (1975); *Chem. Abstr.*, 1975, **83**, 10598.
[37] K. Junghans, G. A. Hoyer and G. Clere, *Ber.*, 1979, **112**, 2631.
[38] R. A. Benkeser, E. M. Kaiser and R. F. Lambert, *J. Am. Chem. Soc.*, 1964, **86**, 5272.
[39] L. J. Throop, *US* 344057 (1969); *Chem. Abstr.*, 1969, **71**, 50359.
[40] D. Ginsberg and W. J. W. Mayer, *US* 4251332 (1981); *Chem. Abstr.*, 1981, **94**, 164824.
[41] R. A. Benkeser and S. J. Mels, *J. Org. Chem.*, 1969, **34**, 3970.
[42] D. Pasquariello, J. Foise, R. Kershaw, G. Zoshi, K. Dwight and A. Wold, *J. Phys. Chem.*, 1985, **89**, 1243.
[43] H. W. Sternberg, R. E. Markby, I. Wender and D. M. Mohilner, *J. Am. Chem. Soc.*, 1969, **91**, 4191.
[44] R. A. Misra and A. K. Yadav, *Bull. Chem. Soc. Japan*, 1982, **55**, 347.
[45] A. Misono, T. Osa, T. Yamagishs and T. Kodama, *J. Electrochem. Soc.*, 1968, **115**, 266.
[46] T. Hatakeyama, K. Udo, Y. Hamano and G. Inoue, *Japan* 7433955 (1974); *Chem. Abstr.*, 1975, **82**, 117890.
[47] A. Misono, T. Osa and T. Yamagishi, *Bull. Chem. Soc. Japan*, 1969, **41**, 2921.
[48] P. E. Hansen, O. Blaabjerg and A. Berg, *Acta Chem. Scand. B*, 1978, **32**, 720.
[49] C. Mettler, *Ber.*, 1906, **39**, 2933.
[50] T. Ohno, M. Ozaki, A. Inagaki and I. Nishiguchi, *Tetrahedron Letters*, 1993, **34**, 2629.
[51] Badische Anilin und Soda Fabrik A.-G., *Fr.* 1559752 (1970); *Chem. Abstr.*, 1970, **72**, 74127.
[52] A. Beyer, *Liebigs Ann. Chem.*, 1892, **269**, 145.
[53] A. Beyer, *Liebigs Ann. Chem.*, 1888, **245**, 103.
[54] F. Fichter and C. Simon, *Helv. Chim. Acta*, 1934, **17**, 1219.
[55] N. M. Przhiyelgovslaya, G. T. Mondodoev and V. N. Belov, *J. Gen. Chem. USSR*, 1961, **31**, 3145.
[56] G. T. Mondodoev, N. M. Przhiyelgovslaya and V. N. Belov, *Zhur. Organ. Khim.*, 1965, **1**, 1244 and 2008.
[57] N. M. Przhiyelgovslaya, G. T. Mondodoev and V. N. Belov, *J. Gen. Chem. USSR*, 1964, **34**, 1580.
[58] J. P. Coleman and J. H. Wagenknecht, *J. Electrochem. Soc.*, 1981, **128**, 322.
[59] E. Kariv-Miller, K. E. Swenson, and D. Zemach, *J. Org. Chem.*, 1983, **48**, 4210.
[60] E. Kariv-Miller, K. E. Swenson, G. K. Lehman and R. Andruzzo, *J. Org. Chem.*, 1985, **50**, 556.
[61] V. S. Mikhailov, V. P. Gul'tyai, S. G. Mairanovskii, S. Z. Taits, I. V. Proskurovskaya and Yu. G. Dubovik, *Izv. Akad. Nauk. SSSR Ser. Khim.*, 1975, 888.

[62] V. I. Zdanovich, M. G. Ezenitskaya, I. A. Lobanova, B. V. Lokshin and N. E. Kolobova, *Izv. Akad. Nauk SSSR Ser. Khim.*, 1981, 687.
[63] O. Carrasco, *Gazz.*, 1908, **38** ii, 301.
[64] H. Hannebaum, H. Nohe and H. R. Müller, *Ger. Offen.* 20403446 (1975); *Chem. Abs.*, 1975, **83**, 210783.
[65] W. H. Perkin and S. G. R. Plant, *J. Chem. Soc.*, 1927, **129**, 2676.
[66] A. R. Bader, R. J. Bridgewater and P. R. Freeman, *J. Am. Chem. Soc.*, 1962, **83**, 3319.
[67] A. Ladenberg, *Ber.*, 1894, **27**, 3062.
[68] M. Ferles, *Coll. Czech. Chem. Commun.*, 1959, **24**, 2221.
[69] W. Cocker, N. W. A. Geraghty and P. V. R. Shannon, *J. Chem. Soc.Perkin Trans. 1*, 1984, 2241.
[70] B. Emmert, *Ber.*, 1913, **44**, 1716.
[71] Yu. D. Smionov, A. P. Tpmilov, V. D. Shitava and G. F. Shajdulina, *USSR SU* 1048718 (1993); *Chem. Abstr.*, 1994, **120**, 191549.
[72] R. D. Chambers, W. K. R. Musgrave and F. G. Drakesmith, *Tetrahedron*, 1981, **37**, 591.
[73] P. Lebeau and M. Pinson, *Compt. rend.*, 1921, **173**, 1178.
[74] B. D. Shaw, *J. Chem. Soc.*, 1937, 300.
[75] A. J. Birch, *J. Chem. Soc.*, 1947, 1270.
[76] J. E. Colchester and J. H. Entwistle, *US* 3478042 (1970); *Chem. Abstr.*, 1070, **72**, 31627.
[77] J. E. Colchester and J. H. Entwistle, *Ger.* 1913149 (1970); *Chem. Abstr.*, 1970, **72**, 21610.
[78] H. Jaegfeldt, *Bioelectrochem. Bioenerg.*, 1981, **8**, 355.
[79] M. Micheletti, L. F. Franco, V. Carelli, A. Arnone, I. Carelli and M. E. Cardinali, *J. Org. Chem.*, 1978, **43**, 3420.
[80] J. C. Leprêtre, D. Limosin, G. Pierre, *J. Electroanal. Chem.*, 1992, **324**, 115.
[81] E. Steckhan, S. Herrmann, R. Ruppert, J. Thömmes and C. Wandry, *Angew. Chem. Int. Ed. Engl.*, 1990, **29**, 388.
[82] F. B. Ahrens, *Z. Elektrochem.*, 1896, **2**, 577.
[83] G. Heller, *Ber.*, 1914, **47**, 2893.
[84] H. C. Dunathan and I. W. Elliot, *Tetrahedron Letters*, 1961, 781.
[85] I. W. Elliott, E. S. McCaskill, M. S. Robertson and C. H. Kirksay, *Tetrahedron Letters*, 1962, 291.
[86] A. M. Jones, C. A. Russell and O. Meth-Cohn, *J. Chem. Soc. C*, 1971, 2453.
[87] J. W. Bunting and w. G. Meathrel, *Tetrahedron Letters*, 1971, 133.
[88] M. Freund and K. Fleischer, *Liebigs Ann. Chem.*, 1915, **409**, 188.
[89] E. Späth and A. Burger, *Ber.*, 1927, **60**, 705.
[90] G. Goldschmidt, *Monatsh*, 1886, **7**, 485.
[91] A. R. Battersby and R. Binks, *J. Chem. Soc.*, 1955, 2888.
[92] I. W. Elliott and R. B. Griff, *J. Org. Chem.*, 1957, **22**, 515.
[93] L. Michaelis and G. Schwartzenbach, *J. Biol. Chem.*, 1938, **123**, 527.
[94] R. C. Kayne and H. I. Stonehill, *J. Chem. Soc.*, 1952, 3244.
[95] D. Ege-Serpkenci and G. Dryhurst, *Bioelectrochem. Bioenerg.*, 1983, **11**, 51.
[96] J. Pinson and J. Armand, *Compt. rend. C*, 1969, **268**, 620.
[97] J. Armand, C. Bellec, L. Boulaves, P. Chaquin, D. Masure and J. Pinson, *J. Org. Chem.*, 1991, **56**, 4840.
[98] P. E. Rowe and G. P. Lewis, *Methods in Enzymology*, 1986, **122**, 319.

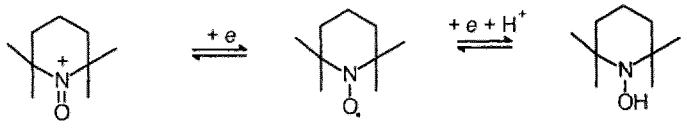
[99] S. Kwee and H. Lind, *Bioelectrochem. Bioenerg.*, 1980, **9**, 175.
[100] S. Kwee and H. Lund, *Biochim. Biophys. Acta*, 1973, **297**, 285.
[101] D. Ege-Serpkenci and G. Dryhurst, *Bioelectrochem. Bioenerg.*, 1982, **9**, 175.
[102] M. Falsig and P. E. Iversen, *Acta Chem. Scand. B*, 1977, **31**, 15.
[103] J. Simonet, M.-A. Michel and H. Lund, *Acta Chem. Scand. B*, 1975, **29**, 489.
[104] P. E. Hansen, A. Berg and H. Lund, *Acta Chem. Scand. B*, 1976, **30**, 267.
[105] C. Degrand and H. Lund, *Acta Chem. Scand.*, 1977, **31**, 593.
[106] U. Hess, D. Huhn and H. Lund, *Acta Chem. Scand. B*, 1980, **34**, 413.
[107] D. W. Root, R. D. Pendarvis and W. H. Smith, *J. Org Chem.*, 1978, **43**, 778.
[108] M. Hammouche, D. Lexa, M. Momenteau and J.-M. Savéant, *J. Am. Chem. Soc.*, 1991, **113**, 8455.
[109] D. Michelet, *Fr. Demande* 2444030 (1980); *Chem. Abstr.*, 1981, **94**, 164821.
[110] P. Fuchs, U. Hess, H. H. Holst and H. Lund, *Acta Chem. Scand. B*, 1981, **35**, 185.
[111] S. Wawzonek and D. Wearring, *J. Am. Chem. Soc.*, 1959, **81**, 2067.
[112] L. L. Miller and C. L. Christensen, *J. Org. Chem.*, 1978, **43**, 2059.
[113] B. Mahdwi, P. Los, M. J. Lessard and J. Lessard, *Can. J. Chem.*, 1994, **72**, 2268.
[114] B. Mahdavi, J. M. Chapuzet and J. Lessard, *Electrochim. Acta*, 1993, **38**, 1377.
[115] D. Robin, M. Comtois, A. Martel, R. Lemieux, A. K. Cheong, G. Belot and J. Lessard, *Can. J. Chem.*, 1990, **68**, 1218.

CHAPTER 8

OXIDATION OF ALCOHOLS, AMINES AND AMIDES

Nitroxyl Radicals

Oxidation of dialkylhydroxylamines with no α-hydrogen substituents proceeds in two reversible one-electron steps. The intermediate nitroxyl radical **2** is the stable species under ambient conditions. The more highly oxidised form **1** finds use as

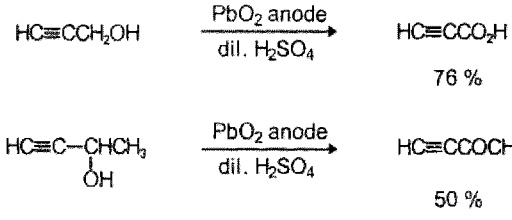


1 **2**

a reagent for the oxidation of alkanols to the carbonyl compound. Standard reduction potentials for these species are give in Table 8.1.

Oxidation of Alcohols

Early electrochemical processes for the oxidation of alcohols to ketones or carboxylic acids used platinum or lead dioxide anodes, usually with dilute sulphuric acid as electrolyte. A divided cell is only necessary in the oxidation of primary alcohols to carboxylic acids if the substrate possesses an unsaturated function, which could be reduced at the cathode [1, 2]. Lead dioxide is the better anode material and satisfactory yields of the carboxylic acid have been obtained from oxidation of primary alcohols up to hexanol [3]. Aldehydes are intermediates in these reactions. Volatile aldehydes can be removed from the electrochemical cell in a



Ref. [4]

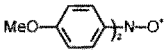
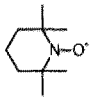
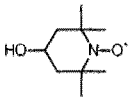
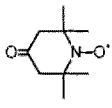
stream of air, and then condensed. In general though, this is not a satisfactory route

to aldehydes since they are easily oxidised to the carboxylic acid at the anode potentials used.

The oxidation of propargyl alcohol to the acid and of but-2-yne-1,4-diol to acetylene dicarboxylic acid is carried out on a technical scale at a lead dioxide anode in sulphuric acid [4, 5]. Electrochemical oxidation of acetylenic secondary alcohols to the ketone at lead dioxide in aqueous sulphuric acid [4], gives better results than the chromic acid based process of Jones [6]. Oxidation of aminoalkan-1-ols to the amino acid at a lead dioxide anode in sulphuric acid is achieved in 31 – 73 % yields [7]. This route is applied to the technical scale production of β-alanine from 3-aminopropanol in an undivided cell [8].

TABLE 8.1

Redox behaviour of nitroxyl radicals in acetonitrile with tetraethylmmonium perchlorate as electrolyte.

Substrate	Reduction process $E_{½}$ / V *vs.* sce	Oxidation process E° / V *vs.* sce
	–	+0.544 [b]
	-1.04 [a]	+0.49 [a]
	-1.49 [a]	+0.608 [b]
	–	+0.668 [b]
	–	+0.781 [b]

Footnotes: (a) Data from [9], adjusted to sce using data for oxidation of 2,2,6,6-tetramethylpiperidinyl-1-oxyl.
(b) Data from [10], adjusted to sce using data from [11].

Alcohol oxidation is inhibited at platinum surfaces with high surface step densities due to the formation of an organic film [12]. More recent attempts to improve the direct electrochemical oxidation of alcohols involve the use of a platinum

catalyst supported on graphite particles in a packed bed reactor, combined with an oxygen diffusion electrode as cathode. The overall cell reaction is given in Equation 8.1. Preparation of the catalyst requires careful control to achieve best results in the oxidation process [13].

$$R{-}CH_2OH + O_2 \longrightarrow R{-}CO_2H + H_2O \qquad \text{Eq. 8.1}$$

The direct electrochemical oxidation of alcohols involves removal of one electron from a non-bonding pair on oxygen. Relatively anodic potentials are required and the use of reagents, which can provide another mechanism for the oxidation step, has been extensively explored. Electrochemistry is then involved in the re-oxidation of spent reagent and often the system can be adapted so as to require only a catalytic amount of reagent.

Aqueous chromic acid acting on a solution of the alcohol in an inert water insoluble solvent [14] is a well known oxidation procedure giving the carbonyl compound. A stoichiometric amount of reagent is required. The aqueous solution of chromium(III) residues can be electrochemically oxidised to the chromium(VI) state [15], however few studies have been made on coupling this process with the excell the oxidation of alcohols.

Nitrogen oxide radicals, derived from the anodic oxidation of nitrate ions in methanol, will oxidise primary alcohols. In the first stage of reaction, an α-

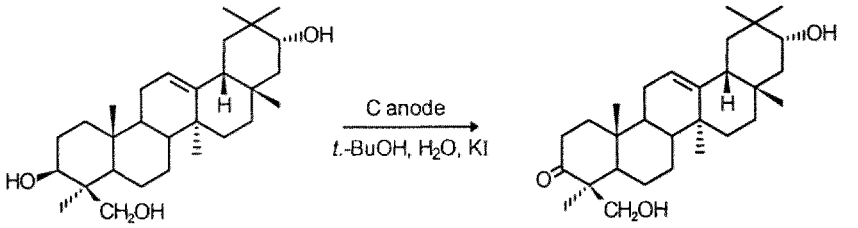
$$RCH_2OH \xrightarrow[MeOH,\ LiNO_3,\ H_2SO_4]{\text{Pt anode}} RCH(OMe)_2 + RCO_2Me$$

62 - 73 % trace Ref. [16]

hydrogen atom is removed and subsequent steps lead to the aldehyde dimethyl acetal [16]. The reaction will not tolerate other functional groups that are attacked by the reagent. The process resembles the oxidation of primary alcohols groups in carbohydrates using nitric acid [17]. Anodic oxidation of secondary alcohols proceeds in low current yields using lithium nitrate in acetonitrile [18].

Anodic oxidation of iodide ions at a graphite electrode in aqueous *tert*-butanol generates a reagent which will oxidise secondary alcohols to ketones and primary alcohols to the ester formed between the related carboxylic acid and the original alcohol [19]. Iodine is first formed and then either further oxidised to iodine(I) or converted to hypoiodite. One of these reagents is the active oxidising agent. Oxidation of iodide ion or iodine in water at sufficiently anodic potentials generates hypoiodite [20]. Related oxidations of alcohols can be achieved using bromide ions at a graphite electrode. The reactions and global electrochemical steps involved

may be written as in Scheme 8.1. The process is catalytic and when an undivided cell is used, proceeds in the presence of base generated in the first stage. The iodine reagent is regioselective for the oxidation of a 3-hydroxyl function in polyhydroxylated triterpenes with a *trans*-A/B-ring junction [21]. Oxidation of the remaining hydroxyl functions in partly protected sugars is also accomplished using calcium iodide as electrolyte [22, 23].



Soyasapogenol

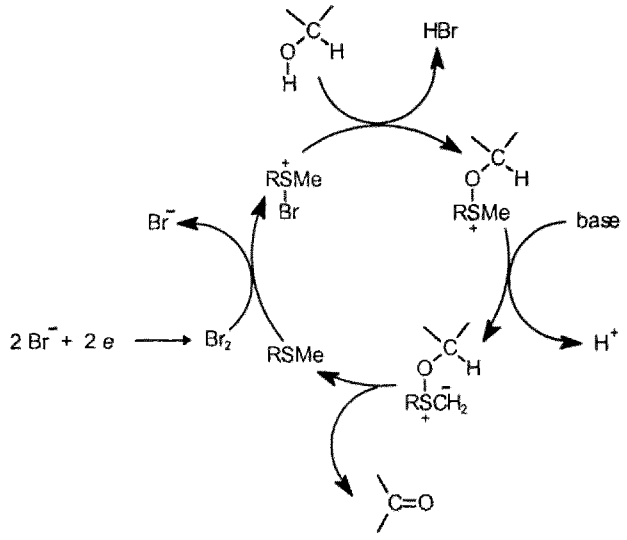
Ref. [21]

Generation of the halogen	$2\,X^- + H_2O \longrightarrow X_2 + H_2 + 2\,HO^-$
Oxidation of the alcohol	$>CHOH + X_2 \longrightarrow >C{=}O + 2\,HX$
Regeneration of the halogen	$2\,HX \longrightarrow H_2 + X_2$

Scheme 8.1. Global reactions during the electrochemical oxidation of alcohols catalysed by halide ions in an undivided cell.

Electrochemical oxidation of carbohydrates is catalysed by the bromide ion – bromine system, which rapidly converts any potential aldehyde function to the carboxylic acid. Gluconic acid is manufactured from glucose in this way using a cell consisting of a stack of parallel graphite plates, separated from each other by narrow gaps through which the reaction solution is pumped. A potential is placed across this pile of electrodes. One side of each electrode functions as anode to a solution stream and as cathode to the stream of solution on the opposite side [24]. Isolated aliphatic secondary alcohols are oxidised very slowly in this system so that current efficiency for ketone formation in an undivided cell is low due to reduction of some bromine at the cathode. The bromide ion – bromine system is satisfactory for the oxidation of benzyl alcohols [25] and α-hydroxyphenylacetate esters [26], although in some cases bromination of the aliphatic system has been observed. Cross-linked poly(4-vinylpyridine) hydrobromide can be electrochemically oxidised so that the protonated pyridine traps the tribromide ion to form a reagent that

will slowly oxidise secondary alcohols in acetonitrile. The exhausted reagent is then re-activated electrochemically [27].

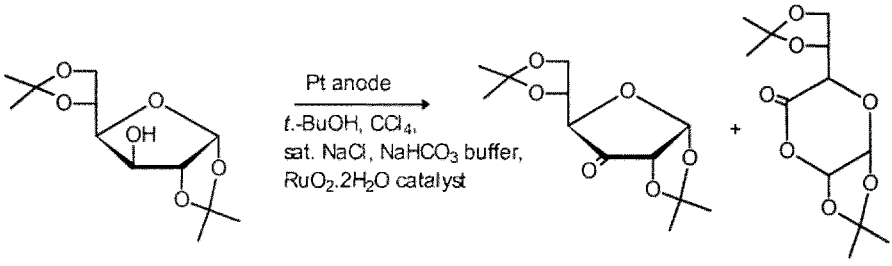


Scheme 8.2. Anodic oxidation of alkanols catalysed by bromide ion and methyl octyl sulphide.

A combination of bromide ions and methyl octyl sulphide is able to oxidise secondary alcohols at the potential necessary to form bromine. Conversion of the alcohol to the ketone follows the Scheme 8.2 and uses an undivided cell with benzonitrile as the solvent containing 2,6-lutidine as base and tetraethylammonium bromide. The reaction occurs using a platinum anode at 1.1 V *vs.* sce [28]. Thioanisole alone, in absence of bromide, will function as a catalyst for the oxidation of secondary alcohols but in these cases a more positive anode potential of 1.5 V *vs.* sce is needed to oxidise the thioether [29].

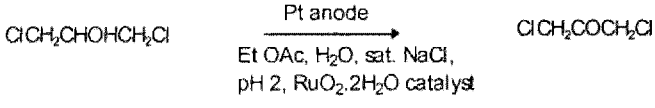
The ruthenium tetroxide – dioxide catalytic system is effective for the oxidation of alkanols, although it will also react with any alkene groups or amine substituents that are present. The catalyst can be used in aqueous acetonitrile containing tetrabutylammonium hydroxide with platinum electrodes in an undivided cell Primary alcohols are oxidised to the aldehyde and secondary alcohols to the ketone [30]. Anodic oxidation of ruthenium dioxide generates the tetroxide, which is the effective oxidising agent.

In another procedure, oxidation is carried out in the presence of chloride ions and ruthenium dioxide [31]. Chlorine is generated at the anode and this oxidises ruthenium to the tetroxide level. The reaction medium is aqueous sodium chloride with an inert solvent for the alkanol. Ruthenium tetroxide dissolves in the organic layer and effects oxidation of the alkanol. An undivided cell is used so that the chlorine generated at the anode reacts with hydroxide generated at the cathode to form hypochlorite. Thus this electrochemical process is equivalent to the oxidation of alkanols by ruthenium dioxide and a stoichiometric amount of sodium hypochlorite. Secondary alcohols are oxidised to ketones in excellent yields. 1,4- and 1,5-Diols with at least one primary alcohol function, are oxidised to lactones while



Ref. [32] 82 % 1 %

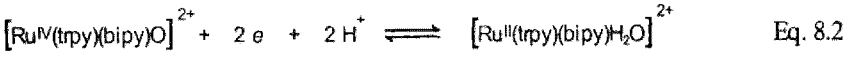
isolated primary alcohols are oxidised to the carboxylic acid. Examples in optimising the use of ruthenium dioxide catalyst include the oxidation of protected carbohydrates [32] and a proposed technical scale production of 1,3-dichloroacetone [33]. The rate of oxidation of the alkanol is considerable increased



Ref. [33]

at high concentrations of sodium chloride [34].

The ruthenium(IV) complex **3** is a powerful oxidising agent. It can be used in catalytic amounts, the residual ruthenium(II) complex being re-oxidised directly at

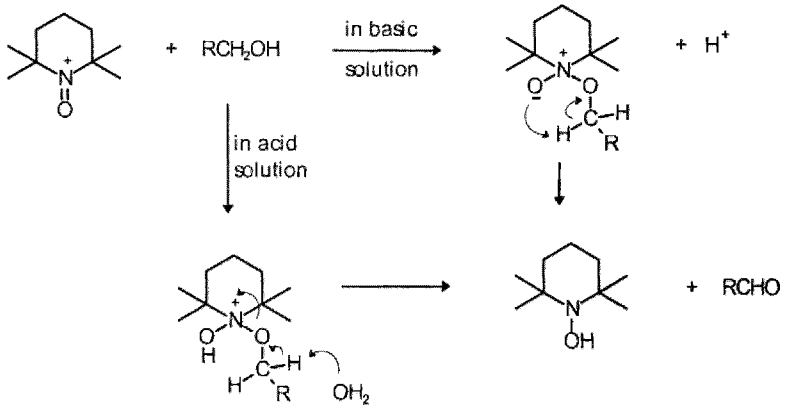


3 Eq. 8.2

the anode according to the redox process in Equation 8.2. This system oxidises secondary alcohols to ketones and primary alcohols to the carboxylic acid in a di-

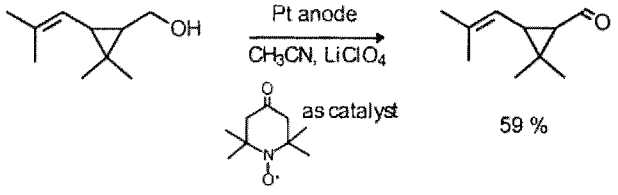
methyl sulphoxide – water solvent mixture [35]. The reagent is also sufficiently powerful to oxidise any benzylic positions in arene derivatives.

An established non-electrochemical system for the catalytic oxidation of alcohols is based on stable nitroxyl radicals such as **2** as catalyst and which are converted to the oxopiperidinium **1** as the effective reagent. Regeneration of the reagent using a stoichiometric amount of an inorganic oxidising agent, such as hypochlorite or periodate, is a common procedure by which alkanols are oxidised to the aldehyde or ketone. Regeneration of the reagent is also effected electrochemically in an anodic process. The mechanism for this oxidation of alkanols is shown in Scheme 8.3 [36]. In basic solution, sterically hindered secondary alkanols are oxidised more slowly than primary alkanols. In acidic solution, primary and secondary alkanols are oxidised at comparable rates.



Scheme 8.3. Pathways for the oxidation of alkanols by 2,2,6,6-tetramethyl-1-oxopiperidinium

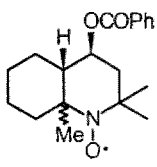
Spent 2,2,6,6-tetramethyl-1-oxopiperidinium can be regenerated directly at a platinum anode in aqueous acetonitrile and aldehyde products do not undergo further oxidation to the carboxylic acid [37]. Either of the two racemic quinolyl-1-oxyls **4** functions better as catalyst for the oxidation of primary and secondary alkanols, but the chiral forms do not achieve selective oxidation of one enantiomer of



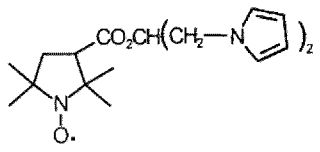
Ref. [37]

a chiral alkanol [38, 39].

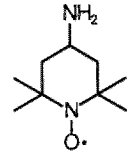
The use of nitroxyls that are amenable to immobilisation in a polymer layer around the anode would be an ideal way of constraining the catalyst where it can be regenerated electrochemically. Attempts to utilise a poly(pyrrole) film formed by anodic oxidation of the monomer **5** led to a system that will oxidise alkanols but which is unstable in continuous use [40]. A more satisfactory polymer layer is



4

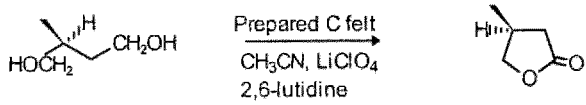


5



6

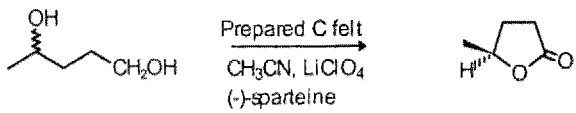
based on poly(acrylic acid). This electrode is prepared from graphite felt coated with poly(acrylic acid) and then lightly cross-linked by amide bond formation using hexamethylenediamine and dicyclohexylcarbodiimide. At this point, the aminonitroxyl **6** is attached to some of the remaining carboxyl groups by amide formation. Finally the remaining carboxyl groups are esterified with dibutyl sulphate [41]. The resulting layer catalyses the oxidation of alcohols in acetonitrile containing lithium perchlorate and a tertiary amine, which functions as a base. This system obeys the general rule that under basic conditions the least hindered alkanol



7

96 % e.e.

Ref. [41]



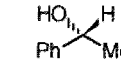
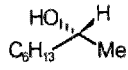
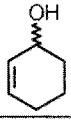
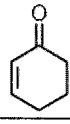
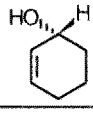
8

48 % yield, 99% e.e.

is preferentially oxidised. Oxidation of the diol **7** is regioselective [41]. When a chiral amine, particularly (-)-sparteine is the base, then one enantiomer of a chiral alkanol is oxidised preferentially. The residual alkanol is enriched in the other enantiomer. Selectivity is very high as indicated in Table 8.3 [42]. Oxidation of the

diol **8** is both regioselective and enantioselective and gives one lactone product in high enantiotopic purity [41].

TABLE 8.2
Enantioselective oxidation of (±)-alcohols using nitroxyl loaded carbon felt in acetonitrile with (-)-sparteine present, ref. [42].

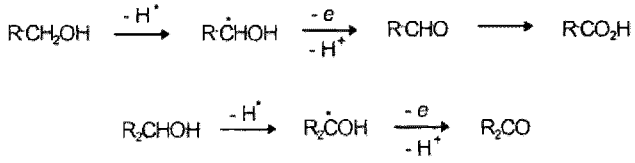
Racemic alcohol	Ketone product	Main remaining enantiomer	Selectivity / %
PhCHOHMe	PhCOMe		92.4
$C_6H_{13}CHOHMe$	$C_6H_{13}COMe$		93
			96.4

Electrochemical regeneration of the 1-oxopiperidinium in bulk solution is facilitated by the use of sodium bromide as both electrolyte and mediator. The tribromide is generated at the anode and re-oxidises the 1-hydroxypiperidine residues [43]. This in-cell regeneration step parallels the use of stoichiometric amounts of sodium hypochlorite as regenerating agent [44]. The electrochemical process is operated in a two-phase system of aqueous sodium bromide and dichloromethane, with vigorous stirring, and with carbon electrodes. It is amenable to the oxidation of water insoluble alcohols. Alkenes and some reactive benzene rings undergo bromination as well as oxidation of the hydroxyl function. These side reactions have been avoided by generating a stoichiometric amount of tetrabutylammonium tribromide in a separate electrochemical step and then adding this to a solution of the alcohol and nitroxyl catalyst in an organic solvent [45].

Nickel(III) oxide, prepared from a nickel(II) salt and sodium hypochlorite, is used for the oxidation of alkanols in aqueous alkali [46]. Residual nickel(II) oxide can be re-activated by reaction with sodium hypochlorite. Nickel oxides have also long been used in the manufacture of the positive pole in the Edison nickel-iron rechargeable battery, now largely superseded by the lead-acid accumulator, and in the Jungner nickel-cadmium batteries used as button cells for calculators [47]. Here, prepared nickel oxide is pressed into a holding plate of perforated nickel. Such prepared plates of nickel(III) oxide have been proposed as reagent for the oxidation, in alkaline solution, of secondary alcohols to ketones and primary alcohols to carboxylic acids [48]. Used plates can be regenerated by anodic oxidation.

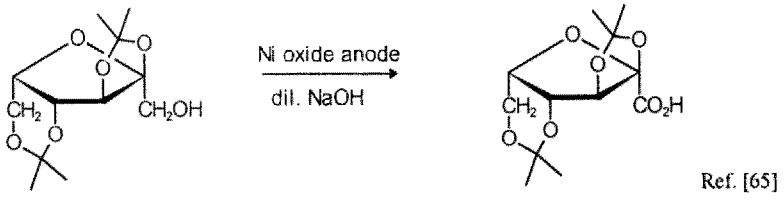
Electrochemically generated nickel(III) oxide, deposited onto a nickel plate, is generally useful for the oxidation of alcohols in aqueous alkali [49]. The immersion of nickel in aqueous alkali results in the formation of a surface layer of nickel(II) oxide which undergoes reversible electrochemical oxidation to form nickel(III) oxide with a current maximum in cyclic voltammetry at 1.13 V *vs.* sce, observed before the evolution of oxygen occurs [50]. This electrochemical step is fast and oxidation at a prepared oxide film, of an alcohol in solution, is governed by the rate of the chemical reaction between nickel oxide and the substrate [51]. When the film thickness is increased to about 0.1 μm, the oxidation rate of organic species increases to a rate that is fairly indifferent to further increases in the film thickness. This is probably due to an initial increase in the surface area of the electrode [52]. In laboratory scale experiments, the nickel oxide electrode layer is prepared by prior electrolysis of nickel sulphate at a nickel anode [53]. It is used in an undivided cell with a stainless steel cathode and an alkaline electrolyte.

Electrochemically generated nickel(III) oxide is approximated as NiO(OH). Analytical figures obtained for the chemically prepared oxide approximate to $NiO(OH).H_2O$. The material behaves as a radical source and the initial step in the oxidation of alkanols is radical attack with removal of the α-hydrogen atom. This is followed by an electron transfer from the carbon radical so generated, see Scheme 8.4 [54]. The same process also attacks aldehydes in the *gem*-diol form. The nickel oxide electrode also attacks nitrogen-containing compounds (p. 281).



Scheme 8.4. Steps in the oxidation of alkanols at a nickel oxide anode.

This nickel oxide coated nickel anode was developed on a technical scale for oxidation of the protected *D*-glucose derivative **9** to the carboxylic acid, as one step in the production of *L*-ascorbic acid [55, 56]. The electrochemical reaction is conducted at a low current density so that a large anode surface area anode is required

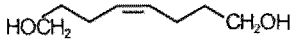
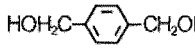


9 93 % Ref. [65]

for rapid throughput. An undivided cell with a stainless steel cathode is used. The electrodes consist of large thin sheets of the metals separated by a polypropylene net insulator, then rolled around a nickel rod, which functions as anode connector, and pushed into a steel cylinder, which functions as the cathode connector. Electrolyte is pumped through this rolled-up electrode system. Anode deactivation is found over a long period of time and this can be retarded by the addition of small amounts of nickel(II) salt to the electrolyte. Several other methods are suggested for improving anode performance [57, 58].

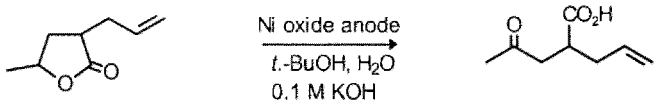
TABLE 8.3

Conversion of primary alcohols, as an emulsion in aqueous sodium hydroxide, to the carboxylic acid at a pre-formed nickel oxide electrode, ref. [59].

Substrate	% Yield of carboxylic acid	Reaction temperature
$C_8H_{17}\ CH_2OH$	89	70 °C
$PhCH_2OH$	86	25 °C
	82	25 °C
$HC{\equiv}CCH_2OH$	51 [a]	5 °C
$HOCH_2(CH_2)_8CH_2OH$	85	80 °C
	80	80 °C
$HOCH_2C{\equiv}CCH_2OH$	55 [a]	20 °C
	99 [b]	

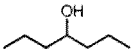
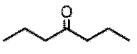
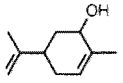
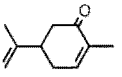
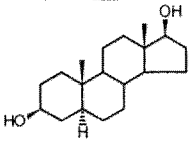
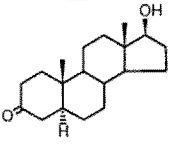
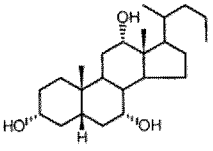
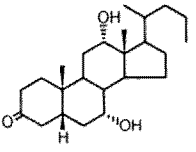
Footnotes: (a) A divided cell is necessary to prevent electrocatalytic reduction of the alkyne bond.
(b) Ref. [60].

The nickel oxide electrode is generally useful for the oxidation of alkanols in a basic electrolyte (Tables 8.3 and 8.4). Reactions are generally carried out in an undivided cell at constant current and with a stainless steel cathode. Water-soluble primary alcohols give the carboxylic acid in good yields. Water insoluble alcohols are oxidised to the carboxylic acid as an emulsion. Short chain primary alcohols are effectively oxidised at room temperature whereas around 70 °C is required for the oxidation of long chain or branched chain primary alcohols. The oxidation of secondary alcohols to ketones is carried out in 50 % *tert*-butanol as solvent [59]. γ-Lactones, such as **10**, can be oxidised to the ketoacid in aqueous sodium hydroxide [59].

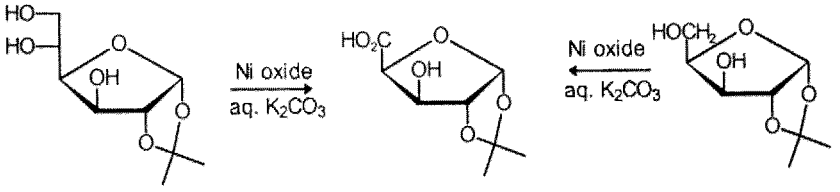


10 **97 %**

TABLE 8.4
Conversion of secondary alcohols to ketones at a pre-formed nickel oxide electrode in 50 % *tert*-butanol, 0.1 M KOH at 25 °C, ref. [59].

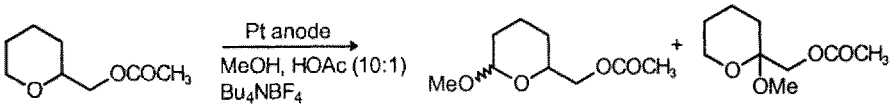
Substrate	Product	% Yield
		70
		75
		75
		28
		38

Primary alcohol groups in protected monosaccharides are efficiently oxidised to carboxylic acid at the nickel oxide anode. Secondary alcohol groups however react very slowly, probably due to steric hindrance from the adjacent protecting group. This allows selective oxidation of polyols such as **12** and **13** [61].



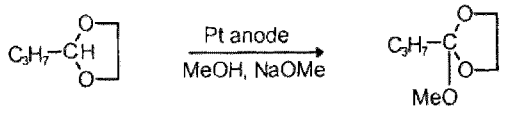
12 53 % **13**

Anodic oxidation of dialkyl ethers in methanol results in the formation of acetals [62]. Reaction is best carried out at a platinum, rather than carbon, anode in methanol containing 10 % acetic acid with tetraethylammonium fluoroborate as



40 % 40 % Ref. [63]

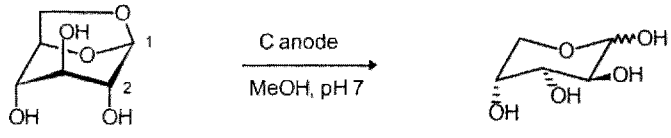
electrolyte, in an undivided cell [63]. The most satisfactory yields are obtained from 5- and 6-ring cyclic ethers and oxidation of unsymmetrical ethers shows no regioselectivity. For these ether substrates, the oxidation can be terminated at the



72 % Ref. [64]

acetal stage. However, chemically prepared 2-substituted 1,3-dioxolanes are readily oxidised to an ortho ester at a platinum anode in methanolic potassium hydroxide [64].

Levoglucosan **14**, which is derived from *D*-glucose, has a strained ether ring system. Oxidation in methanol causes carbon-carbon bond cleavage to yield *D*-arabinose. High yields are obtained in methanol with addition of sodium methoxide

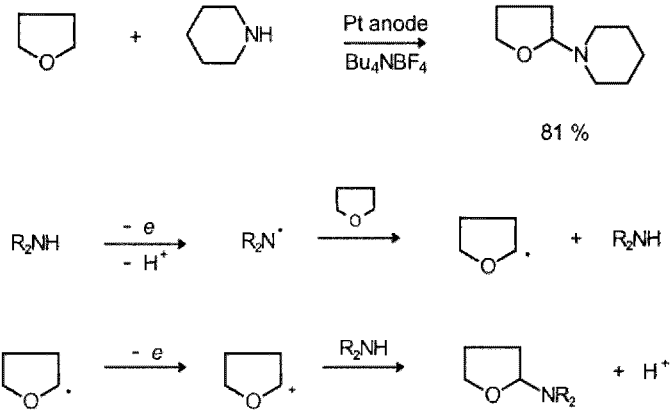


14

to maintain pH 7 [65]. This process is superior to the usual chemical routes for the conversion of glucose to arabinose. In the electrochemical process, probably a radical-cation is generated on the hydroxyl group at position 2, followed by bond cleavage between C_1 and C_2. Further oxidation steps lead to arabinose.

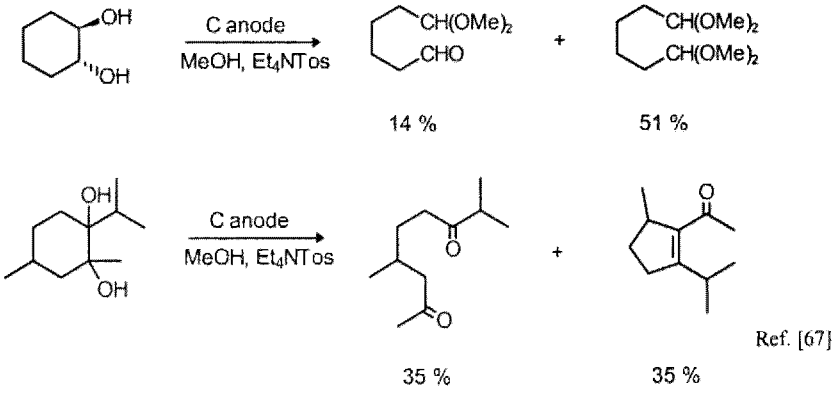
Electrochemical oxidation of tetrahydrofuran containing piperidine leads to efficient formation of the 2-piperidinotetrahydrofuran. However, this process is not

generally useful and open chain dialkylamines give poor yields of the 2-amino-tetrahydrofuran. In these reactions, oxidation of the amine is thought to occur in preference to oxidation of the ether (Scheme 8.5). Tetrahydrofuran is involved in a hydrogen atom transfer to the imine radical, after which further reactions lead to the product [66].



Scheme 8.5. Mechanism for the oxidation of amines in tetrahydrofuran, ref. [66]

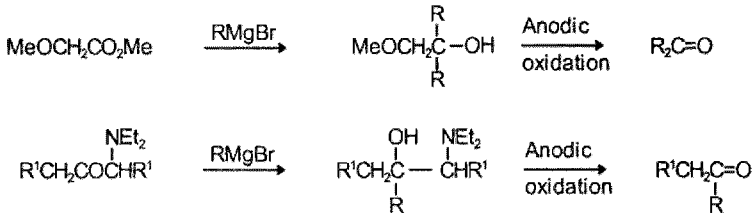
1,2-Glycols are cleaved by electrochemical oxidation at a carbon electrode using potentials around +2.2 V *vs.* sce. Reaction is carried out in methanol in an undivided cell. Secondary alcohol centres lead to the aldehyde dimethyl acetal while



Ref. [67]

tertiary alcohol centres lead to a ketone product. Both *cis*- and *trans*-1,2-glycols are cleaved. 1,2-Dimethoxy and 1-hydroxy-2-methoxy are also oxidisable [67]. Carbon-carbon bond cleavage also results from the anodic oxidation of 2-amino-

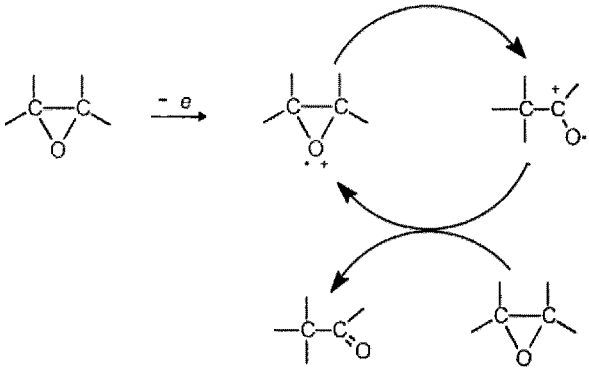
alcohols and 1,2-diamines [68]. These anodic cleavage reactions are incorporated into a novel route for the preparation of symmetrical and unsymmetrical dialkyl ketones illustrated in Scheme 8.6 [69].



Scheme 8.6. Routes for the preparation of dialkyl ketones, ref. [69].

Aqueous periodic acid can be used to achieve glycol cleavage, combined with anodic oxidation of the iodate, which is formed, back to periodate [70]. Oxidation of iodate is catalysed at a lead dioxide anode [71] but at the potentials required, aldehydes are oxidised to the corresponding acids. Due to this further reaction, the redox-mediated cleavage of diols to form an aldehyde may be difficult to achieve with a catalytic amount of periodic acid. Cleavage using a stoichiometric amount of periodic acid, followed by recovery of the iodic acid and then its electochemical oxidation, has been achieved [72].

Electrochemical oxidation of epoxides in absence of nucleophiles, catalyses a rearrangement to the carbonyl compound. The electrolyte for this process is dichloromethane with tetrabutylammonium perchlorate. Reaction, illustrated in Scheme 8.7, involves the initial formation of a radical-cation, then rearrangement to the ketone radical-cation, which oxidises a molecule of the substrate epoxide. The process is catalytic and requires only a small charge of electricity [73].



Scheme 8.7. Mechanism of the electrochemically catalysed rearrangement of epoxides to ketones.

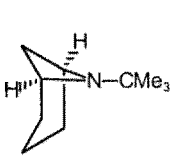
Oxidation of Amines and Sulphonamides

The majority of amines show an irreversible oxidation wave on cyclic voltammetry in acetonitrile at a platinum electrode [74]. Some peak potenial values are given in Table 8.5. An electron is lost from the nitrogen lone pair and the resulting radical-cation loses a proton from the α-position. Further oxidation of the remaining carbon radical then follows. Proton loss is assisted by overlap in the transition-state between the *p*-orbital containing an unpaired electron on nitrogen and the stretching σ-orbital of the carbon-hydrogen bond. Where these two orbitals are orthogonal as in **15**, the amine radical-cation becomes stable on a short time scale so that a value for E° = 0.74 V *vs.* sce can be obtained from cyclic voltammetry and the esr spectrum can be recorded [75].

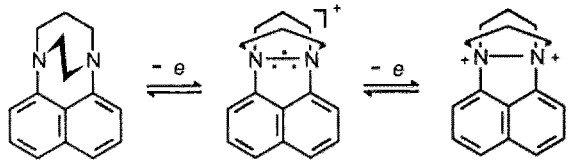
TABLE 8.5

Anodic peak potentials for cyclic voltammetry of amines in acetonitrile, $NaClO_4$, scan rate 6 V s^{-1}. Ref. [74].

Substrate	E_p / V *vs.* sce
Propylamine	1.38
Dipropylamine	0.95
Tripropylamine	0.88



15



16

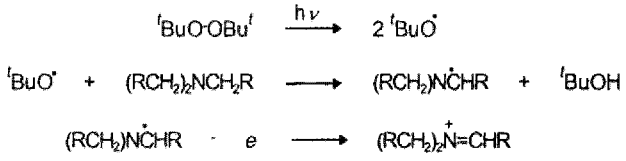
Diamines with a cage-like structure in which the nitrogen atoms are separated by a three carbon chain, form radical-cations where the non-bonding orbital from one nitrogen atom interacts with the radical-cation on the other nitrogen atom to form a three-electron bond [76]. Cyclic voltammetry of **16** in acetonitrile shows two reversible waves with E° = 0.11 and 0.72 V *vs.* sce. The second wave is due to the formation of a dication with a two-electron bond between the nitrogen atoms.

The α-aminoalkyl radical intermediates from electrochemical oxidation of amines show a strong tendency to lose a further electron and form an immonium ion. This process shows an anodic polarographic wave at negative electrode poten-

tials *vs.* sce (Table 8.6) [77]. Measurement of half-wave potentials is achieved by first generating the radical in a photochemical process involving di-*tert*-butyl peroxide, illustrated in Scheme 8.8. In the experiments, *tert*-butoxy radicals are generated using a modulated light beam. These react with the amine to generate a modulated concentration of α-aminoalkyl radicals. Oxidation of the alkyl radicals at an electrode surface gives rise to a modulated electron flow, which is easily amplified. A polarogram is then built up by changing the electrode potential and recording the amplified current flow [78]. The corresponding reduction process for immonium salts, generating the α-amino-alkyl radical, is discussed on p. 359.

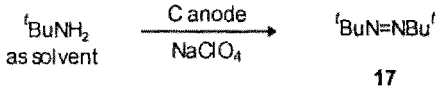
TABLE 8.6
Polarographic half-wave potentials for α-aminoalkyl radical oxidation.

Substrate	$E_{½}$ / V *vs.* sce	Ref.
$Me_2N\dot{C}H_2$	-1.03	[78]
$(PhCH_2)_2N\dot{C}HPh$	-0.92	[78]
$Me_2N\dot{C}HPh_2$	-1.17	[79]



Scheme 8.8. Reaction sequence for the photochemical generation of α-aminoalkyl radicals and determination of oxidation potential, ref. [78].

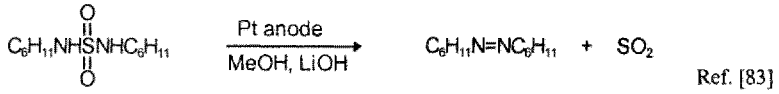
For amines having an α-hydrogen atom, electrochemical oxidation leads to the imine as the first detectable intermediate. In the absence of another nucleophile, this is not usually a useful reaction since the imine is hydrolysed by water present in the solvent leading to a mixture of products [80, 81]. Oxidation of *tert*-butylamine, which has no α-hydrogen atom, leads to loss of a proton from the nitrogen atom and the dimerization of nitrogen centred radicals. The product isolated in moderate yields is azo-*tert*-butane **17** [82]. The reaction can be carried out in an



17

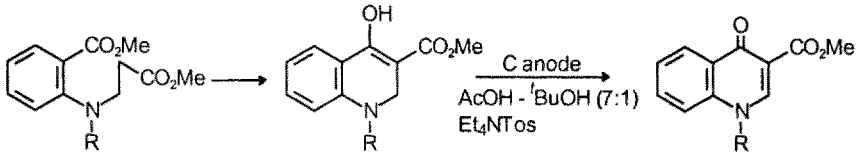
undivided cell where the electrolyte is pumped through a stack of carbon anodes

and stainless steel cathodes. Azoalkanes are obtained from primary and secondary amines by anodic oxidation of the N,N'-dialkylsulphamide in alkaline solution [83]. The same reaction is also effected using sodium hypochlorite as oxidant [84].



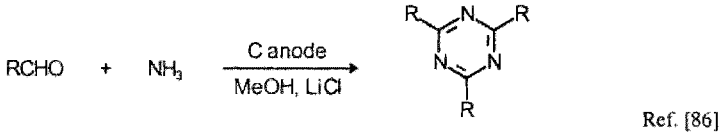
Ref. [83]

For some heterocycles, the imine stage in the oxidation of a secondary or tertiary amine is stable to hydrolysis. Thus oxidation of 1.2-dihydroquinolines gives



18

the quinoline in high yield. This reaction can be carried out in an undivided cell and allows a convenient synthesis of 1,4-dihydro-4-oxoquinolines **18** [85]. A related process is the oxidation of trimeric aldehyde-ammonia condensation products to give the 1,3,5-triazine [86].

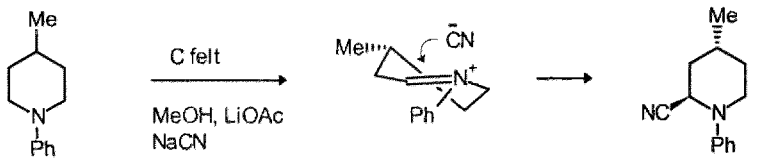


Ref. [86]

R = Me 20 %
R = Me_2CH 30 % yield

Imine intermediates can be trapped by an added nucleophile. However the only reactions of general preparative value are those in which a carbon-carbon bond is formed. In most other cases the product is unstable under the reaction conditions, reverting to the imine which reacts further. Reactions are best carried out in the flow through cell devised by Moinet and Raoult, illustrated in Figure 8.1 [87]. This cell permits total oxidation of the substrate in one pass through the porous anode, thus exposing the product to further oxidation for only a short time. α-aminonitriles are obtained when cyanide ion is added to the electrolyte [88, 89]. In the case of piperidine ring oxidation, addition to the imine is from the less hindered

axial direction onto the more stable conformer, which can lead in some cases to a high degree of stereoselectivity for product formation.



Ref. [89]

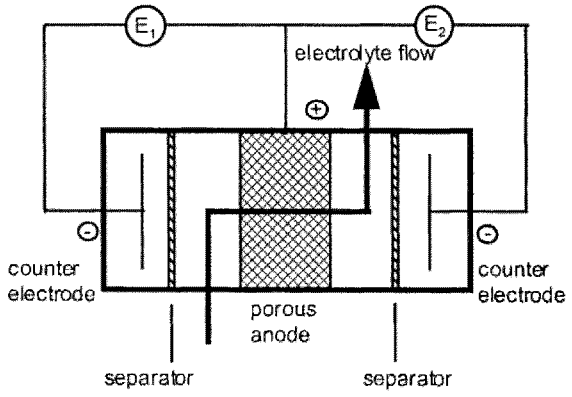
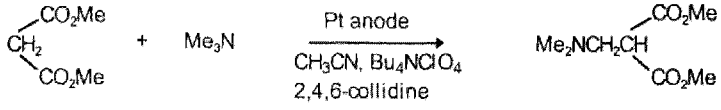


Figure 8.1. Flow cell fitted with a porous carbon felt working electrode fitted between two counter electrodes, see ref. [87].

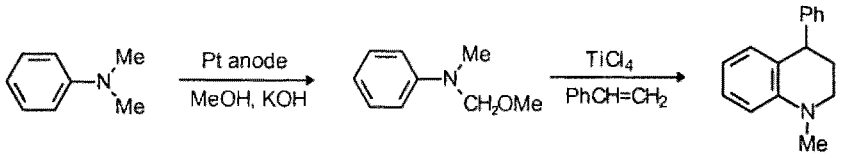
Electrochemical oxidation of aliphatic tertiary amines in acetonitrile together with compounds having weakly acidic hydrogens, such as dimethyl malonate, leads to addition of the malonate anion to the immonium cation intermediate. 2,4,6-Collidine is added to combine with protons, which are released during reaction [90].



Ref. [90]

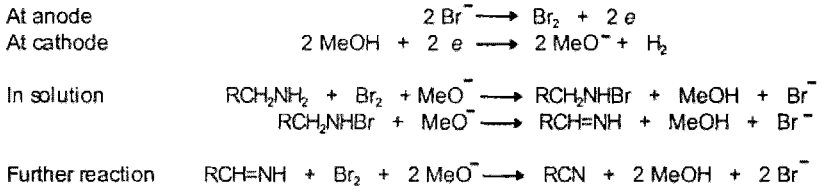
The immonium ion derived from oxidation of N,N-dimethylaniline can be trapped by reaction with methanol to give the relatively stable α-methoxymethyl

compound [91]. Reaction of this with electron rich alkenes, catalysed by Lewis acids, is used to form the tetrahydroquinoline ring [92].



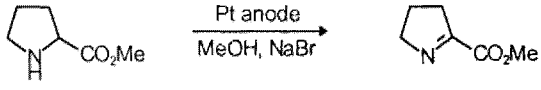
Ref. [92]

Indirect electro-oxidation of primary amines to nitriles is achieved using halogen ion as mediator [93]. The reaction is typically carried out in an undivided cell



Scheme 8.9. Reaction sequence in the indirect electrochemical oxidation of primary amines to nitriles using bromide ion as mediator.

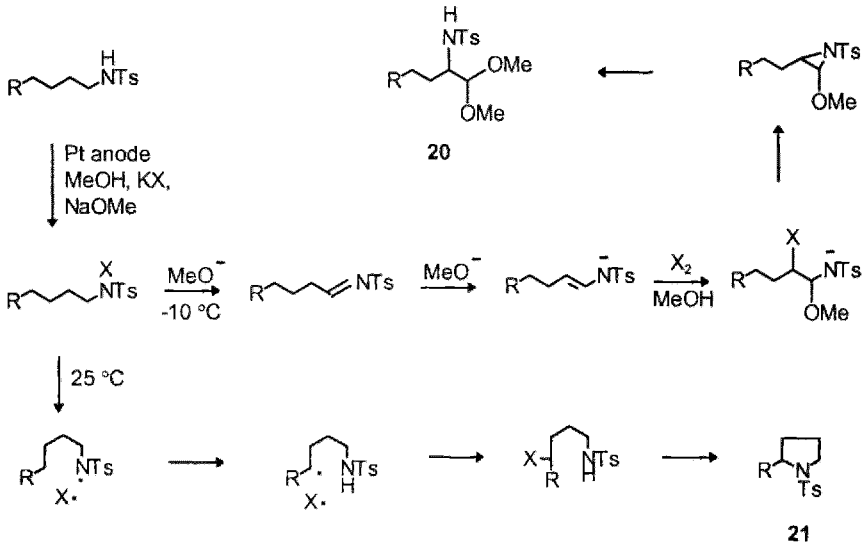
with closely placed platinum anode and cathode. Electrolysis of the amine in methanol containing sodium bromide generates bromine and methoxide ion and these cause dehydrogenation of the amine according to Scheme 8.9. Imines derived from primary amines cannot normally be isolated because they react rapidly to give the nitrile. In the case of proline methyl ester, the relatively stable imine **19** is obtained in 80 % yields.



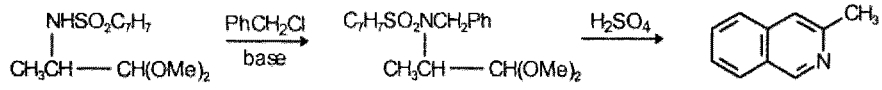
19

Oxidation of sulphonamides in the presence of bromide or iodide ions and sodium methoxide in methanol also leads to formation of the N-halogeno intermediate. The nitrogen-halogen bond in these intermediates is weak and will undergo thermolysis. At –10 °C, reaction proceeds by base catalysed elimination of hydrogen halide and further steps lead to an α-amino acetal **20**. The reaction is carried out in an undivided cell and renders α-aminoacetals readily available for the iso-

quinoline ring synthesis [94]. At room temperature, homolytic cleavage of the nitrogen-halogen bond occurs. When the alkyl chain is long, this step is followed by an intramolecular δ-hydrogen abstraction process and ultimately to the formation of a pyrrolidine ring **21** as indicated in Scheme 8.10 [94, 95].

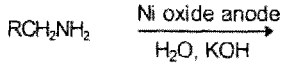


Scheme 8.10. Electrochemical conversion of toluene-4-sulphonamides to α-aminoacetals, catalysed by bromide ion. Ref. [95].



Ref. [94]

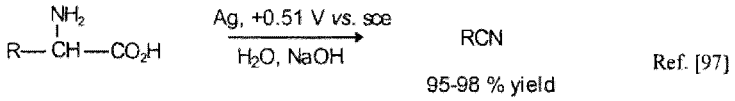
Oxidation of primary amines at a nickel oxide results in the formation of a nitrile. Formation of the nickel oxide electrode was discussed on p. 270. The rate determining stage is the reaction between electrochemically formed nickel(III) ox-



70-90 % yield Ref. [96]

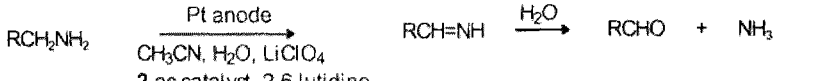
ide and the amine. Overall the reaction is carried out at a pre-oxidised nickel plate anode at low current density and at 50-90 °C [96].

Silver(II) oxide, present on a silver anode in aqueous alkali, will also carry out the oxidation of primary amines to nitriles. Oxidation of the intermediate imine at the silver anode is however relatively slow so that hydrolysis to the aldehyde becomes an important side reaction [97]. α-Amino acids give nitriles in good yields at the silver(II) oxide electrode.



Ref. [97]

Nitroxyl mediated electro-oxidation of primary amines also leads to formation of the imine and the further oxidation to the nitrile. In anhydrous acetonitrile containing 2,6-lutidine as a base, the nitrile is formed. In aqueous acetonitrile, hydrolysis of the imine intermediate is fast and good yields of the aldehyde result

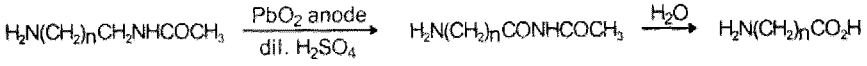


Ref. [98]

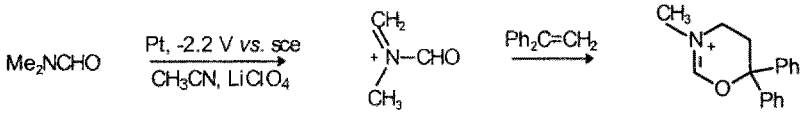
since the amine is oxidised in preference to the product [98]. Continued reaction will convert the aldehyde to the carboxylic acid. The active oxidising agent is the 1-oxopiperidinium and reaction follows a pathway similar to that for the oxidation of alcohols in Scheme 8.3. Electrochemical recycling of the nitroxyl is cost effective relative to the use of a stoichiometric amount of the unstable 1-oxopiperidinium.

Oxidation of Amides and Urethanes

Amines are stable to electrochemical oxidation in acid solution because the nitrogen lone pair is protonated and inaccessible for reaction. This is not the case for N-acetylamines, which are oxidisable at a lead dioxide anode in aqueous sulphuric acid [99]. The primary electron transfer step involves the amide function and leads to a radical-cation, which loses a proton from the carbon atom adjacent to nitrogen. Subsequent steps lead to an acylimmonium ion, which is trapped by water. N-acetylated primary amines are converted to the corresponding carboxylic acid.



N,N-Dialkylamides undergo a related series of reaction steps on anodic oxidation. The immonium ion from dimethylformamide can be generated in solution by oxidation in acetonitrile with no added nucleophile [100]. Solutions of the ion are used in further reactions such as with 1,1-diphenylethene forming **22**. When acetic

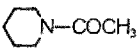
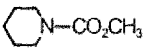
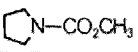


22

acid and sodium acetate are used as solvent and electrolyte, N,N-dimethylamides yield the acetoxymethyl methylamide where the immonium ion has been trapped by acetate [101]. Oxidation in methanol containing ammonium nitrate gives the methoxymethyl methylamide [102].

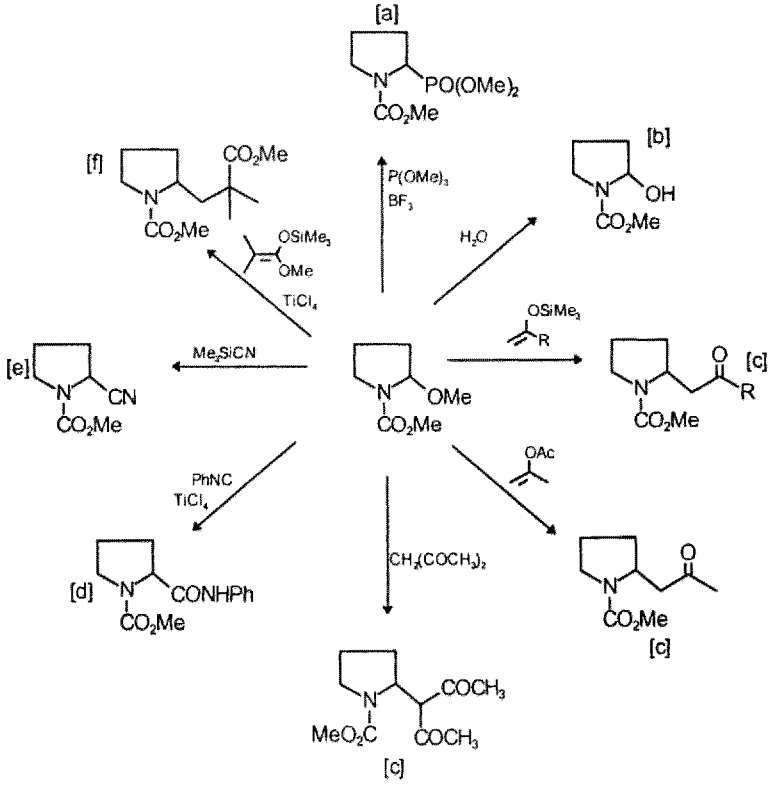
TABLE 8.7

Oxidation of amides at a rotating platinum electrode in acetonitrile with tetraethylammonium 4-toluenesulphonate as electrolyte.

Substrate	$E_{½}$ / V *vs.*sce	Ref.
$C_3H_7NHCOCH_3$	*ca.* 2.2	[108]
$(C_4H_9)_2NCOCH_3$	1.86	[108]
	1.88	[108]
	1.96	[103]
	1.73	[103]

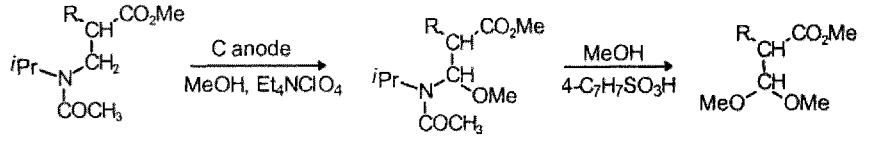
Electrochemical oxidation of amides and urethanes in methanol containing an inert electrolyte has been developed into a useful procedure for the generation of α-methoxy derivatives. Oxidation potentials of some amides and urethanes are given in Table 8.7. The derivatives are easily isolated and have been employed extensively as reaction intermediates. A summary of processes which involve the use of electrochemically generated α-methoxy amides is given in Scheme 8.11. On a small scale, the oxidation has been carried out at platinum electrodes in an undivided cell [104]. Graphite is generally also a serviceable electrode material. Moderate scale laboratory preparations are best carried out in a capillary gap flow through cell with no diaphragm [105]. One design of cell uses a graphite rod as

anode, surrounded by a stainless steel cylinder, which functions as both cathode and outer casing [106]. Large-scale industrial preparations are carried out in a bipolar cell similar to that described on p. 65 but with the electrodes formed from graphite plates [107]. Methyl urethanes, rather than acetamides, are generally preferred as substrates because the products are more stable towards isolation [108, 109]. These reactions are carried out at constant current to the consumption of 2 F. Exhaustive oxidation using 10 F affords the α,α′-dimethoxy product [104, 110, 111]. Urethanes derived from primary amines can also be transformed to α-methoxy products, although a more anodic oxidation potential is required. Methyl urethanes are conveniently synthesised in an electrochemical step from the corresponding formamide (see p. xxx) in a route that does not require the use of methyl chloroformate.



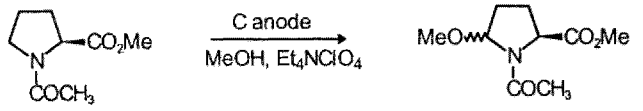
Scheme 8.11. Reactions of electrochemically prepared α-methoxy- amides and urethanes. References: a, [112]; b, [113]; c, [109], d, 114]; e, [115]; f, [116].

The formation of an immonium ion from amides and urethanes is under kinetic control at the stage where a proton is lost from the radical-cation initially formed. In the cases of derivatives of unsymmetrical secondary amines, this leads to preferential reaction at an N-CH_2R group rather than at N-CHR_2 and the kinetically



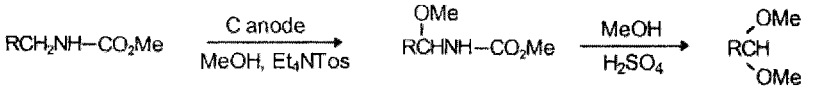
23

Ref. [117]



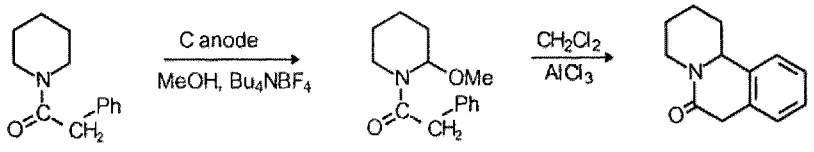
Ref. [118]

formed immonium ion is immediately trapped by reaction with methanol. A strategy for the preparation of dimethyl acetals of α-formyl esters uses the substrates **23** to direct oxidation towards the required carbon centre [117]. A further example of regioselective anodic methoxylation is shown by reaction of N-acetylproline methyl ester [118]. Aldehyde dimethyl acetals can be prepared by oxidation of the primary amine urethanes [119].



Ref. [119]

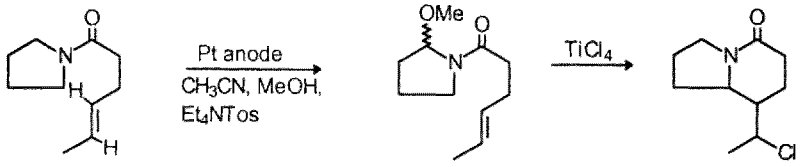
Oxidative transformation of the amide function fails where a more easily oxidisable group is present. Comparison of the oxidation potentials for amides (Table 8.11) with those for aromatic rings (Tables 6.1 and 6.5) and for alkene bonds (Table 2.2) allows the reactivity of a multifunctional compound to be predicted. Whereas phenacylamides are oxidised with no interference from the aromatic ring,



24

Ref. [105]

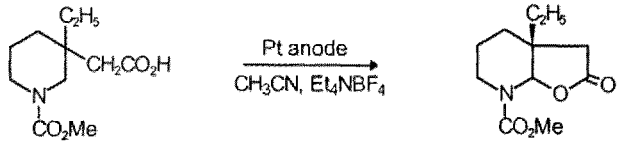
as in the example **24**, more electron rich aromatic rings such as 4-methoxyphenyl are oxidised in preference to give products in which the amide group remains unchanged [120]. An example of the relative reactivity of an alkene group is provided by the dialkyl-substituted ethene **25**, which is oxidised at the amide function. The



25

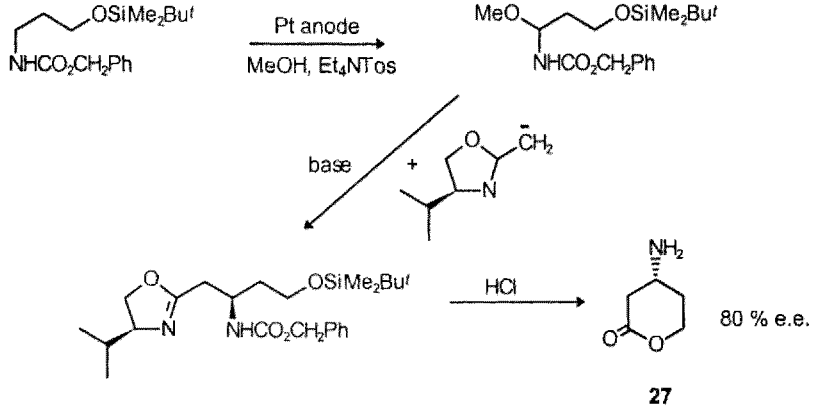
related compound with a trialkyl substituted alkene function in the side chain is oxidised at the alkene group [121].

Substrates such as **26** that possess a suitably placed carboxyl group are converted to the lactone during electrochemical oxidation [122].



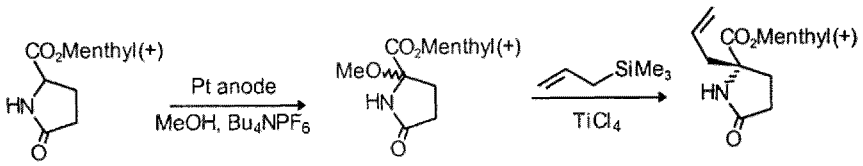
26

Chiral synthesis during the coupling reaction between an α-methoxy amide and a nucleophile can be achieved. One approach to this problem uses a nucleophile derived from a 2-methyloxazoline possessing a chiral centre, for example in the formation of the chiral amine **27** [123]. A second approach uses esters of pyroglu-



27

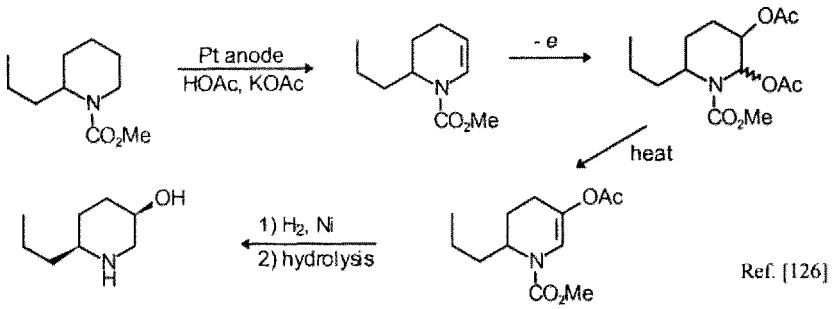
tamide with a chiral alcohol to control the carbon-carbon bond-forming step in the synthesis of **28** [124]. Other work (p. 285) has shown that anodic oxidation at a carbon centre is inhibited by the carbomethoxy substituent and in line with this



28

observation, the oxidation of pyroglutamide esters requires a high current density for success.

Early workers noted that electrochemical oxidation of N,N-dimethyl-amides in acetic acid gives the α-acetoxy compound [101]. Oxidation in acetic acid of amides derived from piperidine and pyrrolidine proceeds differently to yield a mixture of stereoisomers of the α,β-diacetoxy and β-acetoxy-α-hydroxy compounds [125].

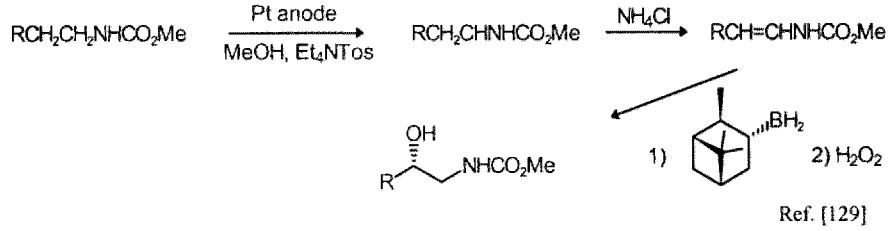


29

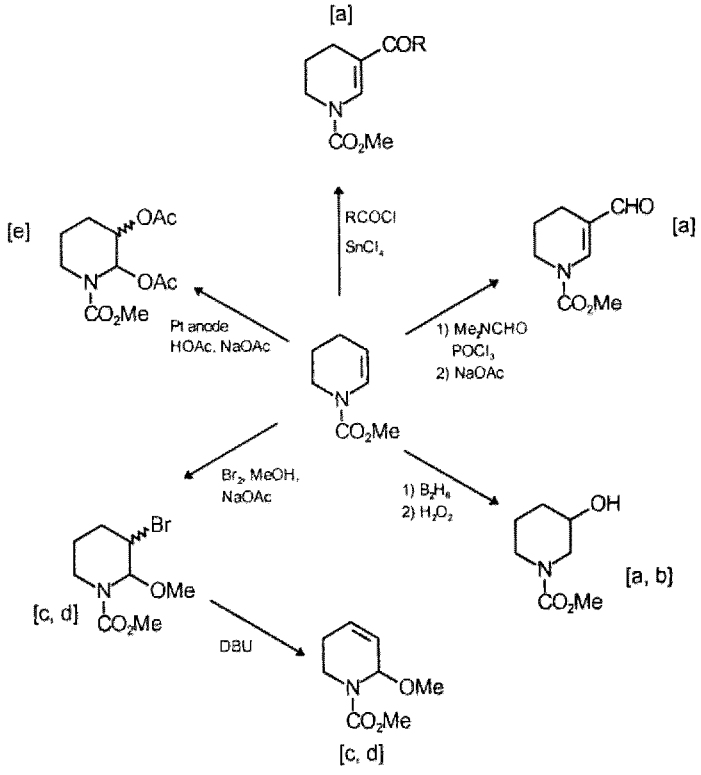
These reactions proceed *via* the α-acetoxy derivative, which then forms the enamide. Further oxidation of the enamide gives the isolated products. A synthesis of *cis*-pseudoconhydrine **29** from 2-propylpiperidine illustrates both this process and also the regioselectivity in oxidation of amides, which favours attack on a methylene rather than a methine carbon atom [126].

α-Methoxyamides are converted to enamides in the presence of a weak acid catalyst [127, 128]. Enamides prepared in this way are oxidised to α,β-diacetoxy compound in acetic acid. Preparation of the α,β-diacetoxy compound from open chain N,N-dialkylamides usually requires the prior formation of an enamide followed by electrochemical oxidation [125]. Further reactions of enamides prepared by this electrochemical route are summarised in Scheme 8.12. Asymmetric hy-

droxylation of the enamide is achieved using (+)-pineneborane followed by oxidation with hydrogen peroxide [129].

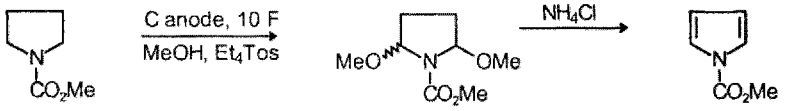


Ref. [129]



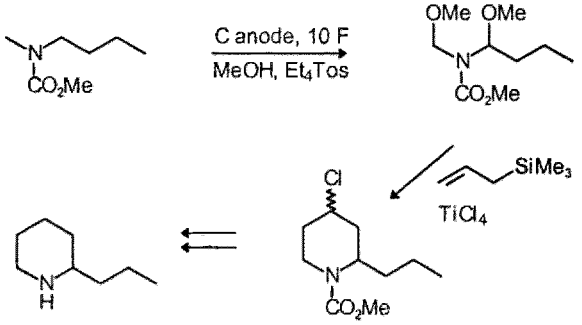
Scheme 8.12. Reactions of electrochemically prepared enamine urethanes.
References: a, [127]; b, [130]; c, [131]; d, [132]; e, [125].

α,α′-Dimethoxyamides, prepared by exhaustive electrochemical oxidation in methanol, also undergo the acid catalysed elimination to form a bis-enamide. This

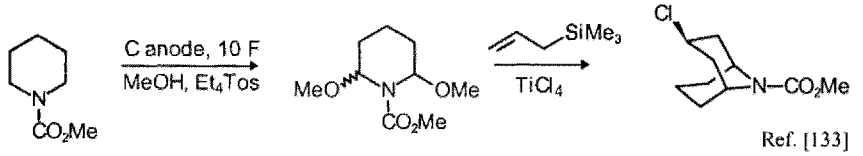


Ref. [125]

process provides a route for the conversion of pyrrolidines to the corresponding pyrrole [125]. Further reactions of the bis-enamides with allyltrimethylsilane also provide a route to the piperidine ring, illustrated by a synthesis of coniine **30** [133].

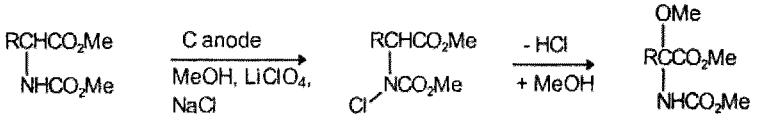


30



Ref. [133]

Direct electrochemical oxidation of protected α-amino acids is generally ineffective. An exception is provided by proline derivatives, which are methoxylated on carbon-5 of the pyrrolidine ring. Open chain protected α-amino acids undergo



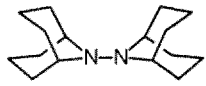
Ref. [135]

α-methoxylation catalysed by chloride ions at a graphite electrode in an undivided cell [134, 135]. The reaction mechanism is different from the direct oxidation pro-

cess so far discussed. The oxidising agent is electrochemically generated hypochlorite and the initially formed intermediate is the N-chloroamide, which loses hydrogen chloride to form an imine. Addition of methanol then gives the isolated product.

Oxidation of Hydrazine Derivatives

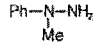
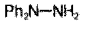
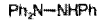
Hydrazine derivatives are more easily oxidised than the corresponding amines. Tetraalkylhydrazines afford the short-lived radical-cation and these redox couples have standard redox potentials in the range 0.0 to +0.1 V *vs.* sce [136]. In the oxidised form, the two nitrogen lone pair *p*-orbitals interact to cause delocalization of the radical-cation centre. Substrates such as **31** where the α-carbon-hydrogen



31

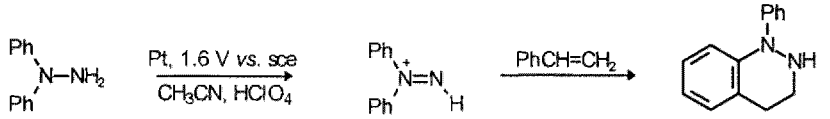
bonds are orthogonal to the nitrogen lone pair afford radical-cations with lifetimes in the range of seconds. For the redox couple derived from **31**, E° = -0.01 V *vs.* sce. A second oxidation step occurs at E° = +1.18 V *vs.* sce and both reactions are reversible in acetonitrile [137]. Tetraphenylhydrazine also gives a stable radical-cation with E° = +0.74 V *vs.* sce [138].

TABLE 8.8
Oxidation of substituted hydrazines at a rotating platinum electrode in acetonitrile.

Substrate	$E_{½}$ / V *vs.* sce			Ref.
	Acid medium	Basic medium		
	1.12	0.23	0.53	[139]
	0.19	0.38	0.75	[138]
	0.25	0.25	0.61	[138]
		0.33		[138]

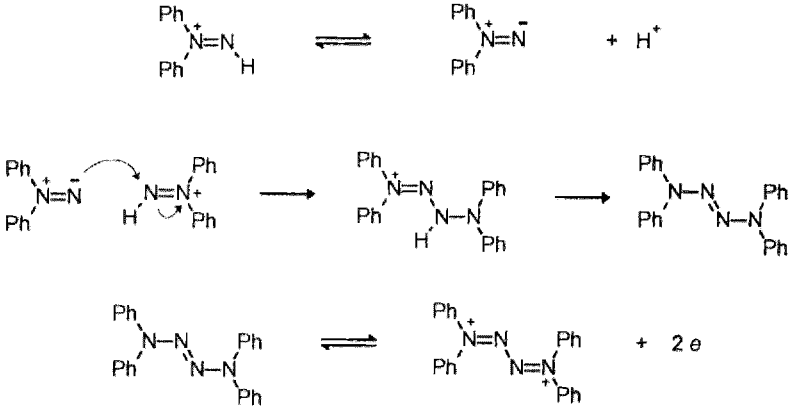
Hydrazines with at least one hydrogen substituent on nitrogen are oxidised in aqueous solution to the substituted diazene. Oxidation takes place in both acid and basic solution. Phenylhydrazine is oxidised by inorganic reagents such as iodine buffered by sodium hydrogen carbonate to form benzenediazonium ion. The latter combines with the substrate to form the isolated product [140]. 1,1-Disubstituted

hydrazines afford the diazenium cation in acid solution and this is deprotonated at higher pH to give the neutral diazene [141]. Oxidation can be carried out with sodium bromate in hydrochloric acid or electrochemically [142, 143] in acetonitrile buffered with either perchloric acid or 2,6-dimethylpyridine (Table 8.8). Diazenium cations are stable at low pH. The species derived from 1,1-diphenylhydrazine will add to the alkene bond in styrenes to generate the cinnoline ring system.

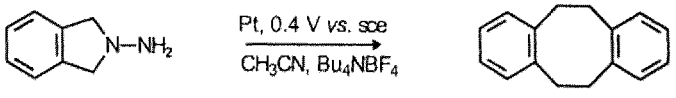


Ref. [142]

In the medium pH range where both the diazenium cation and the diazene exist in solution, these two species react rapidly to afford a substituted tetrazene [141]. The second oxidation wave, observed for disubstituted hydrazenes in acetonitrile with a pyridine base present, is due to the further oxidation of the tetrazene to a dicationic species.



Dialkyldiazenes are unstable and lose nitrogen with the formation of two alkyl radicals. This is the only process observed when the 1,1-dialkylhydrazine is oxidised in alkaline solution where none of the diazenium ion survives [144]. Electrochemical oxidation of the cyclic dialkylhydrazine **32** in an unbuffered solution

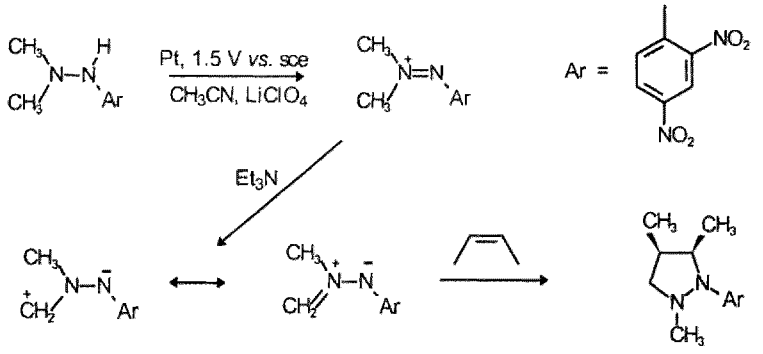


32

Ref. [146]

gives an 8-membered carbocyclic ring product, among other compounds [145].

1,1-Dialkyl-2-arylhydrazines are oxidised in acetonitrile to a stable diazenium ion. Added base will remove an α-proton from one of the alkyl groups to form a 1,3-dipolar species. The latter undergoes a concerted Huisgen-type addition reaction with alkenes [146].



Ref. [146]

Aroylhydrazines are readily oxidised in protic solvents. Benzoylhydrazine and 2-benzoylphenylhydrazine show anodic waves in an acetate buffer at +0.08 and +0.02 V *vs.* sce respectively [147]. The most studied member of this group, because of its importance as the photographic developer phenidone, is 1-phenylpyrazolin-3-one **33**. Phenidone shows a one-electron oxidation wave at a rotating

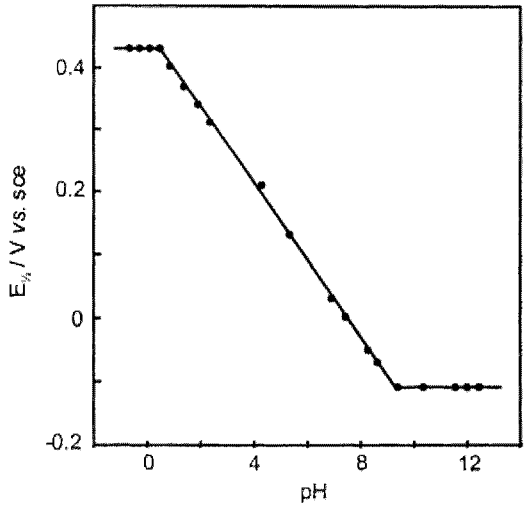
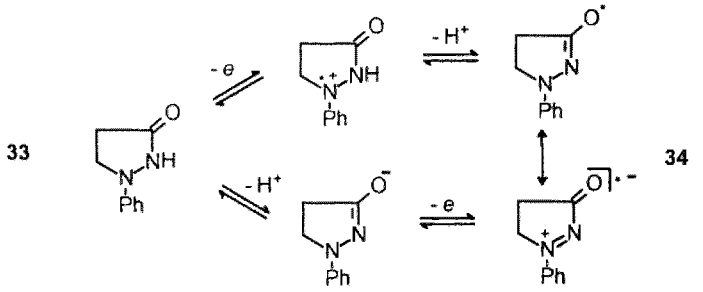
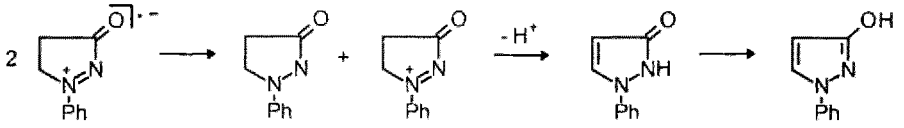


Figure 8.1. Variation of half-wave potential with pH for the first oxidation wave of phenidone **33** in aqueous buffers. Data from ref. [147]

disc electrode and the half-wave potential depends on pH as shown in Figure 8.1. During the oxidation process, the redox and proton transfer processes are in equilibrium at the electrode surface. The radical intermediate **34** can be detected by esr spectroscopy and the unpaired electron is distributed over the hydrazine system. Discontinuities in the graph of half-wave potential versus pH occur due to the acid dissociation of the radical-cation with pK_a = 0.48 and the acid dissociation of

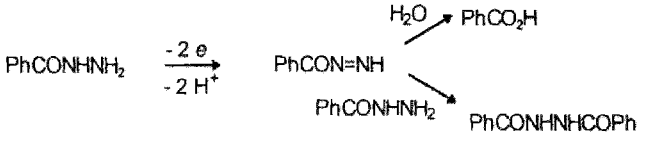


phenidone with pK_a = 9.37 [148]. The radical undergoes dismutation in a second order reaction with rate constant 3.2 x 10^2 M^{-1} s^{-1} as it diffuses away from the electrode. The cationic product from dismutation then loses a proton and forms 1-



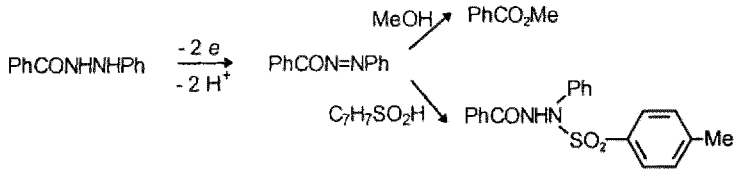
phenyl-3-hydroxypyrazole in two consecutive and slower reactions [149, 150]. A second wave for phenidone appears at more positive potentials due to further oxidation of the radical **34**.

Where there is at least one hydrogen atom on the second nitrogen, electrochemical oxidation of aroylhydrazines leads to the corresponding di-imide [147, 151]. Di-imides undergo rapid addition of a nucleophile onto the carbonyl group, cata-

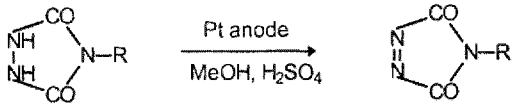


lysed by protons, followed by elimination of the imine [152]. 1-Benzoyl-2-phenyldiimide is sufficiently stable for isolation from rapid chemical oxidation of

the hydrazine [153]. When formed by electrochemical oxidation it can be trapped by addition of toluenesulphinic acid, otherwise it reacts with the solvent [147].



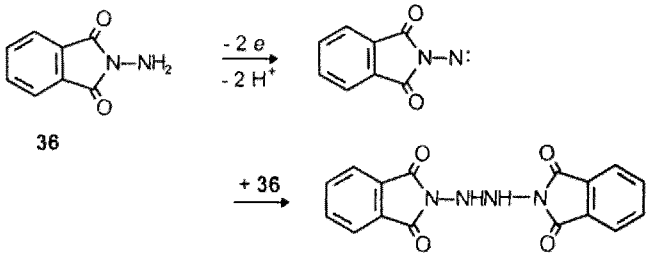
1,2,4-Triazoline-3,5-diones **35**, which are very efficient dienophiles in the Diels-Alder reaction, are easily prepared by anodic oxidation of the hydrazine in methanol. Reaction with a diene is so fast that the Diels-Alder product is obtained by



35, R = H, Me or Ph

oxidation of a mixture of the hydrazine and the diene in an undivided cell with no interference from reduction of the di-imide at the cathode [154].

Electrochemical oxidation of N-aminophthalimide **36** gives an intermediate,



which shows the properties of a nitrene [155]. It will form a dimeric species by insertion into the nitrogen-hydrogen bond of a second molecule of N-aminophthalimide.

References

[1] K. Elbs and O. Brunner, *Z. Elektrochem.*, 1900, **6**, 608.
[2] W. R. Lowstuter and A. Lowry, *Trans. Electrochem. Soc.*, 1940, **77**, 451.
[3] K. I. Kryshchenko, U. Ya. Fioshin, N. G. Bahhchrisaits'yan and G. A. Kokarev, *Khim. Prom. (Moscow)*, 1969, **45**, 496; *Chem. Abstr.*, 1969, **71**, 101253.
[4] V. E. Wolf, *Chem. Ber.*, 1954, **87**, 668.
[5] P Jäger, H. Hannebaum and H. Nohe, *Chem.-Ing.-Technik*, 1978, **50**, 787.
[6] J. Heilbron, E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 1949, 604.
[7] S. Mizuno, *Denki Kagaku*, 1961, **29**, 102; *Chem. Abstr.*, 1965, **62**, 3667.
[8] F. Hoffmann-La Roche and Co., *Swiss* 244600 (1947); *Chem. Abstr.*, 1949, **43**, 5682.
[9] D. Serve, *Electrochim. Acta*, 1975, **20**, 469.
[10] W. Sümmermann and V. Deffner, *Tetrahedron*, 1975, **31**, 593.
[11] R. C. Larson, R. T. Iwamoto and R. N. Adams, *Analyt. Chim. Acta*, 1961, **25**, 371.
[12] D. J. Tarnowski and C. Korzeniewski, *J. Phys. Chem. B*, 1997, **101**, 253.
[13] T. D. Tran, I. Londner and S. H. Langer, *Electrochim. Acta*, 1993, **38**, 221.
[14] H. C. Brown, C. P. Garg and K.-T. Liu, *J. Org. Chem.*, 1971, **36**, 387.
[15] J. P. Millington and I. M. Dalrymple, *Eur. Pat. Appl.* EP 64417 (1982); *Chem. Abstr.*, 1983, **72**, 62164.
[16] S. Kashimura, M. Ishifune, H. Maekawa, Y. Yamaguchi, Y. Murai, S. Kitajima and T. Shono, *Denki Kagaku*, 1997, **65**, 479.
[17] C. W. Scheele, *Kongl. Vetenskaps Academiens Nya Handlingar*, 1780, **1**, 269; A. Laugier, *Ann. Chim. [1]*, 1809, **72**, 81.
[18] J. E. Leonard, P. C. Scholl, T. P. Steckel, S. E. Lentsch and M. R. van de Mark, *Tetrahedron Letters*, 1980, **21**, 4695.
[19] T. Shono, Y. Matsumura, J. Hayashi and M. Mizoguchi, *Tetrahedron Letters*, 1979, 165.
[20] G. Dryhurst and P. J. Elving, *Analyt. Chem.*, 1967, **39**, 607.
[21] M. Yoshikawa, T. Murakami, N. Yagi, N. Murakami, J. Yamahara, H. Matsuda, H. Maeda and H. Ohmori, *Chem. Pharm. Bull.*, 1997, **45**, 570.
[22] P. A. Garcia, R. Velasco and F. Barba, *Chem. Scripta*, 1986, **26**, 579.
[23] P. A. Garcia, R. Velasco and F. Barba, *Synth. Commun.*, 1991, **21**, 1153.
[24] P. Subbiah, K. Jayaraman, C. Seshadri, P. Thirunavukkarasu and K. S. Udupa, *Bull. Electrochem.*, 1988, **4**, 149.
[25] D. Pletcher and N. Tomov, *J. Appl. Electrochem.*, 1977, 501.
[26] H. Maekawa, Y. Ishino and I. Nishiguchi, *Chem. Letters*, 1994, 1017.
[27] J. Yoshida, R. Nakai and N. Kawabata, *J. Org. Chem.*, 1980, **45**, 5269.
[28] T. Shono, Y. Matsumura, J. Hayashi and M. Mizoguchi, *Tetrahedron Letters*, 1980, **21**, 1867.
[29] T. Shono, Y. Matsumura, M. Mizoguchi and J. Hayashi, *Tetrahedron Letters*, 1979, 3861.
[30] S. Torii and A. Yoshida, *Chem. Letters*, 1995, 369.
[31] S. Torii, T. Inokuchi and T. Sugiura, *J. Org. Chem.*, 1986, **51**, 155.
[32] S. Torii, T. Inokuchi, S. Matsumoto, T. Saeki and T. Oki, *Bull. Chem. Soc. Japan*, 1989, **62**, 2108.
[33] S. Torii, T. Inokuchi, S. Matsumoto, T. Saeki and T. Oki, *Bull. Chem. Soc. Japan*, 1990, **63**, 852.
[34] M. L. Tsai and T. C. Chou, *Ind. Eng. Chem. Res.*, 1997, **36**, 3563.

[35] M. S. Thompson, W. F. DeGiovani, B. A. Moyer and T. J. Meyer, *J. Org. Chem.*, 1984, **49**, 4972.
[36] A. E. J. Denooy, A. C. Besemer and H. VanRekkum, *Synthesis*, 1996, 1153.
[37] M. F. Semmelhack, C. S. Chou and D. A. Cortés, *J. Am. Chem. Soc.*, 1983, **105**, 4492.
[38] Y. Kashiwagi, F. Kurashima, J. Anzai and T. Osa, *Heterocycles*, 1999, **51**, 1945.
[39] F. Kurashima, Y. Kashiwagi, C. Kikuchi, J. Ansai and T. Osa, *Heterocycles*, 1999, **50**, 79.
[40] A. Deronzier, D. Limosin and J.-C. Moutet, *Electrochim. Acta*, 1987, **32**, 1643.
[41] Y. Yanagisawa, Y. Kashiwagi, F. Kurashima, J. Anzi , T. Osa and J. M. Bobbitt, *Chem. Letters*, 1996, 1043.
[42] Y. Kashiwagi, Y. Yanagisawa, F. Kurashima, J. Anzai, T. Osa and J. M. Bobbitt, *J. Chem. Soc. Chem. Commun.*, 1996, 2745.
[43] T. Inokuchi, S. Matsumoto and S. Torii, *J. Org. Chem.*, 1991, **56**, 2416.
[44] S. Matsumoto, T. Nishiyama and S. Torii, *J. Org. Chem., 1987, 52, 2559.*
[45] T. Inokuchi, S. Matsumoto, M. Fukushima and S. Torii, *Bull. Chem. Soc. Japan*, 1991, **64**, 796.
[46] K. Nakagawa, R. Konaka and T. Nakata, *J. Org. Chem.*, 1962, **27**, 1597.
[47] A. J. Salkind and M. Klein in Kirk-Othmer Encyclopedia of Chemical Technology, John Wiley and Sons, 4th edition, 1992 Vol. 3 p. 1029.
[48] G. Vértes, G. Horányi and F. Nagy, *Acta Chim. Acad. Sci. Hung.*, 1971, **67**, 145; *Chem. Abstr.*, 1971, **74**, 106534.
[49] H.-J. Schäfer, *Topics in Current Chemistry*, 1987, **142**, 102.
[50] M. Fleischmann, K. Korinek and D. Pletcher, *J. Electroanal. Chem.*, 1971, **31**, 39.
[51] M. Fleischmann, K. Korinek and D. Pletcher, *J. Chem. Soc. Perkin Trans. 2*, 1972, 1396.
[52] P. M. Robertson, *J. Electroanal. Chem.*, 1980, **111**, 97.
[53] J. Kaulen and H.-J. Schäfer, *Synthesis*, 1979, 513.
[54] R. Konaka, S. Terabe and K. Kuruma, *J. Org. Chem.*, 1969, **34**, 1334.
[55] P. M. Robertson, P. Berg, H. Reimann, K. Schleich and P. Seiler, *J. Electrochem. Soc.*, 1983, **130**, 591.
[56] M. Ya. Fioshin and I. A. Avrutskaya, *Russian Chem. Rev.*, 1975, **44**, 982.
[57] Y. Kunugi, T. Fuchigami and T. Nonaka, *J. Electroanal. Chem.*, 1990, **287**, 385.
[58] A. S. Vaze, S. B. Sawant and V, G. Pangarkar, *J. Appl. Electrochem.*, 1997, **27**, 584.
[59] J. Kaulen and H.-J. Schäfer, *Tetrahedron*, 1982, **38**, 3299.
[60] E. G. Bondarenko, A. P. Tomilov, *Zh. Prikl. Khim. (Lenningrad)*, 1969, **42**, 2033; *Chem. Abstr.*, 1970, **72**, 8677.
[61] H.-J. Schäfer and R. Schneider, *Tetrahedron*, 1991, **47**, 715.
[62] T. Shono and Y. Matsumura, *J. Am. Chem. Soc.*, 1969, **91**, 2803.
[63] T. Shono, Y. Matsumura, O. Onomura and Y. Yamada, *Synthesis*, 1987, 1099.
[64] J. W. Scheeren H. J. M. Goossens and A. W. H. Top, *Synthesis*, 1978, 283.
[65] C. Z. Smith, J. H. P. Utley and H. L. Chum, *J. Chem. Res.-S*, 1987, 88.
[66] T. Fuchigani, T. Sato and T. Nonaka, *J. Org. Chem.*, 1986, **51**, 366.
[67] T. Shono, Y. Matsumura, T. Hashimoto, K. Hibino, H. Hamaguchi and T. Aoki, *J. Am. Chem. Soc.*, 1975, **97**, 2546.
[68] T. Fuchiyama, T. Nonaka, C. Watanabe, A. Yoshiyama and T. Sekine, *Denki Kagaku*, 1983, **51**, 812.
[69] T. Shono, H. Hamaguchi, Y. Matsumura and K. Yoshida, *Tetrahedron Letters*, 1977, 3625.

[70] A. Yoshiyama, T. Nonaka, M. M. Baizer and T. C. Chou, *Bull. Chem. Soc. Japan*, 1985, **58**, 201.
[71] A. Hickling and S. H. Richards, *J. Chem. Soc.*, 1940, 259.
[72] A. Yoshiyama, T. C. Chou, T. Fuchigami, T. Nonaka and M. M. Baizer, *Denki Kagaku*, 1985, **53**, 989.
[73] J. Delaunay, A. Lebouc, A. Tallec and J. Simonet, *J. Chem. Soc. Chem. Commun.*, 1982, 387.
[74] C. K. Mann, *Anal. Chem.*, 1964, **36**, 2424.
[75] S. F. Nelsen and C. R. Kessel, *J. Chem. Soc. Chem. Commun.*, 1977, 490.
[76] R. W. Alder, R. Gill and N. L. Goode, *J. Chem. Soc. Chem. Commun.*, 1976, 973.
[77] D. D. M. Wayner, J. J. Dannenburg and D. Griller, *Chem. Phys. Letters*, 1986, **131**, 189.
[78] D. D. M. Wayner and D. Griller, *J. Am. Chem. Soc.*, 1985, **107**, 7764.
[79] C. P. Andrieux and J.-M. Savéant, *Bull. Soc. chim. France*, 1968, 4671.
[80] P. J. Smith and C. K. Mann, *J. Org. Chem.*, 1969, **34**, 1821.
[81] L. C. Portis, J. J. Klug and C. K. Mann, *J. Org. Chem.*, 1974, **39**, 3488.
[82] A. U. Blackham, S. Kwark and J. L. Palmer, *J. Electrochem. Soc.*, 1975, **122**, 1081.
[83] R. Bauer and H. Wendt, *Angew. Chem. Int. Ed. Engl.*, 1978, **17**, 370.
[84] R. Ohme and H. Preuschhof, *Liebigs Ann. Chem.*, 1968, **713**, 74.
[85] S. Torii, H. Okumoto and L. H. Xu, *Tetrahedron*, 1991, **47**, 665.
[86] B. Becker and H. P. Fritz, *Chem. Ber.*, 1976, **109**, 1346.
[87] C, Moinet and E. Raoult, *Bull. Soc. chim. France*, 1991, 214.
[88] S. Michel, E. LeGall, J. P. Hurvois, C. Moinet, A. Tallec, P. Uriac and L. Troupet, *Liebigs Ann.- Receuil*, 1997, 259.
[89] P. E. LeGall, J. P. Hurvois, T. Renard, C. Moinet, A. Tallec, P. Uriac, S. Sinbandhit and L. Troupet, *Liebig's Ann. – Receuil*, 1997, 2089.
[90] G. Bidan and M. Genies, *Tetrahedron*, 1981, **37**, 2297.
[91] N. L. Weinberg and E. A. Brown, *J. Org. Chem.*, 1966, **31**, 4058.
[92] T. Shono, Y. Matsumura, K. Inoue, H. Ohmizu and S. Kashimura, *J. Am. Chem. Soc.*, 1982, **104**, 5753.
[93] T. Shono, Y. Matsumura and K. Inoue, *J. Am. Chem. Soc.*, 1984, **106**, 6075.
[94] T. Shono, Y. Matsumura, S. Katoh, K. Inoue and Y. Matsumoto, *Tetrahedron Letters*, 1986, **27**, 6083.
[95] T. Shono, Y. Matsumura, S. Katoh, K. Takeuchi, K. Sasaki, T. Kamada and R. Shimisu, *J. Am. Chem. Soc.*, 1990, **112**, 2368.
[96] U. Feldhues and H.-J. Schäfer, *Synthesis*, 1982, 145.
[97] N. A. Hampson, J. B. Lee and K. I. MacDonald, *Electrochim. Acta*, 1972, **17**, 921.
[98] M. F. Semelhack and C. R. Schmid, *J. Am. Chem. Soc.*, 1987, **105**, 6732.
[99] S. Mizuno, *Denki Kagaku*, 1961, **29**, 28; *Chem. Abstr.*, 1965, **62**, 2508.
[100] M. Genies, *Bull. Soc. chim. France*, 1975, 389.
[101] S. D. Ross, M. Finkelstein and R. C. Petersen, *J. Org. Chem.*, 1966, **31**, 128.
[102] S. D. Ross, M. Finkelstein and R. C. Petersen, *J. Am. Chem. Soc.*, 1966, **88**, 4656.
[103] T. Shono, *Tetrahedron*, 1984, **40**, 811.
[104] M. Mitzlaff, K. Warning and H. Jensen, *Liebigs Ann. Chem.*, 1978, 1713.
[105] P. D. Palasz, J. H. P. Utley and J. D. Hardstone, *Acta Chem. Scand. B*, 1984, **38**, 281.
[106] L. Cedheim, L Eberson, B. Helgée, K. Nyberg, R. Servin and H. Sternerup, *Acta Chem. Scand. B*, 1975, **29**, 617.

[107] H. Pütter and H. Hannebaum, *Ger. Offen.*, DE 19533733 (1997); *Chem. Abstr.*, 1997, **126**, 244076.
[108] T. Shono, H. Hamaguchi and Y. Matsumura, *J. Am. Chem. Soc.*, 1975, **97**, 4264.
[109] T. Shono, Y. Matsumura and K. Tsubata, *J. Am. Chem. Soc.*, 1981, **103**, 1172.
[110] T. Shono, Y. Matsumura, K. Uchida and H. Kobayashi, *J. Org. Chem.*, 1985, **50**, 3243.
[111] T. Shono, Y. Matsumura, K, Tsubata, Y. Sugihara, S. Yamana, T. Kamazawa and T. Aoki, *J. Am. Chem. Soc.*, 1982, **104**, 6697.
[112] T. Shono, Y. Matsumura and K. Tsubata, *Tetrahedron Letters*, 1981, **22**, 3249.
[113] T. Shono, Y. Matsumura, T. Kanazawa, M. Habuka, K. Unchida and K. Toyoda, *J. Chem. Res. S*, 1984, 320.
[114] T. Shono, Y. Matsumura and K. Tsubata, *Tetrahedron Letters*, 1981, **22**, 2411.
[115] V. Acher, C. BeCu, M. J. O. Aneyunis and R. Callens, *Tetrahedron Letters*, 1981, **22**, 141.
[116] T. Shono, K. Tsubata and N. Okinaga, *J. Org. Chem.*, 1984, **49**, 1056.
[117] S. Torii, T. Inokuchi and M. Kubota, *J. Org. Chem.*, 1985, **50**, 4157.
[118] K. D. Moeller and P. L. Wong, *Bioorg. Med. Chem, Letters*, 1992, **2**, 739.
[119] T. Shono, Y. Matsumura and S. Kashimura, *J. Org. Chem.*, 1983, **48**, 3338.
[120] K. D. Moeller, P. W. Wang, S. Tarazi, M. R. Marzabadi and P. L. Wong, *J. Org. Chem.*, 1991, **56**, 1058.
[121] K. D. Moeller, S. L. Rothfus and P. L. Wong, *Tetrahedron*, 1991, **47**, 583.
[122] K. Irie and Y. Bann, *Heterocycles*, 1981, **15**, 201.
[123] T. Shono, N. Kise, F. Sanda, O. Ohi and K. Tsubata, *Tetrahedron Letters*, 1988, **29**, 231.
[124] K. D. Moeller and L. D. Rutledge, *J. Org. Chem.*, 1992, **57**, 6360.
[125] T. Shono, Y. Matsumura, O. Onomura, M. Ogaki and T. Kanazawa, *J. Org. Chem.*, 1987, **52**, 536.
[126] T. Shono, Y. Matsumura, O. Onomura, T. Kanazawa and H. Habuka, *Chem. Letters*, 1984, 1101.
[127] T. Shono, Y. Matsumura, K. Tsubata, Y. Sugihara, S. Yamane, T. Kanazawa and T. Aoki, *J. Am. Chem. Soc.*, 1982, **104**, 6697.
[128] T. Shono, Y. Matsumura, K. Tsubata and Y. Sugihara, *Tetrahedron Letters*, 1982, **23**, 1201.
[129] Y. Matsumura, T. Onishi, C. Sonoda, T. Maki and M. Watanabe, *Tetrahedron*, 1997, **53**, 4579.
[130] M. Plehiers and C. Hortele, *Can. J. Chem.*, 1996, **74**, 2444.
[131] T. Shono, Y. Matsumura, O. Onomura and Y. Tamada, *Tetrahedron Letters*, 1987, **28**, 4073.
[132] T. Shono, Y. matsumura, M. Ogaki and O. Onomura, *Chem. Letters*, 1987, 1447.
[133] T. Shono, Y. Matsumura, K. Uchida and H. Kobayashi, *J. Org. Chem.*, 1985, **50**, 3243.
[134] T. Shono, Y. Matsumura and K. Inoue, *J. Org. Chem.*, 1983, **48**, 1388.
[135] K. D. Ginzel, P. Brungs and E. Steckhan, *Tetrahedron*, 1989, **45**, 1691.
[136] S. F. Nelsen and P. J. Hovitz, *J. Am. Chem. Soc.*, 1972, **94**, 7108.
[137] S. F. Nelsen and C. R. Kessel, *J. Am. Chem. Soc.*, 1977, **99**, 2392.
[138] G. Cauquis, B. Chabaud and M. Genies, *Bull. Soc. chim. France*, 1973, 3842.
[139] G. Cauquis, B. Chabaud and Y. Gohee, *Tetrahedron Letters*, 1977, 2583.
[140] R. Stollé, *J. prakt. Chem.[2]*, 1902, **66**, 332.

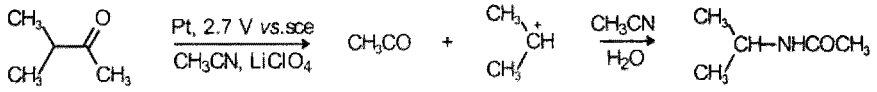
[141] W. R. McBride and E. M. Bens, *J. Am. Chem. Soc.*, 1959, **81**, 5546.
[142] G. Cauquis , B. Chabaud and M, Genies, *Bull. Soc. chim. France*, 1973, 3487.
[143] G. Cauquis, B. Chabaud and Y. Gohee, *Tetrahedron Letters*, 1977, 2583.
[144] L. A. Carpino, *J. Am. Chem. Soc.*, 1957, **79**, 4427.
[145] T. Fuchigami, T. Sato and T. Nonaka, *Denki Kagaku*, 1983, **51**, 133; *Chem. Abstr.*, 1983, **98**, 206877.
[146] G. Cauquis and B. Chabaud, *Tetrahedron*, 1978, **34**, 903.
[147] R. Hazard, M. Le Floch and A. Tallec, *Electrochim. Acta*, 1996, **41**, 2871.
[148] A. Castellan, L. Griggio and E. Vianello, *Atti Accad. Naz. Lincei, Rend. Sci. fis. mat. nat.*, 1965, **39**, 510.
[149] A. Castellan, F. Masetti, U. Mazzucato and E. Vianello, *J. Photographic Sci.*, 1966, **14**, 164.
[150] W. Jaenicke and H. Hoffmann, *Z. Elektrochem.*, 1962, **66**, 814.
[151] H. Lund, *Acta Chem. Scand.*, 1963, **17**, 1077.
[152] S. G. Cohen and J. M. Nicholson, *J. Chem. Soc.*, 1965, **30**, 1162.
[153] E. Mohr, *J. prakt. Chem. [2]*, 1904, **70**, 301.
[154] H. Wamhoff and G. Kunz, *Angew. Chem. Int. Ed. Engl.*, 1981, **20**, 797.
[155] T. Fuchigami, T. Sato and T. Nonaka, *Electrochim. Acta*, 1986, **31**, 365.

CHAPTER 9

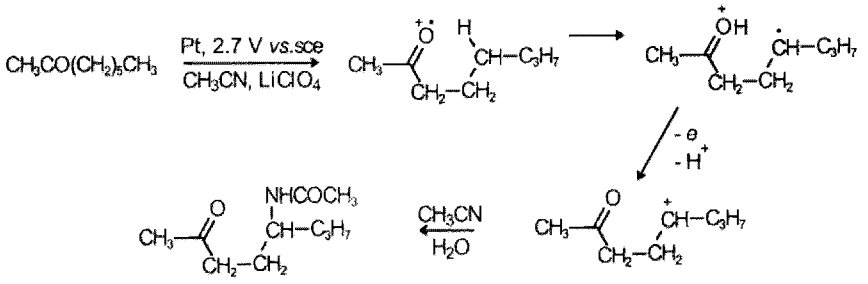
OXIDATION OF KETONES, ALDEHYDES, AND CARBOXYLIC ACIDS

Oxidation of Ketones

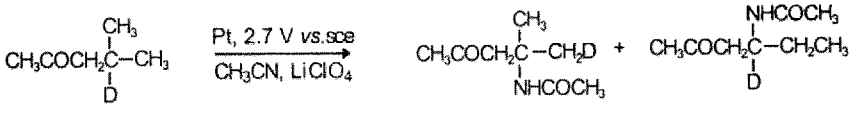
Aliphatic ketones are oxidised in both acetonitrile [1, 2] and trifluoracetic acid [3] at potentials less positive than required for the analogous hydrocarbons. The oxidation process is irreversible in both solvents and cyclic voltammetry peak potentials are around 2.7 V *vs.* sce. Loss of an electron from the carbonyl oxygen lone pair is considered to be the first stage in the reaction. In acetonitrile, two competing processes then ensue. Short chain, α-branched ketones cleave the carbon-carbonyl bond to give the more stable carbocation, which is then quenched by reaction with



acetonitrile and water. The fate of the carbonyl residue has not been clarified. Longer chain ketones show a competition between this carbon-carbonyl bond cleavage and γ-hydrogen transfer due to attack of the carbonyl oxygen function. Further oxidation of the resulting carbon radical leads to the carbocation, which may rearrange before being quenched by acetonitrile. Rearrangement is illustrated

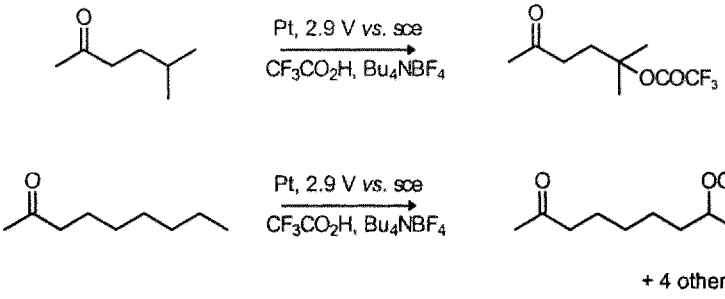


by the oxidation of **1** leading to both methyl and deuterium migration steps [2].

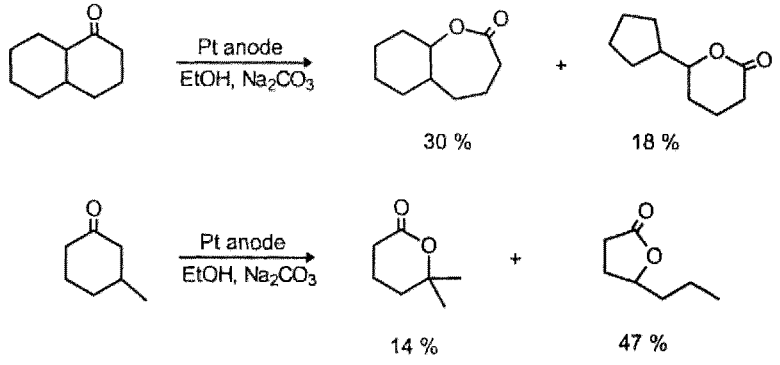


1

Oxidation of aliphatic ketones in trifluoroacetic acid leads to hydrogen abstraction by the carbonyl oxygen radical-cation forming a carbon radical, then further oxidation of the radical to the carbocation and migration of this centre along the carbon chain by a series of hydride transfer steps. Long chain ketones yield a mixture of alcohol trifluoroacetates by reaction of the carbocation centres with the solvent [3].



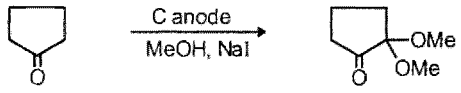
Oxidative ring cleavage of cyclohexanones is achieved in ethanol at a platinum anode. Cleavage of the carbon-carbonyl bond occurs and the carbonyl centre is trapped as the carboxylic acid. The radical centre formed after bond cleavage is oxidised to the carbocation. This rearranges to the most stable centre and is then trapped by the carboxyl group to form a lactone [4, 5]. An identical process is



achieved during oxidation of cyclopentanone and cyclohexanones in trifluoroacetic acid when five and six membered ring lactones are formed [6].

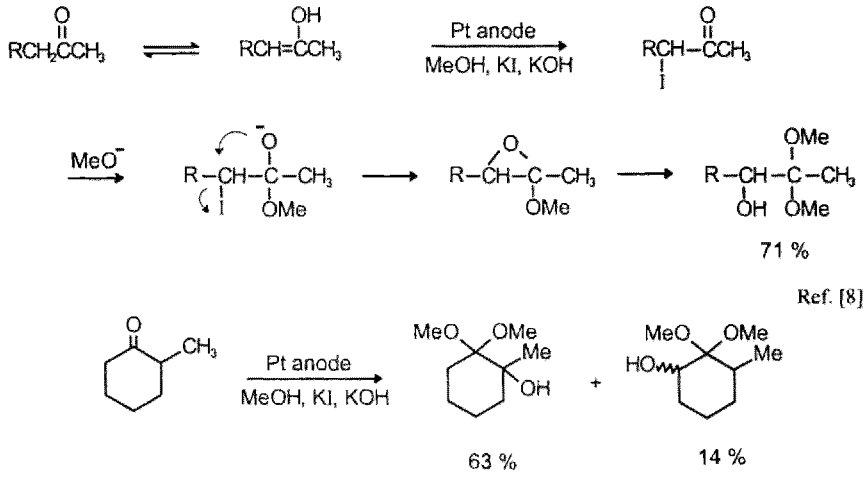
Ketones react with electrochemically generated halogens to form the α-halogenocompound. In the presence of potassium hydroxide and potassium iodide, the more stable enolate is formed from the ketone and this reacts with electrochemically generated iodine. The outcome from reactions in methanol is governed by

competition between either replacement of halogen by methoxide, or the Favorskii rearrangement. Cyclopentanones undergo the simple displacement reactions to give the 2,2′-dimethoxy compound [7]. Open chain aldehydes and ketones, also

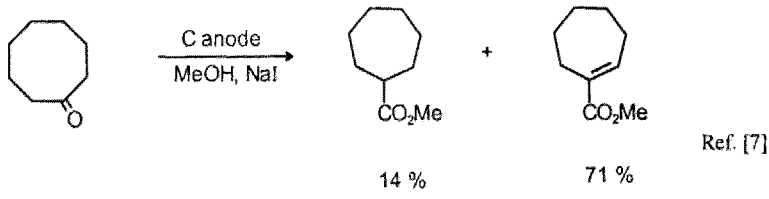


Ref. [7]

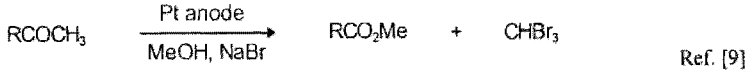
cyclohexanones, react *via* an intermediate epoxide to give the α-hydroxy dimethyl acetal [8]. 7-Membered or higher ring ketones prefer to undergo the Favorskii rearrangement [7]. Some methyl ketones undergo the bromoform degradation to a carboxylic acid during anodic reaction with methanol and sodium bromide [9].



Ref. [8]



Ref. [7]

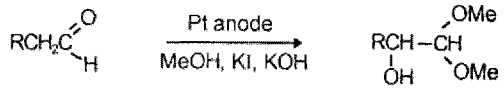


Ref. [9]

Oxidation of Aldehydes

Electrochemical oxidation of aldehydes to the carboxylic acid, catalysed by bromide or iodide ions, is an extensively exploited process. It is the preferred route for the oxidation of reducing sugars to the aldonic acid and replaces the older technique where bromine in stoichiometric amount was used as oxidising agent [10]. Reaction is carried out in aqueous solution in an undivided cell at a graphite anode using an electrolyte of sodium bromide containing suspended calcium carbonate. The calcium salt of the oxidation product separates. Monosaccharides [11, 12, 13], their methylated derivatives [14] and reducing disaccharides [11] have been converted to the carboxylic acid. Conversion of glucose to gluconic acid is carried out on a technical scale.

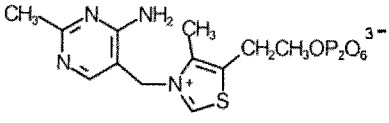
Oxidation of aliphatic aldehydes in methanol with potassium iodide as mediator follows a reaction path like that of the saccharides. The corresponding carboxylic acid methyl ester is formed [15]. With excess potassium hydroxide present, the reaction follows a different pathway. The aldehyde enol is iodinated and subse-



Ref. [8]

quent steps, like the related oxidation of ketones, lead to the α-hydroxyaldehyde dimethyl acetal [8].

In nature, an enzyme requiring two co-factors, thiamine diphosphate **2** and flavin adenine dinucleotide, accomplishes the oxidation of pyruvate to acetyl phosphate. The thiazole ring in thiamine condenses at the 2-position with pyruvat eliminating carbon dioxide to give an activated species that is oxidised by the flavin. An enzymatic oxidation process then reactivates the reduced flavin. The redox

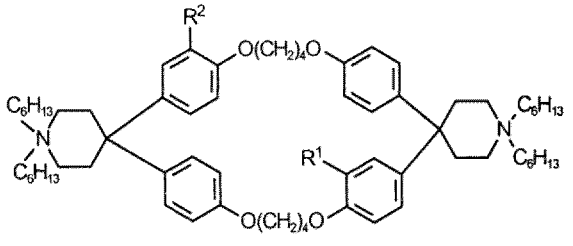


2

behaviour of flavin adenine dinucleotide is discussed on p. 253. Acetaldehyde reacts with the thiamine ring to give the same activated species with elimination of a proton. An electrocatalytic system where the reduced flavin is oxidised at the anode has been applied on a millimolar scale for the oxidation of aldehydes to the carboxylic acid methyl ester, using methanol as solvent [16].

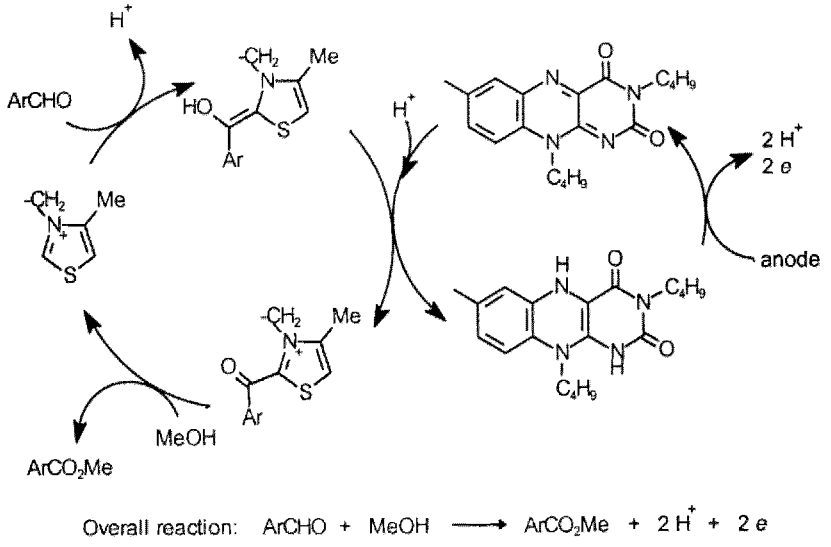
The most catalytically active system uses the thiazolium unit **3** and the flavin unit **4** both covalently attached to a macrocycle in **5**. A binding site shielded within

3 **4**



5

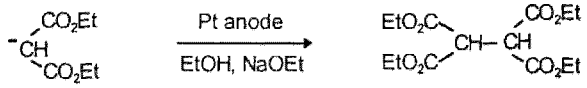
the macrocyclic ring is thus created for attachment of the aldehyde. Oxidation of an aldehyde then takes place by the catalytic cycle in Scheme 9.1, mimicking the enzymic process.



Scheme 9.1. Oxidation of aldehydes at a platinum anode catalysed by macrocycle **5** in methanol.

Oxidation of Enolate Ions

Anodic oxidation of malonate esters in alkaline solution gives the dehydrodimerization product by carbon-carbon coupling. The reaction mechanism has been



Ref. [19]

demonstrated using 5-substituted barbituric acids **6** as substrates [17]. Cyclic voltammetry at sweep rates up to 20 V s^{-1} shows no evidence of reversibility. At slow sweep rates a single one-electron oxidation wave is observed at platinum and the peak potential varies with pH as indicated in Figure 9.1. The point of inflection on this graph corresponds to the pK_a of the barbituric acid. For 1,3-dimethylbarbituric acid, $pK_a = 4.68$ [18]. At low pH values, the electrochemical step involves loss of a proton and an electron. Above pH 4, the process is loss of an electron from the enolate ion. A carbon-centered radical is formed and this dimerises at the diffusion-controlled rate. Preparative scale oxidation of 5-substituted barbituric acids at pH 1.0 gives the dehydrodimer.

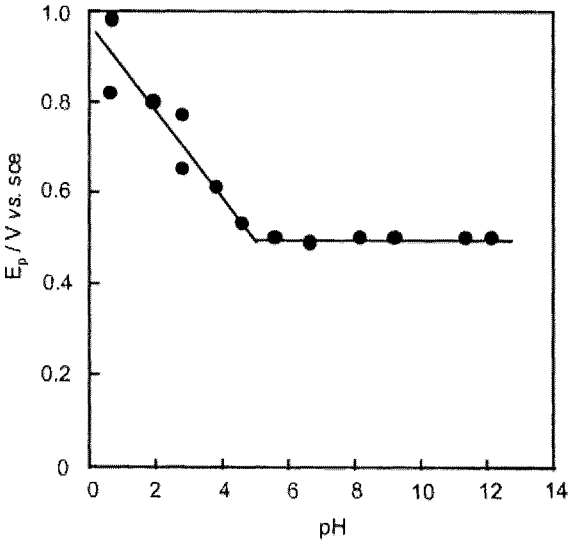
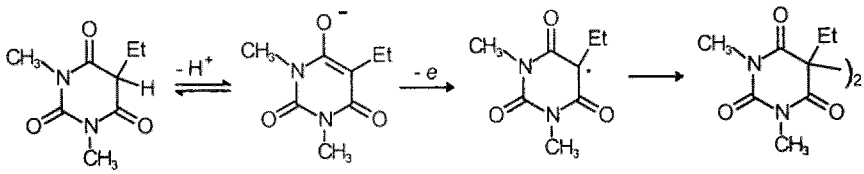
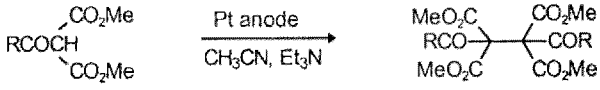


Figure 9.1. Variation of peak potential with pH for the oxidation of 1,3-dimethyl-5-ethylbarbituric acid **2** at a platinum electrode in aqueous solution, sweep rate 5 mV s^{-1}. Data from ref. [17].



6

Early workers employed ethanol as solvent for these oxidations in an undivided cell with electrodes of either platinum or carbon, Good yields are obtained from oxidation of the sodium enolate of diethyl malonate and of acetylacetone [19]. Ethyl acetoacetate however gives poor yields of the coupled product [19, 20]. The dehydrodimerization of malonate esters is best carried out in acetonitrile in the presence of suspended sodium methoxide using carbon electrodes [21]. Most alkylmalonates show this reaction but the presence of a large *tert.*-butyl group prevents the dehydrodimerization process. Ethyl acetoacetate gives poor yields but the relatively acidic acylmalonate esters 7 readily form the dehydrodimerization product. Nitroalkane anions undergo the related oxidative coupling reaction in metha-



7 Ref. [21]

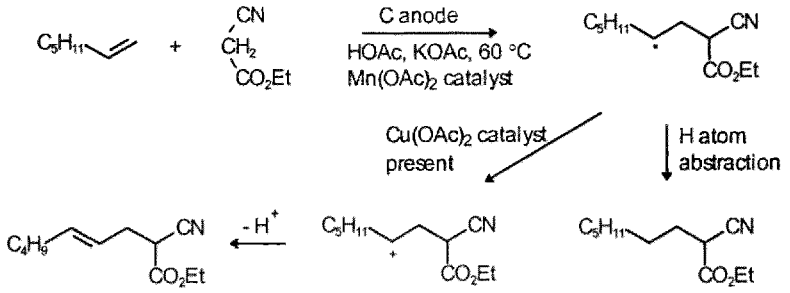
nol containing benzyltrimethylammonium hydroxide [22].

The chemical dehydrodimerization of malonate esters can be carried out by the action of iodine on the sodium enolate [23]. This route is adapted as an electrochemical process using alcoholic sodium iodide as electrolyte in an undivided cell with carbon electrodes [24, 25]. Base generated at the cathode and iodine generated at the anode serve in a catalytic cycle.

Manganese(III) acetate is known to oxidise enolate ion to the radical and a large body of literature is concerned with the generation and further reactions of these carbon radicals, using a stoichiometric amount of the reagent [26]. Diethyl malonate, ethyl cyanoacetate, ethyl acetoacetate and acetylacetone all function as substrates as does acetic anhydride. Recycling of the spent manganese(II) acetate has been proposed by electrolysis at 80 °C using a graphite anode in acetic acid containing lithium tetrafluoroborate as electrolyte.

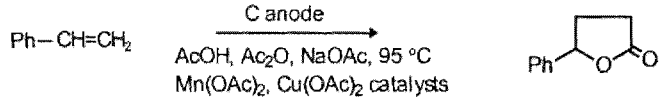
Some reactions can be carried out using a catalytic amount of manganese(II) acetate in acetic acid or acetic acid, acetic anhydride using a graphite anode to convert the reagent to the manganese(III) state. A complex is formed between manganese(III) and the enolizable substrate after which a carbon radical is generated by

intramolecular electron transfer from the enol to manganese. The overall rate for generation of the carbon radical is generally slow and reactions are carried out at 60-90 °C. Once formed, the radical will add to an alkene. Carbon radicals are so slowly oxidised by manganese(III) that reaction is terminated by abstraction of a hydrogen atom from either the solvent or the enolate complex. A change in product structure is found when the coupling between an enolate and an alkene is catalysed by a mixture of manganese(II) acetate and copper(II) acetate. Copper(II) is very effective for the oxidation of carbon radicals to the carbonium ion which leads to another series of products. Scheme 9.2 illustrates the two possible catalytic reactions for addition of ethyl cyanoacetate to hept-1-ene [27, 28].



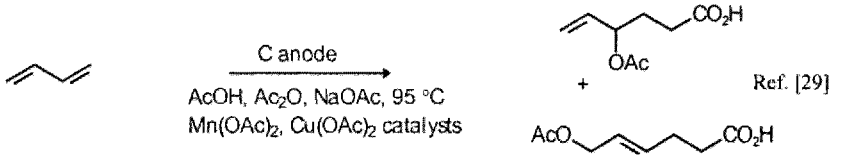
Scheme 9.2. Coupling of active methylene compounds with alkenes catalysed by manganese and copper ions.

Application of the manganese and copper catalysed electrochemical reaction between acetic anhydride and styrenes is as efficient as the process using stoichiometric amounts of reagent [27]. The reaction between acetic anhydride and buta-



Ref. [27]

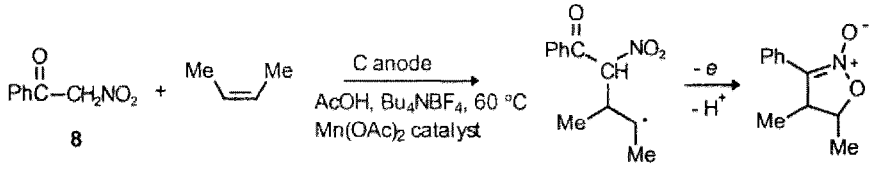
diene has been developed as one stage in the technical scale production of sorbic acid [29].



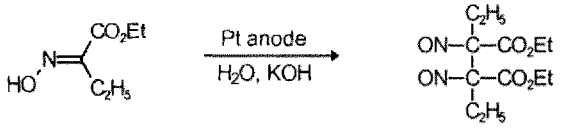
Ref. [29]

Generation of the carbon based radical in these processes involves the prior formation of a complex between manganese(III) and the enol of the carbonyl reactant. Intramolecular electron transfer occurs within this complex. Addition to the olefin then takes place within the co-ordination sphere of manganese. When manganese is present in catalytic amount, the relative values of the equlibrium constants between manganese and both the carbonyl compound and the alkene are important. If the olefin is more strongly complexed then no radical can form and reaction ceases. Reactions are usually carried out at constant current and the current used must correspond to less than the maximum possible rate for the overall chemical steps involved. Excess current caused the anode potential to rise into a region where Kolbe reaction of acetate can occur and this leads to side reactions [28].

The addition to alkenes of radicals derived from an α-nitroketone is also catalysed by manganese(III) [30]. During the reaction between α-nitroacetophenone **8** and *cis*-but-2-ene, the stereochemical relationship between the methyl substituents is not preserved. The process terminates with the formation of a nitrone. A related process will generate nitromethyl radicals from nitromethane and these add to benzene to give phenylnitromethane [31].



Anodic oxidation of the alkali metal salts of α-oximinoesters results in dehydrodimerization [32].



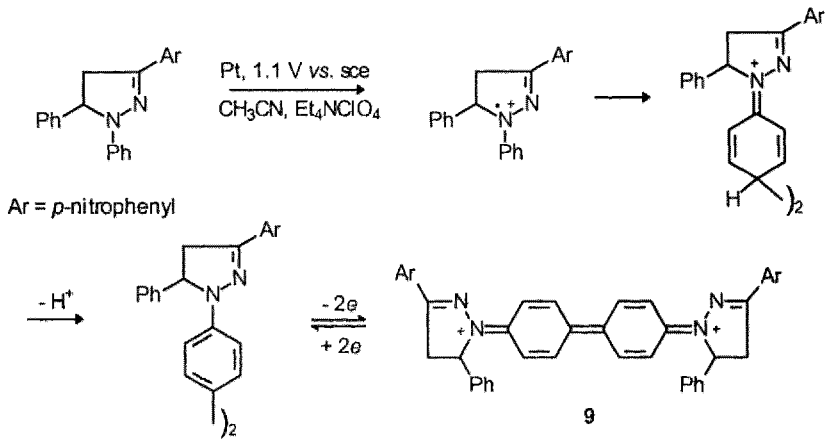
Ref. [32]

Oxidation of Hydrazones and Oximes

Oxidation of ketone phenylhydrazones generates a radical-cation centre on the nitrogen atom adjacent to the benzene ring. The radical-cation is delocalised by both the hydrazone group and the phenyl ring. Reactions of 1,3,5-triphenyl-Δ^2-pyazolines illustrate the properties of these radical-cations. Two one-electron waves are seen at a rotating disc electrode in acetonitrile and for 1,3,5-triphenyl-pyrazoline, $E_{½}$ = 0.82 and 1.68 V *vs.* sce [33]. The delocalised radical-cation is

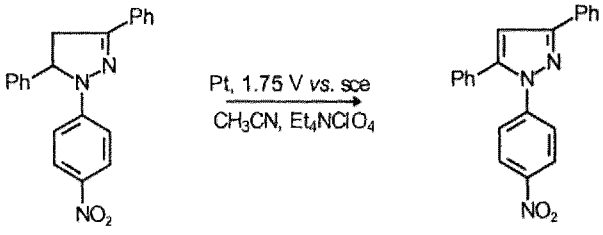
formed at the potential of the first wave by loss of an electron from the 1-nitrogen atom lone-pair. The second oxidation wave is due to further oxidation of this radical-cation.

The radical-cation is relatively stable when the 1-aryl group has a *para*-substituent and can be characterised by uv-spectroscopy [34]. When this *para*-substituent is not present, two radical-cations dimerise by carbon-carbon bond formation at this position, followed by loss of two protons. The rate constant for this dimerization step can be deduced from the variation of the rotating disc elec-



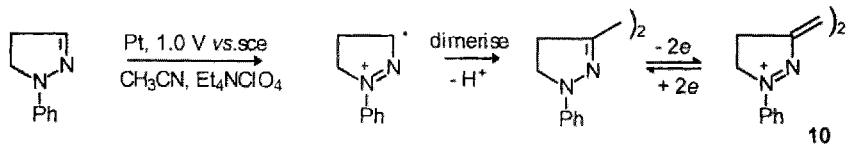
trode response with rotation speed and substrate concentration. It has a value of 5.5 x 10^4 M^{-1} s^{-1} for 1,3,5-triphenyl-Δ^2-pyrazoline [35]. The resulting dimer undergoes an oxidation to the dication **9** in two one-electron steps at less positive potentials than that required for oxidation of the original pyrazoline [33]. The oxidised derivative **9** is responsible for the fushin colour developed in the Knorr test for pyrazolines where the compound under examination is exposed to sodium bichromate and sulphuric acid [36, 34].

When the dimerization step is blocked, oxidation yields the pyrazole [33] and



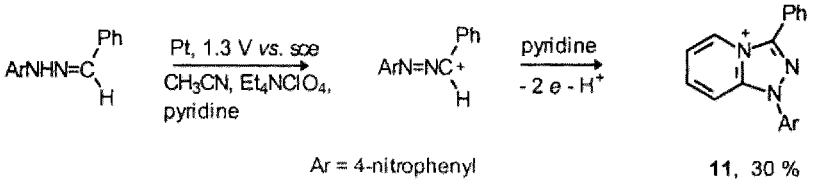
many chemical oxidising agents will effect the dehydrogenation of pyrazolines to

the pyrazole. When no 3-substituent is present, dimerization of the one-electron oxidation product occurs through the 3-position [37]. Two further one-electron

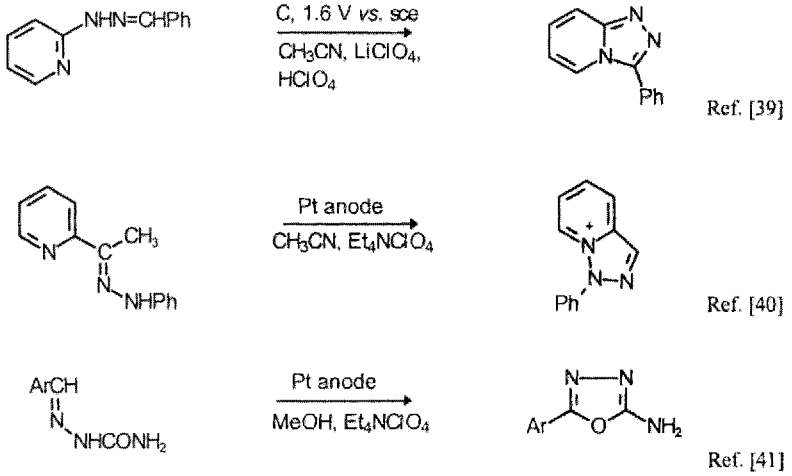


oxidation steps then lead to the dication **10**.

Open chain ketone phenylhydrazones take part in a number of cyclization reactions to form heterocyclic rings. Many of the electrochemical reactions describe can also be achieved using chemical oxidising agents. In general, electrochemical oxidation proceeds to the two-electron level to generate an electrophilic species

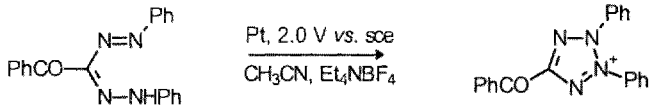


that will react with a nucleophilic nitrogen centre. The intermolecular reaction with pyridine, quinoline or isoquinoline leads to the formation of *s*-triazolo[4,3 – *a*]pyridinium salts **11** [38]. Related intermolecular cyclization reactions are found with 2-substituted pyridine hydrazones [39, 40], with aldehyde semicarbazones [41] and

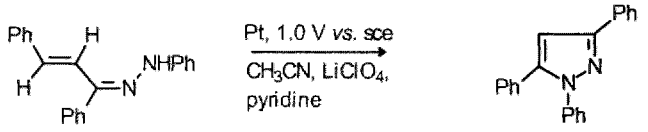


also are involved during the oxidation of formazans **12** [42].

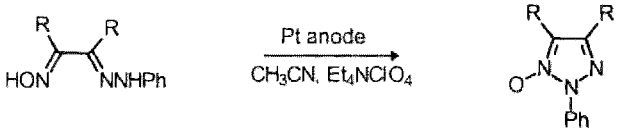
Oxidation of chalcone phenylhydrazone **13** leads to a pyrazole and the expelled proton catalyses formation of a pyrazoline from the chalcone phenyl-hydrazone [43]. The latter undergoes further anodic oxidation (p. 308). In the presence of pyridine as a proton acceptor, the pyrazole becomes the major product. A further example of oxidative cyclization is the conversion of α-oximino phenylhydrazones to 1,2,3-triazole-1-oxides **14** [44].



12

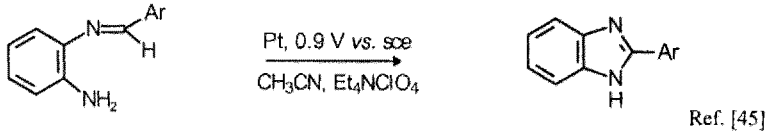


13



14

Schiff bases derived from *o*-phenylenediamine and from 2-hydroxyaniline show a two-electron wave on cyclic voltammetry in acetonitrile and further waves at more positive potentials due to oxidation of the product from the first wave. Preparative scale reaction at the potential of the first wave leads to formation of a heterocyclic ring product [45].



Ref. [45]

Ar = 4-methoxyphenyl

Oxidation of Carboxylates – Introduction and Mechanism

The oxidation of alkylcarboxylates is one of the first organic electrochemical reactions to be investigated. Faraday (1834) noted that during the electrolysis of potassium acetate, hydrogen is evolved at the cathode and a mixture of carbon dioxide and hydrocarbons is evolved at the anode [46]. Later, Kolbe (1849) carried out an extensive examination of the organic products from electrolysis of acetate and valerate (2-methylbutanoate) [47]. Analytical data and vapour density measurements on the hydrocarbon products are in agreement with the formation of C_2H_6 and C_8H_{18} respectively but, because of a poor understanding of the relationship between vapour density and relative molecular mass, the hydrocarbons were assumed to be the methyl and valyl radicals. Wurtz (1855) demonstrated that electrolysis of a mixture of valerate and oenanthylate (heptanoate) gives the product $C_{10}H_{22}$ from cross combination of the two radicals formed [48]. This observation was of fundamental importance to chemical theory since it defined the value of the proportionality constant between vapour density and relative molecular mass. Values for relative molecular mass deduced by Kolbe had to be multiplied by two. Thus electrolysis of acetate gives ethane. Correct molecular formulae were written for the hydrocarbon products when, a few years later, the relative atomic mass of carbon was established as 12 and not 6 as assumed by Kolbe and Wurtz.

Today the coupled product is described as being formed by union of two alkyl radicals formed by loss of one electron and carbon dioxide from the carboxylate ion. Extensive early use of the Kolbe reaction was made for the synthesis of long chain α,ω-dicarboxylate esters starting from the half esters of shorter chain α,ω-diacids [49].

Kolbe noted also the formation of traces of methyl acetate and butyl valerate from electrolysis of acetate and valerate respectively. Careful analysis of reaction products by Petersen (1900) identified compounds which are today formulated as being derived from carbocations formed by loss of one electron from the alkyl radical [50]. Propanoic acid gives mostly ethene while butanoic acid and 2-methylpropanoic acid give mostly propene. Acetate and long chain alkylcarboxylates give mostly the Kolbe type dimer hydrocarbon on electrolysis of their potassium salts in concentrated solution at a platinum electrode, using high current density and low temperatures [51].

The second Kolbe reaction, proceeding via a carbocation, was found by Hofer and Moest (1902) to be promoted by the addition of an indifferent electrolyte [52]. Using a 1 – 2 molar solution of the carboxylate, addition of potassium hydrogen carbonate at a level of 0.2 molar was sufficient to give a good yield of methanol from acetate and similar products from longer chain carboxylates. Sodium perchlorate and sodium sulphate at the molar concentration level also promoted alcohol formation. This second Kolbe reaction involving carbocationic intermediates is

frequently termed the Hofer-Moest reaction. Modern literature refers to it as the non-Kolbe reaction.

Oxygen evolution competes with the Kolbe reaction at any anode material. Smooth platinum is the usual anode material and at low temperatures and high current densities, oxygen evolution is suppressed in favour of the desired Kolbe process [51]. Other suitable anode materials are iridium and rhodium [53, 54]. Soft graphite gives negligible amounts of the Kolbe product but some hard vitreous carbons are as effective anode materials as platinum (Table 9.1). The most effective glasslike hard-carbons are those with a very low apparent porosity [55]. The list of failed anode materials includes platinised platinum, gold, titanium, MnO_2, PbO_2 and Fe_3O_4 where oxygen evolution is the preferred process [56, 53].

Table 9.1. Chemical yields (%) of dodecane from electrolysis of heptanoic acid. Data from ref. [57].

Solvent	Pt	Vitreous carbon	Baked carbon	Graphite [a]
MeOH	52	24-33	30	1
EtOH	62	45-53	39	5-9
H_2O	45	45-50		2

Footnote: (a) Major products are esters $C_6H_{13}CO_2R$ where R = hex-1-yl, hex-2-yl, and hex3-yl.

Physico-chemical studies on the Kolbe reaction are largely restricted to the behaviour of acetate in aqueous solution at a smooth platinum anode. The polarization curve (Figure 9.1) exhibits two linear Tafel regions. At low current densities, the principal reaction is evolution of oxygen. Evolution of ethane and carbon dioxide takes over completely when the anode potential exceed 2.0 V *vs.* sce and the Tafel line above this potential is due to the Kolbe reaction. Iridium anodes show a similar behaviour in that the Kolbe reaction is only found when the anode potential exceeds 1.85 V *vs.* sce. At a gold anode there is only one Tafel region corresponding to the evolution of oxygen [58]. Similar results have been found during electrolysis of potassium ethyl succinate at bright platinum. Synthesis of diethyl succinate begins at anode potentials greater than 2.3 V *vs.* sce when practically no oxygen is evolved [56].

Transition into the Kolbe region at platinum is associated with the formation of an oxide layer. Acetate ions are believed to be more strongly adsorbed on this layer than is water. Conversion of water to oxygen is then suppressed in favour of the oxidation of acetate ions [59, 60]. Electron transfer from acetate is synchronous with cleavage of the alkyl-carboxylate bond leaving adsorbed carbon dioxide and

alkyl radicals. Alkyl radicals now undergo two principal competing reactions, dimerization at a diffusion controlled rate or further electron transfer from the electrode. Since there is almost complete surface coverage by acetate, the alkyl radicals are in high local concentration and dimerisation is the preferred process.

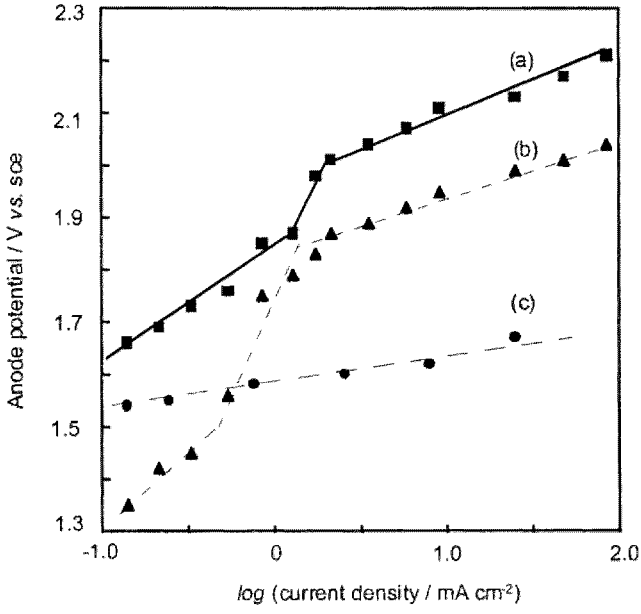


Figure 9.1. Anode potential versus current density for a solution of 1 M sodium acetate and 1 M acetic acid in water; (a) Pt anode, (b) Ir anode, (c) Au anode. Data fron ref. [58].

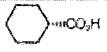
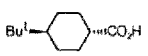
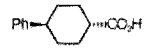
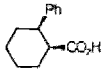
Under the classical Hofer-Moest reaction conditions, a second ion from hydrogen carbonate, sulphate or perchlorate is present in the solution and this competes with acetate for adsorption sites. Methyl radicals are then generated in a diluted local concentration so that further oxidation to give methanol becomes the dominant reaction. The Kolbe reaction of phenylacetic acid to give bibenzyl in methanol is also diverted by addition of sodium perchlorate so that benzyl methyl ether becomes the main product [61]. Reactions, which in the modern literature are defined as non-Kolbe processes, are generally carried out using the usual experimental conditions for the true Kolbe reaction. They are associated with carboxylic acids bearing an electron donating α-substituent such as hydroxyl or alkoxy. In contrast, when an electron withdrawing α-substituent such as nitrile or ethoxycarbonyl is present the normal Kolbe reaction is observed. This chemistry illustrates the competition between dimerization and further oxidation of the radical intermediates.

Electron donating substituents favour further oxidation to the carbonium ion and thus suppress the Kolbe dimerization process [62].

The non-Kolbe reaction of trichloroacetic acid at platinum shows competition with oxygen evolution. The formation of trichloromethyl trichloroacetate only begins when the anode potential exceeds 2.35 V *vs*, sce [63]. At lower anode potentials oxygen only is evolved.

In many cases both Kolbe and non-Kolbe products are isolated from a reaction. Carboxylic acids with an α-alkyl substituent show a pronounced dual behaviour. In these cases, an increase in the acid concentration improves the yield of the Kolbe product. An example of the effect of increased substrate concentration is given in Kolbe's classical paper [47] where 2-methylbutyric acid in high concentration affords mostly a dimethylhexane whereas more recent workers [64], using more dilute solutions, obtained both this hydrocarbon and butan-2-ol. Some quantitative data is available (Table 9.2) for the products from oxidation of cyclohexanecarboxylic acids to show the extent of Kolbe versus non-Kolbe reactions. The range of products is here increased through hydrogen atom abstraction by radical intermediates in the Kolbe reaction, which leads to some of the monomer hydrocarbon

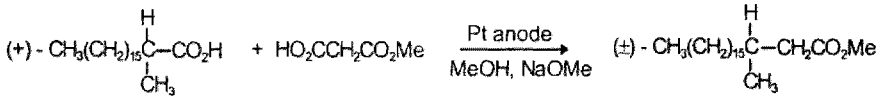
Table 9.2. Products from Kolbe electrolysis at a platinum anode in methanol containing sodium methoxide. Data from ref. [65].

Substrate	Concn. / M	Product distribution / %		
		Cyclohexane	Carbocation derived	Bicyclo-hexanes
	0.33	10.7	71.1	19.2
	0.33	19.3	55.4	25.1
	0.33	19.4	68.4	12.3
	0.33 1.63	6.3 11.2	92.6 81.6	– 7.2

The Kolbe reaction is carried out in an undivided cell with closely spaced platinum electrodes. Early examples used a concentrated, up to 50 %, aqueous solution of an alkali metal salt of the carboxylic acid and the solution became strongly alkaline due to hydrogen evolution at the cathode. Ingenious cells were devised with a renewing mercury cathode, which allowed removal of alkali metal amalgam. These experimental conditions have been replaced by the use of a solution of the carboxylic acid in methanol partially neutralised by sodium methoxide or trieth-

ylamine. A methanol pyridine solvent mixture is used for the more insoluble acid substrates. Under these conditions the solution becomes alkaline only at the end of the reaction. A solvent mixture of 2-methoxyethanol and water has also been recommended [66]. Use of dimethylformamide or acetonitrile favours the Kolbe reaction but these solvents are rarely used in practice since radicals react with these solvents to give a range of unwanted by-products [65].

Experimental evidence indicates that the alkyl radical intermediates from the anodic oxidation of carboxylates are generated in free solution and have no memory of the configuration of the carboxyl group that was eliminated. Where the carboxylic acid function is attached to an asymmetric carbon atom as in **15**, the Kolbe coupling reaction leads to complete racemization [67]. Anodic oxidation of (+)-2-



15

methylbutanoic acid affords racemised Kolbe [68] and non-Kolbe products [64]. More remote asymmetric centres are unaffected in the reaction.

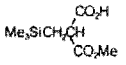
4-*tert*-Butylcyclohexanecarboxylic acid yields a statistical distribution of the three isomeric bicyclohexyls with no evidence for adsorption at the electrode surface, which would distort the distribution of products. In this case the radical intermediates has negligible activation energy for combination so that statistically weighted coupling in the ratio 1:2:1 for *a-a*, *a-e* and *e,e* carbon-carbon bond formation ensues [65]. 2- Phenylcyclohexanecarboxylic acid gives mostly non-Kolbe products. The low yield of dimeric Kolbe product shows a preference for *e-e* bond formation [65]. This evidence can be explained by assuming a larger, but still small, energy of activation for radical coupling in this case, which allows further oxidation to the carbonium ion to compete more successfully and which directs product formation along the least hindered route.

The Kolbe Reaction

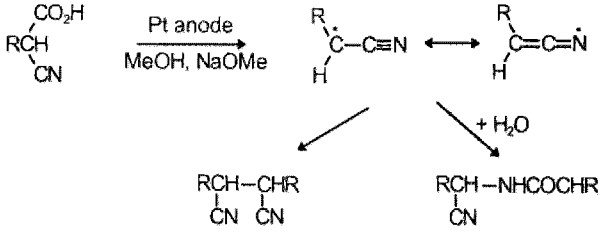
The Kolbe reaction is an important carbon-carbon bond forming reaction Examples of its use as given in Tables 9.3 and 9.4 where either one or two acid components are employed. The range of tolerance of other functional groups is illustrated. Among the halogen substituents, the iodine group is oxidised in preference to carboxylate ion [69]. Most of the examples chosen use methanol as the solvent with about 10 % of the acid neutralised by sodium methoxide or potassium hydroxide. The earlier practice of using a concentrated aqueous solution of a carboxylate salt is considered to give inferior yields. Electron donating α-substituents favour the

formation of a carbonium ion. Electron withdrawing α-substituents favour the radical dimerization. Sterically hindered tetraalkylsuccinic acids can be prepared from the half esters of dialkylmalonic acids, in spite of the electron donating alkyl groups attached to the reaction site [70].

Table 9.3. Kolbe reactions with a single component acid, usually partially neutralised with sodium methoxide.

Substrate	Product yield / %	Solvent	Ref.
$CH_2{=}CH(CH_2)_8CO_2H$	43	MeOH	[71]
$F(CH_2)_6CO_2H$	58	MeOH	[69]
$Cl(CH_2)_6CO_2H$	54	MeOH	[69]
$HO(CH_2)_8CO_2H$	28	MeOH	[72]
$CH_3CONH(CH_2)_5CO_2H$		MeOH	[73]
$PhCH_2CH_2CH_2CO_2H$	37	MeOH / C_5H_5N	[74]
(+)-$MeO_2CCH_2CHMeCH_2CO_2H$	80	MeOH / H_2O	[75]
$MeO_2CCRR'CO_2H$, R R' = H or Alkyl	20-30	MeOH	[70]
$H_2NCOCH_2CO_2H$	56	MeOH	[76]
$EtO_2CCH_2COCH_2CO_2H$	low	H_2O, KOH	[77]
	37	MeOH	[78]

Anodic oxidation of α-cyanocarboxylates generates a delocalised radical. Dimerization occurs by both carbon-carbon and carbon-nitrogen coupling [79]. Oxidation of β-ketocarboxylates using a platinum anode and a mercury pool cathode, to prevent the solution becoming alkaline, causes the dimerization process. The alternative non-Kolbe process, giving an α,β-unsaturated ketone, is followed when the solution is strongly alkaline [80].



Ref. [79]

Δ^2-Enecarboxylic acids do not undergo the Kolbe coupling reaction. Δ^3-Enecarboxylic acids give poor yields in the Kolbe reaction and a mixture of products

results from coupling between the two canonical forms of the allyl radical intermediate [81, 82]. The radical is more efficiently trapped by cross coupling with the radical from a second acid and a synthesis of brevicomin has been achieved in this way [83].

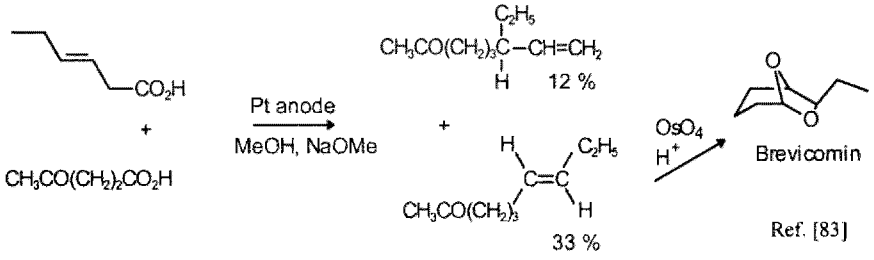
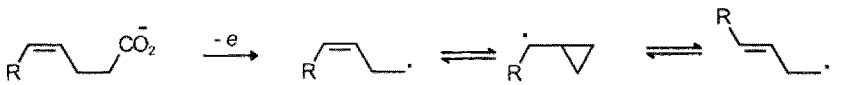
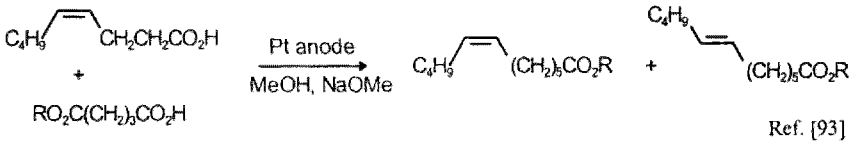


Table 9.4. Mixed Kolbe reactions in methanol. Yields for the mixed product are based on component 1, which is in deficiency. Acids are partially neutralised with sodium methoxide.

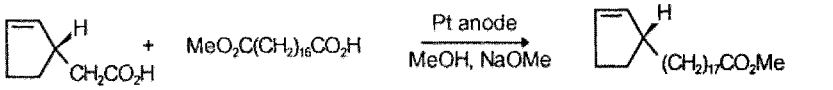
Components 1 and 2	Ratio 1 : 2	Yield / %	Ref.
1) $MeO_2C(CH_2)_4CO_2H$ 2) $CH_3(CH_2)_8CO_2H$	1 : 2	38	[84]
1) Stearic acid 2) $PhCH_2O_2C(CH_2)_2CO_2H$	1 : 4	28	[85]
1) (+)-$MeO_2CCH_2CHMeCH_2CO_2H$ 2) Octanoic acid	1 : 2	48	[86]
1) Oleic acid 2) $MeO_2C(CH_2)_4CO_2H$	1 : 3	34	[87]
1) $CH_3(CH_2)_7CC(CH_2)_7CO_2H$ 2) $MeO_2C(CH_2)_4CO_2H$	1 : 4	28	[88]
1) 9,10-Dihydroxystearic acid 2) $MeO_2C(CH_2)_4CO_2H$	1 : 4	30	[89]
1) Cholic acid 2) $MeO_2CCH_2CH_2CO_2H$	1 : 13	20	[90]
1) $F(CH_2)_9CO_2H$ 2) $Cl(CH_2)_4CO_2H$	1 : 2	24	[69]
1) $MeO_2C(CH_2)_4CO_2H$ 2) $CH_3COCH_2CH_2CO_2H$	1 : 4	32	[91]

Z/E isomerization of the alkene bond in Δ^4-enecarboxylic acids occurs during Kolbe electrolysis because the intermediate radical reacts reversibly with this function to form a cyclopropane [92]. This process leads to a partial loss of stereochemistry in the synthesis of long chain alkenes [93]. However, it does not present stereochemical problems during the synthesis of cycloalkenes such as chaulmoogric acid [94].





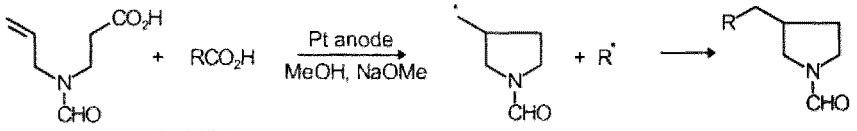
Ref. [93]



Methyl (+)-chaulmoograte

Ref. [94]

Some Δ^6-enecarboxylic acids undergo a rapid intramolecular cyclization reaction of the 5-*exo-trig* type prior to the radical coupling step. Substituted tetrahydrofurans [95] and pyrrolidines [96] can be prepared by this Kolbe route. It is preferable to protect the amine function in the pyrrolidine synthesis by N-formylation in

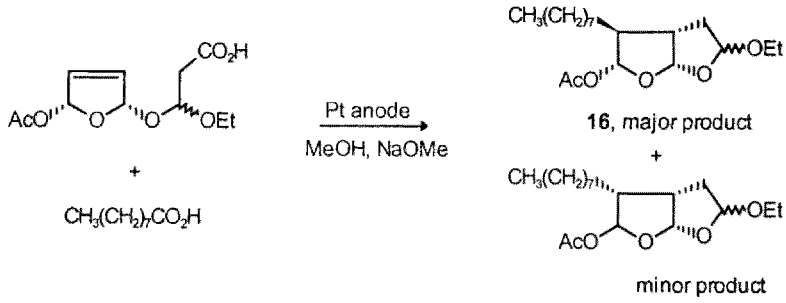


Ref. [96]

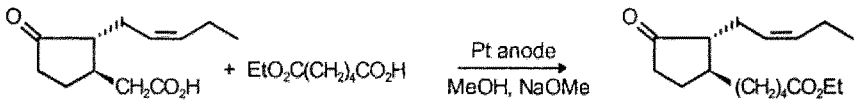
46 - 58 %

order to suppress α-methoxylation of the amide. However, under vigorous conditions, the N-formyl group can be converted to a urethane (p. xxx). One of the advanced prostaglandin-synthesis precursors **16** has been prepared using this intramolecular cyclization as one step in the reaction sequence [97]. The ring junction formed in this process is *cis*-fused due to energy considerations and the incoming radical is attached from the least hindered direction. Two carbon-carbon bonds are introduced with the required stereochemical relationship. Such behaviour

can be contrasted to the reaction of substrate **17** where now the intramolecular cyclization process is hindered because it would lead to a strained *trans-* junction between two five membered rings [98]. Substrate **18** undergoes two successive 5-*exo-trig* cyclizations before the radical intermediate is captured by methyl [99].

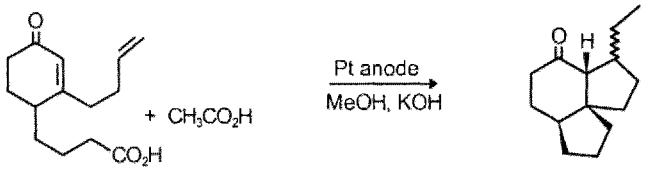


Ref. [97]



17

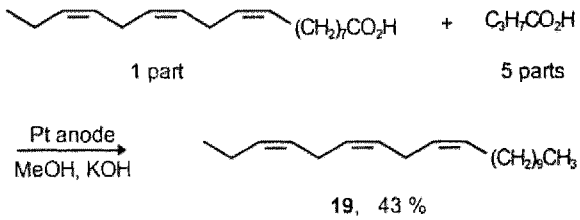
Ref. [98]



18

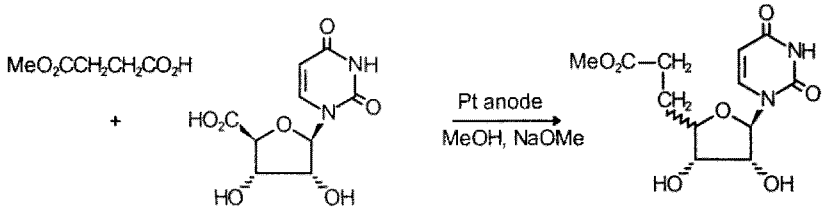
Ref. [99]

Alkene bonds more remote from the carboxyl function do not interfere with the normal Kolbe coupling reaction. An example of this point during a polyene synthesis is given by the formation of the insect pheromone **19** [100].



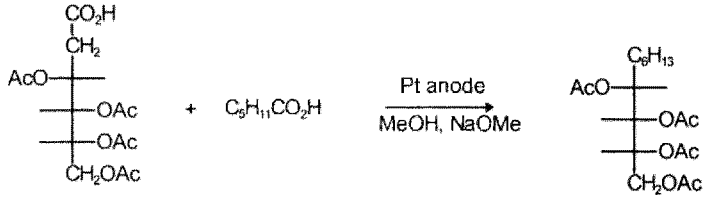
19, 43 %

Electron donating α-substituents favour the non-Kolbe reaction but the radical intermediates in these anodic processes can be trapped during co-electrolysis with an alkanoic acid. Anodic decarboxylation of sugar uronic acids leads to formation of the radical which is very rapidly oxidised to a carbonium ion, stabilised by the adjacent ether group. However, in the presence of a tenfold excess of an alkanoic acid, the radical intermediate is trapped as the unsymmetrical coupling product [101]. Highly functionalised nucleotide derivatives such as **20** will couple successfully in the mixed Kolbe reaction [102]. Other examples include the co-electrolysis of 3-oxa-alkanoic acids with an alkanoic acid [103] and the formation of 3-alkylindoles from indole-3-propanoic acid [104]. Anodic oxidation of indole-3-propanoic acid alone gives no Kolbe dimer [105].



20

Ref. [102]

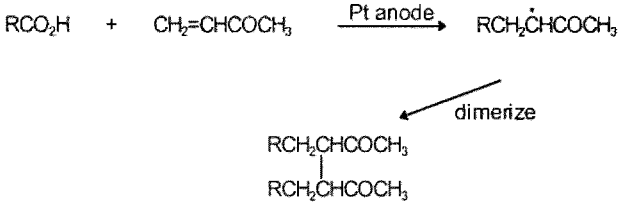


1 part 10 parts 69 %

Ref. [106]

Protected sugar derived acids, having no α-hydroxy substituent, have also been used in the mixed Kolbe reaction [106]. The Kolbe reaction is used to graft short functionalised alkyl chains onto poly(acrylic acid) [107].

The enone function undergoes very fast intermolecular radical addition reactions and will trap the intermediate from oxidation of the carboxylate group. This step leads to a radical centre adjacent to the electron withdrawing carbonyl function of the original enone and this centre is not readily oxidised to the carbonium ion. Dimerization to a diketone is thus the final stage in the reaction [108].

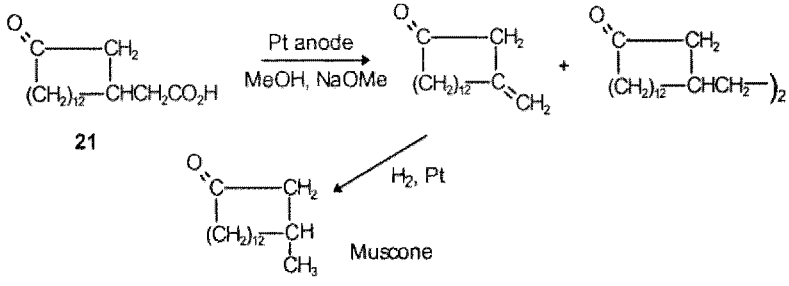


Ref. [108]

Oxidation of carboxylate ions in homogeneous solution using some one-electron transfer agents gives in varying proportions the Kolbe dimer and the product from hydrogen atom abstraction from the solvent by the intermediate alkyl radical. Persulphate ion [109], hexachloco-osmate(V) [110] and the radical-cation from tris(4-bromophenyl)amine [111] all have been used to promote this reaction.

The Non-Kolbe Reaction

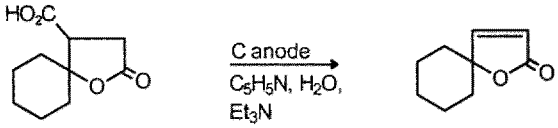
Substituents stabilising a carbonium ion influence the course of the anodic oxidation of carboxylic acids by promoting fast oxidation of the radical intermediate to the carbonium ion. Subsequent chemical steps are those expected of this ionic intermediate and the overall process is termed the non-Kolbe reaction. Reaction at a graphite anode strongly favours the non-Kolbe carbonium ion process, although frequently the platinum anode has been used. For many carboxylic acids with α– or β-alkyl substitution, products at a platinum anode are formed by further chemical reaction of both the radical and the carbonium ion intermediate. The non-Kolbe reaction of **21** was used in an early synthesis of muscone where workers tolerated



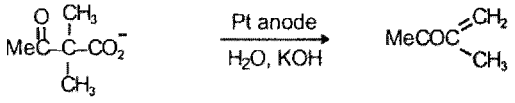
21

the normal Kolbe by-product [112]. Here, carbonium ion formation is probably concerted with proton loss to form the alkene. This is a commonly observed path-

way. It has been exploited for the formation of butenolides [113] and for the conversion of α-ketocarboxylates to enones [80].

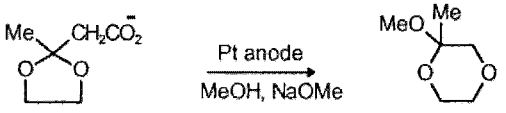


Ref. [113]



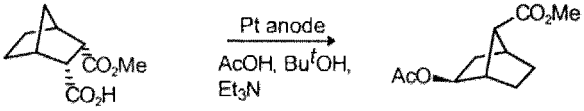
Ref. [80]

Non-Kolbe reactions are often favoured by skeletal rearrangements which generate a more stable carbonium ion. Reaction of the cyclic ketal **22** is driven by formation of a carbonium ion stabilised by the oxygen substituent [114]. Reactions of nor-bornanecarboxylic acids are driven by the norbornane carbonium ion rearrangement [115, 116]. Oxidation of adamant-1-ylacetic acid in methanol affords 1-methoxyhomoadamantane *via* a skeletal rearrangement [117].

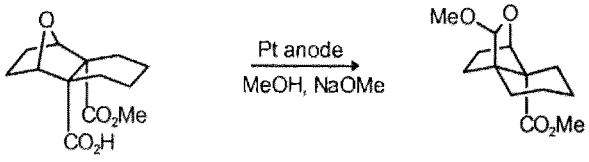


22

Ref. [114]

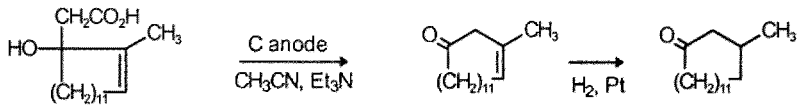


Ref. [115]



Ref. [116]

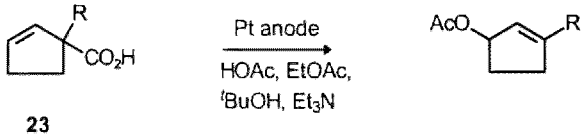
A carbonium ion rearrangement, triggered by anodic oxidation of a carboxylic acid, has been used as one stage in another synthesis of muscone [118].



Muscone

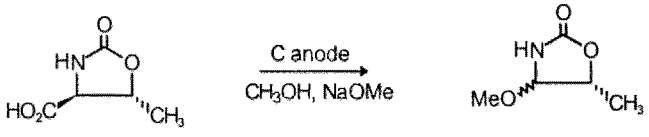
Ref. [118]

The combined effects of an electron donating alkyl substituent and the adjacent alkene bond in **23** leads to reaction solely by the carbonium ion intermediate and in acetic acid the more stable allyl acetate is formed [119].



23

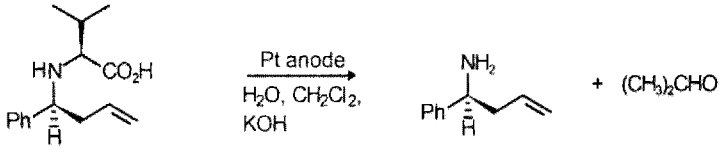
The anodic oxidation of N-acyl α-amino acids in an alcohol solvent leads to the formation of N-acyl α-alkoxyamines. This route is an alternative to the direct oxi-



Ref. [121]

dation of amides to the α-methoxy derivative (p. 284). Stereochemistry at the α-position is lost during the process [120, 121]. Reaction in acetic acid with sodium acetate as the electrolyte leads to the α-acetoxyamide [122].

The reaction is applicable to carboxylic acid derivatives of secondary amines such as **24** when only the acid function is oxidised. Starting materials of this type



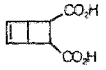
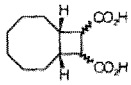
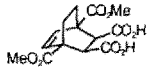
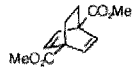
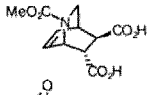
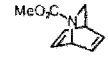
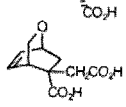
24

are prepared in two chemical steps from valine methyl ester. The chiral centre in valine directs introduction of the second chiral centre. Overall the reaction se-

quence causes transfer of chirality between valine and the allylamine product and the non-Kolbe reaction is used to remove the chiral auxiliary [123]. Anodic oxidation of quinuclidine-2-carboxylic acid leads to 2-methoxyquinuclidine [124].

Anodic oxidation of 1,2-dicarboxylic acids as their alkali metal salts in concentrated aqueous solution gives the alkene with the loss of two molecules of carbon dioxide [125]. Succinic acid affords ethene and methylsuccinic acid propene [50]. Allene is obtained from itaconic acid and the isomeric methylmaleic and methylfumaric acids give propyne

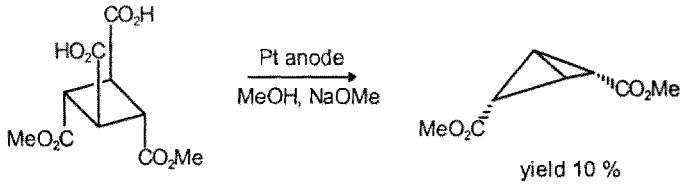
Table 9.5. Anodic decarboxylation of *vic*-diacids to form alkenes in pyridine, water containing triethylamine.

Substrate	Product	Yield / %	Ref.
		35	[126]
		24	[126]
			[127]
		17	[128]
			[129]

Reaction of 1,2 -dicarboxylic acids has been used for the formation of a number of strained alkenes and also applied to the Diels-Alder addition products from maleic anhydride (Table 9.5). Both *cis*- and *trans*-diacids take part in the process. Aqueous pyridine containing, triethylamine as a strong base, is considered the best solvent and higher yields are obtained at temperatures of around 80 °C [130]. Use of a divided cell avoids a possibility of electrocatalytic hydrogenation of the product at the cathode. The addition of *tert*-butylhydroquinone as a radical scavenger prevents polymerization of the product [127]. An alternative chemical decarboxylation process is available which uses lead tetraacetate [131] but problems can arise because of reaction between the alkene and lead tetraacetate.

1,3-Dicarboxylic acids give very poor yields of the cyclopropane under Kolbe reaction conditions. The cyclobutanedicarboxylic acid **25** affords a bicyclobutane [132]. 2,2-Dimethylglutaric acid gives low yields of a hydrocarbon, which is not

completely identified and could be either 1,1-dimethylcyclopropane or 2-methylbut-1-ene [133]. Other α,ω-dicarboxylic acids afford no cycloalkane on anodic



25

yield 10 %

Ref. [132]

oxidation. Pimelic acid gives carbon dioxide and equal amounts of ethene and propene by fragmentation of the carbon chain [134].

References

[1] J. Y. Becker, L. L. Miller and T. M. Siegel, *J. Am. Chem. Soc.*, 1975, **97**, 849.
[2] J. Y. Becker, L. R. Byrd, L. L. Miller and Y.-H. So, *J. Am. Chem. Soc.*, 1975, **97**, 853.
[3] C. B. Campbell and D. Pletcher, *Electrochim. Acta*, 1978, **23**, 923.
[4] F. Barba, A. Guirado, I. Barba and M. Lopez, *Tetrahedron Letters*, 1982, **23**, 463.
[5] M. Lopex-Segura, F. Barba and A. Aldaz, *Electrochim. Acta*, 1986, **31**, 83.
[6] K. Fugimoto, N. Yamashita, Y. Tokuda, Y. Matsubara, H. Maekawa, T. Mizuno and I. Nishiguchi, *Electrochim. Acta*, 1997, **42**, 2265.
[7] F. Barba, M. N. Elinson, J. Escudero and S. R. Feducovich, *Tetrahedron*, 1997, **53**, 4427.
[8] T. Shono, Y. Matsumura, T. Hayashi, K. Inoue, F. Iwasaki and T. Itoh, *J. Org. Chem.*, 1985, **50**, 4967.
[9] M. N. Elinson, I. V. Makhova and G. I. Nikishin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 122; *Chem. Abstr.*, 1991, **114**, 194721.
[10] H. Kiliani and S. Kleemann, *Ber.*, 1884, **17**, 1296.
[11] C. G. Fink and D. B. Summers, *Trans. Electrochem. Soc.*, 1938, **74**, 625.
[12] M. Steiger, *Helv. Chim. Acta*, 1936, **19**, 189.
[13] H. Kiliani, *Ber.*, 1932, **65**, 1269.
[14] O. Th. Schmidt and A. Simon, *J. prakt. Chem. [2]*, 1939, **152**, 190.
[15] T. Shono, Y. Matsumura, K. Inoue and F. Iwasaki, *J. Chem. Soc. Perkin Trans. I*, 1986, 73.
[16] P. Mattei and F. Diederich, *Helv. Chim. Acta*, 1997, **80**, 1555.
[17] S. Kato and G. Dryhurst, *J. Electroanal. Chem.*, 1977, **79**, 391.
[18] A. J. Biggs, *J. Chem. Soc.*, 1956, 2485.
[19] S. P. Mulleken, *Am. Chem. J.*, 1893, **15**, 526.
[20] T. D. Binns and R. Brettle, *J. Chem. Soc. C*, 1966, 336.

[21] R. Peek, M. Streukens, H. G. Thomas, A. Vanderfuhr and U. Wellen, *Chem. Ber.*, 1994, **127**, 1257.
[22] S. Wawzonek and T.-Y. Su, *J. Electrochem. Soc.*, 1973, **120**, 745.
[23] C. A. Bischoff and C. Rach, *Ber.*, 1884, **17**, 2781.
[24] D. A. White, *J. Electrochem. Soc.*, 1977, **124**, 1177.
[25] M. N. Elinson, S. K. Fedukovich, T. L. Lizunova and G. I. Nikishin, *Soviet Electrochem.*, 1992, **28**, 464.
[26] G. C. Melikyan, *Synthesis*, 1993, 833.
[27] R. Shundo, I. Nishiguchi, Y. Matsubara and T. Hirashima, *Tetrahedron*, 1991, **47**, 831.
[28] J.-Y. Nédélec, I. LaChaise, K. Nohair, J. P. Paugam and M. Hakihi, *Bull. Soc. chim. France*, 1995, **132**, 843.
[29] J. P. Coleman, R. C. Halleher, D. E. McMackins, T. E. Rogers and J. H. Wagenknecht, *Tetrahedron*, 1991, **47**, 809.
[30] R. Warinsky and E. Steckhan, *J. Chem. Soc. Perkin Trans. 1*, 1994, 2027.
[31] A. J. Bellamy, *Acta Chem. Scand. B*, 1979, **33**, 208.
[32] C. Ulpiani and G. A. Rodano, *Gazz. chim. Ital.II*, 1906, **36**, 81.
[33] F. Pragst and B. Siefke, *J. prakt. Chem.*, 1974, **316**, 267.
[34] F. Pragst and B. Vieth, *Z. phys. Chem. (Leipzig)*, 1976, **257**, 849.
[35] F. Pragst and W. Jugelt, *J. prakt. Chem.*, 1974, **316**, 981.
[36] L. Knorr, *Ber.*, 1893, **26**, 100.
[37] F. Pragst and R. Nastka, *Z. Chem.*, 1976, **16**, 487.
[38] E. Gunic and I. Tabakovic, *J. Org. Chem*, 1988, **53**, 5081.
[39] S. Crljenak, I. Tabakovic, D. Jeremic and I. Gaon, *Acta Chem. Scand. B*, 1983, **37**, 527.
[40] M. Batusic, I. Tabakovic and S. Crljenak, *Croat. Chim. Acta*, 1981, **54**, 397; *Chem. Abstr.*, 1982, **97**, 127558.
[41] J. Gunic, I. Tabakovic and Z. Sanicanin, *Croat. Chem. Acta*, 1989, **62**, 545; *Chem. Abstr.*, 1990, **112**, 86667.
[42] I Tabakovic, M. Trkovnik and Z. Grujic, *J. Chem. Soc. Perkin Trans. II*, 1979, 166.
[43] I. Tabakovic, M. Lacan and S. Damoni, *Electrochim. Acta*, 1976, **21**, 621.
[44] N. Henning, T. Dassler and W. Jugelt, *Z. Chem.*, 1982, **22**, 25.
[45] M. Lacan, V. Rogic, I. Tabakovic , D. Galijas and T. Solumun, *Electrochim. Acta*, 1983, **28**, 199.
[46] M. Faraday, *Phil. Trans. (London)*, 1834, 95. This paper also introduces the definitions of anode, cathode, anion and cation.
[47] H. Kolbe, *Liebigs Ann. Chem.*, 1849, **69**, 257.
[48] A. Wurtz, *Ann. Chim. [3]*, 1855, **44**, 291.
[49] A. Crum Brown and J. Walker, *Liebigs Ann Chem.*, 1891, **261**, 107.
[50] J. Petersen, *Z. phys. Chem.*, 1900, **33**, 99; 295; 698.
[51] T. S. Murray, *J. Chem. Soc.*, 1892, **61**, 10.
[52] H. Hofer and M. Moest, *Liebigs Ann. Chem.*, 1902, **323**, 284.
[53] Yu. M. Tyurin, E. P. Kovsman and E. A. Karavaeva, *Zh. Prikl. Khim.*, 1965, **38**, 1818; *Chem. Abstr.*, 1966, **64**, 3045.
[54] T. Dickinson and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, 1962, **58**, 382.
[55] T. Ohno, T. Fukumoto, T. Hirashima and I. Nishiguchi, *Chem. Letters*, 1991, 1085.
[56] J. B. Robertson, *J. Chem. Soc.*, 1925, **127**, 2057.
[57] M. J. P. Brennan and R. Brettle, *J. Chem. Soc. Perkin Trans. I*, 1973, 257.

[58] T. Dickinson and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, 1962, **58**, 382.
[59] M. Fleischmann, J. R. Mansfield and Lord Wynne-Jomes, *J. Electroanal. Chem.*, 1965, **10**, 522.
[60] Y. B. Vassiliev and V. A. Grinberg, *J. Electroanalyt. Chem.*, 1991, **308**, 1.
[61] J. P. Coleman, R. Lines, B. C. L. Weedon and J. H. P. Utley, *J. Chem. Soc. Perkin Trans. II*, 1974, 1064.
[62] L. Eberson, *Acta Chem. Scand.*, 1963, **17**, 2004.
[63] R. E. Gibson, *J. Chem. Soc.*, 1925, **127**, 2057.
[64] J. Brenner and K. Mislow, *J. Org. Chem.*, 1956, **21**, 1312.
[65] G. E. Hawkes, J. H. P. Utley and G. B. Yates, *J. Chem. Soc. Perkin Trans. II*, 1976, 1709.
[66] V. G. Gurjar, *J. Appl. Electrochem.*, 1978, **8**, 207.
[67] L. Eberson, K. Nyberg and R. Servin, *Acta Chem. Scand. B*, 1976, **30**, 906.
[68] E. S. Wallis and F. H. Adams, *J. Am. Chem. Soc.*, 1933, **55**, 3838.
[69] F. L. M. Pattison, J. B. Stothers and R. G. Woolford, *J. Am. Chem. Soc.*, 1956, **78**, 2255.
[70] L. Eberson, *Acta Chem. Scand.*, 1959, **13**, 40.
[71] D. G. Bounds, R. P. Linstead and B. C. L. Weedon, *J. Chem. Soc.*, 1953, 2393.
[72] K. Saotome, H. Komoto and T. Yamazaki, *Bull. Chem. Soc. Japan*, 1966, **39**, 480.
[73] H. A. Offe, *Z. Naturforsch. B*, 1947, **2**, 182.
[74] E. A. Evans and M. Whalley, *J. Chem. Soc.*, 1954, 3642.
[75] R. P. Linstead, J. C. Lunt and B. C. L. Weedon, *J. Chem. Soc.*, 1950, 3333.
[76] L. Eberson, *Acta Chem. Scand.*, 1963, **17**, 1196.
[77] R. Willstätter and A. Pfannensteil, *Liebigs Ann. Chem.*, 1920, **422**, 1.
[78] L. Eberson, *Acta Chem. Scand.*, 1956, **10**, 629.
[79] L. Eberson, *J. Org. Chem.*, 1962, **27**, 2329.
[80] M. Chkir, D. Lelandais and C. Bacquet, *Can. J. Chem.*, 1981, **59**, 945.
[81] R. F. Garwood, Naser-ud-Din, C. J. Scott and B. C. L. Weedon, *J. Chem. Soc. Perkin Trans. I*, 1973, 2714.
[82] J. Knolle and H. J. Schäfer, *Electrochim. Acta*, 1978, **23**, 5.
[83] J. Knolle and H. J. Schäfer, *Angew. Chem. Int. Edn. Engl.*, 1975, **14**, 758.
[84] W. S. Greaves, R. P. Linstead, B. R. Shephard, S. L. Thomas and B. C. L. Weedon, *J. Chem. Soc.*, 1950, 3362.
[85] R. P. Linstead, B. C. L. Weedon and B. Wladislaw, *J. Chem. Soc.*, 1955, 1097.
[86] R. P. Linstead, J. C. Lunt and B. C. L. Weedon, *J. Chem. Soc.*, 1951, 1130.
[87] D. G. Bounds, R. P. Linstead and B. C. L. Weedon, *J. Chem. Soc.*, 1954, 448.
[88] B. W. Baker, R. P. Linstead and B. C. L. Weedon, *J. Chem. Soc.*, 1955, 2218.
[89] D. G. Bounds, R. P. Linstead and B. C. L. Weedon, *J. Chem. Soc.*, 1953, 2393.
[90] T. Kazuno, A. Mori and T. Goto, *J. Biochem.*, 1955, **42**, 77.
[91] S. Motoki, Y. Yamada, *Nippon Kagaku Zasshi*, 1960, **81**, 665; *Chem. Abstr.*, 1962, **56**, 396.
[92] M. Huhtasaari, H.-J. Schäfer and H. Luftmann, *Acta Chem. Scand. B*, 1983, **37**, 537.
[93] W. Seidel, J. Knolle and H.-J. Schäfer, *Chem. Ber.*, 1977, **110**, 3544.
[94] K. Mislow and I. V. Steinberg, *J. Am. Chem. Soc.*, 1955, **77**, 3807.
[95] M. Huhtasaari, H.-J. Schäfer and L. Becking, *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 980.
[96] L. Becking and H.-J. Schäfer, *Tetrahedron Letters*, 1988, **29**, 2797.
[97] J. Weiguny and H.-J. Schäfer, *Liebigs Ann. Chem.*, 1994, 225.

[98] K. Schierle, J. Hopke, M. L. Niedt, W. Boland and E. Steckhan, *Tetrahedron Letters*, 1996, **37**, 8715.
[99] A. Matzeit, H.-J. Schäfer and C. Amatore, *Synthesis*, 1995, 1432.
[100] H. J. Bestmann, K. Roth, K. Michaelis, O. Vostrowsky, H.-J. Schäfer and R. Michaelis, *Liebigs Ann. Chem.*, 1987, 417.
[101] A. Weiper and H.-J. Schäfer, *Angew. Chem. Int. Ed. Engl.*, 1990, **29**, 195.
[102] A. S. Jones and J. R. Tittensor, *Carbohydr. Res.*, 1970, **12**, 403.
[103] E. Klocke, A. Malzeit, M. Glockelm and H.-J. Schäfer, *Chem. Ber.*, 1993, **126**, 1623.
[104] A. K. Yadav, A. Singh and L. Prakash, *Indian J. Chem. B*, 1998, **37**, 1274.
[105] B. Wladislaw and R. Rittner, *Ann. Ass. Brazil Quim.*, 1966, **25**, 122.
[106] A. Malzeit and H.-J. Schäfer, *Liebigs Ann. Chem.*, 1996, 55.
[107] G. Smits, X. van der Borght and G. van Haeren, *J. Polymer Sci. A*, 1964, **2**, 5187.
[108] M. Chkir and D. Lelandais, *J. Chem. Soc. Chem. Commun.*, 1971, 1369.
[109] L. Eberson, S. Gränse and B. Olofsson, *Acta chem. Scand.*, 1968, **22**, 2462.
[110] L. Eberson and M. Nilsson, *J. Chem. Soc. Chem. Commun.*, 1992, 1041.
[111] W. Schmidt and E. Steckhan, *J. Electroanal. Chem.*, 1978, **89**, 215.
[112] L. Ruzicka and M. Stoll, *Helv. Chim. Acta*, 1934, **17**, 1308.
[113] S. Torii, T. Okamoto and H. Tanaka, *J. Org. Chem.*, 1974, **39**, 2486.
[114] D. Lelandais, C. Bacquet and J. Einhorn, *Tetrahedron*, 1981, **37**, 3131.
[115] S. Torii, H. Tanaka and T. Mandai, *J. Org. Chem.*, 1975, **40**, 2221.
[116] T. Imagawa, S. Sugita, T. Akiyama and M. Kawanisi, *Tetrahedron Letters*, 1981, **22**, 2569.
[117] F. N. Stepanov and S. S. Guts, *Zh. Org. Khim.*, 1968, **4**, 1931; *Chem. Abstr.*, 1969, **70**, 28456.
[118] T. Shono, J. Hayashi, H. Omoto and Y. Matsumura, *Tetrahedron Letters*, 1977, 2667.
[119] S. Torii, H. Tanaka, T. Inokuchi and K. Tomozane, *Bull. Chem. Soc. Japan*, 1982, **55**, 3943.
[120] H. Horikawa, T. Iwasaki, K. Matsumoto and M. Miyoshi, *Tetrahedron Letters*, 1976, 191.
[121] A. Zietow and E. Steckhan, *J. Org. Chem.*, 1994, **59**, 5658.
[122] T. Iwasaki, H. Horikawa, K. Matsumoto and M. Miyoshi, *J. Org. Chem.*, 1977, **42**, 2419.
[123] H. Tanaka, K. Inoue, U. Pokorski, M. Taniguchi and S. Torii, *Tetrahedron Letters*, 1990, **31**, 3023.
[124] P. G. Gassman and B. L. Fox, *J. Org. Chem.*, 1967, **32**, 480.
[125] A. Kekule, *Liebigs Ann. Chem.*, 1864, **131**, 79.
[126] P. Radlick, R. Klem, S. Spurlock, J. S. Sims and E. E. van Tamelen, *Tetrahedron Letters*, 1968, 5117.
[127] G. B. Warren and J. J. Bloomfield, *J. Org. Chem.*, 1973, **38**, 4011.
[128] H. Sliwa and Y. LeBot, *Tetrahedron Letters*, 1977, 4129.
[129] K. R. Kopecky and M. P. Lau, *J. Org. Chem.*, 1978, **43**, 525.
[130] H. Plieniger and W. Lehert, *Chem. Ber.*, 1967, **100**, 2427.
[131] R. Criegee in *Oxidation in Organic Chemistry* (A. K. Wiberg Editor), Part A, Chapter 5, Academic Press, New York (1965),.
[132] A. F. Vellturo and G. W. Griffin, *J. Org. Chem.*, 1966, **31**, 2241.
[133] J. Walker and J. K. Wood, *J. Chem. Soc.*, 1906, **89**, 598.
[134] B. L. Vanzetti, *Gazz. Chim. Ital. II*, 1907, **37**, 390.

CHAPTER 10

REDUCTION OF CARBONYL COMPOUNDS, CARBOXYLIC ACIDS AND THEIR DERIVATIVES

Carbonyl Compounds Radical-Anions

The first step in the reduction of carbonyl compounds is addition of an electron to the LUMO of the carbonyl group to form a radical-anion in which the unpaired electron is delocalised over the π-system. For unconjugated aliphatic aldehydes and ketones, the LUMO has a high energy level and electron addition only takes place at very negative potentials. An irreversible polarographic wave at mercury with $E_{½}$ = -2.45 V *vs.* sce is seen for aliphatic ketones in some solvents although under most protic or aprotic conditions no clear reduction wave can be seen. Conjugated aliphatic enones, aromatic aldehydes and aromatic ketones show reversible polarographic waves at more accessible potentials in aprotic solvents (Table 10.1) due to one-electron addition with formation of the radical-anion.

TABLE 10.1
Reduction potentials for carbonyl compound - radical-anion systems in dimethylformamide

Substrate	$E_{½}$ / V *vs.* sce		Ref.
	1st Wave[b]	2nd Wave	
2,2,6,6-Tetramethylhept-3-en-2-one	-2.22		[1]
Benzaldehyde[a]	-1.81	-2.37	[2]
Acetophenone[a]	-1.98	-2.40	[2]
Benzophenone[a]	-1.73	-1.98	[2]

Footnotes: a: Data scaled using E° for the 1st wave of acetophenone from ref. [3].
b: Reversible process for which $E_{½}$ = E°.

Radical-anions can be characterised by esr-spectroscopy. Those derived from simple carbonyl compounds such as acetone or 3-methylbutan-2-one are highly reactive and can only be detected in a glassy matrix prepared by the alternate deposition of layers of sodium and the ketone at 77 K [4]. The radical-anion from the

sterically hindered ketone, 2,2,4,4-tetramethylpentan-2-one, is sufficiently stable to be detected in tetrahydrofuran at room temperature using a potassium mirror as reductant [5]. Aromatic carbonyl compounds including benzaldehyde, acetophenone and benzophenone all form radical-anions detectable by electrochemical reduction in dimethylformamide within the cavity of the esr spectrometer [6]. The radical-anions from conjugated aromatic carbonyl compounds have a planar arrangement of atoms bearing the *p*-orbitals. When the carbonyl group is adjacent to an aromatic ring that is not symmetrically substituted about the point of attachment two rotational isomers of the radical-anion exist. Interconvertion between these two rotamers is slow on the time scale of esr spectrometry resulting in either a poorly resolved esr spectrum [7] or a superpositioning of two individual spectra. Thus thiophene-2-aldehyde radical-anion exists as two stereoisomers because the carbonyl oxygen can be either *cis* or *trans* to the ring sulphur atom [8]. The highly sterically hindered di-*tert*-butylketone radical-anion has a non-planar arrangement of bonds about the carbonyl carbon atom [9].

TABLE 10.2
Uv-absorption of carbonyl compound radical-anions and values of pK_a for their conjugate acids

Radical-anion from	λ_{max} / nm	Conjugate acid pK_a	Ref.
Ethanal		11.5	[10]
Acetone		12.1	[11]
Propenal		9.6	[12]
Benzaldehyde	445	10.5	[13]
		8.1	[14]
Acetophenone	445	9.9	[15]
	450	10.9	[13]
Benzophenone	615	9.3	[15]
	630	9.2	[13]

Radical-anions of carbonyl compounds are basic and undergo protonation at the oxygen centre generating highly reactive radical species.

$$R_2CO + e \rightleftharpoons R_2CO^{\bullet -}$$

$$R_2CO^{\bullet -} + H^+ \rightleftharpoons R_2\dot{C}-OH$$

The pK_a values for some of these conjugate acid species have been determined by the methods of fast reaction kinetics. In one approach, solvated electrons are generated by a short pulse of high-energy radiation and allowed to react with the carbonyl compound in an aqueous buffer. Electrons are scavenged quantitatively in a diffusion-controlled reaction and subsequently the proton equlibrium is very rapidly established. In another experimental approach, the same proton equlibrium can be established from radicals generated by flash photo-reaction of the carbonyl compounds in buffered aqueous isopropanol. Experiments using one of these two techniques are performed in solutions of different pH and a uv-spectrum is recorded before the radicals have time to dimerise. The variations in absorbance constitute a titration curve from which the pK_a value can be determined. Some values are given in Table 10.2. Conjugated ketone radical-anions form coloured solutions and the long wavelength absorption maxima can be obtained from these experiments.

An estimate of the pK_a value for benzaldehyde radical-anion has also been obtained from fast cyclic voltammetry experiments over a range of pH values [14]. Interpretation the results obtained in this case requires first deduction of an overall reaction scheme followed by numerical solution of the corresponding set of differential equations allowing simulation of the cyclic voltammogram. Reaction constants are then adjusted to give good simulations over a range of experimental conditions. The pK_a can then be extracted from these reaction constants.

Values of 1554 cm^{-1} for the carbonyl stretching frequency in the radical-anion of benzophenone [16] and of 1558 cm^{-1} for the radical-anion of di-*tert.*-butyl ketone [17] suggest that in general ν_{CO} will be found at lower frequencies for the radical-anion than for the parent carbonyl compound.

Aromatic Carbonyl Compounds - Mechanistic Studies

Stages in the reduction of the carbonyl group conjugated to an aromatic ring have been elucidated from studies of the polarographic behaviour for a range of compounds in aqueous alcohol buffers [18,19]. In general, heterocyclic analogues show similar behaviour to that of their benzene counterparts, benzaldehyde, acetophenone and benzophenone in the pH range 2-12. Both benzaldehyde and benzophenone show two separated one-electron polarographic waves in the acidic region. For the first wave, $E_{½}$ varies with pH and for the second wave, $E_{½}$ is almost independent of pH. As the pH of the solution increases, the two waves approach and finally coalesce around pH 7 into one two-electron wave for which $E_{½}$ varies with pH. Data from the polarography of furan-2-carboxaldehyde [20] given in Fig. 10.1 illustrates behaviour analogous to that of benzaldehyde. Acetophenone shows a single one-electron wave in the acidic region The expected second wave probably occurs at potentials more negative than the accessible potential window. Around pH 7-8 the observed response becomes a two-electron wave. Coulometry for the

reduction of acetophenone and propiophenone carried out on small scale preparative experiments demonstrate a bell shaped behaviour for electron demand in the

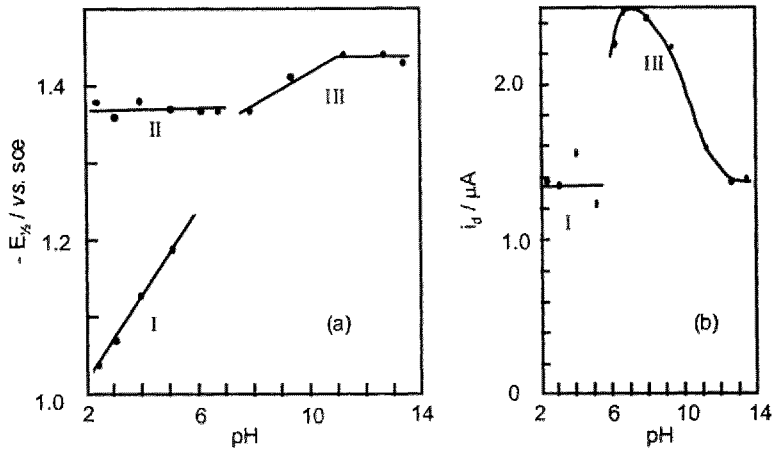
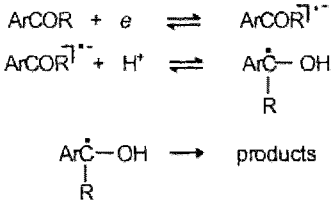


Figure 10.1. Changes with pH of the half-wave potential ($E_{½}$) and diffusion plateau height (i_d) for the polarographic waves of furan-2-carboxaldehyde. Waves I and II have the same height and i_d for wave I only is illustrated. Data from ref. [20].

pH range 3 to 12.5 showing a 1F process in acidic or basic solution and approaching a 2F process around pH 10.5. For all aromatic carbonyl compounds, the height of the two-electron wave falls with increase in pH until it reaches the value for a one-electron process around pH 11. Studies on benzaldehyde and acetophenone have been extended [14, 21] into the strongly alkaline region using buffers in ethanol with estimated pH values up to 18.9. At pH > 13.6 for benzaldehyde and at pH 18.9 for acetophenone, a second one-electron wave is found at more negative potentials. For the two waves in alkaline solution, $E_{½}$ is independent of pH. Benzophenone behaves differently in that it shows only one two-electron wave in alkaline regions [21].

The experimental data is interpreted in the following mechanistic scheme. In acidic solution, the first one-electron wave is due to the following reactions:



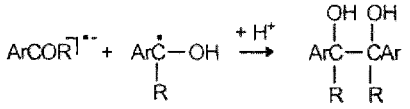
The shape of this wave and the variation with pH are both consistent with fast equilibrium reactions In the pH region lower than the value of pK_a for the hydroxyl radical, the reactions of this hydroxyl radical dominate the electrochemical process. Controlled potential reduction at the potential of this first wave indicates a 1F process and the principal products are dimers of the hydroxyl radical. The second wave in this acidic region is due to addition of an electron and a proton to the neutral radical. This process competes with dimerization in the mid-pH range where the two polarographic waves merge. Over the pH range 7-9, monohydric alcohol is the principal product. At pH <3 or >12, pinacols are the main products. Unsymmetrical carbonyl compounds afford mixtures of (±)- and *meso*-pinacols. Data (Table 10.3) for the (±) / *meso* isomer ratio for pinacols from acetophenone and propiophenone indicate different dimerization mechanisms in acid and in alkaline solutions.

TABLE 10.3.
Isomer ratio for pinacols formed by controlled potential reduction in aqueous alcohol medium.

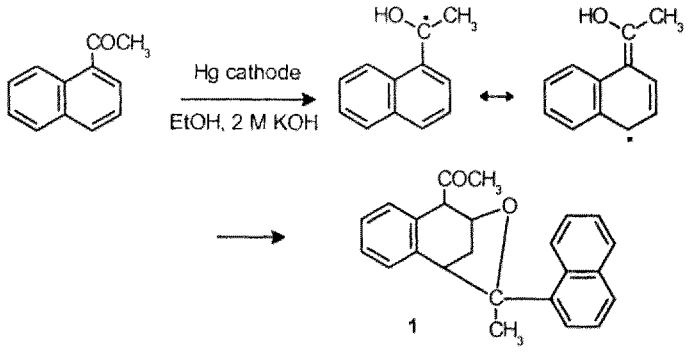
Substrate	Conditions	Pinacols (±) / *meso* ratio	Ref.
PhCHO	acidic	1.12 (n = 1)	[22]
	basic	1.19 ± 0.06 (n = 5)	[22]
p-HOC_6H_4CHO	acidic	0.93 (n = 1)	[23]
	basic	0.51 ± 0.05 (n = 4)	[23]
$PhCOCH_3$	acidic	1.12 ± 0.20 (n = 5)	[24]
	basic	2.88 ± 0.22 (n = 15)	[24]
p-$MeOC_6H_4COCH_3$	acidic	1.24 (n = 1)	[25]
	basic	3.03 (n = 1)	[25]
$PhCOCH_2CH_3$	acidic	1.40 ± 0.01 (n = 2)	[23]
	basic	2.86 ± 0.22 (n = 6)	[22]

At low pH values, dimerization must involve the combination of two neutral carbon radicals since the same (±) / *meso* ratio is obtained as from the photochemical reaction of the carbonyl compound in methanol [26], a process which also involves neutral radicals. The switch in isomer ratio to that characteristic of alkaline media occurs in the region of pH close to the value of pK_a for the neutral radical. Dimerization then occurs in a fast reaction between the radical-anion and the neutral radical. In strongly alkaline solutions where the pH >> pK_a the major reactive species formed at the potential of the first reduction wave is the radical-anion. Reaction between two radical-anions is relatively slow due to coulombic repulsion so that dimerization in strongly alkaline solution still occurs by reaction

between the radical-anions and neutral radicals present in a low equlibrium concentration [14].



The radical-anion has a significant negative charge density on the oxygen atom and hydrogen bonding between this centre and the hydroxyl group of the approaching neutral radical becomes important leading to a preference in favour of the (±)-pinacol for the dimerization process in alkaline solution. In the case of benzaldehyde, the (±) / *meso* ratio for pinacol formation does not change significantly over the pH range spanning the pK_a value for the hydoxybenzyl radical, an unexpected result in view of the argument proposed for the pinacolisation of acetophenone and propiophenone. However, the hydroxybenzyl radical is less sterically hindered than the corresponding neutral radical from phenyl alkyl ketones. This results in a lower activation energy for the dimerization step so that



no additive	94.8	0.7	4.5 %
with α-cyclodextrin	40.0	4.9	55.4 %

reaction can occur on collision and before hydrogen bonding forces are able to orientate the two species within the encounter complex. Enhanced steric repulsion

is also responsible for decreased total yield of pinacols from reduction of phenyl alkyl ketones as the alkyl group R increases in size [27].

In dry aprotic solvents such as acetonitrile [28] with tetraethylammonium bromide as supporting electrolyte or dimethylformamide [29] with sodium perchlorate as supporting electrolyte, the (±) / *meso* ratio for pinacols rises substantially in favour of the (±)-form. Reduction of acetophenone in dimethylformamide in the presence of europium(III) chloride leads to the (±)-pinacol only. Under these reaction conditions, europium(II) is formed and dimerization occurs with the involvement of this ion and the ketone in a complex [30]

The radical site of the intermediates in the dimerization reaction is stabilised by resonance and examples have been noted where dimerization occurs by substitution onto the aromatic ring. This is the major reaction course for the reduction of 1-acetylnaphthalene [31] which yields **1** in alkaline solution by a radical-ion radical coupling. In the reduction of acetophenone, small amounts of related reaction products, **2** and two diastereomers of **3**, can be detected. The yields of these compounds are increased by the reduction of acetophenone encapsulated in a cyclodextrin [32].

Aromatic Carbonyl Compounds – Enantiomeric Reduction

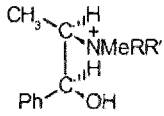
Some compounds form a surface excess concentration at the mercury - water interface and optically active compounds in this class can generate a chiral surface layer. Asymmetric induction during the protonation of carbanions is to be expected when these ions are generated electrochemically within this chiral surface layer. Efforts have been made to achieve significant induction during the protonation of carbanions generated by the two-electron reduction of phenyl alkyl ketones. Chiral conducting salts **4** and **5** form a surface excess at the mercury interface. Reduction of acetophenone in aqueous alcohol in the presence of these salts has been shown by Horner [33, 34, 35] to give 1-phenylethanol with a low optical induction. Pinacol is also formed and the (±)-pinacol showed no asymmetric induction. Experiments with ephedrine **4a** in buffered aqueous alcohol show that the protonated form of this alkaloid is responsible for generation of an enantiomeric excess of (R)-1-phenylethanol. In strongly alkaline solution where the free base is present, an excess of (S)-1-phenylethanol results [36]. Some values for the enantiomeric excess from reduction of acetophenone and related compounds are collected in Table 10.4. The highest enantiomeric excess of 18% for 1-phenylethanol has been obtained from quaternary ammonium salts containing the nitrile function [35, 37].

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 [38]. This result further confirms the importance of some counter ions in orientating radical-anion and radical species during the dimerization step to form the (±)-pinacol.

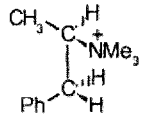
TABLE 10.4

Chiral alcohols isolated from reduction of ketones at a mercury cathode in aqueous methanol containing an asymmetric electrolyte. Data from refs. [34] and [35].

Substrate RCOPh	Asymmetric electrolyte anion							
	4a		**4b**		**5**		**4c**	
R =	e.e / % of isomer		e.e / % of isomer		e.e / % of isomer		e.e / % of isomer	
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		



4a: R = R' = H; **4b**: R = R' = Me
4c: R = Me, R' = $(CH_2)_3CN$



5

Certain alkaloids are able to effect asymmetric induction during a reduction process at a mercury cathode even when present in low concentration in an aqueous alcohol acetate buffer. Asymmetric induction under these conditions was first observed [39] during the conversion of 4-methylcoumarin to 4-methyl-3,4-dihydrocoumarin (see page 60). Induction results because a layer of alkaloid is strongly adsorbed on the electrode surface thus permitting transfer of a proton to a carbanion intermediate in an asymmetric environment. Up to 16% asymmetric induction has been achieved in 1-phenylethanol recovered from reduction of acetophenone in a buffer of pH 4.8 containing a low concentration of quinidine. The pinacol formed simultaneously shows no optical activity. However quinidine is itself reduced at the potential employed so that the actual catalyst for the asymmetric process is not defined [34, 40].

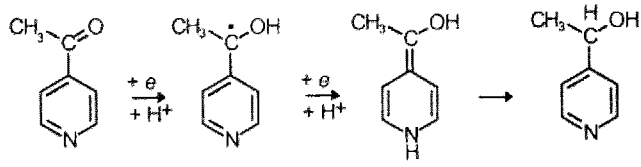
A range of chiral alkaloids have been screened for the asymmetric reduction of 2- and 4-acetyl pyridine [41] and results are given in Table 10.5. Brucine and strychnine give the highest enantiomeric excess in the pyridinylethanols produced. Reduction of 3-acetylpyridine however affords no optically active alcohol under all conditions employed. A further effect of the added alkaloid is to raise the yield of secondary alcohol at the expense of the pinacols relative to reactions where no alkaloid is present. The high enantiomeric excess found during reduction of 4-

acetylpyridine is thought to be due to formation first of the enol **6**, which later tautomerises in presence of the chiral alkaloid. Reduction of 2-acetylpyridine can give an equivalent enol but this route is not open to 3-acetylpyridine.

TABLE 10.5

Enantiomeric excess in pyridinylethanols from reduction of 2- and 4-acetylpyridine at mercury. The electrolyte contains an alkaloid (5×10^{-4} M) in aqueous acetate buffer (pH 4.5) - ethanol (1:1) at 0° C. Data from ref. [41].

Alkaloid	Enantiomeric excess of pyridinylethanol from	
	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 **4a**	(±)-form only	(±)-form only



6

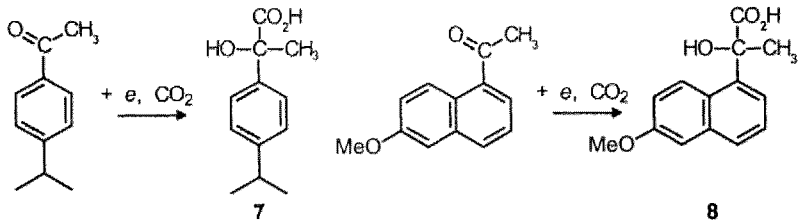
Mandelic acid with a 13 - 20 % enantiomeric excess of the (R)-isomer has been obtained from reduction of phenylglycolic acid in aqueous alcohol buffers containing strychnine in low concentration. The optical yield depends upon pH and is highest (20 - 24 %) at pH 0 or 9.2 and at low current density. In the pH range 2-4, the optical yield drops to 2-8% [42]. The higher result compares well with the maximum value of 20% excess R-isomer found from reduction of (-)-menthyl phenylglycolate in aqueous buffers where the (-)-menthyl ester is the only chiral reagent present [43].

Attempts to achieve optical induction during the reduction of aromatic ketones to the secondary alcohol by immobilising a single layer of chiral catalyst on a solid electrode surface have been much less successful. The preparation of such coatings

on a graphite electrode first involves baking to introduce acidic groups through air oxidation. Treatment with thionyl chloride forms surface carbonyl chloride groups and these are reacted with a chiral amine such as (S)-phenylalanine methyl ester to generate a surface layer of asymmetric centres. Modification of graphite crystallites by this route occurs on the edge and not the basal face [44]. Reduction of 4-acetylpyridine at this prepared surface in aqueous ethanol acetate buffer afforded an excess of the (S)-(-)-2-(pyridin-4-yl)ethanol. In other experiments, ethyl glyoxylate afforded (-)-ethyl mandelate with 9.7% enantiomeric excess [45] Asymmetric induction using this form of surface modification has however proved highly irreproducible [46].

Aromatic Carbonyl Compounds - Carboxylation Reaction

Wawzonek [47] first noted that the radical-anion from benzophenone can be trapped by carbon dioxide in dimethylformamide to yield benzilic acid. The radical-anion of carbon dioxide has $E^\circ = -2.2$ V *vs.* sce [48] and will not be formed in preference to the ketone radical-anion. The reaction has been developed into a convenient synthesis of aryllactic acids from aryl alkyl ketones. Modern technology has applied constant current conditions to this process. A divided cell with a mercury cathode has been used to obtain benzilic acids from benzophenones and carbon dioxide in 70-90% yields [49]. 4-Isopropylacetophenone affords the corre-



sponding lactic acid **7** in 85% yield [50]. A minor byproduct from these carboxylation processes is the pinacol derived from the aryl alkyl ketone substrate and the yield of this byproduct increases in the presence of proton donors. On a technical scale, carboxylation reactions are best carried out in an undivided cell fitted with a lead cathode and a sacrificial aluminium anode using dimethylformamide as solvent and employing a moderate pressure of carbon dioxide [51]. The product is protected as the aluminium(III) chelate from further reaction. Acidification of the reaction mixture affords the aryllactic acid. With this technique, benzaldehyde can be converted to mandelic acid in around 40% yields [52] and optimum conditions for the production of **7** and **8** have been investigated [53].

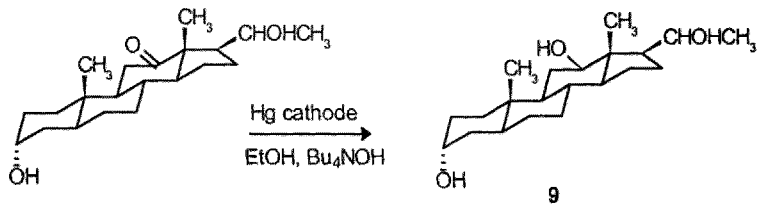
Aliphatic Carbonyl Compounds

Reduction of unconjugated aldehydes and ketones in buffers over the pH range 1-14 affords the corresponding alcohol as the principal product. Examples from the early literature include the formation of borneol from camphor in 45 % yield [54] and the formation of menthol from menthone in 82 % yield [55], both by reduction at lead or mercury in aqueous sulphuric acid alcohol mixture. The polarographic waves for these compounds occur at negative potentials and are not well defined Reduction is assumed to pass through the same type of intermediates as for aromatic carbonyl compounds. Satisfactory yields of pinacol can be obtained only from aldehydes and from acetone by reduction in acid solution. In general, the yield of pinacol from aliphatic aldehydes improves with increasing length of the attached hydrocarbon chain. An electrolyte of pH 2 - 5 and a tin cathode give best results for pinacol formation [56]. The pilot plant scale production of acetone pinacol has been achieved [57] in 52% yield with propan-2-ol as the main byproduct and a route for obtaining glycol from formaldehyde [58] has been pioneered.

Table 10.6
Stereochemistry of alcohols from reduction of cyclohexanones

Substrate	Conditions Solvent-electrolyte-cathode	Yield / %	*Trans* / %	*Cis* / %	Ref.
3-Methylcyclo-hexanone	PrOH-Et_4NTs-C	58	22	78	[59]
	MeOH-dil. H_2SO_4-C	48	52	48	[59]
4-Methylcyclo-hexanone	PrOH-Et_4NTs-C	60	78	22	[59]
	MeOH-dil. H_2SO_4-C	45	38	62	[59]
4-*t.*-Butylcyclo-hexanone	PrOH-Et_4NTs-C	56	85	15	[59]
	MeOH-dil. H_2SO_4-C	55	48	52	[59]
			endo / %	*exo* / %	
Camphor	PrOH-Et_4NTs-C	55	76	24	[59]
			Product		
Androstan-17βol-3-one	EtOH-Bu_4Cl-Bu_4OH-Hg		3β,17β-diol		[61]
Pregnan-3α,20β-diol-12-one	EtOH-Bu_4Cl-Bu_4OH-Hg		3α,12β,20β-triol **9**		[61]

The *axial* : *equatorial* isomer ratio for cyclohexanols obtained by reduction of cyclohexanones depends upon the solution pH (see Table 10.6). In alkaline or initially neutral but unbuffered solutions [59, 60], this ratio approaches the value at thermodynamic equilibrium The *equatorial*-alcohol, for example **9**, is generated [61] from reduction of steroid ketones. In acid buffers, the thermodynamically less



9

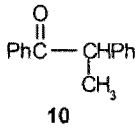
stable isomer is generally preferred. Originally these results were rationalised in terms of steric effects at the electrode surface but a much simpler explanation can be found from the effect of the pH gradient developing close to the cathode surface. This pH gradient arises because transfer of electrons from the cathode to the substrate and generates basic conditions around the electrode surface. Solutions, which in the bulk are neutral or weakly alkaline, develop a strongly alkaline region close to the cathode and this catalyses the equlibration of epimeric alcohols through interaction with unreacted ketone in a type of Meerwein - Ponndorf reaction. Acidic buffers do not develop this surface alkaline region and equlibration of epimers is not achieved. Results from reduction in acid solution indicate that the carbanion intermediate is usually protonated with almost equal probability on either face.

The addition of zinc or magnesium ions to the electrolyte promotes protonation from the least sterically hindered face and results in a dramatic change in the isomer ratio for the alcohol mixture formed. The more hindered alcohol is now strongly favoured. It was originally proposed that these ions interact to stabilise the carbanion centre [62] in the least hindered position. A more likely explanation is that in these solutions, protonation occurs by interaction with the aquated metal ion and the size of this species favours attack from the least hindered side of the cyclohexane ring.

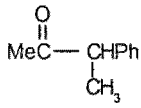
Both 2-cyanocyclohexanone and 2-cyanocyclopentanone give good yields of the *cis*-alcohol by reduction at a mercury cathode in aqueous alcohol at pH 8 [63]. Reduction of 2-carbethoxy substituted cyclopentanone and cyclohexanone under the same conditions favours the *cis*-alcohol at -6° C but the thermodynamically preferred *trans*-isomer at 80° C [64].

Relatively few studies have been made of the isomer ratio obtained by reduction of open chain ketones possessing a prochiral centre adjacent to the carbonyl func-

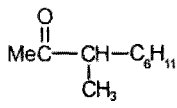
tion. Reduction of **10** in aqueous alcohol at pH 14 favours [65, 66] the *erythro*-alcohol with an *erythro* : *threo* ratio of 80:20, which is different to the equlibrium



10



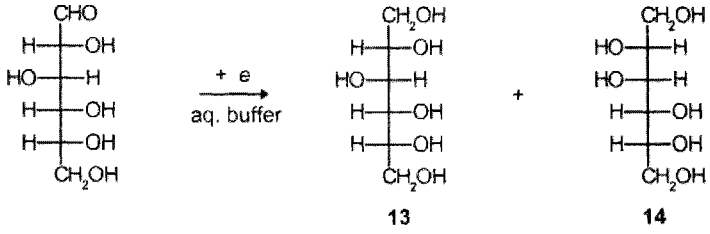
11



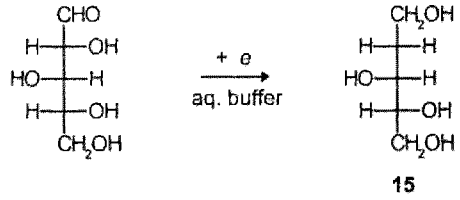
12

ratio of 64:36. Ketone **11** gave an *erythro* : *threo* ration of 45:55 for the isolated alcohol mixture while compound **12** gave a ratio of 65:35 [66].

Sugars having a potential aldehyde function can be reduced electrochemically in alkaline solution at a mercury or amalgamated lead cathode. Because the aldehyde function is masked as the cyclic acetal, the rate of electrochemical reduction is



13 **14**



15

controlled by the rate for conversion of acetal to aldehyde. A commercial process developed for the conversion of glucose to either sorbitol or mannitol [67] has been largely ousted by the high-pressure hydrogenation route. The major product from electroreduction depends on the pH of the electrolyte. Glucose is converted to sorbitol **13** without a change in stereochemistry at low pH. Strongly alkaline solutions catalyse the equlibration between glucose fructose and mannose after which reduction affords some mannitol **14** along with sorbitol. A byproduct of this reduction is the pinacol-type dimer from the glucose aldehyde function [68]. The reduction of ribose or xylose to the pentitol can also be achieved [69]. A byproduct isolated in

low yield from these reactions is the 2-deoxypolyol formed by reductive elimination of the hydroxyl function next to the carbonyl group. Deoxygenation becomes an important process in the reduction of D-xylose in a solution of pH 9 at amalgamated lead, leading to 2- deoxy-D-xylitol **15** in 62 % yield [70].

Several attempts have been made to revive the electrochemical production of sorbitol. It has been shown [71] that the reaction can be carried out in an undivided cell with a lead cathode and a porous hydrogen diffusion anode. Overall, protons consumed at the cathode are regenerated at the anode by oxidation of hydrogen. Other approaches have used electrocatalytic hydrogenation at a Raney-nickel cathode [72] which has been combined with the oxidation of glucose to gluconic acid (see page 264) using bromine generated from calcium bromide electrolyte at a graphite anode [73]. A simple flow-through cell illustrated in Fig. 10.2 has been

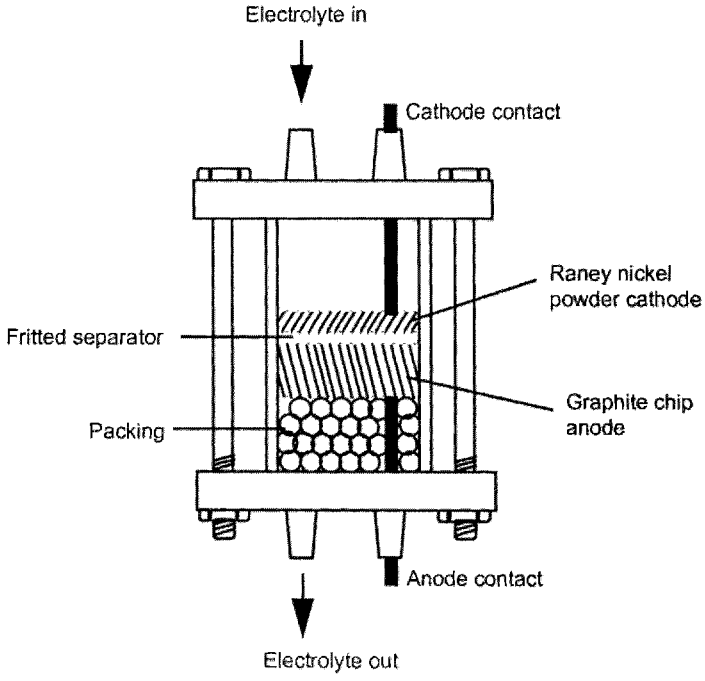


Figure 10.2. Flow through cell for the simultaneous reduction of glucose to sorbitol and oxidation to glucuronic acid. Ref. [73].

devised for achieving the tandem combination of reactions.

The Electrochemical Clemmensen Reaction

The intermediates from reduction of aldehydes and ketones can attack the cathode material particularly in the presence of a high concentration of sulphuric acid. Aliphatic ketones show an anomalous polarographic wave in acid solution with a humped maximum just prior to the negatively displaced hydrogen discharge. This wave is thought to be due to the formation of an insoluble film of mercury compounds on the electrode surface [74]. The formation of organolead compounds has been observed in the reduction of acetone [75] and of benzaldehyde [76] at lead electrodes and organomercury compounds are formed from acetone [77] and 1-acetylnaphthalene [31] at a mercury cathode under strongly acid conditions.

The overall reaction a strongly acid medium is usually reduction of the carbonyl function to methylene in a process involving acid hydrolysis of organometallic intermediates. Tafel [78] in 1911 observed the reduction of 4-ketopentanoic acid at a lead cathode in aqueous alcoholic sulphuric acid to give pentanoic acid in 80% yield whereas 4-hydroxypentanoic acid resulted from reaction in aqueous sodium hydroxide. A series of ketoacids have been converted to the alkanoic acid by reduction at a mercury cathode in sulphuric acid medium [79]. In general, cadmium [80] or amalgamated zinc [81] are the most effective cathode materials for the conversion of a carbonyl function to methylene [82]. The electrochemical process at zinc strongly resembles the Clemmensen reaction where a zinc stabilised carbene is thought to be the important reactive intermediate [83] and reaction at other cathode materials probably follows a similar route.

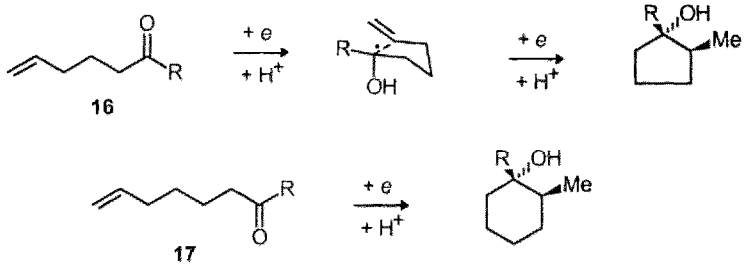
Cyclohexanones are readily reduced to the hydrocarbon in a sulphuric acid electrolyte. Reduction of ketosteroids in dioxan - aqueous sulphuric acid at a lead cathode in a divided cell is a convenient process for converting the carbonyl group to methylene [84,85] and affords as good yields as the alternative non-electrochemical processes. Menthone is reduced to the hydrocarbon under mild conditions at a mercury cathode when the electrolyte is either magnesium chloride or zinc perchlorate in ethanol [86].

Coupling with Unsaturated Functions

Radical additions to alkenes and aromatic systems are well known reactions. The trapping in this manner of radicals obtained by reduction of the aliphatic carbonyl function has proved to be a versatile electrochemical route for the formation of carbon-carbon bonds. Such reactions are most frequently carried out in protic solvents so that the reactive species is a σ-radical formed by protonation of the carbonyl radical-anion. The cyclization step must be fast in order to compete with further reduction of the radical to a carbanion at the electrode surface followed by protonation. Cyclization can be favoured and further reduction disfavoured by a

suitable choice of the cathode material because the rate of electron transfer to the intermediate σ-radical is dependent on the characteristics of this surface.

Cross coupling reactions between acetone and an alkene have been achieved in low yields at a mercury cathode potential of -1.4 V *vs.* sce with acetone as the solvent and either sulphuric acid or *p*-toluenesulphonic acid as electrolyte [87, 88]. Acetone is known to be reducible at around this potential in aqueous sulphuric acid [89]. Intramolecular radical cyclization is faster than intermolecular coupling and Shono (1971) first demonstrated a ring closure reaction by reduction of nonconjugated eneones **16** and **17** where R = alkyl [90, 91]. The process is best effected in a mixed solvent of methanol - dioxan with carbon electrodes in an undivided cell. Cyclization forms a 5- or a 6-membered ring with reaction occuring on the more substituted alkene carbon atom to give exclusively a *cis*-arrangement of alkyl groups on the resulting ring. This stereoselectivity can be explained on the hypothesis that the transition structure resembles the chair form of cyclohexane [92] and that the most favourable conformation will have bulky substituents in *pseudo-*

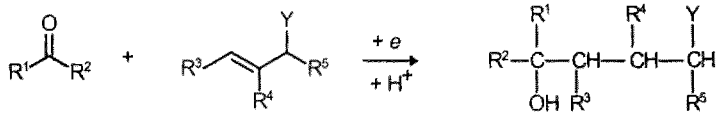


equatorial positions. No ketones of the type **16** or **17** with R = aryl have been reported to undergo this cyclization reaction. From known bond dissociation energies [93], the enthalpy of addition of the hydroxybenzyl radical to an alkene can be estimated to be 67 kJ mol^{-1} less favourable than the addition of the hydroxyalkyl radical so that the driving force for cyclization is diminished.

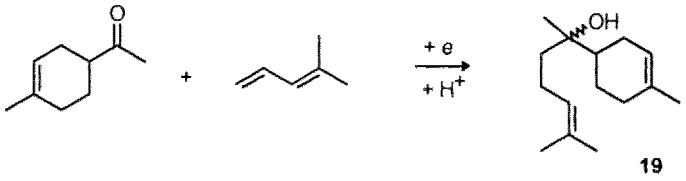
The cyclization process can be promoted by using a single electron transfer mediator. Electron transfer from the mediator generates the carbonyl radical-ion away from the electrode surface so that cyclization can occur before there is opportunity for a second electron transfer. Thus reduction of **16**, R = Me, in dimethylformamide at mercury in the presence of tetraethylammonium fluoroborate leads only to conversion of the ketone function to the secondary alcohol. However addition of a low concentration of N,N-dimethyl pyrrolidinium fluoroborate alters the course of reaction and the cyclized tertiary alcohol is now formed. This pyrrolidinium salt is reduced at -2.7 V *vs.* sce at mercury to yield a complex DMP(Hg_5) which is thought to act as a single electron transfer mediator [94]. Cyclization can

also be effected at a mercury cathode in dimethylformamide using a homogeneous redox catalyst such as phenanthrene or 2-methoxybiphenyl, with redox potential in the range -2.4 to -2.7 V *vs.* sce [95]. The catalyst is reduced at the electrode surface to the radical-anion and this delivers an electron to the substrate in homogeneous solution. Cyclization can then occur before a second electron donor is encountered.

Radical species derived from reduction of ketones are also trapped by alkenes in an intermolecular reaction. Reaction only occurs with terminal alkenes of the type

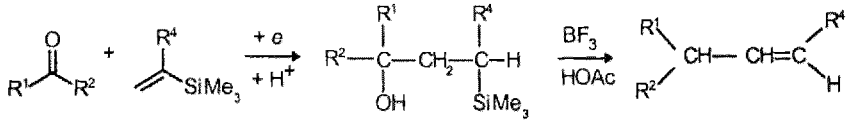


18



19

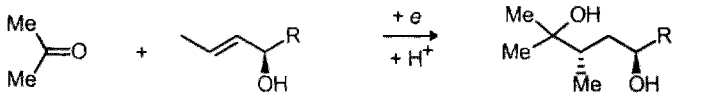
18 ($R^3 = R^4 = Y = H$) and dimethylformamide is the best solvent with carbonised polyacrylonitrile fibre as cathode material in a divided cell under constant current current conditions [96]. The process has been used as one stage in the synthesis of



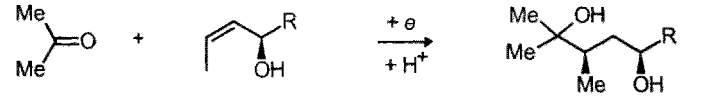
20

the bisabolol skeleton **19** [96]. Substitution on the alkene function, for example in **18** ($R^3 = Y = H$, R^4 = Alkyl), substantially decreases the yield of coupled product and non-terminal alkenes **18** (R^3 = Alkyl) do not react at all. Better and more consistent yields are obtained from related coupling reactions using trimethylsilyl substituted alkenes **20** as substrates. The silicon substituent promotes the desired reaction by stabilising both radical and carbanion centres formed by reaction on the alkene bond [97]. This process provides an alternative to the purely chemical route where a 2-(trimethylsilyl)ethyl Grignard reagent is reacted with the ketone. The *tert*-alcohol products are converted to alkenes with loss of the hydroxyl and trimethylsilyl groups by the action of borontrifluoride in acetic acid [98].

Allylic alcohols **18** (Y = OH) are uniquely active in this coupling process [99]. Even non-terminal alkenes such as **21** are activated towards coupling by the adjacent hydroxyl function. The allyl alcohol centre also plays an important role in



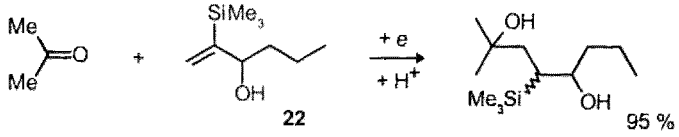
trans-(R)-**21** Yield 60 %, > 85 % *d.e.*

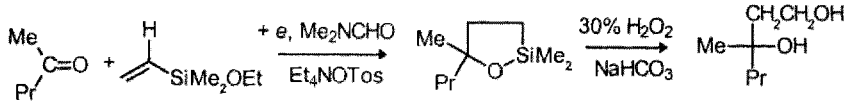


cis-(R)-**21** Yield 70 %, > 85 % *d.e.*

promoting coupling with a high degree of diastereoselectivity. The transition-state for these reactions is stabilised by hydrogen bonding between the ketone radical anion and the allyl hydroxyl group. Stereoselectivity in the product arises from minimising interactions between substituents in the transition-state.

Cathodic coupling of ketones to trimethylsilyl substituted allyl alcohols such as



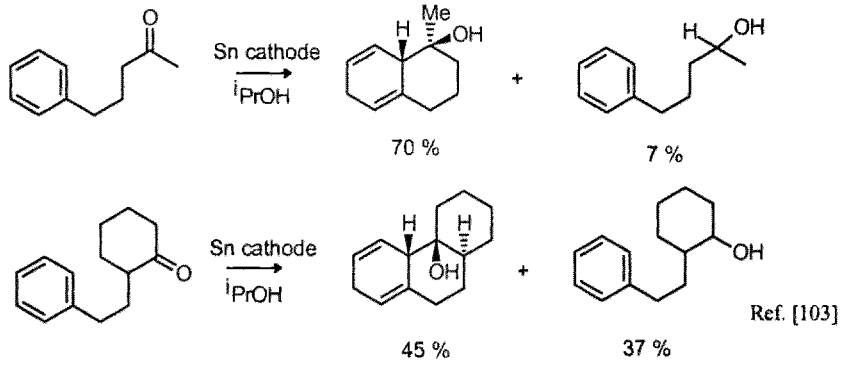


Ref. [101]

22 is very effective and gives up to 95 % of diol product [100]. Even more effective is the coupling between ketones and alkenes bearing a ethoxydimethylsilyl substituent [101]. The primary products formed in this reaction can be chemically oxidised to the corresponding 1,3-diols in good yields.

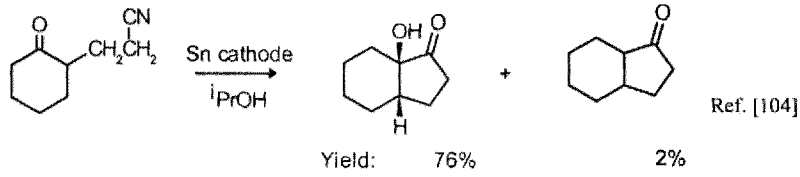
Benzene hydrocarbons are known to undergo radical coupling reactions and the intramolecular reductive coupling of carbonyl compounds with a benzene ring has been achieved. Best conditions for this process are at a tin cathode with isopropanol solvent and tetaethylammonium tosylate as supporting electrolyte [102, 103]. The reaction is performed at constant current in a divided cell. A single stereoiso-

mer of the cyclized product is obtained. Deuterium labeling experiments show that the radical formed after cyclization onto the benzene ring abstracts a hydrogen atom from the solvent and does not undergo further reduction and protonation.



Ref. [103]

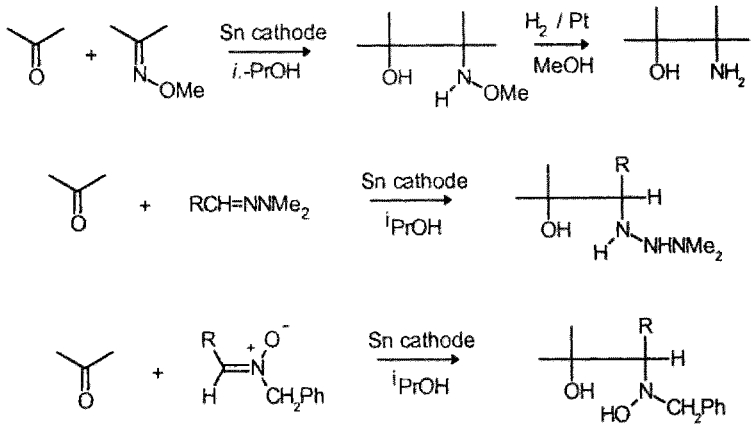
Intramolecular coupling between the carbonyl group and a nitrile function can be accomplished by reduction at a tin cathode in isopropanol. The use of cadmium lead or zinc as cathode materials and of dimethylformamide as alternative solvent



Ref. [104]

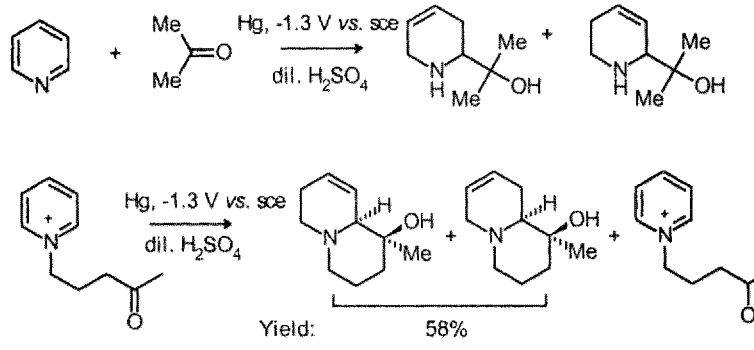
resulted in decreased yields of coupled product. This reaction allows the formation only of 5- or 6-membered rings in good yields [104]. The isolated products are α-hydroxyketones together with ammonia and further reduction causes cleavage of the hydroxyl group (see p. 175). Intramolecular coupling of cyclohexanone and acetonitrile occurs in low yield by reduction at a tin cathode in a mixture of acetonitrile and isopropanol as solvent. In the absence of isopropanol as a proton source, reduction of ketones in acetonitrile generates a strong base which catalyses the nucleophilic addition of acetonitrile anion to the carbonyl group.

Intermolecular coupling between ketones and O-methyl oximes, hydrazones and nitrones is achieved on reduction at a tin cathode in isopropanol [105]. It is not clear which of the reacting species accepts the initial electron in these processes. The reaction with O-methyloximes, followed by catalytic reduction of the first formed O-methylhydroxylamine, is a convenient synthetic route to 2-amino-alcohols.



Ref. [105]

Radical addition to the pyridine ring is another known facile process and coupling of radical intermediates from the reduction of ketones to pyridines in



Ref. [106]

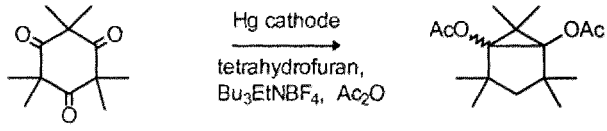
Ref. [107]

sulphuric acid solution has been achieved in both intermolecular [106] and intramolecular reactions [107]. The dihydropyridines initially formed are reduced further under the reaction conditions to the tetrahydropyridine level. The ketone must be present in considerable excess during the intermolecular reactions with pyridine derivatives. An extension of this intermolecular reaction to isoquinoline affords the 1-substituted tetrahydroisoquinoline in 78 % yields [108]. In acid solution, the carbonyl function is the site for initial electron transfer followed by protonation to give a carbon radical which attacks the pyridine ring.

Reduction of Dicarbonyl Compounds

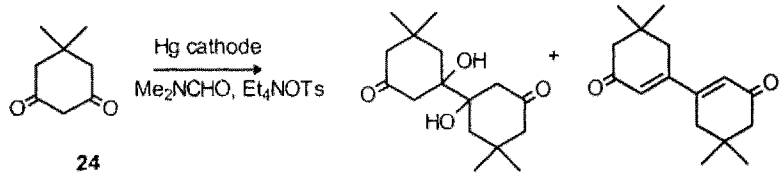
Reduction of dicarbonyl compounds can be expected to lead to a cyclic 1,2-glycol formed by the intramolecular coupling of radical intermediates.

The initial product from reduction of aliphatic 1,3-dicarbonyl compounds is either a cyclopropane derivative formed by intramolecular condensation or a glycol



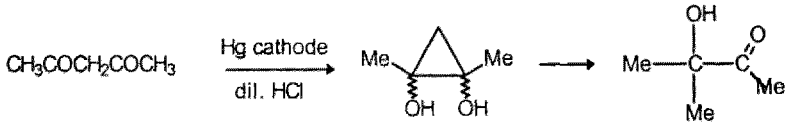
23

formed by intermolecular condensation. *Gem.*-dialkyl substitution, the Thorpe-Ingold effect [109], has long been known to favour ring-forming reactions. The non-enolizable diketones such as **23** afford cyclopropanes [110] whereas the enolizable diketones like **24** undergo intermolecular reactions [111]. Electrogenerated



24

base will accumulate around the cathode so the species reduced in the latter reactions is the enolate ion. Acetylacetone is reduced [112] in aqueous hydrochloric acid to the intramolecular glycol which undergoes ring opening catalysed by protons to form the skeletal rearrange product **25**. Mechanistic studies of these



25

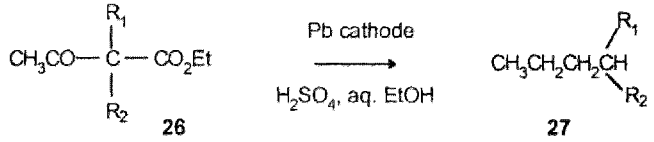
reactions are limited to the cyclization of 1,3-dibenzoylpropane in acetonitrile and suggest that the rate determining step is addition of the radical-anion from one ketone function onto the second carbonyl group, followed by further one-electron addition and protonation [113].

Attempts to prepare a bicyclobutane by reductive cyclization of cyclobutane-1,3-diones have been unsuccessful [114]. α,ω-Dibenzoylalkanes are reduced at a mercury cathode to cycloalkanediols only when a ring size of 5 or 6 results. These reactions have been achieved using either aqueous ethanolic sodium hydroxide [115] or acetonitrile containing tetramethylammonium tetrafluoroborate [113] as electrolyte. Attempts to extend the process to formation of 7-membered rings lead only to oligomeric materials.

1,8-Dibenzoylnaphthalene gives mainly the *cis*-acenaphthenediol by reduction in acid solution, together with some ketone formed by the pinacol rearrangement of the initial product. In alkaline solution this diketone gives mainly *trans*-acenaphthenediol together with a bis-secondary alcohol [115, 116].

Reduction of β-Ketoesters - The Tafel Rearrangement

Reduction of β-ketoesters in aqueous ethanolic sulphuric acid leads to removal of both functional groups and the formation of a hydrocarbon. This reaction which was discovered in 1907 [117] and recognised in 1912 [118] as involving a skeletal rearrangement is now termed the Tafel rearrangement. Conversions of the type **26** into **27** occur in 30 - 60 % yields [118, 119] and the hydrocarbon is easily separated

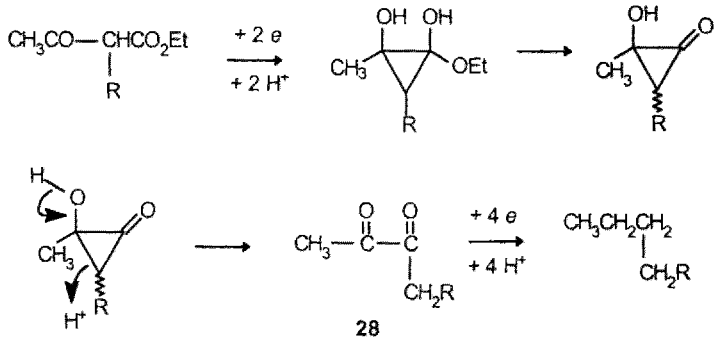


R_1 = alkyl or benzyl, R_2 = H or alkyl Yields 30 - 60%

from the other reaction products. Lead and mercury have been used as cathode materials but the best cathode is from cadmium [118]. Confirmatory evidence for the structures of a number of rearrangement products has been given [120, 121] and the reaction mechanism was established in 1976 by Wawzonek and Durham [122]. Ethyl acetoacetate gives butane by reduction under acid conditions [119], probably by the Tafel rearrangement mechanism.

The Tafel rearrangement only occurs in acid medium. Simultaneous reduction of both carbonyl groups leads to interaction and formation of a cyclopropane. Acid catalysed cyclopropane ring opening follows to yield an α-diketone **28** which undergoes the electrochemical Clemmensen reduction step to the hydrocarbon. Side products include the two monoketones derived by partial deoxygenation of the α-diketone and the secondary alcohols from reduction of these monoketones. Separate experiments show that the α-diketone **28** can be reduced to the hydrocarbon.

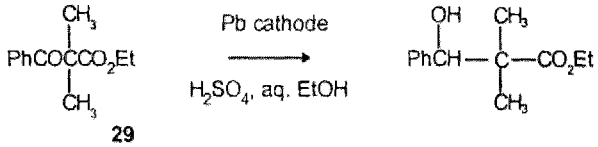
By contrast, reduction in aqueous acetonitrile leads to the generation of basic



28

conditions as a consequence of the hydrogen evolution process and base attacks the β-ketoester to give products of hydrolysis.

A condition for rearrangement is that both carbonyl functions must have similar reduction potentials, otherwise the cyclopropane intermediate cannot be formed. In compound **29** and in ethyl benzoylacetate where the ketone function has a much less negative reduction potential due to conjugation with a benzene ring, only products from reduction of the ketone group are found [123, 124]. Reduction of ethyl benzoylacetate in dimethylformamide gives a dimeric pinacol and subsequently this undergoes the Dieckmann cyclization reaction due to the presence of electrogenerated base [125]. Reduction of β-ketoesters such as ethyl 1-methylcyclohexan-2-onecarboxylate derived from alicyclic ketones gives negligible



29

yields of the hydrocarbon expected from a skeletal rearrangement [122, 126].

Carboxylic Acid Reduction

Carboxylic acid groups attached to an aromatic ring are reducible at cathodes of lead or mercury in sulphuric acid [127]. Oxalic acid is also reduced but in general, where the carboxyl group is attached to an aliphatic carbon as in phenylacetic acid

or cyclohexanecarboxylic acid, it remains unchanged in this reaction. Conjugated alkenecarboxylic acids undergo reduction at the alkene site (see chapter 3), the carboxyl function remaining unchanged.

Oxalic acid is reduced at lead or mercury cathodes in 10% sulphuric acid solution to give glyoxylic acid [128] in 87% yield. The aldehyde function in glyoxylic acid is protected from further reduction because it exists in solution in the dihydroxy form. Preparation of glyoxylic acid by this route has been developed to a pilot plant scale using a flow through divided cell with a lead cathode and a lead dioxide on titanium anode [129, 130]. The catholyte is a concentrated aqueous solution of oxalic acid, which is separated by a cationic ion-exchange membrane from the anolyte of sulphuric acid. Very high chemical yields of glyoxylic acid are obtained and a tedious process for removal of sulphuric acid is avoided.

Benzoic acid gives a polarographic wave in dilute hydrochloric acid at lead or mercury with $E_{½}$ = -1.5 V *vs.* sce [131]. Preparative scale reduction proceeds best at either lead or cadmium cathodes to give benzyl alcohol [132, 133] and an electrolyte of 20-30% sulphuric acid in aqueous ethanol is usually employed. Before the advent of lithium aluminium hydride, this was a convenient synthetic route to benzyl alcohols [132, 134, 135, 136]. It remains a useful procedure because it tolerates a wide variety of substituents including hydroxyl and amino which react with hydride reagents. Chloro- and bromo-substituents survive the reaction but iodobenzoic acid gives only benzyl alcohol with loss of the iodo-substituent. 2,3,4,5,6-Pentafluoro-benzoic acid is reduced in 20% sulphuric acid to mixtures of the pentafluorobenzyl alcohol and 2,3,5,6-tetrafluorobenzyl alcohol. At a lead cathode in 5% sulphuric acid containing tetraethylammonium tosylate the tetrafluorobenzyl alcohol is formed in 93% yield [137]. Phthalic acid and terephthalic acid are reduced in 20% sulphuric acid to dihydrobenzenedicarboxylic acids in contrast to benzene-1,3-dicarboxylic acid which affords the bisbenzyl alcohol. However, terephthalic acid in aqueous ammonia at a lead cathode affords 4-hydroxymethylbenzoic acid in 91% yields [138]. Naphthalene-2-carboxylic acid in 20% sulphuric acid affords the corresponding primary alcohol. Reduction of naphthalene-1-carboxylic acid however yields a hydrocarbon, probably 1-methylnaphthalene [134].

Reduction of the carboxylic acid group passes through the intermediate aldehyde. For a number of examples in the heterocyclic series, the aldehyde becomes a major product because it is trapped as the hydrated *vic.*-diol form. Examples include imidazole-2-carboxylic acid [139], thiazole-2-carboxylic acid [140] and pyridine-4-carboxylic acid [141] reduced in dilute aqueous acid solution. Reduction of imidazole-4-carboxylic acid proceeds to the primary alcohol stage, the aldehyde intermediate is not isolated. Addition of boric acid and sodium sulphite to the electrolyte may allow the aldehyde intermediate to be trapped as a non-reducible complex. Salicylaldehyde had been obtained on a pilot plant scale in this way by

reduction of salicylic acid at a rotating amalgamated copper cathode [142]. 4-Hydroxybenzoic acid is also reduced to the aldehyde under the same conditions [143].

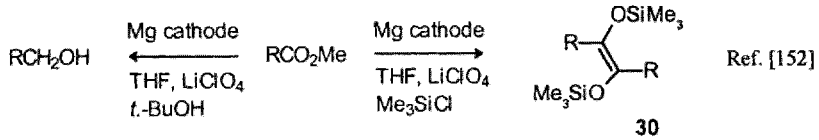
Esters and Lactones

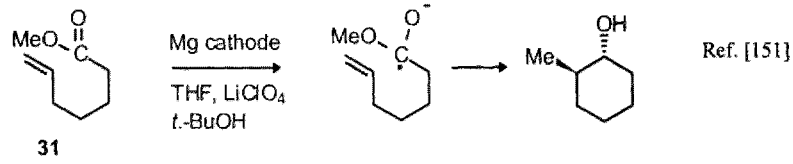
Esters of aromatic acids in aprotic solvents form radical-anions detected by cyclic voltammetry on a short time scale [144]. Ethyl benzoate has E° = -2.19 V *vs.* sce [145]. Follow-up reactions of radical-anions from methyl and ethyl benzoate result from protonation by extraneous water. *tert*-Butyl benzoate radical-anion undergoes very rapid cleavage of the alkyl-oxygen bond to give benzoate ion and *tert*-butyl radical.

Reduction of aliphatic esters with sodium in ethanol results in the primary alcohol corresponding to the original carboxylic acid moiety [146]. This was an important step in organic synthesis (the Bouvault-Blanc reaction) before the advent of hydride reagents. Under Bouvault-Blanc conditions, aromatic esters undergo reduction on the benzene ring but ethyl benzoate can be reduced electrochemically in ethanol - 30% sulphuric acid to a mixture of benzyl alcohol and benzyl ethyl ether [147]. Electrochemical reduction of benzoate esters is best effected at a mercury cathode in ethanol containing acetic acid with tetramethylammonium chloride as supporting electrolyte. Benzyl alcohol together with 1,2-diphenylethan-1,2-diol are formed. In absence of acetic acid, base is generated electrochemically as the reaction proceeds and ethyl benzote then affords a mixture of benzyl alcohol and ring hydrogenation products. Phenyl benzoate in acid solution is reduced quantitatively to benzyl alcohol at mercury, cadmium or lead. A series of benzoate phenyl ester have been converted in this way to the benzyl alcohol [148].

The aldehyde has been shown to be an intermediate in reduction of aromatic esters in both acid [149] and alkaline solutions [148]. It can be trapped in good yield in the form of an acetal by reduction of benzoate esters in acetonitrile in the presence of chlorotrimethylsilane [150]. Intermediates in the reduction of diphenyl-2,2'-dicarboxylate esters undergo a cyclization reaction to form 5,6-dihydroxyphenanthrene [148].

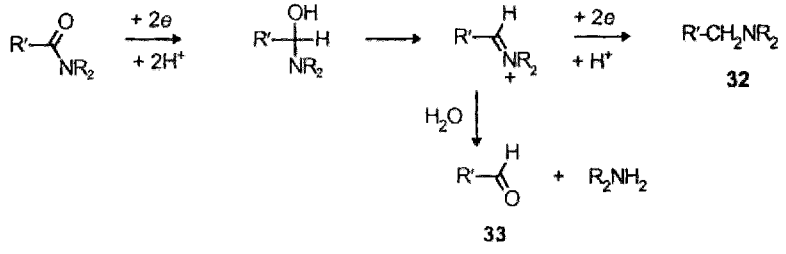
Alkyl alkanoates are reduced only at very negative potentials so that preparative scale experiments at mercury or lead cathodes are not successful. Phenyl alkanoates afford 30-36% yields of the alkan-1-ol under acid conditions [148]. Preparative scale reduction of methyl alkanoates is best achieved at a magnesium cathode in tetrahydrofuran containing *tert*-butanol as proton donor. The reaction is carried out in an undivided cell with a sacrificial magnesium anode and affords the alkan-1-ol in good yields [151]. In the absence of a proton donor and in the presence of chlorotrimethylsilane, acyloin derivatives **30** are formed in a process related to the acyloin condensation of esters using sodium in xylene [152]. Radical-anions formed initially can be trapped by intramolecular addition to an alkene function in substrates such as **31** to give alicyclic products [151].





Acid Amides

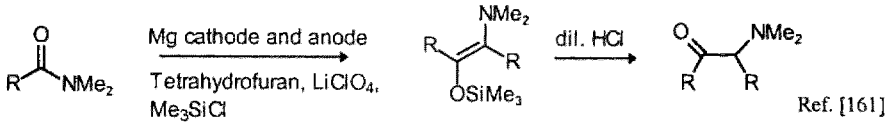
Reduction of acid amides leads to a series of reactions in which the aldimine is a key intermediate. Aldimines are reduced at much less negative potentials than amides. The relative amounts of amine **32** and aldehyde **33** products formed depend



on factors controlling the rate of hydrolysis of the imine. The electron withdrawing properties of substituents, as well as acidity of the electrolyte, play a role in determining the product ratio. Early workers [153, 154] used 50-90% sulphuric acid as solvent and electrolyte to obtain amines by reduction aromatic amides at a lead cathode in a divided cell. Later, ethanol containing hydrochloric acid was used as solvent. Benzamide yields a mixture of benzyl amine and benzaldehyde under these conditions. N-alkyl substituents improve the yield of amine and reduction of thioamides gives still better yields of the amine [155, 156]. Sensitivity of the product ratio to the reaction conditions is illustrated by the reduction of phthalimides to give either the masked aldehyde or the phthalimidine [157, 158, 159].

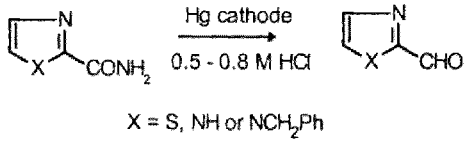
The α–hydroxyamino intermediates from reduction of aromatic amides in acetonitrile can be trapped in the presence of chlorotrimethylsilane and subsequent work-up yields the aromatic aldehyde in good yields. This reaction has been car-

ried out in a divided cell [160] and also in an undivided cell with magnesium cathode and anode [161]. Aliphatic amides behave differently in the undivided cell reaction. In the absence of protons, magnesium ions from the sacrificial anode promote the dimerization of radical-anion intermediates and α–aminoketones are obtained in good yields after acid work-up [161].



Ref. [161]

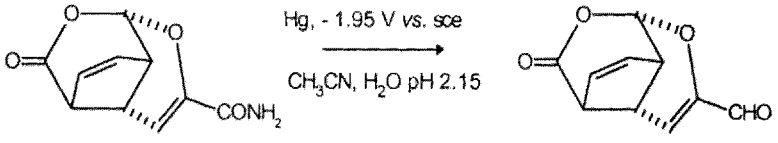
A number of heterocyclic acid amides in dilute hydrochloric acid are reduced to the aldehyde level where this is protected from further reaction as the dihydroxy



Ref. [162]

compound [162, 163].

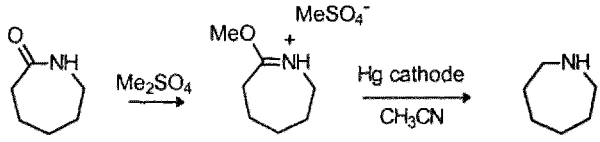
The electrochemical reduction of aliphatic amides in dilute hydrochloric acid will tolerate other functional groups active towards the alternative hydride reducing agents. With aliphatic amides the electrochemical step generally leads to the aldehyde because the intermediate imine is rapidly hydrolysed under the conditions



34

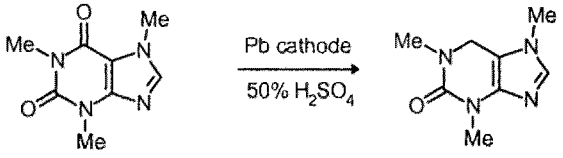
employed. This reaction has been used to generate the aldehyde function of the antitumor agent echinosporine **34** [164] and for the conversion of L-asparagine to L-homoserine [165] where the aldehyde intermediate is further reduced to the primary alcohol. Dialkylamides of alkanoic acids are converted to aldehydes in good yield in an undivided cell with magnesium anode and cathode using tetrahydrofu-

ran and lithium perchlorate as solvent and electrolyte and *tert*-butanol as proton donor [151]. Cyclic amides **35** have been converted to the azacycloalkane by reduction of the O-methyl ether [166].



35

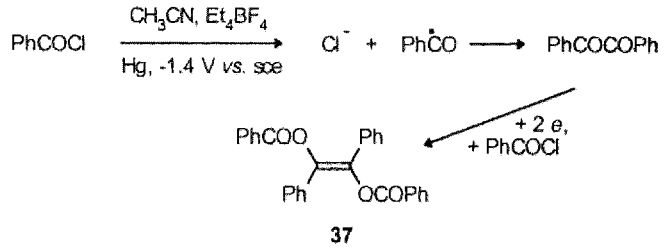
Xanthine, caffeine **36** and other N-methylxanthines are selectively reduced in 75% sulphuric acid at a lead cathode to the 4-desoxy compounds in good yields [153,167,168].



36 70% yield

Acid Chlorides

Linear sweep voltammetry of benzoyl chloride in acetonitrile containing tetraethylammonium fluoroborate shows E_p = -1.4 V *vs.* sce and for heptanoyl chloride E_p = -2.2 V *vs.* sce [169] The one-electron reduction of acid chlorides at these potentials is a source of carbonyl radicals. Reduction of benzoyl chloride at the peak



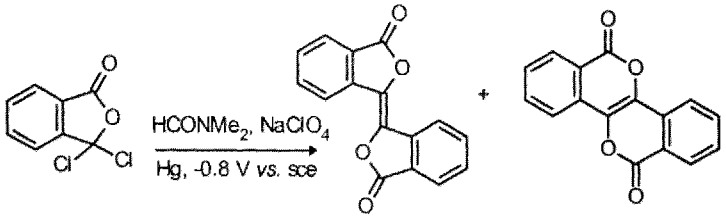
37

potential gives the stilbene derivative **37**. In this reaction, benzil is generated by the union of two benzoyl radicals, then further reduction followed by reaction with benzoyl chloride yields the final product [169]. A number of aroyl chlorides have

been shown to undergo this reaction in good yields at a mercury cathode in acetone containing lithium perchlorate [170]. The standard reduction potentials of carbonyl radicals are in the region -1.68 to -1.75 V *vs.* sce [171] so that carbonyl radicals generated from heptanoyl chloride and other acyl chlorides are immediately reduced further to the carbanion and protonation affords the aldehyde. Overall RCOCl is converted to RCHO [169, 172]. In competing processes, carbonyl radicals lose carbon monoxide to form the alkyl or aryl radical which yield the alkane or arene after further reduction and protonation [169].

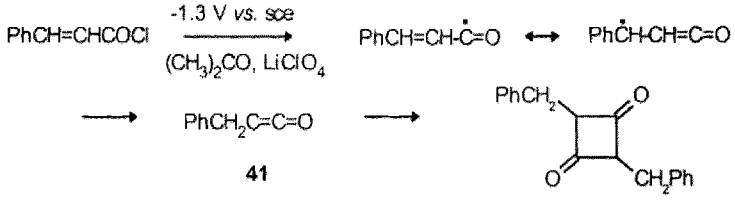
The reduction of aroyl chlorides take a different course in the presence of Ni(II) salts. Reaction is best effected in an undivided cell with a nickel anode and a nickel foam cathode with acetonitrile containing tetrabutylammonium fluoroborate as electrolyte. Symmetrical ketones are formed [173]. Substituted benzoyl chlorides yield the benzophenone in 47-72% yields. Phenacetylchloride also gives the ketone in good yield but in general, alkanoyl chlorides do not react.

Both phthaloyl chloride and the unsymmetrical isomer **38** give an almost quantitative yield of the two isomers **39** and **40** on reduction [174, 175]. Each of these



38 **39** **40**

can be transformed to the other under appropriate conditions [176, 177] so that the electrochemical process is a viable route to either compound. The radical from

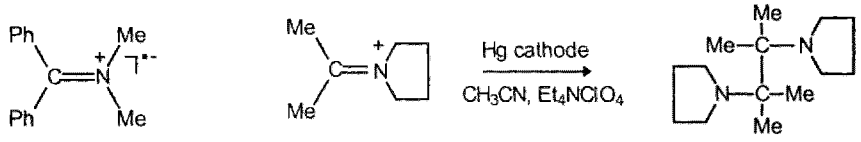


41

reduction of cinnamonyl chloride reacts as the ketene tautomer and abstracts a hydrogen atom from a solvent molecule to give the ketene **41** which dimerizes in a subsequent chemical reaction to yield a cyclobutan-1,3-dione [178].

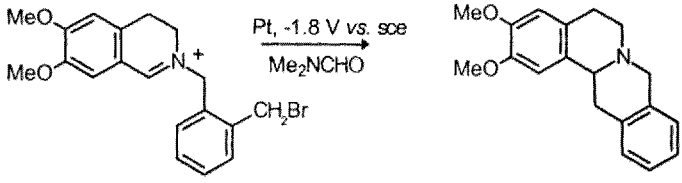
Imines, Oximes and Hydrazones

The carbon-nitrogen double bond in imines is reduced at less negative potentials than the corresponding carbonyl function. Also imine radical-anions are more basic than carbonyl radical-anions. Imines with at least one phenyl substituent on the carbon-nitrogen double bond are sufficiently stable for examination in aprotic solvents and reversible one-electron reduction of benzaldehyde anil [179] or benzophenone anil [180] can be demonstrated with rigorous exclusion of moisture.



42 **43**

Under ordinary conditions, reduction of these imines in dimethylformamide is a two-electron process involving saturation of the carbon-nitrogen double bond [181] because the radical from protonation of the radical-anion is more easily reduced than the starting imine. Immonium salts with two or more phenyl substituents are reduced reversibly in acetonitrile to the radical-zwitterion such as **42**. Other immonium salts, e.g. **43**, are reduced irreversibly to the dimer [182]. Radical-zwitterion intermediates generated from immonium salts exhibit nucleophilic character on carbon. Intramolecular interaction between the reduced immonium function and a



Ref. [183]

benzyl bromide is a route for the formation of heterocyclic ring systems [183].

Benzophenone anil [184] and benzaldehyde anil [185] are both sufficiently stable in aqueous solution above pH 5 for polarographic examination. Both compounds show two one-electron waves in the less alkaline region, as illustrated for benzophenone anil in Figure 10.3. For the more anodic wave, $E_{½}$ varies with pH due to the rapid establishment near the electrode surface of the equlibria:

$$Ph_2C{=}NPh + e \rightleftharpoons Ph_2C{=}NPh^{\bullet-}$$

$$Ph_2C{=}NPh^{\bullet-} + H^+ \rightleftharpoons Ph_2\dot{C}{-}NHPh$$

The more cathodic wave is due to further reduction of the radical intermediate formed at the potential of the first wave.

$$Ph_2\dot{C}\text{-}NHPh + e + H^+ \longrightarrow Ph_2CH\text{-}NHPh$$

At higher pH values the two waves merge to a single two-electron wave which divides into separate single-electron waves at pH 13. The first wave of these waves

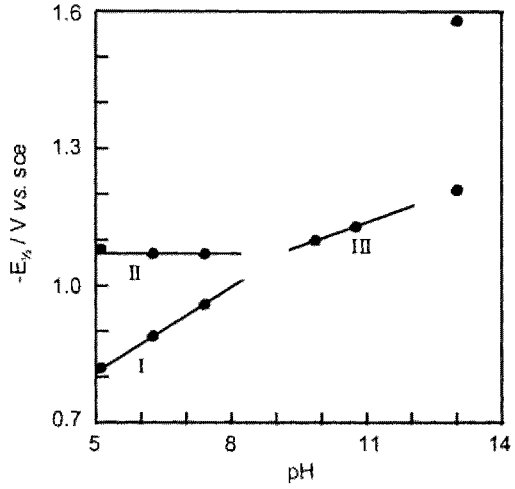
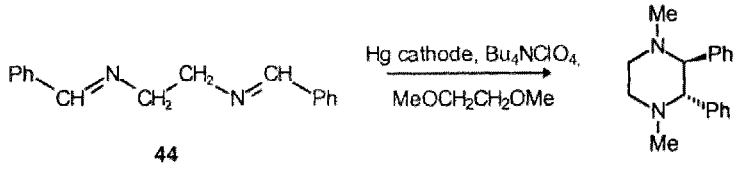


Figure 10.3. Changes with pH of the half-wave potential ($E_{½}$) for the polarographic waves of benzophenone anil. Waves I and II have the same height while wave III has double their height. Each of the two waves seen at pH 13 has the same height as wave I. Data from ref. [184].

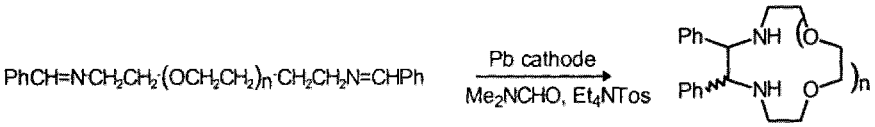
is due to formation of the radical-anion while the more cathodic wave is due to further reduction of the radical-anion. Reduction of benzophenone anil in an ethanol methyl acetate water mixture yields N-phenylbenzylamine together with the dimers from union of two radical intermediates [186].

Reduction of aryl substituted bis-azines in an aprotic solvent allows trapping of intermediates through intramolecular carbon-carbon bond formation as with **44** [187]. Cyclization is achieved in an aprotic solvent and the process is adaptable to



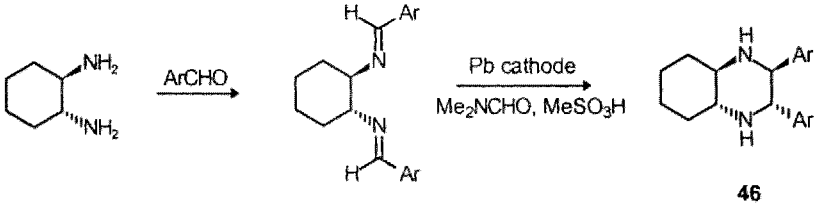
44

formation of 1,4-diazacrown ethers **45** having 9 - 21 atoms in the ring [188]. Other examples of this cyclization process, which give rise to substituted piperazines **46**,

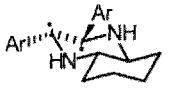


45, n = 0 - 4 50 -70 %

are carried out in dimethylformamide containing a strong protic acid such as methanesulphonic acid. In these cases the radical-anion intermediate is protonated and the cyclization step involves union of two radical centres. The transition state for piperazine ring formation adopts a *pseudo*-chair conformation **47** with the



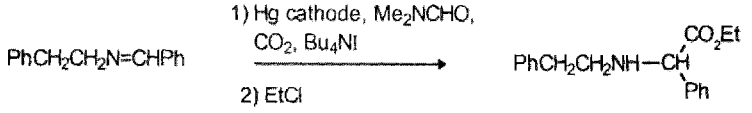
46



47

maximum number of equatorial-like substituents, and this decides the stereochemistry of the major product [189]. Chiral substituted piperazines are synthesised effectively from chiral 1,2-diamines.

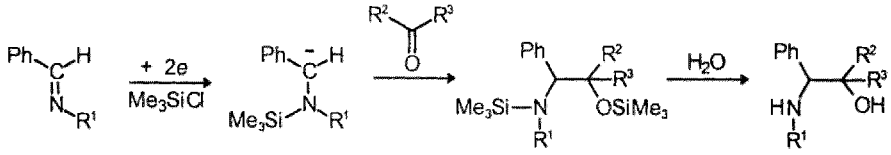
The radical-anion intermediates derived from aromatic imines behave as nucleophiles towards carbon dioxide, as with **48** [190, 191]. This nucleophic character is enhanced by reduction in the presence of chlorotrimethylsilane. A carbanion



48

centre is generated which will add to the carbonyl bond [192]. Coupling is carried

out at a lead cathode in dimethylformamide with tetraethylammonium tosylate as electrolyte in the presence of excess chlorotrimethylsilane and triethylamine.



Ref. [192]

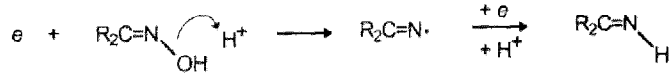
In the presence of excess monoalkylamine, carbonyl compounds in aqueous solution are in equilibrium with the corresponding imine. In most cases these imines cannot be isolated but they are reduced at a less negative potential than the carbonyl compound. Selective reduction of such equilibrium mixtures is a useful route to alkylamines from ketones in yields of 70-90%. The process fails with hindered ketones such as camphor and with bulky amines such as *tert.*-butyl amine. Overall the reaction has advantages of lower costs and simpler work-up compared to the use of cyanoborohydride reducing agents. In the electrochemical reaction, protonation of carbanion intermediates occurs from the more hindered side and where two isomeric products are formed, the least hindered amine predominates [193].

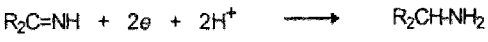
TABLE 10.7

Polarography of oximes and phenylhydrazones in aqueous buffers at pH 1.0. All give four-electron waves with half-wave potential dependent on pH.

Substrate	$-E_{½}$ / V *vs.* sce	Ref.
2-Methylpropanal oxime	1.08	[184]
Mesityloxide oxime	1.01	[184]
Acetophenone oxime	0.78	[194]
Benzaldehyde phenylhydrazone	0.75	[184]

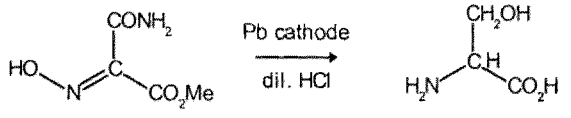
Reduction of aliphatic oximes is specifically catalysed by protons. The process exhibits a single four-electron wave on polarography and $E_{½}$ is dependent on pH. Some half-wave potentials are given in Table 10.7. Around pH 6-8 this wave decreases in height and finally disappears because protons can no longer be supplied



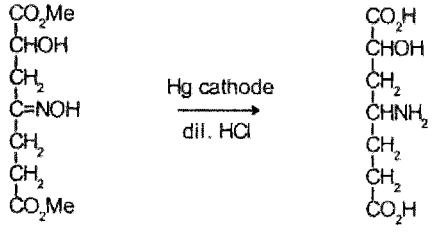


to the electrode surface at a rate sufficient to maintain the electron transfer process [184]. The rate-determining step for reduction of oximes must involve electron and proton addition with elimination of water. In strongly acid solution, enone oximes show two two-electron waves and reduction of testosterone oxime at the potential of the first of these waves leads to testosterone as the sole product [184]. Here the reduction process is halted at the imine stage and the imine is hydrolysed to the ketone and ammonia. Half-wave potentials for the more cathodic waves displayed in acidic media correspond to those found for the imines. In the reaction of non-conjugated oximes, this imine is immediately reduced at the potential used.

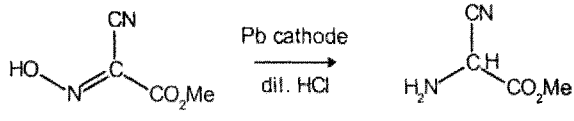
Preparative scale reduction of oximes at a mercury or lead cathode in acid solution has been used in the conversion of the carbonyl function to amine. Originally, 30-50% sulphuric acid was used as solvent [195] but ethanol with dilute hydrochloric acid is usually satisfactory. Aliphatic and aromatic oximes give amines in 64-86% yields [196]. Aromatic ketoximes are also reducible in alkaline solution and acetophenone oxime has been converted to 1-phenylethylamine in a tri-potassium orthophosphate solution [197]. The reduction of oximes in acid solution is tolerant of many other substituents as indicated by a number of examples [198, 199, 200]. Phenylglyoxal monoxime in acid solution is however reduced at both the carbonyl and the oxime centres by sodium amalgam to yield 2-amino-1-phenylethanol [201]



Ref. [198]



Ref. [199]



Ref. [200]

Large-scale reduction of phenylhydrazones at mercury or lead in ethanolic hydrochloric acid or 30-50% sulphuric acid results in cleavage of the nitrogen-

nitrogen bond to yield aniline and the amine corresponding to the original carbonyl compound [184,195]. Cleavage of the nitrogen-nitrogen bond in phenylhydrazones requires specific acid catalysis. The polarography of this group resembles the polarography of oximes. Benzaldehyde phenylhydrazone gives one four-electron wave, the half-wave potential of which varies with pH (Table 10.7). The wave height falls to zero around pH 6-8 because protons can no longer be supplied to the electrode surface at sufficient rate for the reaction to proceed [184]. In contrast to the reaction in acid, reduction of phenylhydrazones using sodium amalgam under alkaline conditions saturates the carbon-nitrogen double bond to give the N-alkyl-N'-phenyl-hydrazine [202].

Electrocatalytic Hydrogenation

Cathodic surfaces of finely divided platinum, palladium and nickel have a low hydrogen overvoltage and the dominant electrochemical reaction is the generation of a layer of hydrogen atoms. The electrocatalytic hydrogenation of aldehydes and ketones can be achieved at these surfaces. Cathodes of platinum or palladium black operate in both acid solution [203] and in methanol containing sodium methoxide [204]. The carbonyl compound is converted to the alcohol. Reduction of 4-*tert*-butylcyclohexanone is not stereoselective, however, 1,2-diphenylpropan-1-one is converted to the *threo*-alcohol.

A Raney nickel surface is also suitable for electrocatalytic hydrogenation [205]. This surface is prepared by electrodepositing nickel from a solution containing suspended Raney nickel alloy (Ni 50%; Al 50%). Some alloy particles stick to the surface, which is then activated by leaching the aluminium using hot aqueous sodium hydroxide. Cyclohexanone, acetophenone and benzil have been converted to the corresponding alcohol and there is no stereoselectivity for the formation of hydrobenzoin from benzil.

Electrocatalytic hydrogenation is also achieved by reaction of carbonyl compounds with aluminium and nickel(II) chloride in tetrahydrofuran. Nickel(II) is reduced to finely divided nickel(o) which is deposited on the aluminium.This setsup corrosion cells where aluminium dissolves, liberating electrons which are transferred to the nickel. Protons are then reduced to hydrogen at the nickel surface. Hydrogenation of benzaldehydes to the alcohol has been effected under these conditions [206].

References

[1] K. W. Bowers, R. G. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger and D. K. Roe, *J. Am. Chem. Soc.*, 1970, **92**, 2783.
[2] P. H. Given, M. E. Peover and J. Schoen, *J. Chem. Soc.*, 1958, 2674.
[3] G. Gores, C. E. Koeppe and D. E. Bartak, *J. Org. Chem.*, 1979, **44**, 380.
[4] P. H. Rieger and G. K. Fraenkel, *J. Chem. Phys.*, 1962, **37**, 2811.
[5] N. Hirota and S. I. Weissman, *J. Am. Chem. Soc.*, 1960, **82**, 4424.
[6] N. Steinberger and G. K. Fraenkel, *J. Chem. Phys.*, 1964, **40**, 723.
[7] M. Kazuhiro, T. Rikuhei and G. Ryozo, *Nippon Kagaku Zasshi*, 1963, **84**, 75; *Chem. Abs.*, 1964, **60**, 144.
[8] A. Hudson and J. W. E. Lewis, *Tetrahedron*, 1970, **26**, 4413.
[9] G. R. Underwood, *Mol. Phys.*, 1971, **22**, 729.
[10] G. P. Laroff and R. W. Fessenden, *J. Phys. Chem.*, 1973, **77**, 1283.
[11] P. Toffel and A. Henglein, *Ber. Bunsenges. Phys. Chem.*, 1976, **80**, 525.
[12] D. A. Nelson and E. Hayon, *J. Phys. Chem.*, 1972, **76**, 3200.
[13] A. Beckett, A. D. Osborne and G. Porter, *Trans. Faraday Soc.*, 1964, **60**, 873.
[14] C. P. Andrieux, M. Grzeszczuk and J.-M. Savéant, *J. Am. Chem.Soc.*, 1991, **113**, 8811.
[15] E. Hayon, T. Ibata, N. N. Lichtin and M. Simic, *J. Phys. Chem.*, 1972, **76**, 2072.
[16] A. Bewick, V. W. Jones and M. Kalaji, *Electrochim. Acta*, 1966, **41**, 1961.
[17] D. H. Eargle and R. Emrich, *J. Org. Chem.*, 1970, **35**, 3744.
[18] D. M. Coulson and W. R. Cromwell, *J. Am. Chem. Soc.*, 1952, **74**, 1294.
[19] P. J. Elving and J. T. Leone, *J. Am. Chem. Soc.*, 1958, **80**, 1021.
[20] J. Stradins, *Electrochim. Acta*, 1964, **9**, 711.
[21] L. Nadjo and J.-M. Savéant, *J. Electroanalyt. Chem.*, 1971, **33**, 419.
[22] J. H. Stocker and R. M. Jenevein, *J. Org. Chem.*, 1968, **33**, 2145.
[23] D. F. Tomkins and J. H. Wagenknecht, *J. Electrochem. Soc.*, 1978, **125**, 372.
[24] J. H. Stocker and R. M. Jenevein, *J. Org. Chem.*, 1968, **33**, 294.
[25] J. M. Stocker , D. H. Kern and R. M. Jenevein, *J. Org. Chem.*, 1969, **34**, 2810.
[26] J. H. Stocker, D. H. Kern and R. M. Jenevein, *J. Org. Chem.*, 1968, **33**, 412.
[27] L. Horner and D. Degner, *Tetrahedron Letters*, 1971, 1241.
[28] J. H. Stocker and R. M. Jenevein, *Coll. Czech. Chem. Commun.*, 1971, **36**, 965.
[29] D. W. Sopher and J. H. P. Utley, *J. Chem. Soc. Perkin Trans. 2*, 1984, 1361.
[30] J. Douch and G. Mousset, *Can. J. Chem.*, 1987, **65**, 549.
[31] J. Grimshaw and E. J. F. Rea, *J. Chem. Soc. C*, 1967, 2628.
[32] A. M. Martre, G. Mousset, P. Pouillen and R. Prime, *Electrochim. Acta*, 1991, **36**, 1911.
[33] L. Horner and D. Degner, *Tetrahedron Letters*, 1971, 2141.
[34] L. Horner and D. Degner, *Electrochim. Acta.*, 1974, **19**, 611.
[35] D. Brown and L. Horner, *Liebigs Ann. Chem.*, 1977, 77.
[36] I. A. Titova, I. M. Levinson, V. G. Mairanovskii and A. B. Ershler, *Elektrokhimiya*, 1973, **9**, 424; *Chem. Abs.*, 1973, **78**, 167746.
[37] L. Horner and D. H. Scaletz, *Liebigs Ann. Chem.*, 1977, 1365.
[38] W. J. M. van Tillborg and C. J. Smit, *Rec. Trav. chim. Pays-Bas*, 1979, **98**, 532.
[39] R. N. Gourley, J. Grimshaw and P. G. Millar, *J. Chem. Soc.*, 1970, 2318.
[40] E. Kariv, H. A. Terni and E. Gileadi, *J. Electrochem. Soc.*, 1972, **119**, 639.

[41] J. Kopilov, E. Kariv and L. L. Miller, *J. Am. Chem. Soc.*, 1977, **99**, 3450.
[42] M. Jubault, E. Raoult and D. Peltier, *Electrochim. Acta*, 1980, **25**, 1359.
[43] M. Jubault, D. Raoult and D. Peltier, *Electrochim. Acta*, 1977, **22**, 67.
[44] B. E. Firth, L. L. Miller, M. Mitani, T. Rogers, J. Lennox and R. W. Murray, *J. Am. Chem. Soc.*, 1976, **98**, 8271.
[45] B. Watkins, J. R. Behling, E. Kariv and L. L. Miller, *J. Am. Chem. Soc.*, 1975, **97**, 3549.
[46] L. Horner and W. Brich, *Liebigs Ann. Chem.*, 1977, 1354.
[47] S. Wawzonek and A. Gundersen, *J. Electrochem. Soc.*, 1960, **107**, 537.
[48] M. Hammouche, D. Lexa, M. Momenteau and J.-M. Savéant, *J. Am. Chem. Soc.*, 1991, **113**, 8455.
[49] Y. Ikeda and E. Manda, *Bull. Chem. Soc.* Japan, 1985, **58**, 1723.
[50] Y. Ikeda and E. Manda, *Chem. Letters*, 1984, 453.
[51] G. Silvestri, S. Gambino and G. Filardo, *E.P.*, 189120 (1986); *Chem. Abs.*, 1986, **105**, 180522.
[52] G. Silvestri, S. Gambino and G. Filardo, *Tetrahedron* Letters, 1986, **27**, 3429.
[53] A. S. C. Chang, T. T. Huang, J. H. Wagenknecht and R. E. Miller, *J. Org. Chem.*, 1995, **60**, 742 and 7074.
[54] J. Tafel and K. Schmitz, *Z. Elektrochem.*, 1902, **8**, 288.
[55] H. D. Law, *J. Chem. Soc.*, 1912, **101**, 1026.
[56] V. G. Khomyakov, A. P. Tomilov and B. G. Soldatov, *Elektrokhimiya*, 1969, **5**, 853.
[57] H. Nohe, F. Beck, W. Dietmar and E. J. Schier, *Ger. Offen.*, 2345461 (1975); *Chem. Abs.*, 1975, **83**, 9181.
[58] N. L. Weinberg, *U. S.* 4478694 (1984); *Chem. Abs.*, 1985, **102**, 35368.
[59] T. Shono and M. Mitani, *Tetrahedron*, 1972, 28, 4747.
[60] J. H. P. Utley, J. P. Coleman and R. J. Kobylecki, *J. Chem. Soc. Chem. Commun.*, 1971, 104.
[61] P. Kabasakalian, J. McGlotten, A. Basch and M. D. Yudis, *J. Org. Chem.*, 1961, **26**, 1738.
[62] R. J. Holman and J. H. P. Utley, *J. Chem. Soc. Perkin Tran. 2*, 1976, 879.
[63] G. LeGuillanton, *Nouv. J. Chim.*, 1978, **2**, 157.
[64] G. LeGuillanton, *Electrochim. Acta*, 1980, **25**, 1351.
[65] L. Mandel, R. M. Powers and R. A. Day, *J. Am. Chem. Soc.*, 1958, **80**, 5284.
[66] T. Nonaka, Y. Kusayanagi and T. Fuchigami, *Electrochim. Acta*, 1980, **25**, 1679.
[67] H. J. Creighton, *Can. Chem. Process Inds.*, 1942, **26**, 690.
[68] M. L. Wolfrom, W. W. Binkley, C. C. Spencer and B. W. Lew, *J. Am. Chem. Soc.*, 1951, **73**, 3357.
[69] L. Piszczek, K. Gieldon and S. Z. Wojtkowiak, *J. Applied Electrochem.*, 1992, **22**, 1055.
[70] H. Berbalk, K. Eichinger and F. Fricko, *Synthesis*, 1978, 42.
[71] S. G. Chen, T. Wen and J. H. P. Utley, *J. Applied Electrochem.*, 1992, **22**, 43.
[72] N. G. Belenkaya and N. A. Belozerskii, *J. Gen. Chem. USSR*, 1949, **19**, 93.
[73] K. Park, P. N. Pintauro, M. M. Baizer and K. Nobe, *J. Electrochem. Soc.*, 1985, **132**, 1850.
[74] E. Knobloch, *Coll. Czech. Chem. Commun.*, 1947, **12**, 407.
[75] J. Tafel, *Ber.*, 1906, **39**, 3626.

[76] T. Arai and T. Oguri, *Bull. Chem. Soc. Japan*, 1960, **33**, 1018.
[77] J. Tafel, *Z. Elektrochem.*, 1911, **17**, 975.
[78] J. Tafel and B. Emmert, *Z. Electrochem.*, 1911, **17**, 569.
[79] R. Lukeš and F. Šorm, *Coll. Czech. Chem. Commun.*, 1949, **43**, 3792.
[80] W. Schepss, *Ber.*, 1913, **46**, 2564.
[81] G. Shima, *Mem. Coll. Sci. Kyoto University [A]*, 1929, **12**, 73.
[82] S Swann, E. I. Onstatt and F. H. Baastad, *J. Electrochem. Soc.*, 1955, **102**, 113.
[83] J. Burdon and R. E. Price, *J. Chem. Soc. Chem. Commun.*, 1986, 839.
[84] L. Throop and L. Tökés, *J. Am. Chem. Soc.*, 1967, **89**, 4789.
[85] G. Phillipou, C. J. Seaborn and I. A. Blair, *Austral. J. Chem.*, 1979, **32**, 2767.
[86] R. J. Holman and J. H. P. Utley, *J. Chem. Soc. Perkin Trans. 2*, 1976, 884.
[87] K. Sugino and T. Nonaka, *J. Electrochem. Soc.*, 1965, **112**, 1241.
[88] M. Nicolas and R. Pallaud, *Compt. rend. C*, 1967, **265**, 1044.
[89] T. Sekine, A. Yamura and K. Sugino, *J. Electrochem. Soc.*, 1965, **112**, 439.
[90] T. Shono and M. Mitani, *J. Am. Chem. Soc.*, 1971, **93**, 5284.
[91] T. Shono, I. Nishiguchi and M. Mitani, *J. Am. Chem. Soc.*, 1978, **100**, 545.
[92] A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, 1985, **41**, 3925.
[93] S. W. Benson, *J. Chem. Ed.*, 1965, **42**, 502.
[94] J. E. Swartz, T. J. Mahachi and E. Kariv-Miller, *J. Am. Chem. Soc.*, 1988, **110**, 3622.
[95] J. E. Swartz, E. Kariv-Miller and S. J. Harrold, *J. Am. Chem. Soc.*, 1989, **111**, 1211.
[96] T. Shono, S. Kashimura, Y. Mori, T. Hayashi, T. Soejima and Y. Yamaguchi, *J. Org. Chem.*, 1989, **54**, 6001.
[97] S. Kashimura, M. Ishifue, Y. Murai, N. Moriyoshi and T. Shono, *Tetrahedron Letters*, 1995, **36**, 5041.
[98] I. Flemming and S. K. Patel, *Tetrahedron Letters*, 1981, 2321.
[99] T. Shono, Y. Morishima, N. Moriyoshi, M. Ishifune and S. Kasimura, *J. Org. Chem.*, 1994, **59**, 273.
[100] S. Kasimura, M. Ishifune, Y. Murai and T. Shono, *Tetrahedron Letters*, 1996, **37**, 6737.
[101] S. Kasimura, M. Ishifune, Y. Murai and T. Shono, *Chemistry Letters*, 1996, 309.
[102] T. Shono, N. Kise T. Suzumoto and T. Morimoto, *J. Am. Chem. Soc.*, 1986, **108**, 4676.
[103] N. Kise, T. Suzumoto and T. Shono, *J. Org. Chem.*, 1994, **59**, 1407.
[104] T. Shono, N. Kise, T. Fujimoto, N. Tominaga and H. Morita, *J. Org. Chem.*, 1992, **57**, 7175.
[105] T. Shono, N. Kise, T. Fugimoto, A. Yamanami and R. Nomura, *J. Org. Chem.*, 1994, **59**, 1730.
[106] T. Nonaka and K. Sugino, *J. Electrochem. Soc.*, 1969, **116**, 615.
[107] R. Gorny, H. J. Schäfer and R. Frohlich, *Angew. Chem. Int. Ed. English*, 1995, **34**, 2007.
[108] T. Koizumi, T. Fuchigami, Z. E. Kandeel, N. Sato and T. Nonaka, *Bull. Chem. Soc. Japan*, 1986, **59**, 757.
[109] R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, 1915, **107**, 1080.
[110] T. J. Curphey, C.W. Amelotte, T. P. Layloff, R. L. McCartney and J. H. Williams, *J. Am. Chem. Soc.*, 1969, **91**, 2817.
[111] E. Kariv, B. J. Cohen and E. Gileadi, *J. Electrochem. Soc.*, 1970, **117**, 342.

[112] A. D. Thomsen and H. Lund, *Acta Chem. Scand.*, 1971, **25**, 1576.
[113] B. Aalstad and V. D. Parker, *Acta Chem. Scand. Ser. B*, 1982, **36**, 187.
[114] J. Hoffmann and J. Voss, *Electrochim. Acta*, 1991, **36**, 465.
[115] R. N. Gourley and J. Grimshaw, *J. Chem. Soc. C*, 1968, 2388.
[116] T. Nonaka and M. Aasai, *Bull. Chem. Soc. Japan*, 1978, **51**, 2976.
[117] J. Tafel and H. Hall, *Ber., 1907*, **40**, 3312.
[118] J. Tafel, *Ber.*, 1912, **45**, 437.
[119] J. Tafel and W. Jurgens, *Ber.*, 1909, **42**, 2548.
[120] H. Stenzl and F. Fichter, *Helv. Chim. Acta*, 1934, **17**, 669.
[121] H. Stenzl and F. Fichter, *Helv. Chim. Acta*, 1937, **20**, 846.
[122] S. Wawzonek and J. E. Durham, *J. Electrochem. Soc.*, 1976, **123**, 500.
[123] H. Stenzel and F. Fichter, *Helv. chim. Acta*, 1934, **17**, 669.
[124] J. Tafel and G. Friedericks, *Ber.*, 1904, **37**, 3188.
[125] Y. Brun and G. Mousset, *Compt. rend. C*, 1978, **286**, 525.
[126] H. Stenzel and F. Fichter and H. Arni, *Helv. Chim. Acta*, 1936, **19**, 392.
[127] C. Mettler, *Ber.*, 1906, **39**, 2933.
[128] J. Tafel and G. Friederichs, *Ber.*, 1904, **37**, 3187.
[129] F. Goodridge and K. Lister, Brit. 1 411 371 (1975); F. Goodridge, K. Lister R. E. Plimey and K. Scott, *J. Appl. Electrochem.*, 1980, **10**, 55.
[130] I. Gimenez, S. Maximovitch, M. J. Barbier, Y. Christidis and G. Mattioda, *Nouv. J. Chim.*, 1987, **11**, 733.
[131] R. G. Barradas, *Electrochim. Acta*, 1974, **19**, 49.
[132] C. Mettler, *Ber.*, 1905, **38**, 1745.
[133] S. Swann and G. D. Lacker, *Trans. Electrochem. Soc.*, 1939, **75**, 14.
[134] C. Mettler, *Ber.*, 1906, **39**, 2933.
[135] F. Mayer and F. A. English, *Liebigs Ann. Chem.*, 1918, **417**, 69.
[136] G. H. Coleman and H. L. Johnson, *Org. Syn. Coll.Vol. III*, 1955, 60.
[137] T. Iwasaki, A. Yoshiyama, N. Sato, T. Fuchigami, T. Nonaka and M. Sasaki, *J. Electroanal. Chem.*, 1987, **238**, 315.
[138] H. Nohe and N. Hannebaum, *Ger. Offen*, 2642496 (1978); *Chem. Abs.*, 1978, **89**, 6119.
[139] P. E. Iversen and H. Lund, *Acta Chem. Scand.*, 1967, **21**, 279.
[140] P. E. Iversen and H. Lund, *Acta Chem. Scand.*, 1967, **21**, 389.
[141] H. Lund, *Acta Chem. Scand.*, 1963, 17, 972.
[142] K. S. Udupa, G. S. Subramanian and H. V. K. Udupa, *Industrial Chemist (U.K.)*, 1963, **39**, 238.
[143] H. V. K. Udupa, G. S. Subramanian, K. S. Udupa and K. Natarajan, *Bull. Acad. Polon. Sci. Ser. Chim.*, 1965, **13**, 631.
[144] J. H. Wagenknecht, R. D. Goodwin, P. J. Kinlen and F. E. Woodward, *J. Electrochem. Soc.*, 1984, **131**, 1559.
[145] C. P. Andrieux, I. Gallardo, J.-M. Savéant and K.-B. Su, *J. Am. Chem. Soc.*, 1984, **131**, 1559.
[146] L. Bouvault and G. Blanc, *Bull. Soc. chim. France* [3], 1904, **31**, 1213.
[147] C. Mettler, *Ber.*, 1904, **37**, 1752.
[148] L. Horner and H. Hönl, *Liebigs Ann. Chem.*, 1977, 2036.
[149] A. M. Romulus and A. Savall, *Electrochim. Acta*, 1992, **37**, 625.

[150] P. R. Goetz-Schatowitz, G. Struth, J. Voss and G. Wiegand, *J. prakt. Chem., Chem.-Zeitung*, 1993, **335**, 230.
[151] T. Shono, H. Masuda, H. Murase, M. Shimomura and S. Kashimura, *J. Org. Chem.*, 1992, **57**, 1061.
[152] S. Kashimura, Y. Murai, M. Ishifune, H. Masuda, H. Murase and T. Shono, *Tetrahedron Letters*, 1995, **36**, 4805.
[153] T. B. Baillie and J. Taft, *Ber.*, 1899, **32**, 68.
[154] J. Tafel and M. Stern, *Ber.*, 1900, **33**, 2224.
[155] K. Kindler, *Ber.*, 1924, **57**, 774.
[156] K. Kindler, *Arch. Pharm.*, 1927, **265**, 389.
[157] E. Späth and F. Breusch, *Monatsh.*, 1928, **50**, 349.
[158] M. J. Allen, *U. S. Pat.*, 2846382 (1958); *Chem. Abs.*, 1959, **53**, 2252.
[159] E. W. Cook and W. G. France, *J. Phys. Chem.*, 1932, **36**, 2383.
[160] P. R. Goetz-Schatowitz, G. Struth , J. Voss and G. Wiegand, *J. Prakt. Chem., Chem.-Zeitung*, 1993, **335**, 230.
[161] S. Kashimura, M. Ishifune, Y. Murai, H. Murase, M. Shimomura and T. Shono, *Tetrahedron Letters*, 1998, **39**, 6199.
[162] P. E. Iversen and H. Lund, *Acta Chem. Scand.*, 1967, **21**, 279.
[163] H. Lund and P. E. Iversen, *Acta Chem. Scand.*, 1967, **21**, 389.
[164] D. Deprez, R. Margraff, J. Bizot and J. P. Pulicani, *Tetrahedron Letters*, 1987, **28**, 4679.
[165] Y. Kokusenya and M. Matsuoka, *Denki Kagaku*, 1987, **55**, 174; *Chem. Abs.*, 1987, **107**, 134645.
[166] K. Herbig, W. W. Wiersdorff and D. Degner, *Ger. Offen* 2408532 (1975); *Chem. Abs.*, 1976, **84**, 23765.
[167] J. Tafel and X. Ach, *Ber.*, 1901, **34**, 1166.
[168] J. Tafel and X. Dodt, *Ber.*, 1907, **40**, 3753.
[169] G. A. Urove, D. G. Peters and M. S. Murbank, *J. Org. Chem.*, 1992, **57**, 786.
[170] F. Barba and A. Guirado, *J. Org. Chem.*, 1982, **47**, 142.
[171] D. Occhialini, K. Daasbjerg and H. Lund, *Acta Chem. Scand.*, 1993, **47**, 1100.
[172] M. S. Murbarak, G. A. Urove and D. G. Peters, *J. Electroanal. Chem.*, 1993, **350**, 205.
[173] J. C. Folest, E. Pereiramartins, M. Troupel and J. Périchon, *Tetrahedron Letters*, 1993, **34**, 7571.
[174] A. Guiardo, F. Barba, M. B. Hursthouse, A. Martinez and A. Areas, *Tetrahedron Letters*, 1986, **27**, 4063.
[175] A. Guirado, F. Barba and J. Martin, *Synthetic Commun.*, 1983, **13**, 327.
[176] M. P. Cava, D. R. Napier and R. J. Pohl, *J. Am. Chem. Soc.*, 1963, **85**, 2076.
[177] C. W. Bird and D. Y. Wong, *Tetrahedron*, 1975, **31**, 31.
[178] A. Guirado, F. Barba and J. Martin, *Electrochim. Acta*, 1984, **29**, 587.
[179] J. M. W. Scott and W. H. Jura, *Can. J. Chem.*, 1967, **45**, 2375.
[180] A. G. Evans and J. C. Evans, *J. Chem. Soc. B*, 1966, 271.
[181] A. J. Fry and R. G. Reed, *J. Am. Chem. Soc.*, 1969, **91**, 6448.
[182] C. P. Andrieux and J.-M. Savéant, *J. Electroanalyt. Chem.*, 1970, **28**, 339.
[183] T. Shono, K. Yoshida, K. Ando, Y. Claui and H. Hamaguchi, *Tetrahedron Letters*, 1978, 4819.
[184] H. Lund, *Acta Chem. Scand.*, 1959, **13**, 249.

[185] L. Holleck and B. Kastening, *Z. Elektrochem. Ber. Bunsenges. Phys. Chem.*, 1956, **60**, 127.
[186] L. Horner and D. H. Skaletz, *Liebigs Ann. Chem.*, 1975, 1210.
[187] R. W. Koch and R. E. Dessy, *J. Org. Chem.*, 1982, **47**, 4452.
[188] T. Shono, N. Kise and E. Okazaki, *Tetrahedron Letters*, 1992, **33**, 3347.
[189] T. Shono, N. Kise, E. Shirakawa, H. Matsumoto and E. Okazaki, *J. Org. Chem.*, 1991, **56**, 3063.
[190] U. Hess and M. Ziebig, *Pharmazie*, 1982, **37**, 107.
[191] U. Hess and R. Thiele, *J. prakt. Chem.*, 1982, **324**, 385.
[192] T. Shono, N. Kise, N. Kunimi and R. Nomura, *Chem. Letters*, 1991, 2191.
[193] T. Pienemann and H.-J. Schäfer, *Synthesis*, 1987, 1005.
[194] H. J. Gardner and W. P. Georgans, *J. Chem, Soc.*, 1956, 4180.
[195] J. Tafel and E. Pfeffermann, *Ber.*, 1902, **35**, 1510.
[196] B. M. Prasad, A. K. Yadava, S. C. Mishra and R. A. Misra, *J. Indian Chem. Soc.*, 1991, **68**, 95.
[197] Y. D. Smirnov and A. P. Tomilov, *Russian J. Electrochem.*, 1996, **32**, 106.
[198] Y. Kokusenya, S. Nokajima and M. Matsuoka, *Denki Kagaku*, 1987, **55**, 853.
[199] V. N. Leibzon, L. M. Makarenkova, M. Y. Leonova, T. I. Egorova and S. L. Ioffe, *Russian J. Electrochem.*, 1996, **32**, 110.
[200] Y. Kokusenya, S. Nakajima and M. Matsuoka, *Denki Kagaku*, 1987, **55**, 853.
[201] E. Kolshorn, *Ber.*, 1904, **37**, 2474.
[202] O. Schlenk, *J. prakt. Chem.* [2], 1908, **78**, 50.
[203] T. Nonaka, M. Takahashi and T. Fuchigani, *Bull. Chem. Soc. Japan*, 1983, **56**, 2584.
[204] M. A. Casadei and D. Pletcher, *Electrochim. Acta*, 1988, **33**, 117.
[205] A. K. Cheong, Y. Bolduc and J. Lessard, *Can. J. Chem.*, 1993, **71**, 1850.
[206] B. K. Sarmah and N. C. Barua, *Tetrahedron*, 1991, **47**, 8587.

CHAPTER 11

REDUCTION OF NITRO, NITROSO, AZO AND AZOXY GROUPS

Nitro- and Nitroso-compounds Radical-Anions

Reduction of nitrocompounds involves a series of one-electron additions and chemical steps and an important reaction intermediate is the nitrosocompound. The redox properties of nitro- and nitroso-compounds will be discussed first. Some values of reduction potentials for nitrocompounds are collected in Table 11.1.

TABLE 11.1

Polarographic half-wave potentials for nitrocompounds in aqueous ethanol, pH 13. The radical-anion is formed reversibly so that $E_{1/2} = E°$

Substrate	$E_{1/2}$ / V *vs.* sce	Ref.
2-Methyl-2-nitropropane	-1.09	[1]
Nitrobenzene	-0.70	[2]
ω-Nitrostyrene	-0.40	[3]

The radical-anions of aliphatic nitrocompounds are detectable in aqueous solution as transient intermediates formed during continuous electrolysis in the cavity of the esr spectrometer [4]. Decay of the species occurs by protonation and then further reactions. 2-Methyl-2-nitropropane has no acidic hydrogens so that it can be examined in aqueous alkaline solution where the radical-anion is not protonated. Over the pH range 9-11, this radical-anion decays by a first order process with $k = 0.8 \pm 0.1\ s^{-1}$ at 26° C. Decay results from cleavage of the carbon-nitrogen bond to give a carbon centred radical and nitrite ion. Ultimately, the di-(*tert.*-butyl)nitrone radical is formed in follow-up reactions [5].

Nitrobenzene radical-anion is more stable in aprotic solvents than its aliphatic counterparts. Nitrobenzene shows two one-electron polarographic waves in acetonitrile with $E_{1/2}$ -1.15 and -1.93 V *vs.* sce. The first wave is due to the formation of the radical-anion and this species has been characterised by esr spectroscopy [6]. Nitrobenzene radical-anion can also be generated in steady-state concentration by electrochemical reduction in aqueous solutions at pH 13 [7] and in dimethylformamide [8]. It is yellow-brown in solution with λ_{max} 435 nm. Protonation initiates a series of reactions in which nitrosobenzene is formed as an intermediate and

leading to phenylhydrazine as the first isolatable product. Rate constants for the steps in the conversion of nitrobenzene radical-anion to phenylhydroxylamine have been determined in aqueous solution by fast reaction techniques. When the radical-anion is formed by pulse-radiolysis in aqueous buffer, the absorption spectrum depends upon pH due to the equlibrium (Equation 11.1) for which $pK_a = 3.2$ [9]. In acidic solutions with pH<2, all the nitrobenzene radical-anion is protonated and further reaction is by disproportionation (Equation 11.2) and then formation of ni-

$$PhNO_2^{\bullet -} + H^+ \rightleftharpoons PhNO_2H^{\bullet} \qquad pK_a = 3.2 \qquad \text{Eq. 11.1}$$

$$2\,PhNO_2H^{\bullet} \longrightarrow PhNO_2 + PhN(OH)_2 \qquad 2k = 6 \times 10^8\ M^{-1}\,s^{-1} \qquad \text{Eq. 11.2}$$

$$PhNO_2^{\bullet -} + PhNO_2H^{\bullet} \longrightarrow PhNO_2 + PhNO^{-}(OH) \qquad k = 1.7 \times 10^8\ M^{-1}\,s^{-1} \qquad \text{Eq. 11.3}$$

$$PhNO^{-}(OH) + H^+ \longrightarrow PhN(OH)_2$$

$$PhN(OH)_2 \longrightarrow PhNO + H_2O$$

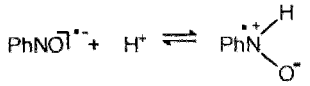
trosobenzene. In the pH range 4 to 11, rapid protonation of the radical-anion is followed by reaction between a radical and a radical-anion (Equation 11.3) followed by the formation of nitrosobenzene [7]. At pH>11.5, disproportionation of nitrobenzene radical-anion with $2k = 1\ M^{-1}\,s^{-1}$ is the predominate reaction leading to nitrosobenzene.

Redox equlibrium (Equation 11.4) between nitrosobenzene and phenylhydroxylamine is fully reversible on the time scales of polarography and preparative elec-

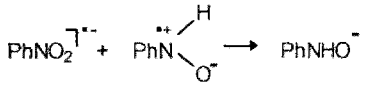
$$PhNO + 2e + 2H^+ \rightleftharpoons PhNHOH \qquad \text{Eq. 11.4}$$

trolysis over the whole pH range. The electrode potential for this process varies with pH, being more anodic in acidic solutions. At pH 4.0, $E^\circ = +0.075$ V *vs.* sce [10].

Nitrosobenzene radical-anion is detected in steady-state concentration during electrolysis of a solution of the nitrosobenzene in acetonitrile within the cavity of the esr spectrometer [11]. Both the radical-anion and the protonated radical are present and protonation occurs at nitrogen, not oxygen, generating a nitroxide. Immediately following generation by pulse-radiolysis, nitrosobenzene radical-anion is detected by absorption spectroscopy with λ_{max} 450 nm. A few milliseconds after generation, the acid-base equlibrium (Equation 11.5) is established. A value of $pK_a = 11.7$ has been obtained from the changes in this absorption spectrum over a pH range [12]. In solution, nitrobenzene radical-anion will transfer an electron to the nitroxide species, (Equation 11.6) with a rate constant of $2.1 \times 10^8\ M^{-1}\,s^{-1}$, and protonation of the resulting ion yields phenylhydroxyl-amine [12].



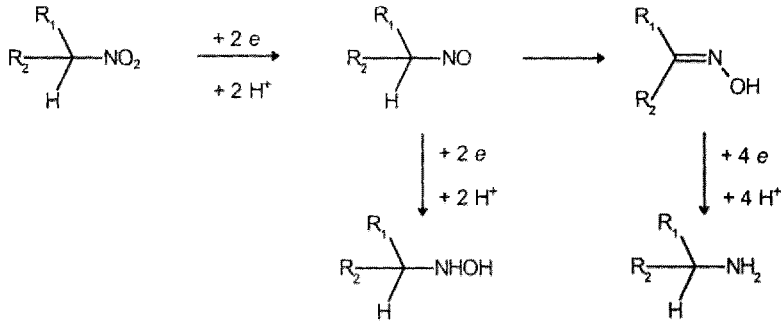
Eq. 11.5



Eq. 11.6

Aliphatic Nitrocompounds

The reduction of aliphatic nitrocompounds in acid solution proceeds in two steps. First the nitrosocompound is formed. A low steady state concentration of 2-methyl-2-nitrosopropane has been detected during the reduction of 2-methyl-2-nitropropane [13]. At the cathode potential necessary to attach the first electron to a nitro group, the nitroso intermediate undergoes further reduction to the hydroxylamine. When the nitrocompound has one α-hydrogen substituent, tautomerism of the nitroso intermediate to an oxime is in competition with further reduction. Both temperature and proton availability affect the rate of this isomerisation. Reduction of aliphatic nitrocompounds to the hydroxylamine is usually carried out in acid solution at 0-5° C to minimise oxime formation [14, 15]. The hydroxylamine is stable towards further reduction in acid solution. Oxines in acid solution are reduced

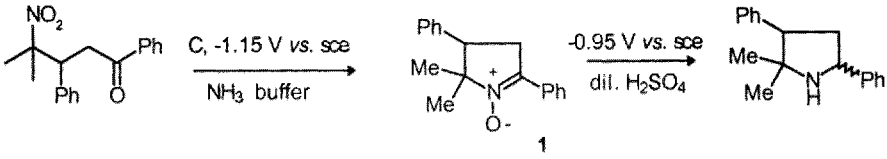


at a more negative potential, relative to the nitrocompound, and the final product is the amine. Oximes are also hydrolysed under reaction conditions so that side products form the conversion of nitrocompounds to hydroxylamines include the oxime and the corresponding carbonyl compound together with some amine [16]. Formation of these side products can be avoided by reduction of nitrocompounds in acetonitrile containing acetic anhydride when the hydroxylamine is isolated as its

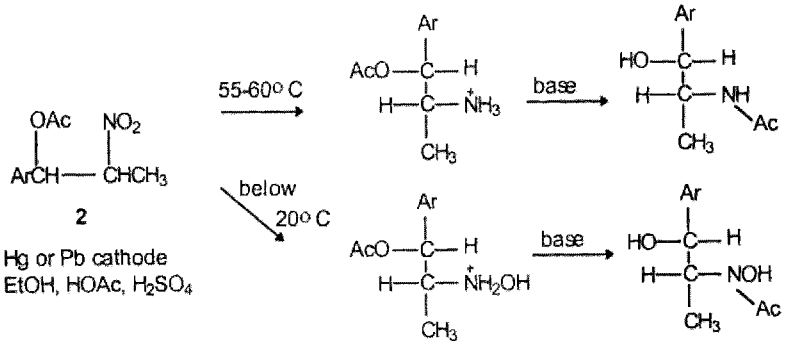
N,O-diacetyl derivative [17]. Reduction of most aliphatic nitrocompounds at 50-70° C in acid solution gives good yields of the amine, the nitrosocompound and the oxime being intermediates [18].

In the cases of phenylnitromethane and 1-phenylnitroethane the intermediate nitrosocompounds isomerise very rapidly because of the driving force to introduce a double bond in conjugation with the aryl ring. Even at -5° C, an oxime is the main reduction product together with some hydroxylamine. A flow through cell using a porous carbon cathode has been devised for the rapid conversion of these nitrocompounds to a mixture of oxime and alkylhydroxylamine. Addition of a solution of iodine to the mixture oxidises any hydroxylamine to the oxime. This overall process converts phenylnitromethane to benzaldehyde oxime in excellent yields [19].

Hydroxylamines from reduction of nitrocompounds are trapped by reaction with any adjacent carbonyl function under slightly basic conditions. This reaction forms a nitrone, e.g. **1**, which can be reduced in acid solution to a pyrrolidine [20].



The effect of temperature on the reduction of nitro-alkanes has been extensively exploited in the synthesis of φ-ephedrine analogues [15, 21, 22] starting from 1-aryl-2-nitropropenes which are easily converted to the substrates **2**. Reduction of these nitrocompounds below 20° C affords the hydroxylamine. The amine is formed above 55° C. Neutralisation of either reaction mixture causes rapid intramolecular migration of the acetyl group from oxygen to nitrogen, a reaction which implies a

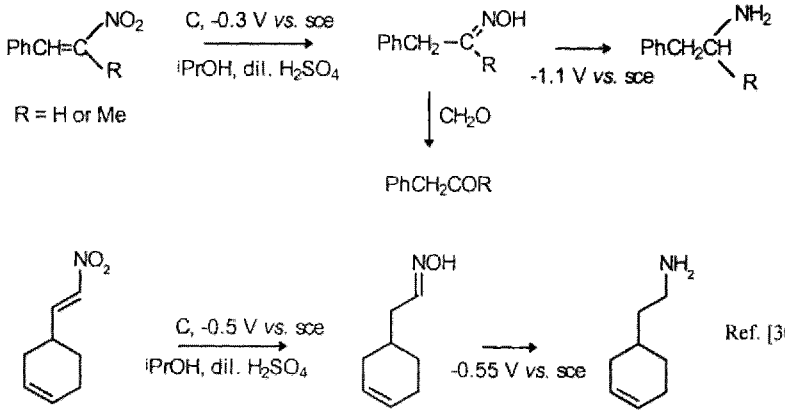


φ-norephedrine stereochemistry for the reduction products [23]. Reduction of the

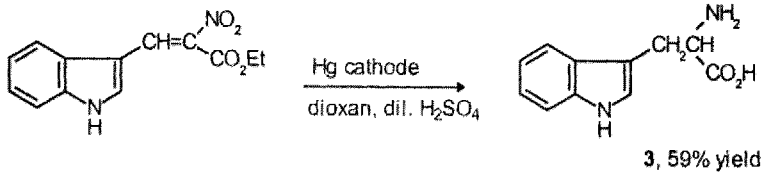
oxime intermediate to a φ-norephedrine product implies a highly stereoselective reaction. This assumption should however be treated with caution since the isomer with norephedrine type stereochemistry may not have been isolated from the reaction mixture. It is known that the reduction of the nitroalcohol related to **2** by tin and hydrochloric acid at 45° C gives a mixture of the diastereomeric amines [24].

Good yields of the hydroxylamine are obtained from nitroalkanes with no α-hydrogen substituent by reduction in acid solution [25, 26]. This step has been used to modify the antibiotic everninomicin, a naturally occuring aliphatic nitrocompound, where the hydroxylamine was obtained by reduction at pH 8 in the presence of other functional groups [27]. Above pH 8 the radical-anion from this class of nitro-alkane is not fully protonated in solution and has a sufficiently long lifetime to undergo carbon-nitrogen bond cleavage giving an alkyl radical. Reaction products are then formed by addition of the radical onto any of the nitroso intermediate which is present [26].

Reduction of 1-nitroalkenes in acid solution gives initially the enehydr-

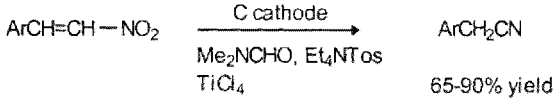


oxylamine. Cathodes of platinum [28], lead [29] and carbon [30] have been used for this reaction. These intermediates are unstable under the reaction conditions and isomerise to an oxime. The isolated product can be either the oxime or an amine



generated by further reduction. Tryptophan **3** [31] and phenylalanine [32] have been prepared by this electrochemical route. When the oxime is a major product,

work-up by addition of formaldehyde leads to conversion of the oxime to the corresponding carbonyl compound. Where the reduction step generates an aldoxime, reaction in the presence of a Lewis acid such as titanium(IV) chloride promotes dehydration of this intermediate to a nitrile. Phenylacetonitrile is isolated from re-



Ref. [33]

duction of ω-nitrostyrene in the presence of titanium(IV) chloride [33].

Formation of Arylamines

Reduction of aromatic nitrocompounds takes place in three overall stages. The first two steps proceed in sequence because nitrosocompounds produced in the first step have a much less negative reduction potential than nitrocompounds. Arylhy-

$$ArNO_2 + 2e + 2H^+ \longrightarrow ArNO + H_2O$$

$$ArNO + 2e + 2H^+ \longrightarrow ArNHOH$$

$$ArNHOH + 2e + 2H^+ \longrightarrow ArNH_2 + H_2O$$

droxylamine is the first product to be isolated. The polarogram of nitrobenzene shows a pH dependent step due to this four-electron process [34]. The relationship between half-wave potential and pH for aromatic nitrocompounds (Fig. 11.1) shows a discontinuity around pH 4 which is more marked with some substituted nitrobenzenes. Discontinuity occurs close to the pK_a of the protonated nitrobenzene radical-anion. The polarogram show a further two-electron wave at more negative potentials due to reduction of phenylhydroxylamine to aniline. This latter process is specifically catalysed by protons [35] and the related polarographic wave disappears at high pH values because protons cannot diffuse sufficiently rapidly towards the electrode surface for the reaction to proceed [34]. To obtain high yields of amine requires careful selection of acid concentration, cathode material reduction potential and stirring conditions. The objective is to decrease the residence time for arylhydroxylamine in the medium because this intermediate can undergo reactions to form a number of side products [36, 37, 38]. Transition metal ions can be added to the electrolyte in order to catalyse the reduction of arylhydroxylamine intermediates. The successful industrial processes for the conversion of nitrocompounds to amines uses iron powder and acid and can achieve yields greater than 99%. Good yields of amine can be obtained from the uncatalysed electrochemical

reduction of di-*ortho* substituted nitrocompounds [39] and from nitrophenols and nitroamines as discussed later.

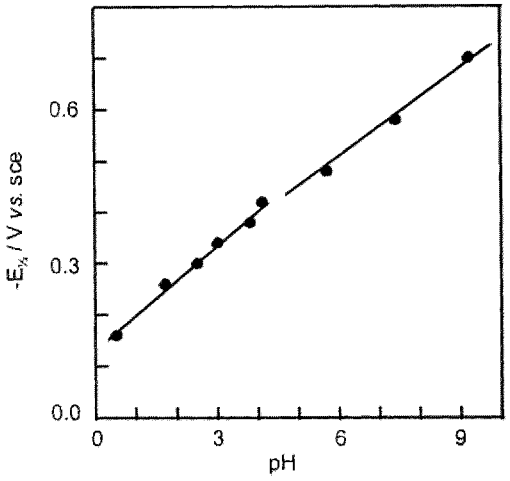
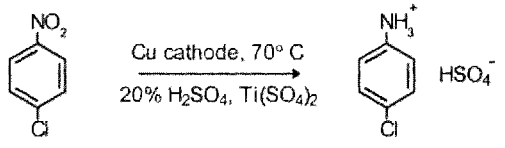


Figure 11.1. Changes with pH of the half-wave potential ($E_{½}$) for the first polarographic wave of nitrobenzene. Data from ref. [34].

The most generally useful conditions for electrochemical conversion of aryl nitrocompounds to the amine involve an electrolyte of 10-25% sulphuric acid containing titanium(IV) sulphate, working with an emulsion of electrolyte and nitrocompound and using a copper cathode. Titanium(III) ions are formed and act as homogeneous reducing agent, increasing the yield of aniline [40]. Titanium ions also function as a Lewis acid, assisting cleavage of the nitrogen-oxygen bond in the



Ref. [42]

intermediate hydroxylamine. The industrial application of this process has been pioneered by Udupa for a number of substituted nitrobenzenes [41, 42]. Isolation of the product is simple in many cases because the amine sulphate precipitates from the reaction mixture and the electrolyte can be recycled.

A further adaptation of the titanium(III) reduction uses di(cyclopentadienyl)-titanium ions as mediator. The mediator is generated in aqueous acid and reacted outside the electrochemical cell with a solution of the nitrobenzene in toluene. The

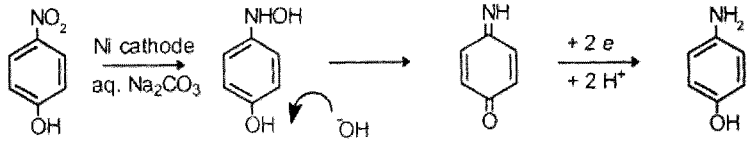
aniline is formed and oxidised titanium complex is reduced at a graphite felt cathode by continuously recycling the aqueous solution [43].

Electrolytic reduction of an emulsion of the nitro compound in 1 M zinc chloride solution at high current density is another proposed method for conversion to the amine. Finely divided zinc is produced and this reduces the nitrocompound. Zinc ions also function as Lewis acid in the reduction of arylhydroxylamines [44].

Reduction of substituted nitrobenzenes under alkaline conditions, usually with aqueous sodium acetate as electrolyte and a nickel cathode, is the classical method due to Elbs [45] for the formation of azo- and azoxy-compounds. Protons are used in the electrochemical reaction so that the catholyte becomes alkaline and under these conditions, phenylhydroxylamine reacts rapidly with nitrosobenzene to form azoxybenzene. Finely divided copper has long been known to catalyse the reduction of nitrobenzene to aniline in alkaline solution at the expense of azoxybenzene production [46]. Modern work confirms that whereas reduction of nitrobenzene at polycrystalline copper in alkaline solution gives mainly azoxybenzene, if the electrode is pre-oxidised in alkaline solution and then reduced just prior to the addition of nitrobenzene, high yields of aniline are obtained with good current efficiency [47]. Pre-treatment of the cathode produces a finely divided copper surface and this catalyses the hydrogenolysis of phenylhydroxylamine to aniline which becomes the principal reaction product. The reaction probably involves promotion of nitrogen-oxygen bond cleavage in the chemisorbed phenylhydroxylamine intermediate.

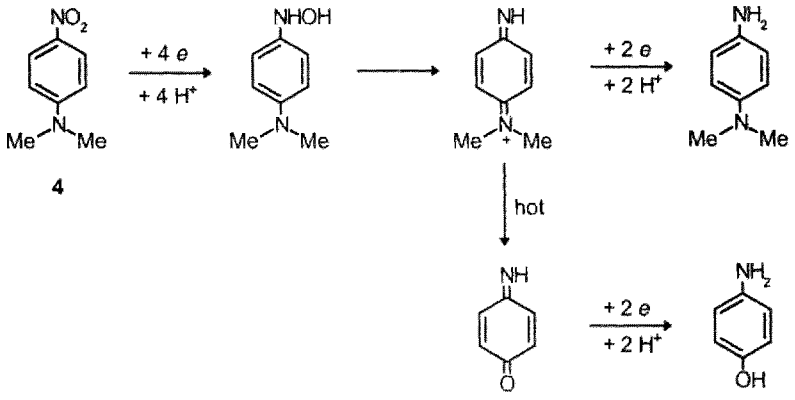
Surfaces of finely divided nickel also promote the formation of aniline. A practical route to the preparation of electrodes coated with a finely divided metal involves electroplating nickel onto a cathode from a solution containing a suspension of finely divided Raney nickel (Ni 50%; Al 50%) or Devarda copper alloy (Cu 50%; Al 45%; Zn 5%). Some alloy particles stick to the cathode surface which is then activated by leaching out the aluminium using hot aqueous sodium hydroxide [48]. Both the copper and nickel surfaces are efficient for the electrochemical reduction of nitrobenzene to aniline. With time however, the properties of this surface are transformed to those of the polycrystalline metal and azoxybenzene becomes as major reduction product [49].

Nitrobenzenes with an *ortho* or a *para* hydroxyl or amino function form an exceptional group of compounds in which the nitro function can readily be reduced to amino in alkaline solution. Heterolytic cleavage of the nitrogen-oxygen bond in the phenylhydroxylamine intermediate is promoted by any 2- or 4-substituent which can donate a lone pair of electrons. Further reduction steps then lead to the overall



conversion of nitro to amino. Early workers demonstrated the reaction with 2- and 4-nitrophenols [50, 51] and indicated that this process gives better yields than the chemical route using tin and hydrochloric acid for the reduction of 2-nitro-4-methylphenol [52]. The conversion of 3-nitro-4-hydroxybenzoic acid to 3-amino-4-hydroxybenzoic acid has been carried out on a pilot plant scale by reduction at a copper cathode in basic medium [53].

2- and 4-Nitroanilines give the phenylenediamine in excellent yields by reduction from alkaline solution [54]. However, because of improved solubility, the best process for conversion of 4-nitroaniline to 1,4-phenylenediamine uses dilute hydrochloric acid and a copper cathode [55] and gives 93% yield of the product hydrochloride. N,N-dimethyl-4-nitroaniline **4** undergoes reduction to the diamine in



alkaline solution at low temperatures but in hot solution the intermediate immonium ion is hydrolysed and the isolated product is 4-aminophenol [56].

Formation of Nitrosoarenes and Arylhydroxylamines

Conversion of substituted nitrobenzenes to the arylhydroxylamine is easily achieved by reduction in neutral or slightly acid solution. In the first classical experiments, Haber [35] used a platinum cathode and ammonia ammonium chloride buffer and the process was improved by Brand [57] using either a nickel or silvered copper cathode in an acetate buffer. The hydroxylamine can also be obtained from reduction in dilute sulphuric acid provided the temperature is kept below 15° C to suppress further reduction [58]. This electrochemical route to arylhydroxylamines due to Brand is superior to the chemical reduction using zinc dust and ammonium chloride solution. The latter process is known to give variable yields depending on

the quality of the zinc dust [59]. Many examples have been given of the reaction carried out in a beaker-type cell fitted with a nickel cathode [60, 61].

Phenylhydroxylamines are unstable in air so that more consistent yields are obtained using rapid conversion in a flow-through cell, followed by rapid isolation of the product with minimum exposure to oxidising conditions. A flow-through porous carbon cathode was developed for industrial use in 1898 [62] and this approach has been perfected more recently for the pilot scale production of either phenylhydroxylamines or nitrosobenzenes. Conversion to the phenylhydroxylamine is effected in a simple flow through cell with a carbon cathode. This step can be coupled with the back oxidation of the phenylhydroxylamine to the nitrosobenzene [63] in a serial flow-through double cell of the type sketched in Fig. 11.2. The first working electrode operates at a potential for reduction of the nitrobenzene while the second working electrode operates from an independent supply unit at a potential for oxidation of phenylhydroxylamine to nitrosobenzene. Solutions of nitroso compounds can be used without purification in further reaction steps [64, 65].

Conversion of nitrobenzenes to the phenylhydroxylamine and then the nitroso-

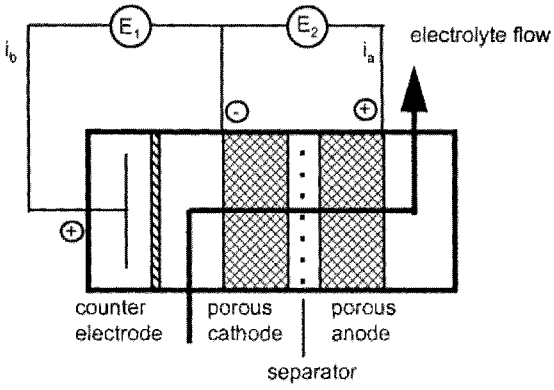


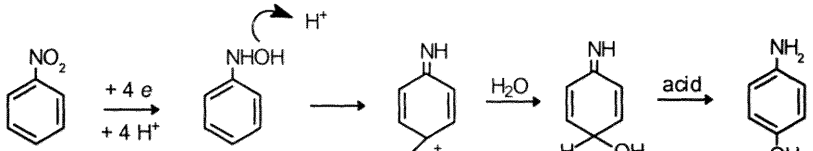
Figure 11.2. Flow cell for conversion of nitrobenzenes to the nitrosobenzene. Both of the porous electrodes are constructed from carbon fibre. They are fed with constant current as indicated with $i_b = 2\ i_a$.. The feedstock containing nitrobenzene is introduced at a rate corresponding to the current i_b for reduction to phenylhydroxylamine. The outflow contains nitrosobenzene, see ref. [62].

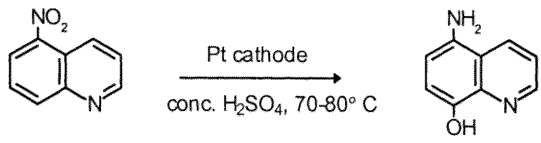
benzene is also achievable in a one-pot process using a conventional beaker-cell provided that the electrolyte pH is maintained in the range 5-8 where the condensation between phenylhydroxylamine and nitrosobenzene is slow. Yields up to 98% of nitrosobenzene are obtained when electron-donating substituents are present in the aromatic ring [66]. Nitrobenzenes possessing an electron-withdrawing substituent give more satisfactory yields using the flow through cell. The conversion of nitrobenzene to nitrosobenzene can also be carried out with 90%

isolated yield by first reducing to phenylhydroxylamine in tetrahydrofuran containing benzoic acid as a proton source, then oxidising the same solution at -30° C [67].

Rearrangement of Phenylhydroxylamines - Formation of 4-Aminophenols

Phenylhydroxylamine rearranges rapidly in sulphuric acid at medium temperatures to give 4-aminophenol **5**. Formation and rearrangement of the phenylhydroxylamine during a one-pot reduction of nitrobenzenes in sulphuric acid is a convenient synthetic route. It usually affords the crystalline sulphate of the 4-aminophenol. The reaction was first achieved in 1893 by Gattermann at a platinum cathode in concentrated sulphuric acid [68] and has been the subject of many patent applications. Some 4-aminophenols are sulphonated under the reaction conditions, particularly when the electrolyte used is concentrated sulphuric acid at 80-90° C [69]. The best yields of 4-aminophenol are achieved by reduction of a suspension of nitrobenzene in 50% sulphuric acid at a nickel cathode in the temperature range 25-60° C when the product precipitates as the hydrogen sulphate in 65% yield [70]. A more recent approach to the technical scale production uses a packed bed reactor where the cathode consists of coarse particles of polycrystalline copper [71]. A

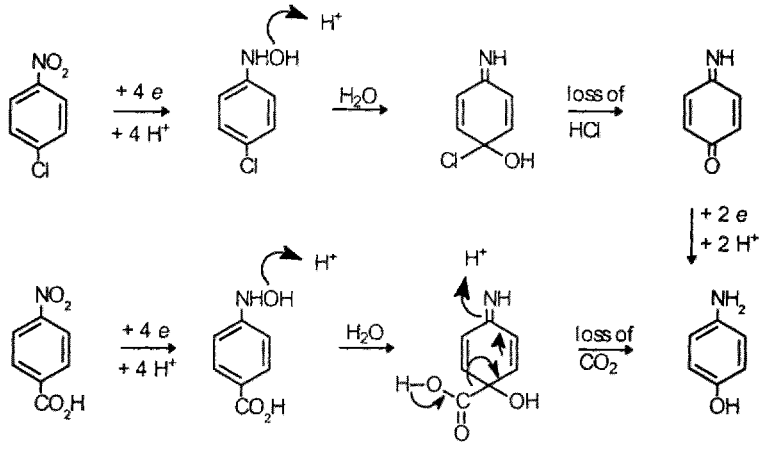




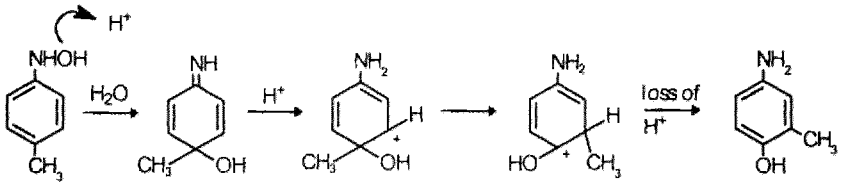
Ref. [72]

large range of substituted nitrobenzenes have been converted to the 4-aminophenol [68, 72, 73] and the method is applicable also to heterocyclic nitrocompounds [73, 74, 75]. The alkoxyamino compound is obtained from reactions carried out in methanol or ethanol containing sulphuric acid. 4-Ethoxyaniline has been obtained in 42% yield from the reduction of nitrobenzene at a Monel metal (Ni 60%; Cu 33%; Fe 7%) cathode in ethanol and sulphuric acid [76].

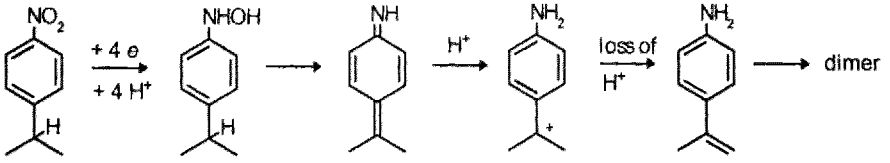
A variety of alternative reactions occur when there is a substituent *para* to the nitro-group. Halogen [77] and carboxyl groups [78] are eliminated while the methyl



group undergoes a 1,2-migration [58].

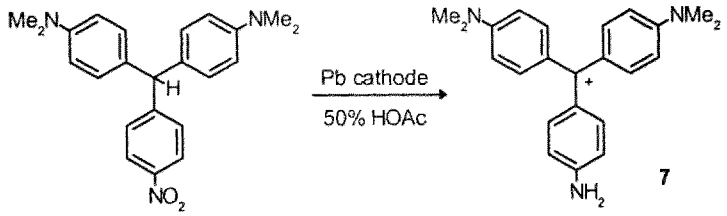


A benzyl carbocation is generated where the substrate has additional substitution stabilising the cationic centre. Thus 4-nitro-isopropylbenzene **6** affords both 4-



6

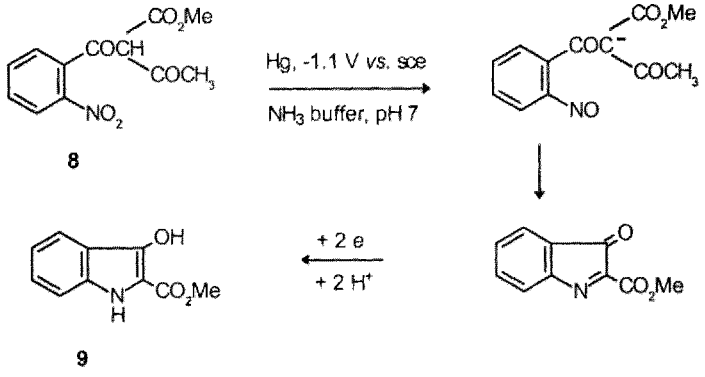
amino-isopropylbenzene and 4-amino-α-methyl-styrene on reduction in acid solution. Under acid conditions, the α-methylstyrene is isolated as a dimer [79]. In a related reaction, 4-nitrophenyl-diphenylmethanes are reduced to the phenylhydroxylamine and then converted to the cationic triphenylmethane dyestuff **7** [80].



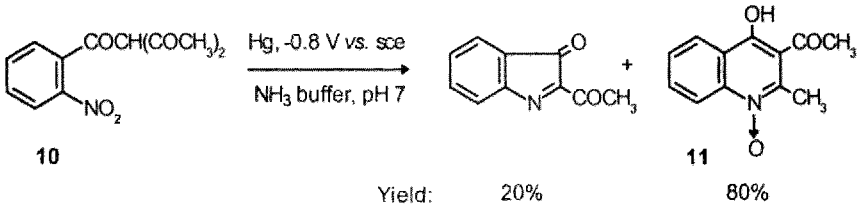
Formation of Heterocyclic Rings

The nitrosogroup reacts with nucleophiles while the hydroxylamino function reacts with electrophiles. After formation in an electrochemical step, these functions will react with suitable *ortho*-substituents to generate 5- or 6-membered rings.

Reaction between the nitroso group and the anion of a β-diketone is often sufficiently rapid to compete with further reduction of the nitroso compound to the hydroxylamine. This process is illustrated by reduction of **8**. The initial ring closure product undergoes further reduction at the cathode and **9** is isolated in good yield

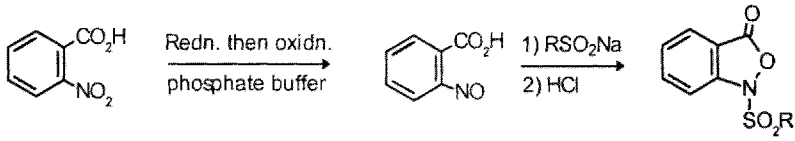


[81]. Not all capture processes are so rapid and for these examples like **10**, a second



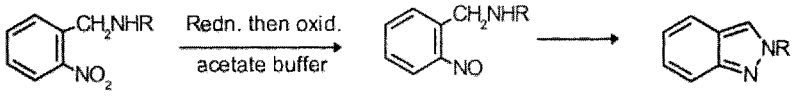
product is the quinoline derivative **11** formed by further reduction to the hydroxylamine which condenses with an adjacent carbonyl function [82].

Most reactions of nitroso intermediates are however too slow to compete with further reduction. In these cases it is necessary to carry out the tandem reduction to the hydroxylamine stage and then oxidation back to the nitroso compounds using the type of double-cell sketched in Fig. 11.2. The intermediate is then allowed to

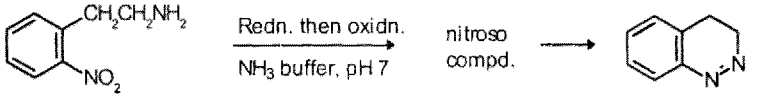


12

react to give the heterocyclic product. Sulphinate ion is used as an external nucleophile for the formation of **12** [83]. An amino group can function as intramolecular nucleophile in the formation of 5-ring [84, 85] and 6-ring [86] heterocycles.

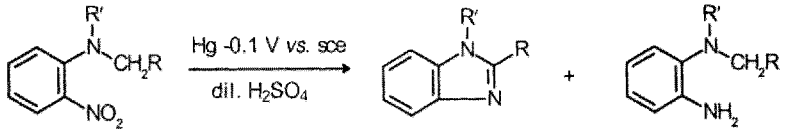


Ref. [84]



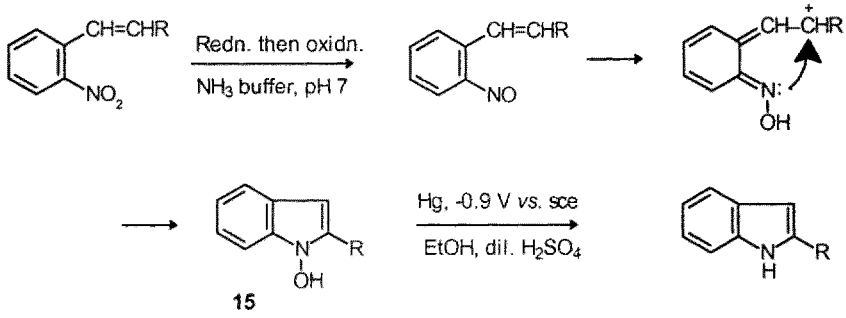
Ref. [85]

2-(Dialkylamino)phenylhydroxylamines undergo a ring closure reaction on standing in acid solution [87]. This process is involved in the conversion of **13** to **14**. The mechanism is thought to involve dismutation of the hydroxylamine into nitroso compound and amine. The nitroso compound is believed to undergo the ring closure and the amine can be isolated as a side product. The nitroso group will

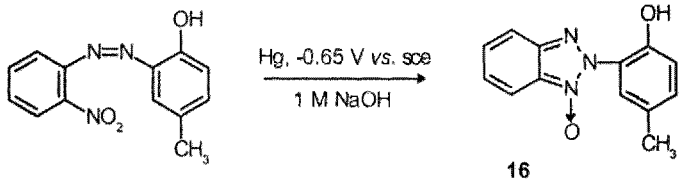


13 **14**

also react with an adjacent alkene bond to give an N-hydroxyindole **15** which can be reduced further to the indole [88].



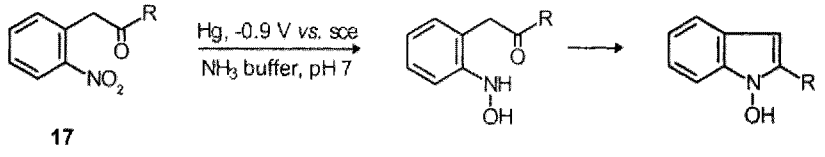
Reduction of 2-nitroazobenzenes in alkaline solution leads to the triazole-N-oxide **16** in excellent yields and this can be reduced further at –1.4 V *vs.* sce to the corresponding triazole [89, 90, 91]. Cyclization is due to reaction between a nitroso group and the azo function. For the reactive groups involved, the order of increas-



16

Ref. [90]

ingly negative reduction potential is nitroso, azo then nitro. The first electrochemical step in this process is formation of the 2-nitrohydrazobenzene. This undergoes a rapid intramolecular redox process to yield the 2-nitrosoazobenzene, formed close to the electrode and then reduced to the relatively stable 2-hydroxylaminoazobenzene. The latter drifts into the bulk of the solution where it undergoes an intermolecular redox reaction with the nitroazobenzene to generate the nitrosoazobenzene. In the bulk of the solution, the nitroso compound has a high

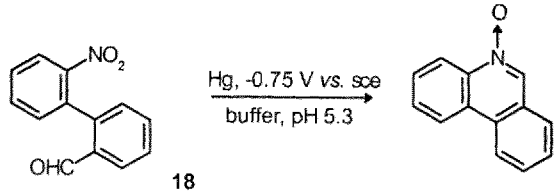


17

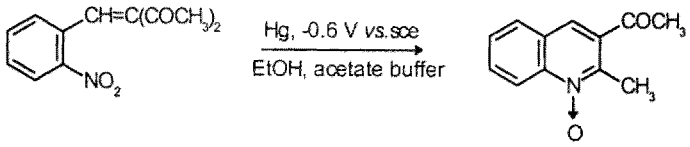
probability for cyclization before it drifts back towards the electrode and is reduced again to the hydroxylamino level.

The hydroxylamino group will react with an adjacent side chain carbonyl function. Thus, 2-nitrobenzyl ketones **17** are reduced to the N-hydroxyindole [92]. Side

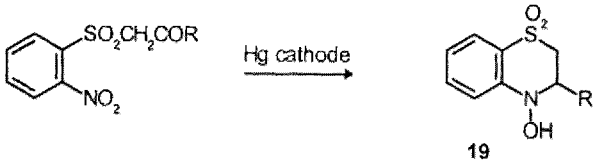
chains of a suitable length lead to formation of a 6-membered ring N-oxide. Examples include cyclization of biphenyl derivatives **18** [93], the formation of quinoline-N-oxides [94, 95] and the preparation of sulphur-nitrogen heterocycles **19** [96].



18

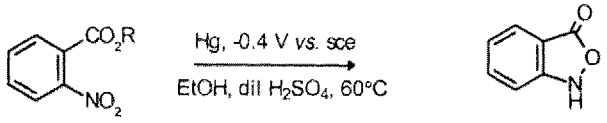


Ref. [93]

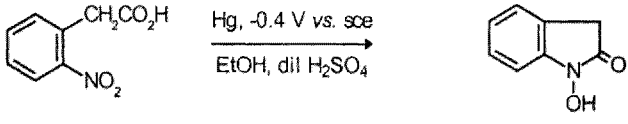


19

Reduction of 2-nitrobenzoic acid or the ester to the hydroxylamine stage in acid solution is accompanied by ring closure to form benzisooxazolone **20** [97]. When



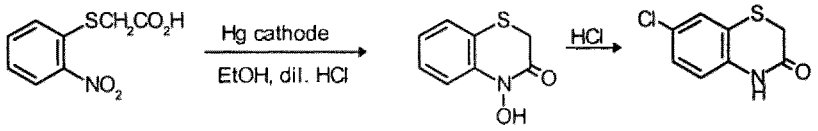
20



Ref. [97]

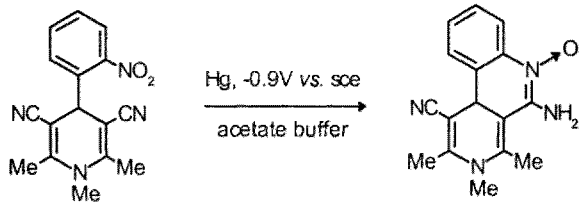
the carboxylic acid function is separated from the nitroaromatic ring by one or two atoms, the hydroxylamine undergoes ring closure to form a 5-membered [98] or 6-

membered ring [98, 99] hydroxamic acid. The hydroxamic acids undergo the Bamberger rearrangement, illustrated for **21**, on warming with hydrochloric acid [99].



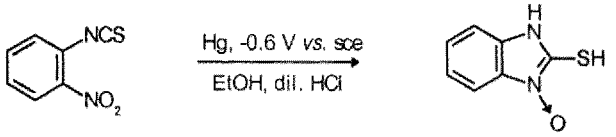
21

Hydroxylamine intermediates will react with an adjacent nitrile function [100, 101]. Interaction with the isothiocyanate group can be achieved in acid solution

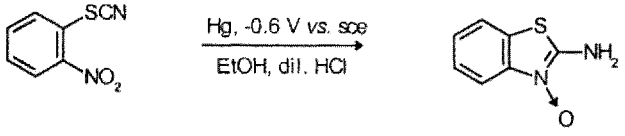


Ref. [100]

[94, 102]. In neutral or alkaline solution the isothiocyanate group is also reduced.



Ref. [93]



Ref. [94]

The hydroxylamine from reduction of 2-nitrophenylthiocyanate also undergoes a ring closure reaction [94].

Azoxybenzenes, Azobenzenes and Hydrazobenzenes

Nitrosobenzene and phenylhydroxylamine condense rapidly in alkaline solution to give azoxybenzene. During the reduction of nitrobenzenes at high pH, the phenylhydroxylamine scavenges nitroso compound so that the azoxybenzene becomes

the isolated product. Experimental conditions are either a copper cathode in refluxing ethanolic sodium acetate [103] or a nickel cathode in a suspension of the nitrocompound in aqueous sodium hydroxide [104]. Reactions are carried out under conditions of constant current, controlling the total charge passed to 3F according to the overall reaction:

$$2\,ArNO_2 + 6\,e + 6\,H^+ \longrightarrow ArN{=}NAr + 3\,H_2O$$
$$\downarrow$$
$$O$$

A wide range of *m*- and *p*-substituted nitrobenzenes give the azoxycompound in 80% yields or higher. Yields of *ca.* 45% are found for *o*-substituted starting materials.

Azoxybenzene is reducible under polarographic conditions. The final product is hydrazobenzene formed in an irreversible process for which the half-wave potential [105] varies with pH as illustrated in Fig. 11.3. The half-wave potential is close to that of the nitrobenzene. Azobenzene, which is an intermediate in the process, is

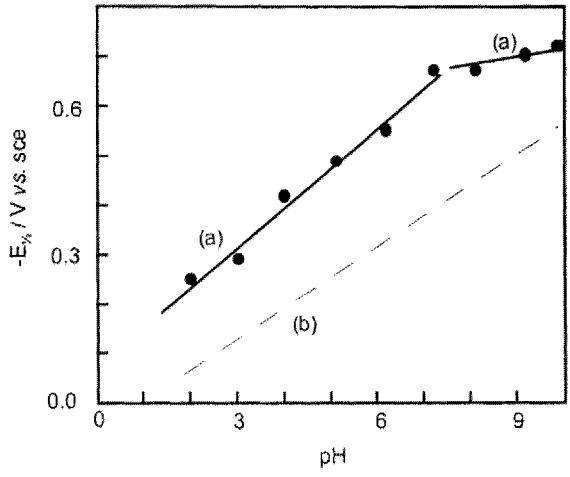


Figure 11.3. Variation of half-wave potential with pH for the polarography of (a) azoxybenzene, a 4-electron wave and (b) azobenzene, a 2-electron wave. Data from refs. [104,105].

reduced at less negative potentials than azoxybenzene itself. The redox system azobenzene - hydrazobenzene is reversible in aqueous solution and shows a polarographic half-wave potential (Fig. 11.3), which varies linearly with pH [106].

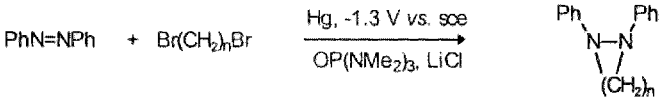
On a preparative scale, the product formed during electrochemical reduction of nitrobenzenes in alkaline solution can be readily controlled by adjusting the total numer of Faraday passed under constant current conditions. The formation of az-

oxybenzenes has already been discussed. Azobenzenes are obtained in a 4F process according to the overall reaction:

$$2\ ArNO_2 + 8\ e + 8\ H^+ \longrightarrow ArN{=}NAr + 4\ H_2O$$

They can be isolated in good yields by reduction of the nitrobenzene in aqueous ethanolic sodium acetate under reflux, passing around 10% excess electric charge [103]. Any hydrazobenzene formed is rapidly oxidised back to the azobenzene by air during work-up. Azoxybenzene is formed first and then reduced to azobenzene and finally hydrazobenzene at the cathode. A solution electron transfer reaction between azoxybenzene and the hydrazobenzene reforms azobenzene.

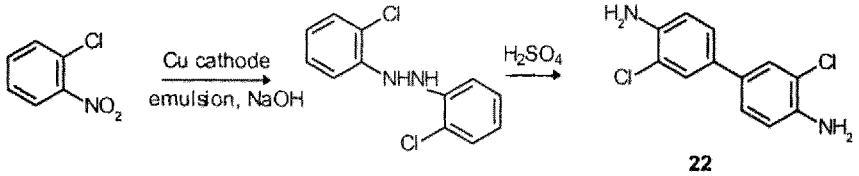
Reduction of azobenzenes in an aprotic solvent generates nucleophilic nitrogen species, which can react with an added alkyl halide. In this way, cyclic hydrazo compounds can be generated from α,ω-dibromoalkanes [107].



Complete reduction of nitrobenzenes to the hydrazobenzene is achieved in alkaline solution at a copper cathode by passage of 5F according to the overall reaction:

$$2\ ArNO_2 + 10\ e + 10\ H^+ \longrightarrow ArNHNHAr + 4\ H_2O$$

Addition of the crude reduction mixture to excess sulphuric acid causes rearrangement of the hydrazobenzene to a benzidine **22** [108, 109]. The nitrogen-nitrogen

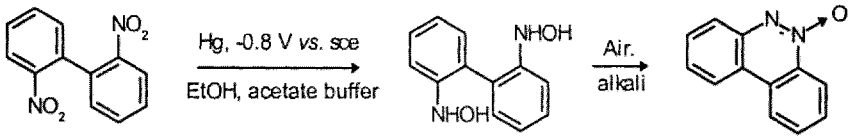


22

bond in hydrazobenzene is not cleaved by direct electrochemical reduction. This bond cleavage can be achieved by reduction with tin(II) or titanium(III) [110] followed by electrochemical regeneration of the reducing agent. Reaction must involve formation of a complex between hydrazobenzene and the metal ion followed by an inner-sphere electron-transfer process.

2,2′-Dinitrobiphenyl **23** can be reduced in faintly acid solution to the bishydroxylamine. In alkaline solution this product undergoes oxidation by air to the mononitroso level. The resulting nitroso-hydroxylamine then undergoes rapid cy-

clization to form a cyclic azoxy compound [111, 112]. 1,8-Dinitronaphthalene un-

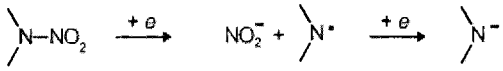


23

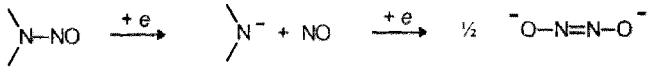
dergoes a similar reaction to form a 5-membered cyclic azoxy compound [113].

Nitramines and Nitrosamines

Secondary nitramines and nitrosamines both show a two-electron wave on polarography in aprotic solvents. Addition of the first electron is synchronous with cleavage of the nitrogen-nitrogen bond in both classes of compounds. Nitramines [114] afford nitrite ion and a nitrogen radical which accepts the second electron:



Nitrosamines [115] probably afford the amide ion and nitrogen oxide. The latter accepts the second electron and is converted to hyponitrite ion:



In the presence of acetic acid, the radical-anion of a nitrosamine is protonated before bond cleavage can occur and further reactions give the dialkylhydrazine:

In acidic aqueous buffers, secondary nitramines [116] show a six-electron polarographic wave which is converted into two two-electron waves above pH 5 (Fig. 11.4). Nitrosamines [117, 118] show a four-electron wave in acid solution and this becomes a single two-electron wave above pH 5 (Fig. 11.5). Above pH 5 the half-wave potentials are independent of pH. Primary nitramines are relatively acidic. They show a six-electron wave in acidic aqueous buffers, the height of which falls to zero around the pK_a value for the nitramine because the anion is not reducible [119].

These patterns of polarographic waves arise because nitramines are reduced to the nitrosamine at all pH values in a two-electron process. Below pH 5, the

nitrosamine is reduced in a four-electron process to the dialkylhydrazine. Primary nitramines give the monoalkylhydrazine in a process involving an intermediate

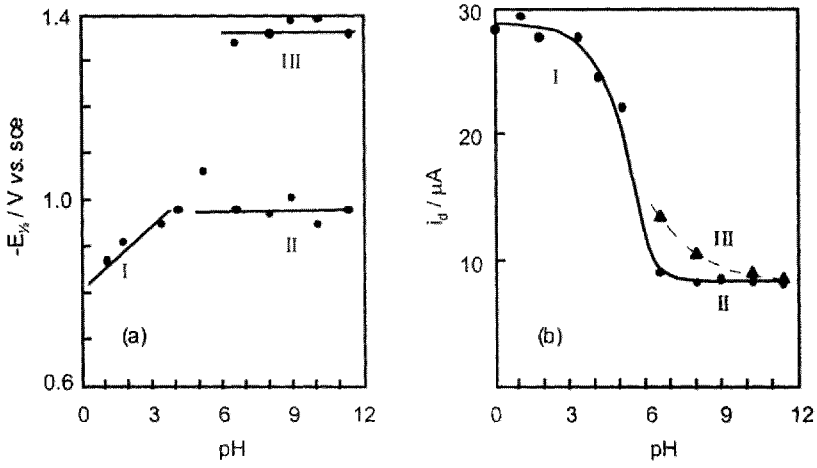


Figure 11.4. Changes with pH of (a) the half-wave potential ($E_{½}$) and (b) diffusion plateau height (i_d) for the polarographic waves of N-nitropiperidine. Data from ref. [115].

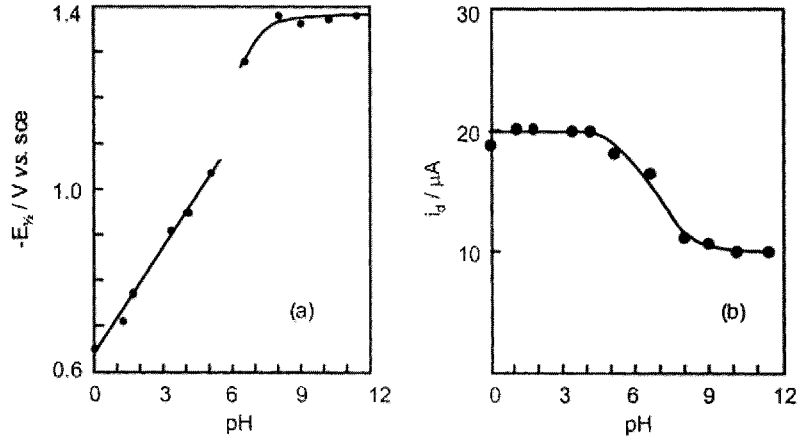


Figure 11.5. Changes with pH of (a) the half-wave potential ($E_{½}$) and (b) diffusion plateau height (i_d) for the polarographic waves of N-nitrosopiperidine. Data from ref.[115].

primary nitrosamine. Such intermediates must be reduced very rapidly because they are unstable due to tautomerism to the diazonium hydroxide followed by loss of dinitrogen. Above pH 5, addition of the first electron to the nitrosamine is ac-

companied by nitrogen-nitrogen bond cleavage to give the secondary amine and nitric oxide. Nitric oxide is then reduced to hyponitrite ion, which decomposes to nitrous oxide.

$$HO{-}N{=}N{-}O^{-} + H^{+} \longrightarrow N_2O + H_2O$$

The secondary amine and nitrous oxide are the only isolated products from reduction of nitrosamines in alkaline solution [117].

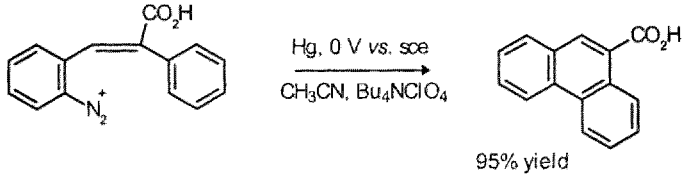
Preparative scale reduction of nitramines and nitrosamines in acid solution is a convenient route to substituted hydrazines. Early workers used a cathode of tinned copper [120]. More recently mercury has been employed as cathode material, although tin would probably be equally suitable. Nitrosamines are conveniently reduced in dilute hydrochloric acid and evaporation of the electrolyte at the end of the reaction affords the hydrazine hydrochloride [121]. Some nitroso compounds are unstable to these acidic conditions. In the case of N-nitrosoindoles, this problem has been overcome in an ingenious manner [122]. The nitroso compound and aqueous sulphuric acid are mixed just prior to reaction and then forced through a porous cathode of bronze coated with mercury at such a rate that the reduction is completed in one pass through the cathode. Other workers have overcome the instability of N-benzyl-N-nitrosoanthranilic acid towards acid by working in an acetate buffer at below room temperature [123].

Nitroguanidine is reduced to aminoguanidine **24** in good yields using aqueous sulphuric acid as electrolyte when the product precipitates as the hydrogen sulphate [124, 125]. Nitrourea affords semicarbazide on reduction in acid solution [126]

Benzenediazonium Salts

Benzenediazonium salts show a single one-electron polarographic wave in aprotic solvents [127]. Benzenediazonium fluoroborate in sulpholane shows a half-wave potential of +0.295 V *vs.* sce. In aqueous acid solution these compounds show two polarographic waves. A one-electron wave is found around 0 V *vs.* sce and this is complicated by reduction of pre-adsorbed material at the mercury surface. A second reduction process is found around -0.9 V *vs.* sce and consisting of two overlapping waves which together are due to a three-electron process [128, 129]. Reduction of diazonium salts at the potential of the first polarographic wave in either aqueous or aprotic solvents yields phenyl radicals. These are trapped by the mercury electrode during small scale reduction in aqueous solution to yield phenylmercuric chloride. Phenylhydrazine is formed at the plateau of the second wave in aqueous solution [130]. Phenyl radicals formed by reduction of benzenediazonium salts in aprotic solvents have been trapped by benzal-*tert*butylnitrone to give the stable nitroxide radical, which is detected by esr spectroscopy [131].

Reduction of phenyldiazonium chloride in acetonitrile containing a high concentration of an aromatic substrate, which can act as a free-radical trap, leads to phenylation of the substrate in 14 - 33% yields together with 50 – 50% of benzene formed by phenyl radical attack on the acetonitrile [132]. Intramolecular capture of the phenyl radical, in an electrochemical equivalent of the Pschorr reaction, is much more successful and phenanthrene derivatives can be prepared in 90 – 96% yield [133].



95% yield

Ref. [132]

Reduction of diazonium salts in aqueous solution under constant current conditions can give up to 30% yield of the phenylhydrazine [134] by interception of the phenyldiazo radical before this loses nitrogen. Reduction of alkali metal diazotates and isodiazotates gives the phenylhydrazine in up to 80 –90% yields [135]. However the starting materials are not very accessible so this method is of little value.

References

[1] V. N. Leibzon, A. S. Mendkovich, S. G. Mairanovski et al., *Dokl. Akad. Nauk S.S.S.R.*, 1976, **229**, 1378.
[2] B. Kastening, *Elektrochim. Acta*, 1964, **9**, 241.
[3] L. Holleck and D. Jannahoudakis, *Z. Naturforsch. B*, 1961, **16**, 396.
[4] L. H. Piette, P. Ludwig and R. N. Adams, *J. Am. Chem. Soc.*, 1962, **84**, 4212.
[5] J. K. Dohrmann, F. Gallusset and H. Wittchen, *Faraday Discussions Chem. Soc.*, 1973, **56**, 330.
[6] A. H. Maki and D. H. Geske, *J. Am. Chem. Soc.*, 1961, **83**, 1852.
[7] B. Kasterning, S. Vavricka, *Ber. Bunsenges. Phys. Chem.*, 1968, **72**, 27.
[8] W. Kemula and R. Sioda, *Nature (London)*, 1963, **197**, 588.
[9] K. D. Asmus, A. Wigger and A. Henglein, *Ber. Bunsenges. Phys. Chem.*, 1966, **70**, 862.
[10] J. W. Smith and J. G. Walker, *Trans. Faraday Soc.*, 1950, **46**, 290.
[11] P. B. Ayscough, E. R. Sargent and R. Wilson, *J. Chem. Soc. B*, 1966, 903.
[12] K. D. Asmus, G. Beck, A. Henglein and A. Wigger, *Ber. Bunsenges. Phys. Chem.*, 1966, **70**, 869.
[13] P. Iversen and H. Lund, *Tetrahedron Letters*, 1967, 4027.
[14] P. Iversen and H. Lund, *Acta Chem. Scand.*, 1965, **19**, 2303.

[15] V. Bruckner, *Liebigs Ann. Chem.*, 1935, **518**, 226.
[16] M. W. Leeds and G. B. L. Smith, *J. Electrochem. Soc.*, 1951, **98**, 129.
[17] L. Christensen and P. E. Iversen, *Acta Chem. Scand. B*, 1979, **33**, 352.
[18] P. Pierron, *Bull Soc. chim. France [3]*, 1899, **21**, 780.
[19] F. Mirallesroch, A. Tallec and R. Tardivel, *Electrochim. Acta*, 1993, **38**, 2379.
[20] M. Cariou, R. Hazard, M. Jubault and A. Tallec, *Canad. J. Chem.*, 1983, **61**, 2359.
[21] V. Bruckner, J. Kovács and K. Kovács, *Ber.*, 1944, **77**, 610.
[22] G. Fodor, *Ber.*, 1943, **76**, 1216.
[23] G. Fodor, J. Kiss and M. Szekerka, *J. Org. Chem.*, 1950, **15**, 227.
[24] W. N. Nagai and S. Kano, *Liebigs Ann. Chem.*, 1929, **470**, 157.
[25] P. E. Iversen and T. D. Christensen, *Acta Chem. Scand. B*, 1977, **31**, 733.
[26] M. Masui, H. Sayo and K. Kishi, *Tetrahedron*, 1965, **21**, 2831.
[27] P. Kabasakalian and S. Kalliney, *US* 3998708 (1976); *Chem. Abs.*, 1977, **87**, 3114.
[28] T. Shono, H. Hamaguchi, H. Mikami, H. Nogusa and S. Kashimura, *J. Org. Chem.*, 1983, **48**, 2103.
[29] S. Torii, H. Tanaka and T. Katoh, *Chem. Letters*, 1983, 607.
[30] M. Wessling and H.-J. Schäfer, *Chem. Ber.*, 1991, **124**, 2303.
[31] V.T. Novikov, I. A. Avrutskaya, M. and Ya. Fioshin, *Elektrokhim.*, 1976, **12**, 1486.
[32] I. A. Avarutskaya, K. K. Babievskii, V. M. Belikov, E. V. Zaporozhets, V. T. Novikov and M. Ya. Fioshin, *Elektrokhim.*, 1975, **11**, 661.
[33] A. Sera, H. Tani, I. Nishiguchi and T. Hirashima, *Synthesis*, 1987, 631.
[34] J. Pearson, *Trans. Faraday Soc.*, 1948, **44**, 683.
[35] Ch. Subrahmanyam and V. R. Krishnan, *Indian J. Chem. A*, 1981, **20**, 462.
[36] F. Harber and C. Schmidt, *Z. phys. Chem.*, 1900, **32**, 271.
[37] M. Suzuki, *J. Electrochem. Soc. Japan*, 1954, **22**, 63.
[38] J. Marquez and D. Pletcher, *Electrochim. Acta*, 1981, **26**, 1751.
[39] S. Torii, H. Okumoto, T. Minoshima and S. Kurozumi, *Synlett.*, 1994, 68.
[40] Y. M. Kargin, B. V. Melnikov, Y. A. Lisitsyn and G. A. Kamalova, *Z. Obshch. Khim.*, 1988, **58**, 2320.
[41] H. V. Udupa, G. S. Subramanian, P. N. Anantharaman, *Indian* 128412 (1974); *Chem. Abs.*, 1975, **82**, 23759.
[42] H. V. K. Udupa, and P. N. Anantharaman, *Indian*, 143584 (1977); *Chem. Abs.*, 1980, **92**, 110652.
[43] D. Floner, L. Laglaine and C. Moinet, *Electrochim. Acta*, 1997, **42**, 525.
[44] D. Pletcher, M. Razaq and G. D. Smilgin, *J. Appl. Electrochem.*, 1981, **11**, 601.
[45] K. Elbs, *Z. Elektrochem.*, 1898, **5**, 108.
[46] W. Löb and R. W. Moore, *Z. phys. Chem.*, 1904, **47**, 418.
[47] A. Martel, A. K. Cheong and J. Lessard, *Can. J. Chem.*, 1994, **72**, 2353.
[48] J. Lesard and G. Belot, *US* 4584069 (1986); *Chem. Abs.*, 1986, **105**, 14281.
[49] A. Cyr, P. Huot, G. Belot and J. Lessard, *Can. J. Chem.*, 1990, **35**, 147.
[50] K. Elbs, *Z. Elektrochem.*, 1900, **7**, 145.
[51] K. Elbs, *J. prakt. Chem.* [2], 1891, **43**, 40.
[52] K. Auwers and E. Eisenlohr, *Liebigs Ann. Chem.*, 1909, **369**, 209.
[53] K. J. Stutts, C. L. Scortichini, T. D. Gregory, S. J. Babinec, C. M. Repucci and R. F. Phillips, *J. Appl. Electrochem.*, 1989, **19**, 349.
[54] A. Rohde, *Z. Elektrochem.*, 1900, **7**, 348.
[55] J. F. Norris and E. O. Cummings, *Ind. Eng. Chem.*, 1925, **17**, 305.

[56] A. Rohde, *Z. Elektrochem.*, 1900, **7**, 338.
[57] K. Brand, *Ber.*, 1905, **38**, 3077.
[58] M. Le Guyader, *Bull. Soc. chim. France*, 1966, 1848.
[59] E. Bamberger, *Ber.*, 1894, **27**, 1548.
[60] K. Brand and H. Zölner, *Ber.*, 1907, **40**, 3330.
[61] K. Brand and Th. Eisenmenger, *J. prakt. Chem. [2]*, 1913, **87**, 501.
[62] K. Messinger, *D.R.P.*, 109051 (1898).
[63] C. Lamoureux and C. Moinet, *Bull. Soc. chim. France*, 1988, 59.
[64] C. Gault,and C,. Moinet, *Tetrahedron*, 1989, **45**, 3429.
[65] B. A. Frontana-Uribe and C. Moinet, *Tetrahedron*, 1998, **54**, 3197.
[66] C. Karokus and P. Zuman, *J. Electrochem. Soc.*, 1995, **142**, 4018.
[67] J. C. Gard, J. Lessard and Y. Mugnier, *Electrochim. Acta*, 1993, **38**, 677.
[68] L. Gattermann, *Ber.*, 1893, **26**, 1844.
[69] A. A. Noyes and A. A. Clement, *Ber.*, 1893, **26**, 990.
[70] F. M. Brigham and H. S. Luckens, *Trans. Electrochem. Soc.*, 1932, **61**, 281.
[71] L. J. J. Janssen and E. Barendrecht, *Electrochim. Acta*, 1981, **26**, 699.
[72] L. Gattermann, *Ber.*, 1894, **27**, 1927.
[73] L. Gattermann, *Ber.*, 1896, **29**, 3035.
[74] L. F. Fieser and E. L. Martin, *J. Am. Chem. Soc.*, 1938, **57**, 1840.
[75] L. F. Fieser and E. L. Martin, *J. Am. Chem. Soc.*, 1935, **57**, 1835.
[76] H. V. Udupa, S. G. Subramanian and P. Subbial, *Indian* 97002 (1967); *Chem. Abs.*, 1974, **81**, 25351.
[77] A. Noyes and J. J. Dorrance, *Ber.*, 1895, **28**, 2351.
[78] A. A. Noyes and A. A. Clement, *Am. Chem. J.*, 1894, **16**, 511.
[79] A.Petsom and H. Lund, *Acta Chem. Scand.*, 1980, **34**, 693.
[80] Gesellschaft für chemische Industrie, *D.R.P.*, 84607 (1895).
[81] R. Hazard, M. Jubault, C. Mouats and A. Tallec, *Electrochim. Acta*, 1988, **33**, 1335.
[82] R. Hazard, M. Jubault, C. Mouats and A. Tallec, *Electrochim. Acta*, 1986, **31**, 489.
[83] C. Gault and C. Moinet, *Tetrahedron*, 1989, **45**, 3429.
[84] R. Hazard and A. Tallec, *Bull. Soc. chim. France*, 1975, 679.
[85] B. A. Frontana-Uribe and C. Moinet, *Tetrahedron*, 1998, **54**, 3197.
[86] R. Hazard and A. Tallec, *Bull. Soc. chim. France*, 1976, 433.
[87] M. Le Guyader and D. Peltier, *Bull. Soc. chim. France*, 1966, 2695.
[88] R. Hazard and A. Tallec, *Bull. Soc. chim. France*, 1971, 2917.
[89] H. Lund and S. Kwee, *Acta Chem. Scand.*, 1968, **22**, 2879.
[90] R. Hazard and A. Tallec, *Bull. Soc. chim. France*, 1971, 2917.
[91] R. Bourgeois, A. Delay, R. Hazard and A. Tallec, *El;ectrochim. Acta*, 1977, **22**, 857.
[92] R. Hazard and A. Tallec, *Bull. Soc. chim. France*, 1973, 3040.
[93] Y. Mugnier and E. Laviron, *Bull. Soc. chim. France II*, 1978, 39.
[94] H. Lund and L. G. Feoktistov, *Acta Chem. Scand.*, 1969, **23**, 3482.
[95] R. Hazard, M. Jubault, C. Mouats and A. Tallec, *Electrochim. Acta*, 1986, **31**, 489.
[96] C. P. Maschmeier, H. Tannenberg and H. Matschiner, *Z. Chem.*, 1981, **21**, 219.
[97] M. Le Guyader, *Bull. Soc. chim. France*, 1966, 1867.
[98] A. Tallec, G. Mennereau and G. Robic, *Compt. rend. C*, 1971, **273**, 1378.
[99] H. Matschiner, H. Tannenberg and C. P. Maschmeier, *J. prakt. Chem.*, 1981, **323**, 924.
[100] A. Chibani, R. Hazard, M. Jubault and A. Tallec, *Bull. Soc. chim. France*, 1987, 795.

[101] J. P. Hurvois, A. Tallec and L. Tropel, *Bull. Soc. chim. France*, 1992, **129**, 406.
[102] J. Hlavaty, J. Volke and O. Manousek, *J. Electrochem. Soc.*, 1975, **61**, 219.
[103] K. Elbs, *Z. Elektrochem.*, 1900, **7**, 137.
[104] W. Löb, *Z. Elektrochem.*, 1900, **7**, 520.
[105] S. Wawzonek and J. D. Fredrickson, *J. Am. Chem. Soc.*, 1955, **77**, 3988.
[106] C. R. Castor and J. H. Saylor, *J. Am. Chem. Soc.*, 1953, **75**, 1427.
[107] T. Troll and W. Elbe, *Electrochim. Acta*, 1977, **22**, 615.
[108] K. Elbs and O. Kopp, *Z. Elektrochem.*, 1898, **5**, 108.
[109] K. S. Udupa, G. S. Subramanian and U. V. K. Udupa, *Bull. Acad. Polon. Sci. Ser. Sci. Chim.*, 1961, **9**, 541.
[110] J. F. Norris and F. O. Cumming, *Ind. Eng. Chem.*, 1925, **17**, 305.
[111] J. Becher and P. E. Iversen, *Acta Chem. Scand. B*, 1974, **28**, 539.
[112] Y. Mungier and E. Laviron, *Bull. Soc. chim. France*, 1976, 1496.
[113] D. Bernard, Y. Mugnier, G. Tainturier and E. Laviron, *Bull. Soc. chim. France*, 1975, 2364.
[114] Yu. N. Kargin, V. Z. Kondranina *et al.*, *J. Gen. Chem. USSR.*, 1977, **47**, 606.
[115] Yu. N. Kargin, V. Z. Latypora, A. N. Supyrev and N. L. Kucherova, *J. Gen. Chem. USSR.*, 1982, **52**, 292.
[116] E. Laviron and P. Fournari, *Bull. Soc. chim. France*, 1966, 518.
[117] H. Lund, *Acta Chem. Scand.*, 1957, **11**, 990.
[118] L. Holleck and R. Schlindler, *Z. Elektrochem.*, 1958, **62**, 942.
[119] E. Laviron, P. Fournai and J. Greusard, *Bull. Soc. chim. France*, 1967, 1255.
[120] H. J. Backer, *Rec. Trav. Chim.*, 1912, **31**, 142.
[121] P. E. Iversen, *Acta Chem. Scand.*, 1971, **25**, 2337.
[122] G. Jacob, C. Moinet and A. Tallec, *Electrochim. Acta*, 1983, **28**, 635.
[123] G. Marrosu, R. Petrucci and A. Trazza, *Electrochim. Acta*, 1995, **40**, 923.
[124] C. F. Boehringer and Söhne, *D. R. P.*, 167637 (1904).
[125] A. W. Ingersoll, L. J. Bircher and M. M. Brubaker, *Org. Synth., Coll. Vol. 1*, 19XX, p.472.
[126] H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, 1912, **31**, 1.
[127] R. M. Elofson and F. F. Gadallah, *J. Org. Chem.*, 1969, **34**, 854.
[128] E. R. Atkinson, H. H. Warren, P. I. Abell and R. E. Wing, *J. Am. Chem. Soc.*, 1950, **72**, 915.
[129] O. Orange, C. Elfakir-Hamet and C. Caullet, *J. Electrochem. Soc.*, 1981, **128**, 1889.
[130] R. M. Elofson, *Can. J. Chem.*, 1958, **36**, 1207.
[131] A. J. Bard, J. C. Gilbert and R. D. Goodin, *J. Am. Chem. Soc.*, 1974, **96**, 620.
[132] F. F. Gadallah and R. M. Elofson, *J. Org. Chem.*, 1969, **34**, 3335.
[133] R. M. Elofson and F. F. Gadallah, *J. Org. Chem.*, 1971, **36**, 1769.
[134] R. E. McClure and A. Lowy, *Trans. Am. Electrochem. Soc.*, 1934, **17**, 1416.
[135] F. Fichter and E. Willi, *Helv. Chim. Acta*, 1943, **17**, 1416.

INDEX