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Organic Reactions Via Electrochemically Generated Intermediates

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Organic reactions via electrochemically generated intermediates

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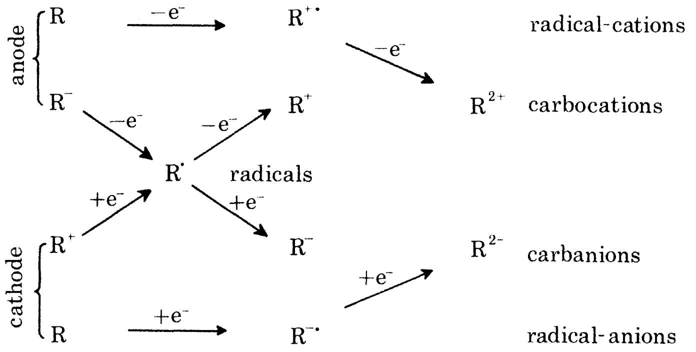
The scope of electrosynthesis is reviewed. Examples are chosen that highlight particular advantages over conventional chemical methods, i.e. the possibility of high-potential oxidation and reduction under chemically mild conditions and selectivity in functional group transformations. The most important mechanistic pathways are also exemplified.

It is my intention in this paper to demonstrate the scope of cathodic and anodic methods for organic electrosynthesis. Particular emphasis will be given to likely advantages over conventional methods and classification according to mechanistic type. The examples are chosen to illustrate: (*a*) selective transformations in organic molecules, (*b*) functionalization, (*c*) coupling reactions (e.g. hydrodimerization), (*c*) cleavage (e.g. deprotection), (*e*) hydrogenation and (*f*) the generation *in situ* of redox reagents.

Perhaps because of the outstanding success of the Monsanto adiponitrile process, attention has in recent years been focused on the possibilities for large-tonnage processes, and, in the U.K. at least, possibilities for the application of electrosynthetic methods to the production of intermediates for the pharmaceuticals and fine chemicals industry have been neglected. For such applications the organic chemistry involved is necessarily more specialized and subtle than for work with smaller molecules; some of the examples used in this paper will develop this point and the whole constitutes a plea for the involvement of more organic chemists in this field. Gone are the days, if ever they existed, when a good physical chemist could 'swot up' organic chemistry in a fortnight.

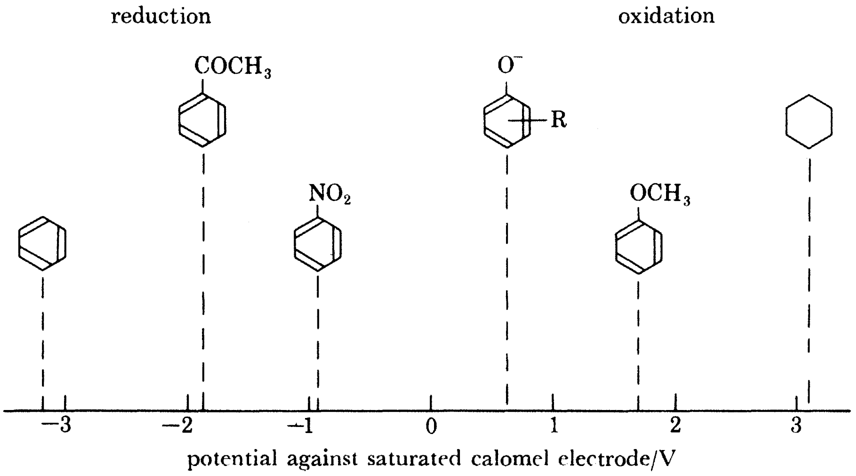
The species formed at electrodes are radicals, carbenium ions, carbanions, radical-ions, dications and dianions (scheme 1). Their chemical behaviour is remarkably similar to that of the same species formed homogeneously, although patterns of reactivity may sometimes be affected significantly by ill-defined surface effects, mass transport phenomena and the high local concentrations of species formed near to the electrodes. Conventional physical–organic wisdom, however, holds well in this area and, indeed, is also useful in the qualitative prediction of the relative ease of oxidation and reduction of organic substrates (scheme 2). Scheme 2 also serves to illustrate the great power of the electrochemical method; in suitable aprotic solvents an electroactive range of 6 V is achievable and, for a one-electron transfer, this effectively allows modification of the energy of activation for electron transfer by *ca.* 290 kJ mol^{-1} (i.e. $z\beta EF$ in equation (1) with $z = 1$ and $\beta = 0.5$). This power enables the production of solvated electrons at the cathodic limit and the oxidative cleavage of carbon–carbon and carbon–hydrogen bonds at the anodic limit.

The precise application of redox power through controlled potential electrolysis has been a persistent motive for research; selectivity may be achieved in this way, although the redox potentials of the relevant functions should differ by several hundreds of millivolts. Another, more obvious, requirement is that the products are not more easily oxidized or reduced than the starting material. The example given in scheme 3 is a case where electroreduction succeeds simply and well (Iversen *et al.* 1973), whereas conventional chemical methods are problematical.

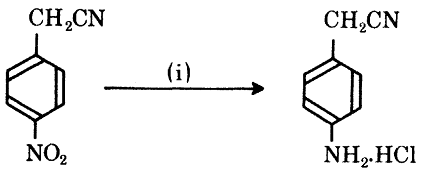


Scheme 1. Organic reactive intermediates produced at electrodes.

$$k = \not{k}(T/h)\exp\{-(\Delta G^{\ddagger}-\beta zEF)/RT\} \qquad (1)$$



Scheme 2.



Scheme 3. Selective electroreduction: (i) $+6e^-$, $7H^+$; -0.9 V against s.c.e.; 4 M HCl–EtOH (1:1). Yield: 95%.

For industrial-scale work, amperostatic rather than potentiostatic operation is desirable; in fact, control of concentration, mass transport or flow conditions may be deployed to allow electrolysis at constant current with, for most of the reaction, effectively constant potential. This corresponds to the situation in figure 1, from which it can be seen that the potential holds at E_1, with accompanying selectivity, as long as the supply of substrate is sufficient to keep the current above the preset value. For some reactions the redox potentials of functional groups, or species in solution, do not determine the selectivity in electrolysis. A good example of this is Kolbe oxidation in aqueous solution (Utley 1974) carboxylates are discharged at *ca.* 2.3 V (compared with the normal hydrogen electrode) whereas hydroxide ion is discharged at *ca.* 1.9 V. Consequently the Kolbe reaction should not be possible in aqueous solution. Various surface effects, however, allow carboxylate discharge to dominate at high overpotentials (figure 2 shows this in the form of a Tafel plot for acetate oxidation (Dickinson & Wynne-Jones 1962)).

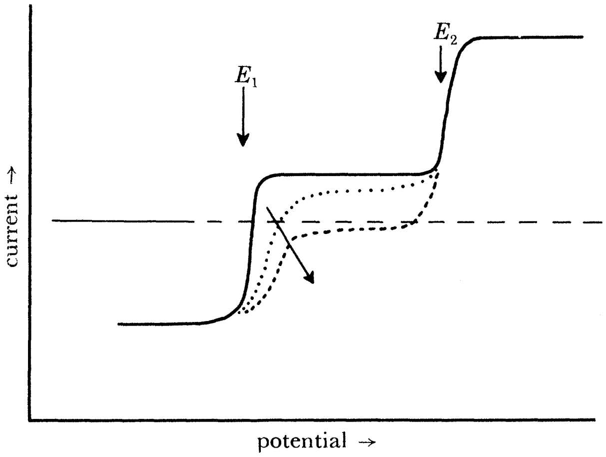


FIGURE 1. Electrolysis at constant current: when the substrate concentration falls, the potential increases to E_2 with a loss of selectivity

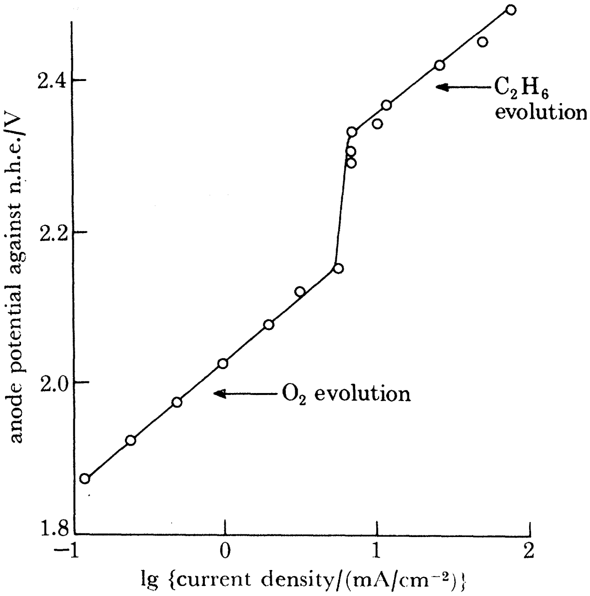


FIGURE 2. Kolbe oxidation of acetate in aqueous solution.

Anodic methods of functionalization have been much studied; the ones cited here (schemes 4–6) may all be performed at constant current. In the first (scheme 4), methyl oleate is converted (Adams *et al.* 1979*a*, *b*) by oxidation of the double bond and subsequent deprotonation into allylic carbenium ions, which are trapped by the relatively nucleophilic solvent (acetic acid). The isomeric monoacetates thus formed are more easily oxidized than the starting material but, once again, the conditions at the electrode are such that only when the methyl oleate concentration is substantially depleted does further oxidation to diacetate take place (figure 3). It should be noted that this method is more selective than alternative chemical methods, e.g. using a palladium(II) catalyst.

The anodic α-alkoxylation of amides provides an entry into a class of previously inaccessible intermediates. In this case a nucleophilic solvent is employed (an alcohol) and the method adapts well to scaling-up (Malmberg & Nyberg 1979). The example given here (scheme 5) also includes an indication of the usefulness of the intermediate in Friedel–Crafts type reactions.

The proton is not always the leaving group in anodic substitution. There are several examples of anodic cyanation in which an alkoxyl group is substituted. An example, particularly interesting because the product is an important liquid crystal (Eberson & Elgee 1977), is featured in scheme 6. The reaction was run at constant current and used as electrolyte an emulsion of water and methylene chloride, which enabled sodium cyanide to be used in conjunction with

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functionalization *anodic substitution*

$$\mathrm{MX}^{+\cdot} \xrightarrow[\text{(e.g. H}^+\text{)}]{-\mathrm{X}^+} \mathrm{M}^{\cdot} \xrightarrow{\quad -\mathrm{e}^- \quad} \mathrm{M}^+ \xrightarrow{\mathrm{Nu}^-} \mathrm{MNu}$$

E.g. Methyl oleate oxidation (grossly simplified);
alternative to Pd$^{\mathrm{II}}$ catalyst:

$$\begin{tikzcd}
\mathrm{CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2Me} \arrow[d, "-\mathrm{e}^-,\ -\mathrm{H}^+,\ -\mathrm{e}^-"] \\
\mathrm{CH_3(CH_2)_6CHCH{=}CH(CH_2)_7CO_2Me}\ \text{(and isomers)} \arrow[d, "\mathrm{AcO}^-"] \\
\text{isomeric monoacetates} \arrow[d, "-2\mathrm{e}^-,\ -\mathrm{H}^+,\ \mathrm{AcO}^-"] \\
\text{isomeric diacetates}
\end{tikzcd}$$

SCHEME 4

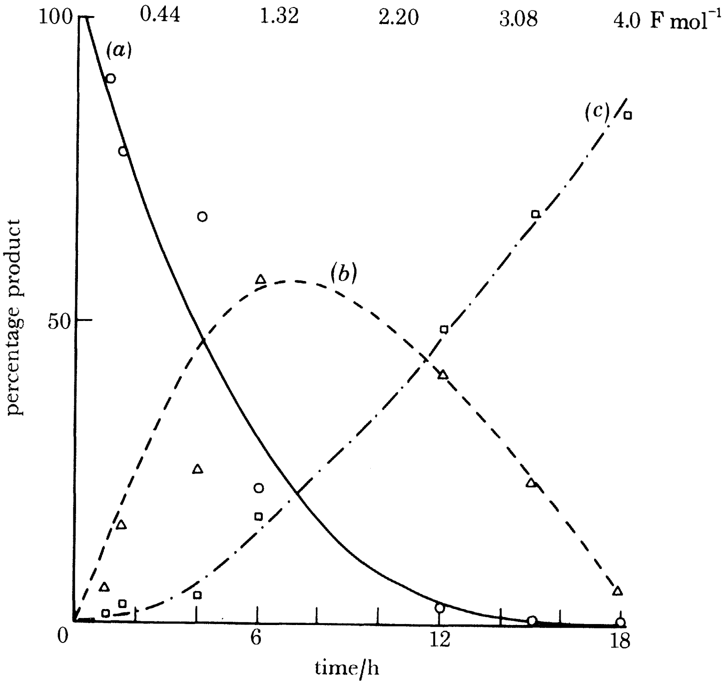
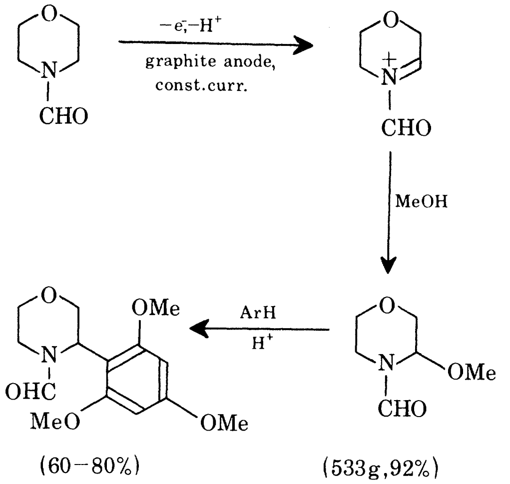
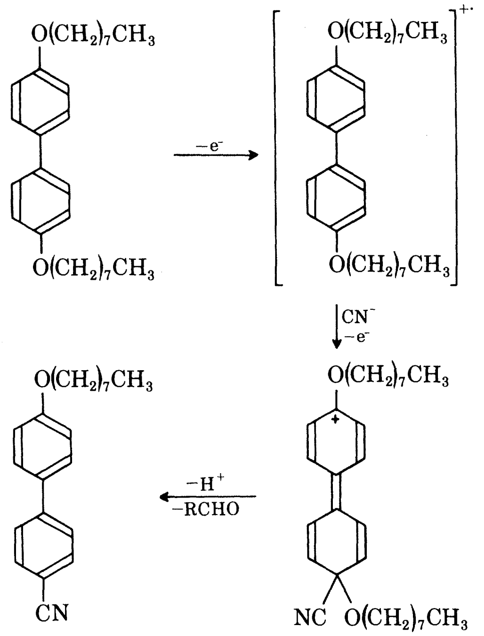


FIGURE 3. Anodic acetoxylation of methyl oleate: (*a*) oleate; (*b*) monoacetoxyoleate; (*c*) diacetoxyoleat *z*-Me$(\mathrm{CH_2})_7$ CH═CH$(\mathrm{CH_2})_7$COOMe; Pt anode; HOAc–LiClO$_4$ (0.1 M); 0.008 A cm^{-2}.

a phase-transfer agent. Reaction in the organic solvent alone would, because of low conductivity, have required larger quantities of supporting electrolyte and higher applied voltages in addition to the inconvenience of using a tetraalkyl cyanide as nucleophile.



SCHEME 5. Anodic substitution: an example of intermediate inaccessible by conventional routes.



SCHEME 6. Anodic cyanation. Overall yield: 65 %.

A frequent consequence of radical-anion formation is dimerization, either directly, after protonation, or by nucleophilic addition to starting material. In scheme 7, which ignores the mechanistic complexities of these reactions, are listed examples of some of the more important types of hydrodimerization (Sioda *et al.* 1976; Sopher & Utley 1979; Baizer 1973; Feoktistov & Lund 1973). The examples are chosen to illustrate the general application of the method to molecules of various structural types and to include the commercially important production of adiponitrile. There are possibly considerable advantages to be exploited for cathodic pinacolization *vis-à-vis* the conventional use of magnesium amalgam; sensitive carbonyl compounds are pinacolized in neutral solution (e.g. retinal and related polyene aldehydes and ketones) (Sopher & Utley 1979; Powell & Wightman 1979), and the stereochemistry of the product may often be controlled by judicious selection of proton donation or ion-pairing conditions.

The importance of ion-pairing in controlling stereochemistry is also demonstrated in scheme 8. Aliphatic ketones reduce cathodically to alcohols with the carbanion $R^1R^2C^-OH$ as a key intermediate. Under conditions consistent with strong ion-pairing, e.g. ethanol containing magnesium or zinc cations (Coleman *et al.* 1976; Holman & Utley 1976), kinetic control may be achieved which, for unhindered ketones, contrasts with thermodynamic control for other reductive methods. It is worth noting that solvated electrons, which are conveniently generated at the cathode, give thermodynamic control for the reduction of hindered and unhindered ketones; this provides a good route for the reduction of camphor to (±) borneol (Holman & Utley 1976).

Accomplishment of difficult oxidations and reductions under chemically mild conditions, particularly with regard to pH and temperature, is a feature of the electrochemical method. A particularly fruitful approach should therefore be the application to syntheses in which conventional chemical reagents cause problems of product degradation, isomerization, etc. The highly selective cathodic hydrogenation of the carotenoid canthaxanthin fits into this category. The high degree of conjugation allows reduction at a potential of -1.5 V (against Ag wire) to the dianion, in which double bonds have rearranged to the retro form (Hall *et al.* 1976). Subsequent acylation and hydrolysis completes the hydrogenation reaction and it is possible in this way to prepare the highly labile 5,5′-dihydro product (scheme 9).

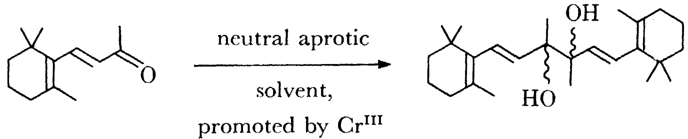
$$2MX^{-\bullet} \longrightarrow {}^{-}XM.MX^{-} \longrightarrow HXM.MXH$$

(MX of type RCOR′, $-CH{=}CH-Y$)

Examples:

(*a*) $$Me_2CO \xrightarrow[\text{strong acid}]{\text{cathode,}} Me_2C(OH)C(OH)Me_2$$

(*b*)

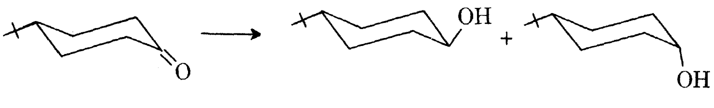


(laboratory scale)

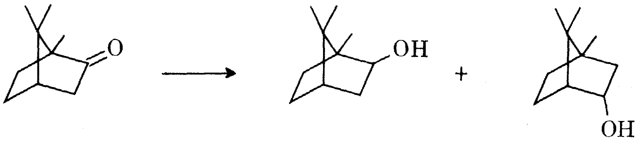
(*c*) $$CH_2{=}CHCN \xrightarrow[\text{cathode, } R_4N^+]{\text{aqueous solvent,}} NC(CH_2)_4CN$$

(plant scale, up to 90 000 t/year)

SCHEME 7. Hydrodimerization.



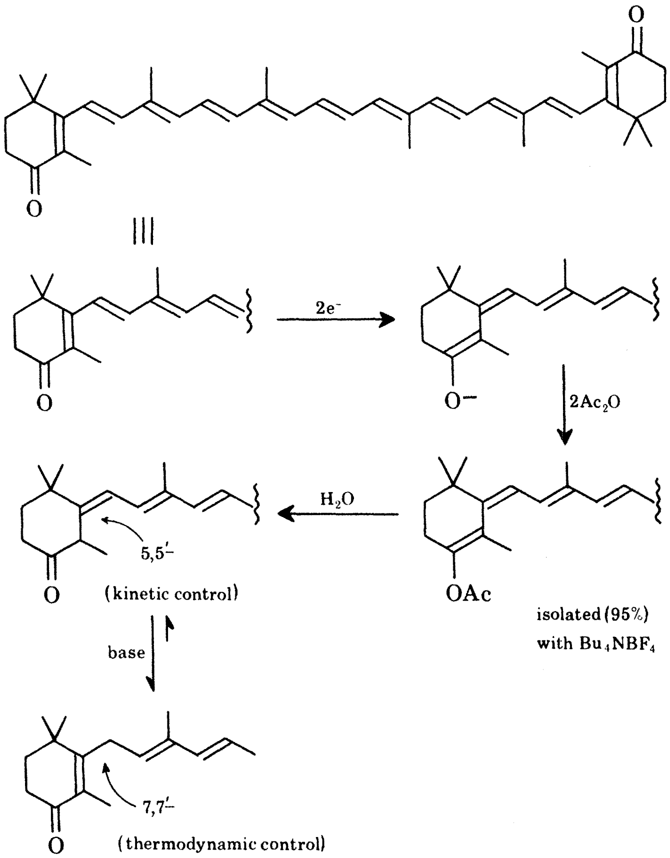
$LiAlH_4$	90%	10% (t)
$e^-_{solv.}$	95%	5% (t)
Hg cathode/Mg^{2+}	<2%	>98% (k)



$LiAlH_4$	90%	10% (k)
$e^-_{solv.}$	16%	84% (t)

SCHEME 8. Kinetic (k) or thermodynamic (t) control.

The canthaxanthin reduction described above introduces the concept of synthesis by reaction between cathodically generated nucleophiles (radical-anions, dianions) and added electrophiles (acetic anhydride in the canthaxanthin case). This approach has also been used to develop an impressive method for the preparation (Knittel & Kastening 1973) of a variety of sulphones (scheme 10); the radical anion of sulphur dioxide is easily generated at the cathode, and its reactions with added electrophiles such as alkyl halides must be good candidates for scaling-up.



Scheme 9. Indirect hydrogenation of canthaxanthin.

$$SO_2 \underset{}{\overset{e^-}{\rightleftharpoons}} SO_2^{-\cdot} \xrightarrow{RX} RSO_2^{\cdot} + X^-$$

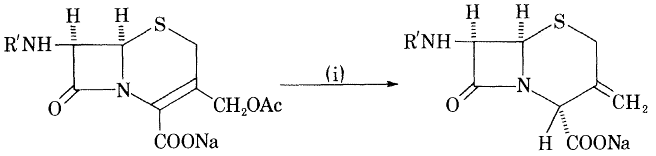
$$RSO_2^{\cdot} + SO_2^{-\cdot} \longrightarrow RSO_2^- + SO_2$$

$$RSO_2^- + RX \longrightarrow RSO_2R + X^-$$

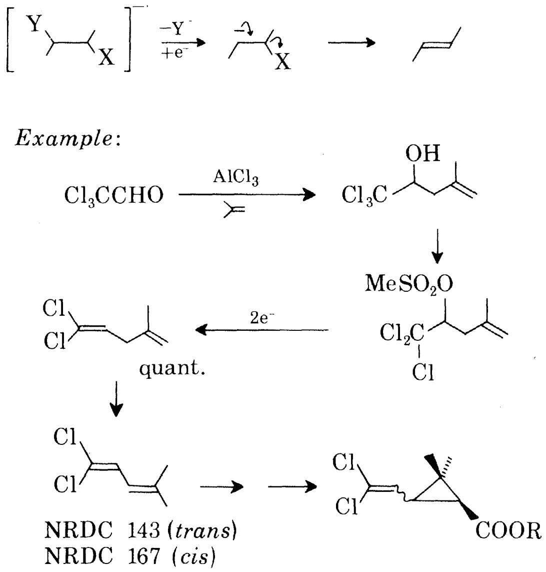
$$\xrightarrow{R'Y} RSO_2R' + Y^-$$

Scheme 10. Cathodic preparation of sulphones.

The fragmentation of radical cations is familiar to organic chemists from their use of mass spectrometry. In solution, also, radical ions may fragment and the rapid loss of protons from radical cations has already received comment (see scheme 5). Electrochemical fragmentation (or cleavage) may often be preparatively useful, and although the factors controlling leaving group abilities are far from well understood (Berenjian & Utley 1979), sufficient is known for the design of anodic and cathodic methods of deprotection. At the anode, for instance, benzylic ethers (Weinreb *et al.* 1975) and dithians (Porter & Utley 1978) may be cleaved. A good example of the use of a cathodic deprotection reaction (Ochiai *et al.* 1974) is given in scheme 11, which highlights the selectivity of the electrochemical method. The cathodic cleavage reaction is usually completed by protonation to give, overall, hydrogenolysis. An interesting and potentially useful situation arises, however, when elimination from the intermediate carbanion is favoured over protonation. These elimination reactions are almost certainly stepwise, and sometimes elimination or protonation will predominate depending upon reaction conditions (Adams *et al.* 1979*a*, *b*). With the correct choice of leaving group, cathodic elimination can be an effective method for alkene synthesis and one example has been put to good use (Alvarez & Fishman 1977) in the preparation of intermediates in pyrethroid synthesis (scheme 12).

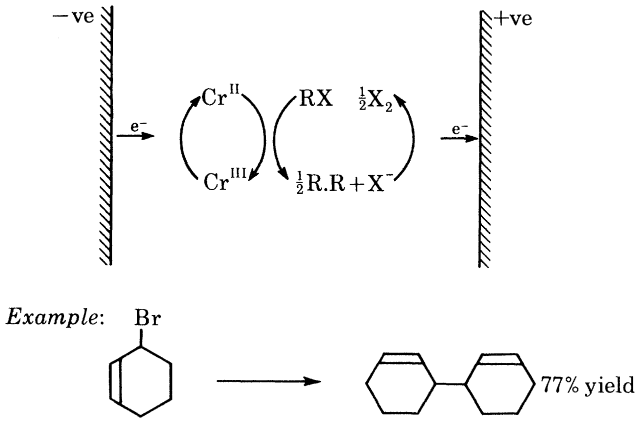


SCHEME 11. Deprotection of cephalosporin derivatives; an example of $MX \underset{}{\overset{e^-}{\rightleftharpoons}} MX^{-\cdot} \xrightarrow{-X^-} M^{\cdot} \xrightarrow{e^-,\,H^+} MH$. (i) Aqueous Na_2HPO_4–HCl, pH 7.0, Hg cathode divided cell, constant current, room temperature. R′ = $HOOC(H_2N)CH(CH_2)_3CO$. Yield = 81%.



SCHEME 12. Reductive elimination: synthetic pyrethroids. The cathode replaces the use of Zn–HOAc. R = *m*-PhO.C_6H_4.CH_2.

The generation *in situ* of inorganic redox reagents and of bases is a burgeoning area of research, which unfortunately can receive but scant attention here. The advantages of using electrochemistry to generate and regenerate species such as Cr^{VI}, Ce^{IV} and Cr^{II} in a controlled manner and in closed systems are obvious. The principles of this method are exemplified for just one (Wellman & Steckhan 1978) of several possible examples (scheme 13).



SCHEME 13. Indirect reduction.

This short account of the reactions of electrochemically generated reactive intermediates cannot possibly be exhaustive, but examples of the most important types of reactions have been given and the principles of intelligent design of electrosyntheses are embodied therein. In summary, it is suggested that much progress will continue to be made in the replacement by electrochemical methods of expensive or undesirable redox reagents. In particular, attention should be paid to selective transformations under mild conditions – processes of interest not only to those practising general organic synthesis but also to those involved in the production of intermediates for fine chemicals and pharmaceuticals.

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