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SYNTHETIC USES OF ANODIC SUBSTITUTION REACTIONS

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Practitioners of organic synthesis, normally content to shuffle around electrons two by two in curved-arrow-mechanisms and work with equipment no more sophisticated than beakers and flasks, have not quite accepted electrolysis as a routine tool for performing oxidation and reduction reactions in spite of the enormous increase in the amount of knowledge about electroorganic reactions in recent years.[1-9] No doubt this is connected with the fact that electrochemical reactions must be expressed in terms of one-electron transfers, must deal with those little known odd-electron intermediates, radical anions and cations, must deal with heterogeneous reaction steps, and must be conducted in seemingly complicated equipment, all combined with a constantly lurking danger of instant electrocution for the experimenter! And yet, the mechanistic and experimental situation in electrolysis is, on the whole, not as complicated as in another heterogeneous reaction, catalytic hydrogenation, which is routinely used in all synthetic organic laboratories without too much hesitation.

We here intend to show that the purchase of a potentiostat and a few electrochemical cells is a profitable investment for any synthetic organic chemist worthy of this designation. This will be done by focussing the treatment on one single type of electroorganic processes, anodic substitution, the choice of which we hope is justified by the wealth of new chemistry uncovered during the exploration of this reaction type. If some anodic additions have sneaked in, it is only because they are so intimately bound to substitutions and, of course, have turned out to give a few interesting synthetic applications too.

1. PRINCIPLES OF ELECTROLYSIS

For the synthetic organic chemist, anxious to perform reactions with the sometimes conflicting aims of obtaining a maximal yield with a minimum of effort, the most direct way to introduce the phenomenon of electrolysis is to emphasize that *electron transfer* from or to an electronic conductor (a metal or semiconductor *electrode*) to or from a species (denoted the *substrate* molecule if we happen to be interested in its transformations under the influence of electric current) dissolved in an ionic conductor (the *electrolyte solution*, composed of a *solvent* and a *supporting electrolyte* to provide ionic conduction) is the central act of electrochemistry (Fig. 1). Thus oxidation and reduction takes place at the anode and cathode, respectively, in Fig. 1 so far shown as one-electron transfers only.

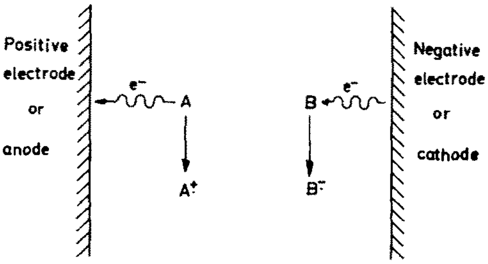

Fig. 1. One-electron transfer from ($A \rightarrow A^{+\cdot}$) or to ($B \rightarrow B^{-\cdot}$) a neutral molecule with formation of a radical cation (anion).

The ensuing reactions of the intermediates generated in the electron transfer step, $A^{+\cdot}$ or $B^{-\cdot}$, are called *follow-up reactions* and ultimately lead to stable products. These reactions are normally composed of a series of chemical and/or electrochemical steps, e.g. as in eqn (1) which schematically depicts an anodic substitution by a nucleophile, Nu^-.

$$A^{+\cdot} \xrightarrow{Nu^-} \dot{A}\text{—}Nu \xrightarrow{-e^-} \overset{+}{A}\text{—}Nu \xrightarrow{-H^+} A\text{—}Nu(-H). \tag{1}$$

Note that electrons are transferred one by one, an important postulate in electrochemistry. It has been shown that the probability of transferring two electrons at the same time is virtually zero.[10]

In order to arrive at a workable understanding of the electron transfer act, we need only resort to the simple picture of molecular energy levels that MO theory provides.[11] Each molecule has available a number of occupied and vacant MO:s; oxidation removes an electron from the highest occupied MO, while reduction adds an electron to the lowest vacant MO (Fig. 2). In electrolysis, electron transfer takes place over a very thin solution layer (10–15 Å thick; this layer is commonly called the *electrical double layer* or the *electrified interface*) adjacent to the electrode surface. In order for an electron to jump between the electrode and a molecule in the solution, the energy level of the electrode, the Fermi level, and the energy level of the MO involved must match eath other *exactly*.[12,13] Otherwise, radiationless transfer of an electron cannot take place (and thermodynamics tells us that it has to be radiationless).

How do we then achieve matching of the energy levels? What we want to do is to change the energy of the Fermi level, and this is simply done by changing the *electrode*

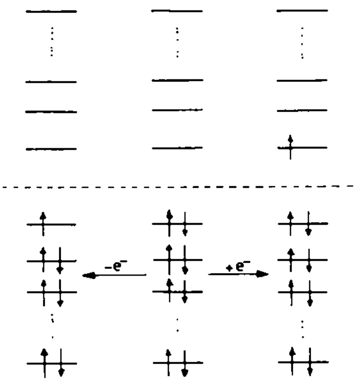

Fig. 2. Molecular orbital picture of one-electron oxidation and reduction, respectively.

potential which is the potential applied across the interface between the electrode and solution. When the energy of the Fermi level has been raised or lowered to fit exactly (which means within ±kT) with the appropriate MO in the substrate molecule, electron transfer can take place. This simplified picture should not obscure the fact that heterogeneous electron transfer theory is a lot more complicated and should be consulted if the reader wants to dig deeper into the subject.[14] For the purpose of understanding the phenomena underlying electroorganic synthesis, we shall rest content with the conceptual apparatus introduced so far.

2. PRACTICE OF ELECTROLYSIS

From these principles, the following pieces of equipment turn out to be essential for an electrolysis experiment to be performed: two electrodes, a vessel, a variable DC source and an ampéremeter. Thus equipped, an innovative organic chemist can set out to do practically all kinds of anodic chemistry but perhaps not so much in terms of cathodic chemistry. If he, however, provides his electrochemical cell with a *cell divider* in the form of some kind of semipermeable *membrane*, separating the cell into an anode and cathode compartment, the whole area of cathodic chemistry will be open for him too. The membrane which in the simplest case can be an ordinary glass frit disc, is introduced to prevent products formed at the cathode from migrating to the anode and thus being oxidized there.

Some words are necessary to explain the difference between anodic and cathodic chemistry with respect to the cell divider. In an ideal case, one would of course like to have both the anode and the cathode do useful organic chemistry, but in laboratory practice one settles for using only one of them for sheer convenience. If this happens to be the anodic reaction, it is nearly always possible to make up the electrolyte so that the cathode process becomes reduction of some protonic species to give hydrogen, especially if the cathode material has a low *overpotential* for proton reduction, i.e. proton reduction occurs at a high rate at the particular material chosen (as an example, stainless steel is excellent from this point of view). The hydrogen evolution reaction suppresses all other reactions at the cathode and thus prevents substrate or products formed at the anode from being reduced. Hence no membrane is needed in most anodic chemistry. It is far more difficult to find a universally applicable anodic process which fulfills the same role vs cathodically formed products and therefore the membrane is a necessary piece of equipment for almost all electroorganic reactions where the cathode process is the desired one. From the experimental point of view, the membrane poses some rather difficult problems, at least in large-scale runs and/or nonaqueous solvents.

The simple cell so far described can be improved upon by adding a few other items. In the first place, we might want to measure the potential of the electrode at which the desired reaction occurs (often called the *working electrode*). This is made by inserting a reference electrode, e.g. an ordinary calomel electrode, in the electrolyte solution with its tip as near the working electrode as possible and measuring the potential between it and the working electrode by a voltmeter with a very high internal resistance. With this arrangement one measures a potential difference which is very close to the electrode potential and can be approximated as such.

If we now run an electrolysis experiment, using the anode as the working electrode, with a low substrate concentration and take measurements of current vs anode potential over a range of potentials we will in many cases obtain a current-voltage curve (voltammogram) of the type shown in Fig. 3. From a region where no current flows (AB) we arrive at a point (B) where substrate molecules start to become oxidized. Here the current will initially increase exponentially (BC) but, as with all exponentially increasing events, will soon level out to a plateau value (at D) due to lack of material to oxidize. Molecules approach the electrode surface by *diffusion* and the rate of diffusion becomes limiting as the potential is increased further. As we increase the anode potential to E, a second electrochemical process begins to run in parallel with the first one (or outrun it, or mix with it; a fair number of complications is possible with two processes that in principle can run simultaneously). This reaction is due to oxidation of the solvent or the anion of the supporting electrolyte or both.

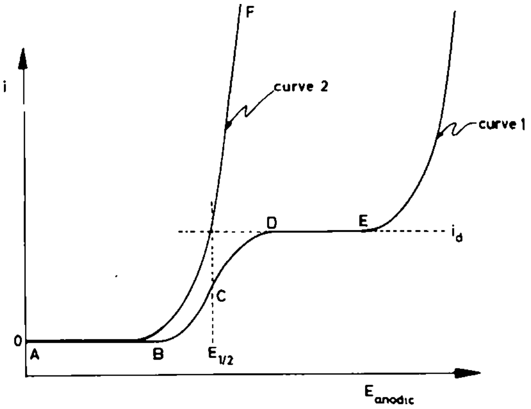

Fig. 3. Voltammogram for anodic process at low (curve 1) and high (curve 2) substrate concentration. Diffusion-controlled current = i_d; half-wave potential = $E_{1/2}$. For explanations, see text.

Thus we can easily understand why it is useful to measure the potential of the working electrode during the experiment in situations of the type depicted in Fig. 3. By doing so and adjusting the potential when it tends to increase—or, at the cathode, decrease—we can avoid running the reaction in a potential region where both reactions can take place, thus avoiding waste of electrical energy or worse, formation of byproducts due to mixing of the two processes. Commercially available electronic devices, potentiostats, in fact allow for presetting the electrode potential at an arbitrary value simply by turning a knob and keeping this value constant during the whole run (controlled potential electrolysis = CPE). The current will then initially be high and decreases exponentially to zero or close to zero, thus signalling the endpoint of the reaction.

One attractive feature of electroorganic synthesis emerges from the rapidly spreading use of potentiostats; it will be recognized as demanding very little work and attention and in general providing a very safe laboratory environment. One sets up the cell (10 min if the equipment is around; it never is), makes up the electrolyte solution (5 min), provides for cooling of the cell, adjusts the potential, and leaves the electrolysis running. No high temperature, no high pressure, no risk for explosions, very little attention required. The experimenter has the entire reaction period free for all those other demanding tasks that fill the day in an organic laboratory. What else can an organic chemist want?

Curve 1 in Fig. 3 gives two other pieces of information that are of interest in connection with electrochemical synthesis. The plateau current or, rather, *current density* which is the true measure of electrochemical rate, is linearly related to the concentration of the substrate. By comparing the plateau current or *diffusion current* with that of a known process one can estimate the number of electrons transferred in the unknown electrode process. Often used standard redox couples for this purpose are the hydroquinone/quinone and ferrocene/ferrocinium systems (two- and one-electron process, respectively). Another way to estimate the number of electrons transferred is to record and plot current vs time during the electrolysis period. The area under the curve corresponds to the number of As (ampere-seconds or coulomb) passing through the electrolyte and is equal to the number of electrons per mol of substrate times the number of mols of starting material times Faraday's constant (96 500 As), provided no other reaction than that of the substrate takes place in the system. The charge passed can be measured directly by aid of an electronic integrator and the method is called *coulometry*.

The second interesting parameter that can be extracted from a voltammetric curve is the half-wave potential, $E_{1/2}$, i.e. the potential at which the current has reached 50% of the diffusion-controlled value. $E_{1/2}$ is conveniently measured by a micro-scale electrolysis procedure commonly called *polarography* and is an approximate measure of the oxidizability or reducibility of a compound. At the anode, a more positive $E_{1/2}$ corresponds to a compound more difficult to oxidize than one with a less positive $E_{1/2}$. An extensive list of $E_{1/2}$ values is available.[15]

Anodic $E_{1/2}$ values correlate very nicely with the energy coefficients of the highest occupied MO of a large range of compounds,[11] as would be expected from the simple theoretical treatment inherent in Fig. 2. It is then not surprising to find that $E_{1/2}$ values also correlate well with ionization potentials in the gas phase. The underlying phenomenon, loss of an electron from the HOMO, is common to both anodic oxidation and gas phase ionization by electron or light quantum impact. It has in fact been shown that the anodic $E_{1/2}$ values of practically all types of organic compounds give a reasonable correlation with vertical ionization potentials.[16] On the cathodic side, energy coefficients of the lowest vacant MO and electron affinities are analogously correlated with $E_{1/2}$ values for reduction.[11] With these correlations available, it is easy to deduce from literature data or calculated quantities a fairly reliable $E_{1/2}$ value for almost any organic compound.

A final remark with respect to Fig. 3 is that the voltammetric curve in a synthetic experiment does not normally appear as in curve 1. Instead the substrate concentration is so high (>0.1 M) that the plateau current is never reached due to lack of capacity of the current source (see curve 2) until the end of the electrolysis is near. It is precisely this state of affairs that allows for running preparative† scale electrolysis at constant current (CCE) instead of constant potential. If we start the electrolysis at a constant current, corresponding to a current density somewhere on curve 2, Fig. 3 (say, at F), we will in effect run a constant potential experiment during most of the run, in fact up to at least 90% of the charge calculated theoretically for the process. We can then either choose to stop the electrolysis at this stage and accept the separation problem created or proceed to 100% using manual control of the potential during the last 10% of the reaction.

Since CPE demands a potentiostat which is roughly 10 times more expensive than a DC source equipped with the option of current control, it is important to stress that CCE in most cases gives very satisfactory results, especially in anodic applications. In fact, CPE operation with a potentiostat becomes prohibitively expensive at high currents and applied voltages (the *applied voltage* or *cell voltage* is the total potential difference between anode and cathode; it is composed by the sum of the two electrode potentials, E_a and E_c, and the potential drop, iR, due to ohmic resistance of the system and has no theoretical meaning whatsoever). Already with a rather moderate requirement of, say, 50 V and 10 A, we approach the price range of middle-sized family cars. And this should be combined with the fact that a current of 10 A must flow for 5.36 hr in order to produce 1 mol of product from a two-electron reaction, if the current efficiency is 100%. On the industrial scale, which means thousands of A, the use of a potentiostat is impossible and CCE imperative. Here we instead have the option of running CCE electrolysis at constant substrate concentration by using a continuous mode of operation. In effect, this is CPE operation.

Thus, a synthetic chemist with no other aim than to use electrolysis as a routine tool can do very well by resorting to very simple equipment and techniques.[17] The appropriate current density for a preparative CCE experiment can be obtained by recording voltammetric curves in a small-scale experiment on electrolyte solutions without and with substrate added. From these curves it is easy to decide which current density should be used in the CCE run. A preparative CCE run to *ca.* 90% conversion will then in essence be a CPE run, albeit with much cheaper equipment. In these days of financial hardship, this is not an entirely trivial observation.

Should the experimenter want to obtain some elementary mechanistic information about a reaction, the technique of voltammetry, in the form of *cyclic voltammetry*, is the first one that should be acquired. We shall not deal with this method here but only assert that it is the single most useful electrochemical method for the organic

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†Opinion is somewhat divided as to what constitutes "preparative scale electrolysis" but we are here talking of producing reasonable amounts of material in a single run, i.e. 0.1 mol or more.

chemist who wants quick mechanistic orientation about an electrode reaction.[1]

As can be seen by even a cursory glance in the literature of electroorganic chemistry, no amount of money and ingenuity has been spared in designing cells of the most perplexing complexity.[6,18] Unfortunately, this has lead to a state where every electrochemist with some self-esteem uses cells of his or her own design. We have always been and still are of the opinion that nothing would advance the routine use of electrolysis in organic synthesis better than the commercial availability of simple standard cells—with some inbuilt flexibility—for preparative scale use. It is an interesting problem to ponder upon why nearly every laboratory glass company sells dozens of rather specialized items for synthetic photochemical applications but essentially nothing for electrochemistry.

3. CLASSIFICATION OF ORGANIC ELECTRODE REACTIONS

From the synthetic point of view, organic electrode reactions are conveniently classified according to the following categories,[3] of which each one has an anodic and cathodic version:

(1) Electron transfer
(2) Conversion of functional groups
(3) Substitution
(4) Addition
(5) Elimination
(6) Coupling
(7) Cleavage
(8) Miscellaneous

It should immediately be stressed that categories 3, 4, 5 and 7, despite their nomenclature being identical to that of ordinary organic reactions, ought to be preceded by the words "oxidative" or "reductive" or "anodic" or "cathodic". As we will see later, they are quite different from their non-redox counterparts.

A detailed discussion of this classification scheme, together with illustrating and clarifying examples, has been presented elsewhere[13,19] and need not be repeated here. It is appropriate, however, to consider the anodic substitution process from the synthetic point of view in some detail, since this reaction type is the main object of this Report. A general formula for anodic substitution is shown in eqn (2), where E^+ and Nu^- denote a general electrophile and nucleophile, respectively (the use of charged species is entirely for convenience).

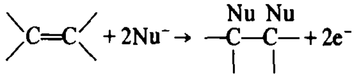
$$R{-}E + Nu^- \rightarrow R{-}Nu + E^+ + 2e^- \qquad (2)$$

Nu^-: HO^-, RO, $RCOO^-$
NO_3^-, NO_2^-, N_3^-
OCN^-, SCN^-, $SeCN^-$, CN^-
F^-, Cl^-, Br^-, I^-
H_2O, ROH, RCOOH, CH_3CN, C_5H_5N, R—E, CO

E^+: most commonly H^+, but can be R^+, RO^+, CO_2.

The overridingly important thing to notice in eqn (2) is that the left side contains two species that would not react with each other *were it not for the fact that two electrons are removed from the system.* It is this feature that makes anodic substitution, and indeed most other electrochemical reaction types, look unfamiliar to the organic chemist, always on the lookout for pairs of compounds that might react with each other. Here we must get used to look for systems that do not react in normal synthetic practice. To give one example of the difficulties involved in grasping this feature, the reader is referred to a very recent review on new directions in aromatic nucleophilic substitution,[20] in which oxidative substitution is described as "a newly emerging class of reactions", which can take place by oxidation by "even an anode". The reaction type has been known in electrochemistry since the days of Hermann Kolbe[21] but very seldom recognized for what it is.

The anodic addition to a carbon–carbon double bond can be formulated as in eqn (3). It should be noted that


(3)

anodic addition can take place across a system of conjugated double bonds, even in aromatic rings (cf. eqns 48 and 49). The list of nucleophiles known to participate in anodic addition is the same as in substitution (eqn 2).

4. DIRECT AND INDIRECT ELECTROLYSIS

Before we can discuss the possible synthetic applications of anodic substitution we must make a mechanistic diversion of rather trivial—today, but not ten years' ago[13]—kind in order to distinguish between *indirect* and *direct* electrochemical processes, i.e. a classification based on the nature of the *electroactive species.* In an indirect process a component of the electrolyte solution *other than the substrate* is oxidized at the anode to form a species that attacks the substrate in a conventional reaction. A typical example would be anodic oxidation of a solution containing chloride ion and an aromatic hydrocarbon which gives chlorinated arenes; chlorine (or possibly Cl_2^{+}) is formed at the anode and attacks the arene in an ordinary electrophilic reaction. Although indirect reactions have considerable practical interest,[22] we shall limit our treatment here to reactions proceeding via direct mechanisms, i.e. where the substrate molecule is the electroactive species. After all, it is in this way that radical cations are formed and consequently new chemistry originates. The indirect mechanism, on the other hand, can be studied in a two-pot experiment; electrolysis gives a solution of an oxidizing agent that can be transferred to a second vessel where it can interact with the substrate.

The experimental distinction between direct and indirect mechanisms is made by voltammetric methods, sometimes in combination with product studies. Usually, this approach suffices to establish this aspect of an electrochemical reaction mechanism beyond doubt. Only in cases where substrate and other components are oxidized in the same range of potentials can decisions be difficult or impossible. Here it is pertinent to point out that despite claims to the contrary electrochemical methods *do not possess any remarkably high power of resolution,* in that a difference of at least 0.15 V, equal to an energy difference of *ca.* 15 kJ/mol, is required to make meaningful CPE experiments. One such ambiguous case is anodic oxidation of alkylaromatic hydrocarbons in acetic acid in the presence of a nitrate salt as the supporting electrolyte. Here the indirect mechanism (eqn 4a) so far has been impossible to distinguish from the direct one (eqn 4b). Current opinion has settled

$$NO_3^- \xrightarrow{-e^-} NO_3^{\cdot} \xrightarrow{ArCH_3} ArCH_2^{\cdot} \xrightarrow{-e^-} ArCH_2^+$$

$$\xrightarrow[NO_3^-]{AcO^-} \begin{matrix} ArCH_2OAc \\ ArCH_2ONO_2 \end{matrix} \qquad (4a)$$

$$\mathrm{ArCH_3} \xrightarrow{-e^-} \mathrm{ArCH_3^{\cdot+}} \xrightarrow{-H^+} \mathrm{ArCH_2^{\cdot}} \xrightarrow{-e^-} \mathrm{ArCH_2^+} \xrightarrow{etc} \qquad (4b)$$

for the simultaneous operation of both mechanisms,[23-27] presumably indicating that there is no definite evidence in either direction.

In the following discussion, only direct electrolytic reactions will be included; the evidence for their direct nature—by no means undisputed in all cases—has been scrutinized in a recent review[13] and will not be repeated here.

5. SYNTHETIC USE OF ANODIC SUBSTITUTIONS

If we express the synthetic scope of a reaction in the usual terms of bonds broken in the substrate and bonds formed in the product we immediately find from eqn (2) an array of reactions that have considerable synthetic interest, namely the one-step replacement of a C–H bond by a C–O, C–N or C–C bond. Only a very limited number of non-electrochemical schemes of this type is available and, since these ultimately depend on electrolytic procedures for the production of the oxidant, generally a high valence state metal ion, they are in essence indirect (two-pot) electrolyses.

The individual synthetic reactions are listed below together with their commonly accepted names:

C–O *Bond formation*		
$\mathrm{R{-}H + R'COO^- \rightarrow R{-}OCOR' + H^+ + 2e^-}$	anodic acyloxylation (e.g. R′ = H, formyloxylation, R′ = $\mathrm{CH_3}$, acetoxylation, R′ = $\mathrm{CF_3}$, trifluoroacetoxylation)	(5)
$\mathrm{R{-}H + R'O \rightarrow ROR' + H^+ + 2e^-}$	anodic alkoxylation	(6)
$\mathrm{R{-}H + OH \rightarrow R{-}OH + H^+ + 2e}$	anodic hydroxylation	(7)
$\mathrm{R{-}H + NO_3^- \rightarrow R{-}ONO_2 + H^+ + 2e^-}$	no name attached yet, but nitratation seems logical	(8)
C–N *Bond formation*		
$\mathrm{R{-}H + CH_3CN + H_2O \rightarrow RNHCOCH_3 + 2H^+ + 2e^-}$	anodic acetamidation	(9)
$\mathrm{R{-}H + C_5H_5N \rightarrow R\overset{+}{N}C_5H_5 + H^+ + 2e^-}$	anodic pyridination	(10)
$\mathrm{R{-}H + N_3^- \rightarrow RN_3 + H^+ + 2e^-}$	anodic azidation	(11)
$\mathrm{R{-}H + OCN^- \rightarrow RNCO + H^+ + 2e^-}$	no name attached yet	(12)
$\mathrm{R{-}H + NO_2^- \rightarrow R{-}NO_2 + H^+ + 2e^-}$	anodic nitration	(13)
C–C *Bond formation*		
$\mathrm{R{-}H + CN^- \rightarrow R{-}CN + H^+ + 2e^-}$	anodic cyanation	(14)
$\mathrm{R{-}H + R{-}H \rightarrow R{-}R + 2H^+ + 2e^-}$	anodic coupling	(15)

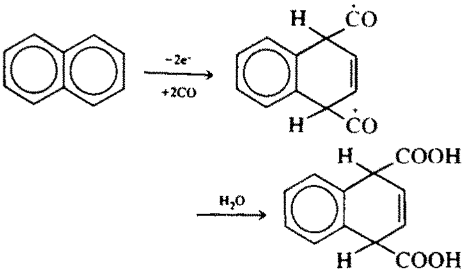
If we add to this list yet a fourth type, anodic fluorination (eqn 16), evidence for the direct nature of which is now emerging after many years of dispute,[28] our present choice of anodic substitution reactions

$$\mathrm{R{-}H + F^- \rightarrow R{-}F + H^+ + 2e^-} \qquad (16)$$

is complete, with the reservation that the anodic nitration mechanism[29] has not been unambiguously established to be a direct one (thus nitration has been shown to occur at a potential as low as 0.9 V, whereas the substrate used, 1,4-dimethoxybenzene, has an $E_{1/2}$ of 1.34 V; the oxidation of nitrite ion takes place already around 0.8 V, so that an indirect mechanism via anodically generated nitric acid or nitronium ion appears to be equally feasible).

Among the reactions listed in eqns (5)–(16), only acetoxylation, alkoxylation, acetamidation, cyanation, coupling, and of course fluorination (eqns 5, 6, 9, 14–16) have been synthetically explored to any appreciable extent. The remaining ones appear in rather isolated cases, sometimes because they are inherently limited as synthetic procedures (like hydroxylation, which often gives products that are easily oxidized further, or nitration which can be done in a simpler way) or for some reason have not been adequately studied in spite of their practical interest (like isocyanation). A very attractive reaction would be anodic carboxylation (eqn 17) which so far is only known as an anodic addition process[30] (as in eqn 18).

$$\mathrm{R{-}H + CO + H_2O \rightarrow R{-}COOH + 2H^+ + 2e^-} \qquad (17)$$



(18)

6. SUBSTRATES

Substrates for anodic oxidation are conveniently classified according to their contents of *electrophores*. In a similar way as a chromophore makes a molecule absorb light quanta in a certain region of wave-lengths, an electrophore conveys electroactivity to a molecule in a certain potential range. As would be expected, interactions (inductive, mesomeric, steric) between several electrophores in a molecule will sometimes affect its oxidation potential beyond the effect of any single electrophore, and therefore the concept is necessarily a crude tool for predictions. Figure 4 thus cannot give more than an approximate idea of how different electrophores influence oxidation potentials.

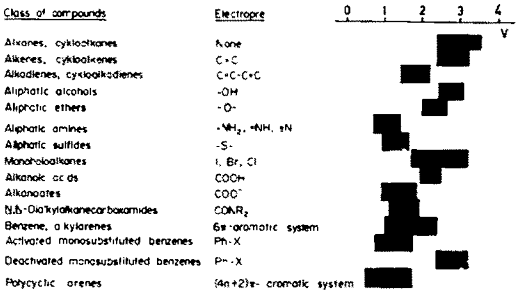


Fig. 4. Approximate ranges of oxidation half-wave potentials for different classes of compounds.

A general rule of thumb, evident from Fig. 4 is that the presence of one or several electron-donating groups strongly decreases the oxidation potential of a molecule whereas the reverse is true for electron-withdrawing ones (cf. also the correlations discussed on p. 2187).

Commonly employed substrates for anodic substitution of C–H bonds have so far been limited to the fairly simple types of compounds listed below together with the mode of attack. A most desirable extension would be a more widespread application to synthetic schemes involving more complex polyfunctional systems in order to define the full scope of this reaction type. Only then can one take maximum advantage of its "short-cut capabilities".

Alkanes and cykloalkanes	(selective attack on tertiary C)
Alkenes, cykloalkenes, dienes	(allylic substitution)
Arenes	(nuclear substitution)
Alkylarenes	(benzylic or α substitution)
Amides	(α to N)
Ethers	(α to O)

It was indicated in eqn (2) that leaving groups other than hydrogen exist. It is enough to note that these cases are relatively rare, except for the case of CO_2 which corresponds to the carbocation pathway of the Kolbe reaction[31] (eqn 19).

$$RCOO^- + Nu^- \rightarrow R\text{—}Nu + CO_2 + 2e^-. \qquad (19)$$

This has been dealt with elsewhere;[31,32] due to the intervention of "hot" carbocations the synthetic scope of this particular process presently appears to be limited to special cases. It should, however, be possible to devise reactions in which a strong nucleophile traps the carbocation before it has had time to rearrange. Indications in this direction can be found in Skell's work using hydroxide ion as the trapping agent;[33] we would like to suggest that azide ion might be an interesting possibility to explore. It has been claimed that the neopentyl system survives the treatment in Eqn (9) intact with this nucleophile present.[34]

So far alkoxy groups function as leaving groups only with cyanide ion[35] (see eqns 2 and 26). Finally, alkyl groups are very rarely deliberately used as leaving groups, and only the t-Bu group has been reported so far.[36]

7. ADVANTAGES OF SYNTHETIC SCHEMES BASED UPON ANODIC SUBSTITUTIONS AND ADDITIONS

Which are then the synthetic advantages of using an anodic substitution or addition process? After all, it is only fair to demand a sizable advantage of any untried method in order for the organic chemist to be coerced out of his ordinary conceptual and practical framework. We suggest that one or several of the following advantageous features should make it worthwhile to look into anodic substitution as a synthetic tool (or indeed into any kind of electrolytic process):

(1) Too many redox steps can be avoided, which at least from the economical point of view is important. Also, the chemist's pride in his profession should militate against, e.g. the following series of reactions presently involved in the large-scale production of hydroquinone (the number of electrons given in each redox step is that required per mol of hydroquinone):

$$\begin{array}{rl}
H_2O \rightarrow H_2 & +3e^- \\
3/2\,H_2 + 1/2\,N_2 \rightarrow NH_3 & \\
NH_3 \rightarrow HNO_3 & -8e^- \\
HNO_3 \xrightarrow{C_6H_6} C_6H_5NO_2 & \\
C_6H_5NO_2 \rightarrow C_6H_5NH_2 & +6e^- \\
C_6H_5NH_2 \rightarrow p\text{-Benzoquinone} & -4e^- \\
p\text{-Benzoquinone} \rightarrow \text{Hydroquinone} & +2e^-.
\end{array}$$

Here 23 redox equivalents are used or, really, wasted to make a product that can be made electrochemically—the process exists on a pilot-plant scale—in one step in a 4-electron oxidation process[37] (eqn 20)! And it is done with considerably less pressure on the occupational and natural environment!

$$C_6H_6 + 2H_2O \rightarrow C_6H_4(OH)_2 + 4H^+ + 4e^-. \qquad (20)$$

(2) To mention an advantage that is easier to appreciate in ordinary laboratory practice, one can often bypass conventional multistep procedures by resorting to the kind of inverted thinking required for the successful application of electrolytic synthesis. As an example, one can summarize the conventional way of preparing aromatic amines and nitriles, biaryls, and phenols in the scheme below (eqn 21). The anodic replacements are shown in eqns (22)–(25). The total number of steps implied in eqn (21), eleven, is replaced by a total of six in eqns (22)–(25). Already in cases somewhat more complex than substitution of simple benzene derivatives, the gain can be quite drastic, as in the anodic synthesis of 4-cyano-4'-octyloxybiphenyl from cheaply available 4,4'-dihydroxybiphenyl in two steps[38] (eqn 26) instead of the hitherto reported (eqn 27) five-step method.[39]

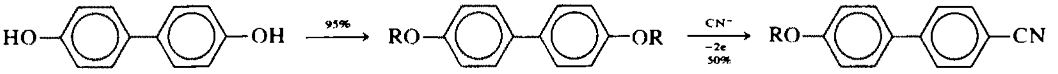
$$\begin{tikzcd}
 & & Ar\text{—}Ar' & \\
ArH \arrow[r] & ArNO_2 \arrow[r] & ArNH_2 \arrow[u] \arrow[r] \arrow[d] & ArOH \qquad (21) \\
 & & ArCN &
\end{tikzcd}$$

$$ArH \rightarrow ArOAc \rightarrow ArOH \qquad (22)$$

$$ArH \rightarrow ArNHCOCH_3 \rightarrow ArNH_2 \qquad (23)$$

$$ArH \rightarrow ArCN \qquad (24)$$

$$ArH \rightarrow Ar\text{—}Ar'. \qquad (25)$$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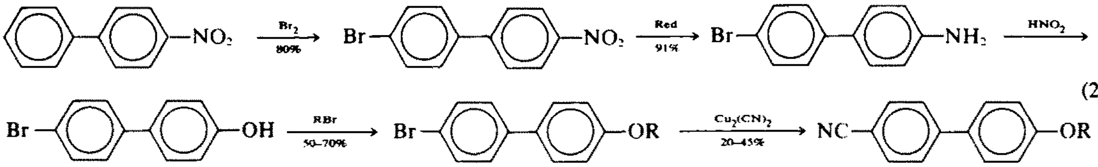

(27)

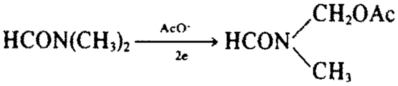
3. Thirdly, the possibility of preparing *unique products* electrochemically will always be a challenge to the synthetic chemist. Of course, very few compounds are likely to be synthesizable via electrolysis only, but we propose that a more sensible operational definition of a unique product would correspond to the following situations:

(a) it can be synthesized by conventional methods but the yields are low,

(b) it can be synthesized by conventional methods but the procedure is so long and tedious that its use by others than pre- and post-doctoral students, the cannon-fodder of organic chemistry, is virtually precluded, and

(c) it has not so far been synthesized by any conventional procedure.

Examples corresponding to (a)–(c) are shown in eqns (28)–(33). Case (a) is demonstrated by the acetoxylation of DMF[40] (eqn 28) which can be done in low yield by other methods; the product is useful for carrying out amidoalkylations.[41] An example of (b) involves an addition reaction (eqn 29) for a change; here the stereochemical course of the anodic reaction is different from that of the homogeneous ones.[42] Finally, case (c) is represented by one addition[43] (eqn 30) and two substitutions (eqns 31[44] and 32[45]), eqn (30) constituting a new and useful method for functionalizing a 3,4-disubstituted furan into a lactone or maleic anhydride derivative.


$$\mathrm{HCON(CH_3)_2} \xrightarrow[2e]{\mathrm{AcO^-}} \mathrm{HCON}\begin{smallmatrix}\diagup \mathrm{CH_2OAc}\\ \diagdown \mathrm{CH_3}\end{smallmatrix} \qquad (28)$$

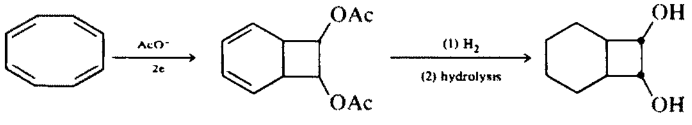
4. Finally, the components on the left side of eqn (2) often represent cheap starting materials and hence these methods ought to have merits in the industrial context.[6,46]

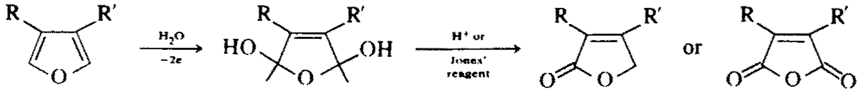
8. MECHANISMS

Since a working knowledge of the mechanism of a reaction is necessary for its successful application to synthetic problems, some basic mechanistic features of anodic substitution and addition will be dealt with in this section.

It is common misconception[47] that the mechanisms of organic electrode processes are so little known that predictions about new phenomena reduce to mere guesswork. Admittedly, some questions have not received satisfactory answers yet and some have not been amenable to treatment so far, but on the whole we possess a reasonably clear picture of the mechanistic framework of electrode reactions.[13] Part of the missing pieces of information should actually be provided by ordinary physical organic chemistry, in that the homogeneous solution chemistry of radical cations—intermediates in most anodic reactions—has been very little explored, presumably due to the experimental difficulties involved.[48] It is nevertheless surprising that this challenge has not been adequately met, considering, e.g. the amount of work that has been and still is spent on rather esoteric details of carbocation chemistry. The radical cation may constitute the last class of important intermediates in organic chemistry!

It is useful to think of mechanistic problems in electrochemistry as being ordered in a hierarchy, where the


cis/trans = 62:38
(29)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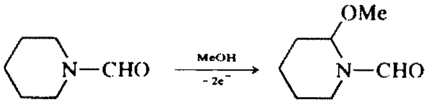
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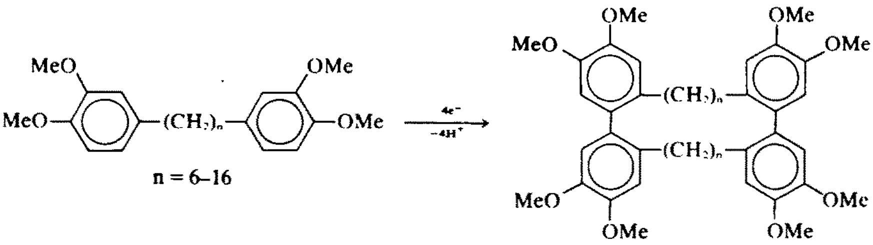

(32)

degree of complexity increases as we move up in the organization (not entirely different from real hierarchies like, e.g. university bureaucracies). With this principle in mind, we can list the most important problem areas as shown below:

4 Effect of electrode material
3 Effect of adsorption
2 Reaction sequence
1 Nature of electroactive species

Increasing complexity

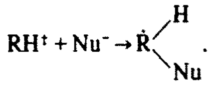
At the lowest and simplest level, we have to find out the nature of the electroactive species, in most cases either easily done by voltammetric methods and CPE product studies (Section 4) or predictable on the basis of known and/or extrapolated values of $E_{1/2}$ (Section 2). We would, however, like to warn against the indiscriminate use of predictions based on $E_{1/2}$ values since they sometimes lead the experimenter astray. This is especially serious if a planned experiment is not carried out at all due to "theoretical" reasoning of this kind. Consider for example an electrolyte solution composed of methanol, sodium cyanide, and anisole with anodic $E_{1/2}$ values of *ca.* 2.5, 0.9 and 1.7 V, respectively. A logical prediction is then that cyanide ion should be oxidized at a fairly low potential to a species, most probably $CN^{\cdot}$, which would then attack anisole, i.e. the reaction would proceed according to an indirect mechanism. Due to the expected radical character and concomitant low selectivity of the reaction the experimenter might never attempt to run it if he is looking for and expecting better results from a direct cyanation mechanism. In this particular case he would, however, be wrong.

The voltammetric curve for methanol/sodium cyanide rises steeply above 0.9 V. On addition of anisole, the voltammetric curve is displaced by *ca.* 0.5 V toward more positive potentials and CPE/product studies unambiguously show that the substrate is the electroactive species. Here we have a situation where a high-potential process suppresses a low-potential one, something that might look rather unfamiliar to a chemist versed in the chemistry of homogeneous media. It is, however, no more peculiar than the possibility to catalyze or inhibit reactions that we often exploit in solution chemistry. In the electrochemical case, adsorption (see further below) of the substrate at a higher potential is believed to force out cyanide ions, adsorbed at a lower potential, from the electrode surface and hence inhibit its oxidation.[17] This phenomenon is fairly common; one prominent case is the Kolbe oxidation of carboxylates on a platinum or iridium anode in aqueous solution.[31,32] Here water oxidation in the region of 1.4–1.8 V is completely suppressed as the potential is increased to above 2.3 V, presumably as a result of increasing coverage of the surface by adsorbed carboxylate ions. No other anode material sustains this behavior in aqueous medium.

At level 2, the problem of elucidating the reaction sequence, i.e. the nature of the follow-up reactions, is very similar to that of finding out which intermediates participate in any reaction mechanism. Since the electroactive species very often is a neutral molecule, the first possible and most important branching reaction after initial 1-e transfer is directly related to the chemical properties of radical cations. It is largely the reactivity of the radical cation which determines the preparative outcome of an anodic process, and it is in the area of radical cation chemistry that we still have a lot of mechanistic detail to unveil before we can be reasonably sure of our predictive abilities.

With the reservation that much mechanistic reasoning about radical cations is hypothetical in character, we can summarize their reaction modes in eqns (33)–(38).

Reaction with nucleophile (eqn 2)



$$RH^{+\cdot} + Nu^- \rightarrow \dot{R}\begin{matrix} H \\ Nu \end{matrix}. \quad (33)$$

Reaction with base

$$RH^{+\cdot} + B\colon \rightarrow R\cdot + BH. \quad (34)$$

Dimerization

$$RH^{+\cdot} + RH^{+\cdot} \rightarrow H\overset{+}{R}—\overset{+}{R}H. \quad (35)$$

Oxidation to dication
At anode

$$RH^{+\cdot} \xrightarrow{-e^-} RH^{2+} \quad (36)$$

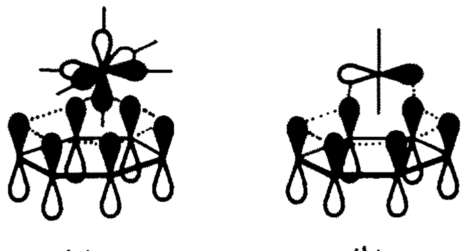
Via disproportionation in solution

$$2RH^{+\cdot} \rightleftarrows RH + RH^{2+} \quad (37)$$

Reduction:

$$RH^{+\cdot} + Nu^- \rightarrow RH + Nu\cdot. \quad (38)$$

To start with nucleophilic attack upon a radical cation (eqn 33) it is seen that a competing process, one-electron reduction (eqn 38) is possible too. A survey of the behaviour of certain aromatic and heteroaromatic radical cations in homogeneous media revealed a rather scattered and certainly not understandable picture with respect to the preference of either of these reaction modes.[50] Application of the Dewar–Zimmerman rules to a probable transition state for the nucleophilic interaction seems to resolve some of the apparent anomalies (Fig. 5). If a nucleophile uses its interacting orbital in a suprafacial manner in the reaction with a radical cation derived from a 4n + 2 aromatic system, the transition state has antiaromatic character and hence the reaction corresponds to an unfavorable pathway. For the same interaction with the nucleophile using its orbital in an antarafacial manner,



(a) (b)

Fig. 5. Orbital representation for the transition state of the reaction between a benzene radical cation and (a) a nucleophile interacting suprafacially (exemplified by a halide ion) or (b) a nucleophile interacting antarafacially. Reprinted by courtesy of The Chemical Society.[50]

the transition state has aromatic character. Thus halide ions, belonging to the first category (Fig. 5) should not react as nucleophiles with radical cations from 4n + 2 systems; instead electron transfer occurs (Cl^-, Br^-, I^-) or the reaction should not take place at all (F^-). Available data on the reactivity of perylene radical cation are in agreement with this reasoning. For radical cations derived from 4n parent systems, no restriction is imposed upon any type of nucleophilic interaction.

The interesting part of this set of predictions is, in the Popperian sense, of course the restrictions imposed upon the reactions between halide ions and aromatic radical cations from 4n + 2 parent systems. Anodic halogenations have been known since the turn of the century,[51] and it has generally been concluded from mechanistic investigations that they proceed via anodically generated halogens (I_2, Br_2, Cl_2) or, in the case of fluorination, high valence metal fluorides like NiF_3,[28] generated on a nickel anode by oxidation of a fluoride ion containing electrolyte solution (usually HF/KF). More recently, two types of anodic aromatic halogenation reactions have, however, been proposed to be direct reactions. Anodic bromination of arenes was one case,[52] and fluorination of aromatics in acetonitrile/$R_4N^+H_3F_4^-$ at a Pt anode was another and perhaps more wide-ranging one.[53–57] In both cases radical cations were assumed to be the primarily formed species, reacting further with halide ion in a step that was postulated above to correspond to a "forbidden" pathway.

While we do not quite place ourselves in the group of chemists defined by the statement "there is a fair body of chemists who hold that you must not believe any data that are not confirmed by theory",[58] we would nevertheless like to suggest that the problem of anodic halogenation mechanisms by no means is settled and that eqns (36)–(38) in principle may provide other pathways for anodic halogenation besides the direct one via the radical cation. Dication formation at the anode (eqn 36) has been studied extensively[59] and is a well established process; it should occur at higher potentials, the difference between the first and second $E_{1/2}$ values, $\Delta E_{1/2}$, having been determined to vary between 0.2 and 0.7 V for a series of aromatic radical cations. The disproportionation equilibrium (eqn 37) should give a kinetically significant dication concentration if $\Delta E_{1/2}$ is not too large. Finally, at least for bromination eqn (38) provides a route for the formation of halogen at high potential, i.e. an indirect mechanism. This pathway would result in a current density dependent upon substrate concentration[52] and be very similar to the direct mechanism in many respects, more so with increasing reactivity of the arene toward electrophilic bromination.

For the anodic fluorination of aromatic compounds in acetonitrile in the presence of fluoride ion donating anions, the situation is summarized in Table 1. In this case formation of the free halogen is claimed to be excluded at potentials below 3.0 V and possibly higher potentials. Table 1 shows that CPE experiments leading to fluorination products in most cases have been performed at potentials close to the region where a second electron transfer can take place (i.e. at $E_{1/2}$ of the first step plus 0.3–0.5 V or more).

Electron transfer mechanisms have been discussed in great detail[28] recently for fluorinations performed by high valence metal fluorides like CoF_3. Also here fluoride ion-aromatic radical cation reactions have been proposed, and also here the same problem of possible mechanistic diversification should be taken into account.

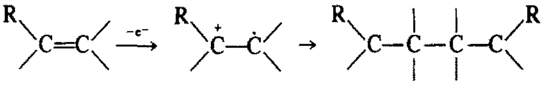
Table 1. CPE conditions for anodic aromatic fluorinations in acetonitrile/$Me_4N^+H_2F_3^-$ (for 9,10-diphenylanthracene)[53] or $Et_4N^+H_3F_4^-$ (all other compounds)[54–57]

Compound	Anode potential in CPE run/V vs SCE[a]	$E_{1/2}$ of substrate first step/V vs SCE
9,10-Diphenylanthracene	1.65	1.27
Benzene	2.4	
1,4-Di-t-butylbenzene	1.9	
4-t-Butyltoluene	1.9	
Naphthalene	1.8	1.6
Fluorobenzene	2.4	2.0
Chlorobenzene	2.4[b]	2.2
Bromobenzene	2.4[c]	2.1
Benzotrifluoride	3.2	

[a] Saturated calomel electrode. [b] Higher yields were obtained at 2.8 V. [c] Higher yields were obtained at 2.6 V.

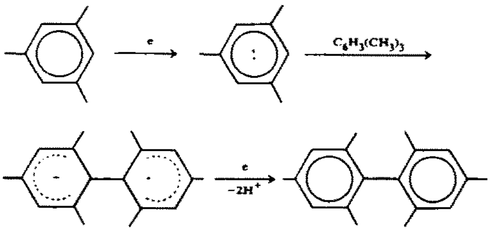
Proton abstraction by base on a radical cation (eqn 34) occurs readily in many cases, e.g. if the radical cation has a hydrogen α to an oxygen or nitrogen function, α to aromatic and double bond systems (benzylic or allylic attack), or even in a non-activated position. Generally, the higher the stability of the neutral radical formed, the more favored is proton abstraction. On the opposite side, proton abstraction from ring positions in aromatic radical cations does not occur; it has been postulated in some cases,[60] but the reactions involved might as well be explained in other terms.

The direct coupling of two radical cations (eqn 35) has been firmly established only for stable or relatively stable radical cations (derived from olefins, stabilized by electron-donating groups). Coupling occurs in the position where a positive charge would be least stabilized according to resonance theory (eqn 39). The question-mark for R = Ar is due to the mechanistic uncertainty still attached to the reactions of this type of radical cations.[9] Attack by the radical cation on the parent olefin (corresponding to eqn 33) is equally feasible for less stable systems. For biaryl coupling both CPE studies[61] and direct spectroscopic



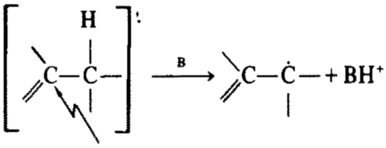
(39)

observation of anodically generated intermediates[62] indicate that this mechanism operates, as illustrated in eqn (40) for mesitylene:



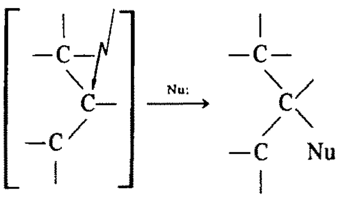
(40)

To generalize, the following reactivity pattern for radical cations has emerged so far: (1) Radical cations derived from saturated systems will preferentially lose a proton (eqn 34) to give a neutral radical, since for other reaction types we will have to invoke the intervention of intermediates with pentacoordinate carbon centers (in principle possible in view of Olah's demonstration of the generality of this concept in carbocation chemistry). (2) Radical cations derived from unsaturated compounds can react via either or any combination of the reaction modes depicted in eqns (33)–(35), but, as mentioned above, the coupling process appears to be relatively rare. Instead, nucleophilic and/or base interaction are predominant. The tendency for a given reaction to follow either of these pathways is dependent upon the positive charge density at different carbon atoms in the radical ion (eqns 41 and 42). If it has



(41)

Position of highest positive charge density



(42)

a high value at the carbon atom adjacent to a center capable of C-H ionization, proton abstraction will take place predominantly, whereas a high value at a carbon atom without any removable β hydrogen favors nucleophilic attack at that particular hydrogen. Some examples of the selectivity of α vs nuclear anodic acetoxylation of alkylarenes is shown below (positive charge densities were calculated by the INDO method;[63] for experimental data, see Table 6).

Also the isomer distribution in nuclear acetoxylation and trifluoroacetoxylation of aromatic compounds (for data, see Table 5) is reasonably well correlated with positive charge densities[63] (Figs. 6 and 7). Positive charge distributions also suffice very well to describe aliphatic reactivities like, e.g. the anodic trifluoroacetoxylation of decane[64] and methoxylation of N,N-dimethylbenzylamine.[65]

According to the reasoning outlined above, it is the reactivity of the radical cation towards different species present in the electrolyte that plays the dominant role for the synthetic outcome of the reaction. This first crucial chemical step is then followed by one or several electrochemical/chemical steps, but these involve the chemistry of more familiar species—neutral radicals and/or carbocations—and are therefore amenable to predictions based upon the vast empirical and theoretical material available for these intermediates.

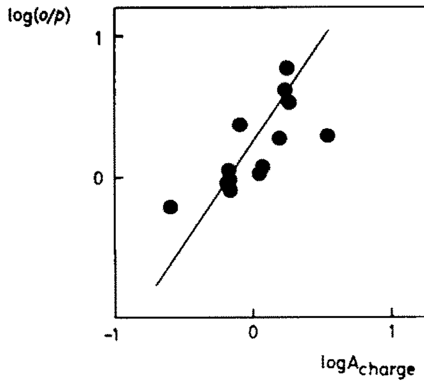


Fig. 6. Logarithmic plot of experimentally determined o/p ratio *vs.* ratio between the positive charge density in the *ortho* and *para* position, respectively (A_{charge}), for anodic acetoxylation and trifluoroacetoxylation (Table 5).

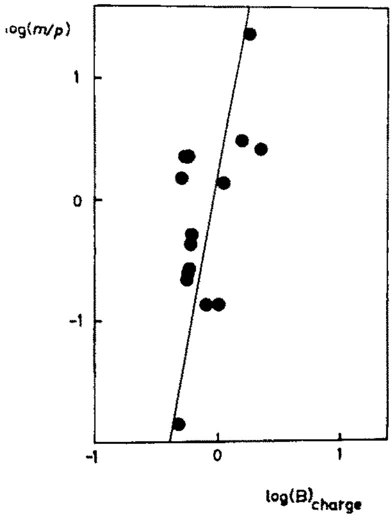


Fig. 7. Logarithmic plot of experimentally determined m/p ratio *vs.* ratio between the positive charge density in the *meta* and *para* position, respectively (B_{charge}) for anodic acetoxylation and trifluoroacetoxylation (Table 5).

At the third level of mechanistic electrochemistry—adsorption and its role in the mechanism—we leave the realm of relatively familiar phenomena and enter the complicated microcosm called the *electric double layer* or *electrified interface* (EI). The EI is a layer adjacent to the electrode surface, 10–15 Å thick, which is composed of adsorbed ions and molecules (Fig. 8). At a given surface, potential and composition of the bulk electrolyte the structure and composition of the EI is considered to be rather well defined, although we cannot at present put any reliable quantitative data into this model.[66]

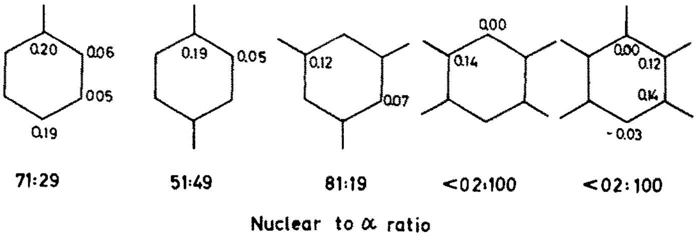


Figure 8 shows at schematic drawing of an anodic EI (positively charged surface), in which the characteristic features of adsorption are represented. Starting from the flat surface—in itself a drastic simplification but at the present state of knowledge there is little else to substitute with that is not pure guesswork—we first encounter a layer of desolvated anions, electrostatically and specifically[†] adsorbed to the anode, and solvent molecules, electrostatically attached to the surface. The next layer is composed of solvated anions, held in their positions by purely electrostatic forces, and interspersed solvent molecules. From this fairly rigid structure we enter less ordered and disturbed regions of the electrolyte solution (the diffuse layer) until the composition and structure of the bulk solution is approached.

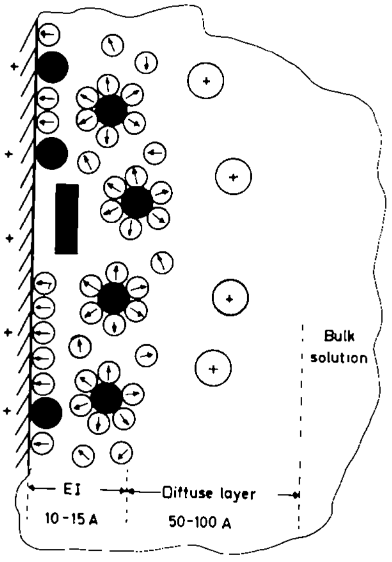


Fig. 8. Schematic representation (cross-section) of an anodic EI. Filled circles, anions; small circles with arrow, solvent molecules with the arrow indicating the direction of the dipole; rectangle, cross-section of an aromatic hydrocarbon, adsorbed with its plane parallel to the electrode surface; large circles with +; cations.

The rectangular symbol in Fig. 8 is intended to symbolize a cross-section of an aromatic hydrocarbon, adsorbed with its planar face to the anode via the same type of bond as in π-donor-acceptor complexes. This type of bonding and orientation is well documented from adsorption studies on aromatic hydrocarbons at platinum anodes.[67]

It is immediately obvious that this situation, with an EI structure and composition dependent upon the largely unknown adsorption behaviour of the species present in the electrolyte solution, does not easily lend itself to predictions about its possible influence upon mechanism and product distribution. Some attempts at a more detailed discussion have been made, but amount to no more than empirical findings clad in theoretical language garb. On the other hand, one would imagine intuitively that important consequences of the EI structure might be possible due to the simple fact that the follow-up reactions of highly reactive intermediates must take place in the EI.

We have spent a great deal of effort on trying to find such effects of adsorption, but cannot say that we have been very successful in finding unambiguous cases. A few, hopefully significant experimental findings that *can* be attributed to adsorption effects have, however, been found: (1) Anomalous nucleophilicity orders, such as acetonitrile being a stronger nucleophile than water in the competing acetamidation and hydroxylation reaction[13,68] (eqns 7 and 9) and water being a stronger nucleophile than RCOO$^-$ or pyridine in the carbonium ion pathway of the Kolbe reaction,[13] (2) anomalous stereochemistry, in that a thermodynamically less stable *cis* isomer is formed to a larger extent in the anodic process than in an analogous homogeneous reaction,[69] and (3) anomalous regiospecificity, as for example in the change of the *o/p* ratio for the anodic acetoxylation of anisole by addition of naphthalene or another aromatic hydrocarbon to the electrolyte solution.[70]

Recently, the very important observation was made that one can chemically modify the surface of a graphite electrode and thus influence the product distribution.[71] The surface was oxidized, thus becoming covered by carboxyl groups. By treatment with thionyl chloride and (−)-phenylalanine methyl ester, the graphite surface assumed the property of a chiral electrode. Thus, anodic intramolecular coupling of laudanosine gave the product, O-methylflavinantine, with up to 40% asymmetric induction.[72] This experiment shows that the layer of electrode next to the solution does play a role in the follow-up reactions. By inference, it would be surprising if the EI would not have similar effects. On the cathodic side, it is known that the presence of optically active cations in the electrolyte solution can induce optical activity in the reduction products formed,[73] but here alternative explanations besides adsorption effects are possible. And finally it should be kept in mind that the effects that have been mentioned are very small energywise, at most 5–6 kJ/mol. Can we really interpret effects in this range?

From what has been said above concerning adsorption and its role in organic electrode processes, we can be sure that it is often important in determining the ***nature*** of the process(es) possible in a given electrolyte at a given electrode material. On the other hand, as a first approximation we can state that adsorption plays little or no role in determining the *product distribution* from a given reaction, i.e. if we could simulate the electrode process by some homogeneous electron transfer reaction, the product distribution would be similar or identical (Section 12). In other words, we cannot make much use of the adsorption phenomenon in organic electrosynthesis, in spite of the fact that the energetics of adsorption (e.g. adsorption enthalpies of arenes on platinum from aqueous solutions are of the order of −(24–40) kJ/mol)[67] in principle would seem to allow for experimentally rather dramatic effects. This is maybe a pessimistic conclusion but nevertheless the only possible one at the present level of knowledge.

At the fourth level, the mechanistically very complex problem of the effect of electrode material appears. In anodic chemistry it is somewhat simplified by the fact that only relatively few materials resist the strongly corroding conditions prevailing at anodic potentials. For general use only platinum, different kinds of carbon, a few metal oxides (e.g. lead dioxide, magnetite) and some carbides (e.g. boron carbide) are available. Table 2 shows how a standard reaction, anodic acetoxylation of mesitylene,[74] is influenced by the nature of the electrode material. The

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[†] In this context, "specific" denotes that the strength of the adsorption bond is dependent upon the chemical nature of the anion.

Table 2. Anodic acetoxylation of mesitylene[74] (0.2 M) in acetic acid/1 M sodium acetate at constant current density (10 mA/cm^2 of geometrical area)

Anode material[a]	Ratio between 2,4,5-trimethylphenyl acetate and 3,5-dimethylbenzyl acetate	Current yield of acetates (%)
Gold	3.6	23
Platinum	4.4	19
Palladium	4.9	13
Rhodium	7.6	57
Platinum on graphite	14	38
Lead dioxide on graphite	9.6	37
Magnetite, bulk material	10	22
Magnetite on titanium[b]	7.7	38
Boron carbide	22	27
Carbon cloth	23	34
Glassy carbon	21	35
AUC graphite	23	56
Sigriflex graphite[c]	15	45

[a] Source of anode materials, see Ref. 74 unless otherwise noted. [b] From KemaNord, Ljungaverk, Sweden. [c] From Sigri AG.

measured variables are the nuclear vs side-chain substitution ratio and current yield of products. The reaction was chosen because its oxidation potential is situated in a region where the Kolbe oxidation of the supporting electrolyte competes to an easily measurable extent. Some interesting features are discernible in Table 2; bright gold, platinum palladium and rhodium sustain a less selective reaction than the porous materials (glassy carbon very quickly converts to a porous surface under the conditions employed) and a lower current yield (except for rhodium). This is a fairly general observation in anodic synthesis and makes graphite of different types or lead dioxide the materials of choice for anyone who contemplates running a new anodic reaction. Platinum or other noble metals, indispensible as they are in mechanistic studies, are of limited use for runs on any reasonable scale because of their high price (platinum can be electrolytically deposited or glued onto graphite in layers *ca.* 0.01 mm thick, but even so the cost of platinum only is in the range of US $0.50 per cm^2).

It has been proposed that the difference between a bright noble metal and a porous material surface might be due to the large difference in surface roughness factor,[13] which is defined as the ratio between the real electrode area and the geometrical area. For a porous material the roughness factor can easily be 20 or larger which means that reactions run at seemingly identical current densities (as for example in Table 2) may actually be run at drastically different current densities. Then the concentration profiles near the electrode surface (EI and diffuse layer, see Fig. 8) will be different in the two cases, and this would certainly be expected to affect the relative concentrations of radical cation and nucleophile. So far no measurements of roughness factors have been combined with product distribution studies, but it seems necessary to explore the possible influence of this "trivial" difference before one attempts to explain the effect of the electrode material in more sophisticated terms. As one example, the role of the anode material in the Kolbe reaction (radical vs carbocation pathway) has been the subject of much speculation but may really be as simple as indicated above.

9. PROBLEMS OF PRINCIPAL DIFFICULTY IN ANODIC SYNTHESIS

Before we proceed with discussing synthetic applications of anodic substitution, it is only fair to present some problems that in principle are connected with anodic reactions.[75] We have already mentioned the first two below, and can add two others to the list:

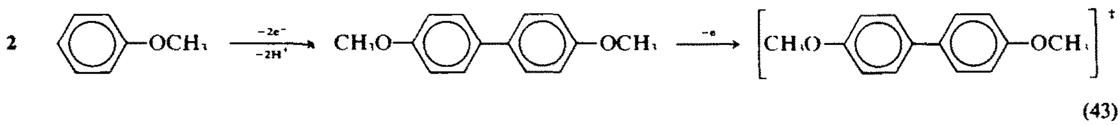
(1) Radical cations do not seem to react with all kinds of nucleophiles (Section 9.2).

(2) The selectivity of electrolytic reactions is not very high, contrary to what is commonly claimed. A $\Delta E_{1/2}$ of at least 0.15 V between two compounds is necessary to separate the corresponding electrode processes in CPE experiments, which cannot be termed an exceptionally high resolution. An investigation of the feasibility of defining anodic "reactivities" from competition experiments designed in the manner of homogeneous solution chemistry has actually shown[70] that this type of reactivity is not very well related to $E_{1/2}$ values. Besides, the span of reactivities thus determined is relatively narrow ($\sim 3 \times 10^2$ for a range of $E_{1/2}$ of 1.62–2.23).

(3) With few exceptions, a carbocation will be formed at some stage of an anodic reaction sequence. With the known tendency of carbocations to undergo elimination, cleavage, rearrangement, etc. it is hardly surprising that complex product mixtures are often formed in anodic reactions. As a reasonably reliable rule of thumb we may state that the more difficulty oxidizable a substrate is, the more complex will the product mixture be due to the intervention of high-energy cationic species, e.g. in the form of non-solvated ions. Except for those improvements which sometimes can be achieved by a change in electrode material—and, as mentioned above, these are not predictable at our present state of knowledge—this situation is not amenable to experimental corrections. Work with the aim of finding new electrode materials is highly desirable since it might alleviate this problem.

(4) The product from an anodic process is often as easily as or more easily oxidized than the starting material, so that already at low conversion further oxidation of the desired product might become a serious side-reaction. In the discontinuous procedures of the laboratory this problem is sometimes troublesome, but it is more easily handled on a technical scale. Here continuous flow processes with work-up at low conversion are at least in principle feasible.

In some cases over-oxidation may actually be an advantage, as in the dehydrodimerization of anisole where the product is stabilized in the form of its radical cation in the electrolyte solution[76] (eqn 43). This can be reduced back to the product at the end of the experiment.



(43)

10. PRACTICAL PROBLEMS IN ELECTROLYSIS

For small-scale electrolysis (up to, say, the 0.2 molar scale), it is no problem whatsoever to set up an electrochemical cell, especially not for anodic reactions. A beaker, equipped with a cooling coil or a water jacket, two electrodes (Pt or graphite as anode, stainless steel as cathode), and a magnetic stirring unit is quite sufficient for a simple preparative experiment. For CPE a reference electrode is needed too. Very few anodic reactions require a divided cell, but if it should be necessary, a glass frit will serve well as a divider. One example where an anodic process requires a divider, is acetamidation (eqn 9). In nonaqueous acetonitrile, the intermediate nitrilium ion (eqn 44) is stable

$$\mathrm{R{-}H} \xrightarrow[-\mathrm{H}^-]{-2e} \mathrm{R}^+ \xrightarrow{\mathrm{CH_3CN}} \mathrm{R}\overset{+}{\mathrm{N}}{\equiv}\mathrm{C{-}CH_3} \xrightarrow{\mathrm{H_2O}} \mathrm{RNHCOCH_3} \qquad (44)$$

and, being an easily reducible species, it must be prevented from reaching the cathode. With traces of water present acetamidations can be run in nondivided cells[77] but yields are still considerably lower than in divided ones.

As one increases the scale of operation, a few experimental difficulties begin to make themselves felt. Especially the need for passing high currents through the cell in order to attain reasonable reaction times, creates needs for special equipment. To illustrate the problem, eqn (45) shows the amount of electrical energy (and hence, the cost) needed for an electrochemical reaction run at 100% current yield

$$\text{Electrical energy needed} = 27\, E_{\mathrm{app}} \frac{n}{M} \quad \text{kWh/kg of product} \qquad (45)$$

with respect to the desired product. Here E_{app} is the applied voltage (as pointed out above, equal to the sum of the two electrode potentials and the ohmic potential drop, $E_a + E_c + Ri$), n the number of electrons transferred per molecule of product, and M the molecular weight of the product. The latter two quantities cannot be manipulated for a given reaction, but they tell us that the cost of electrical energy of a many-electron process for a small molecule is prohibitively high (an example would be the cathodic reduction of nitrogen to ammonia; it is a very interesting reaction in itself but has very little prospect for practical applications).

What we can manipulate is E_{app}, and here we have several possibilities. Firstly, and most difficult, one can try to develop better electrode materials in order to have E_a and E_c approach the thermodynamic potentials as closely as possible at the current densities prevailing during electrolysis. Secondly, one can try to minimize the potential drop due to ohmic resistance by decreasing the distance between the electrodes, and/or increasing the conductance of the electrolyte. The latter possibility may lead to higher costs due to higher expenditure on supporting electrolytes, so the most employed way of reducing iR has been to reduce the distance between the electrodes to the extent that one can talk about *capillary gap* cells. In such a cell the distance between anode and cathode is 1 mm or less, the present limit being something around 10^{-3} mm in the rotating shear flow cell.

Capillary gap cells exist in different designs,[78,79] and we shall not here dwell upon the merits of any of these designs. It suffices to say that we constructed a concentric version a few years ago[44,75,79] to meet the criteria listed below:

(1) Operation at currents up to 50 A should be possible, which means the transfer of about 2F/h or formation of one mol of product per h in a two-electron process.

(2) Graphite should be used as anode material, since designs based on platinum would be too expensive.

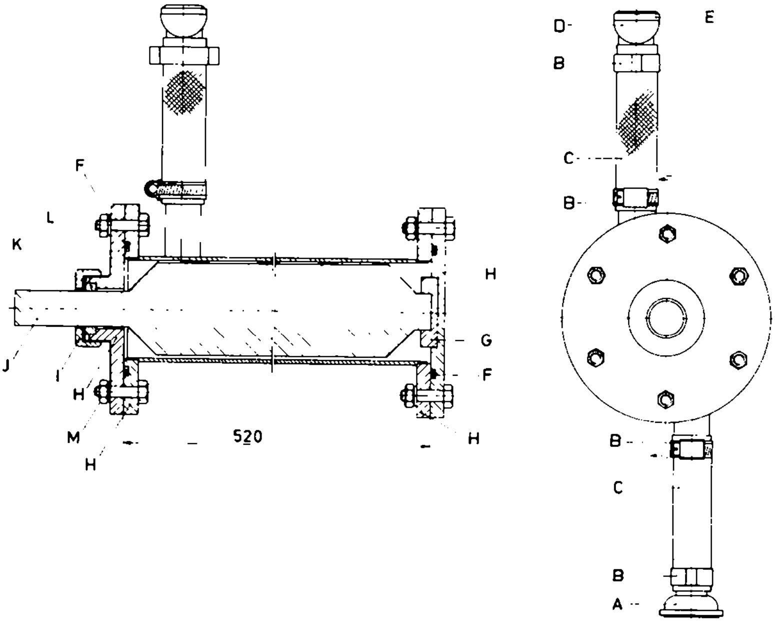


Fig. 9. Drawing of a concentric capillary gap cell with an anode area of *ca.* 800 cm². A, cup of a flexible joint (Rotulex® 4.692-15); B, hoseclip; C, PTFE tubing with steel wiring support (Texan® 4201-12); D, ball of a flexible joint (Rotulex® 4.691-15); E, PTFE sealing ring (Rotulex® 4.690-04); F, Viton® O-ring (65.09 × 3.53); G, glass-fiber reinforced PTFE anode support; H, stainless steel (Uddeholm 24L, D17730), flange and end support; I, polypropylene; J, graphite (AUC quality from Union Carbide) anode; K, stainless steel washer; L, sealing ring (Sovirel® 4701-26); M, M6 × 25 bolt + nut and washer. Reprinted by courtesy of Acta Chemica Scandinavica, Ltd.[79]

Table 3. Examples of anodic substitutions run in the concentric capillary gap cell[79]

Process	Substrate	Product isolated	Scale/mol of substrate	E_{app}/V	Current (A)	Material yield (%)
Acetoxylation	$HCON(CH_3)_2$	$HCON(CH_3)CH_2OAc$	5	40–60	50	92
Acetoxylation	4-t-Butyltoluene	4-t-$BuC_6H_4CH_2OAc$	2	60	20	73
Acetoxylation	Mesitylene	2,4,6-$Me_3C_6H_2OH^a$	1	20	20	40
Dehydrodimerization	Mesitylene	Bimesityl	8	10	25	42
Dehydrodimerization	Naphthalene, pentamethylbenzene	1-(Pentamethylphenyl)-naphthalene	3	22	20	54
Dehydrodimerization	Durene	2,3,4,5,2′,4′,5′-Heptamethyldiphenylmethane	1	31	10	20
Methoxylation	$HCON(CH_3)_2$	$HCON(CH_3)CH_2OMe$	5	26	50	75
Methoxylation	*N*-Formylpyrrolidine	*N*-Formyl-2-methoxy-pyrrolidine	4	15–20	50	97
Methoxylation	*N*-Formylmorpholine	*N*-Formyl-3-methoxy-morpholine	4	15–20	50	92

[a] Isolated after hydrolysis of the crude product.

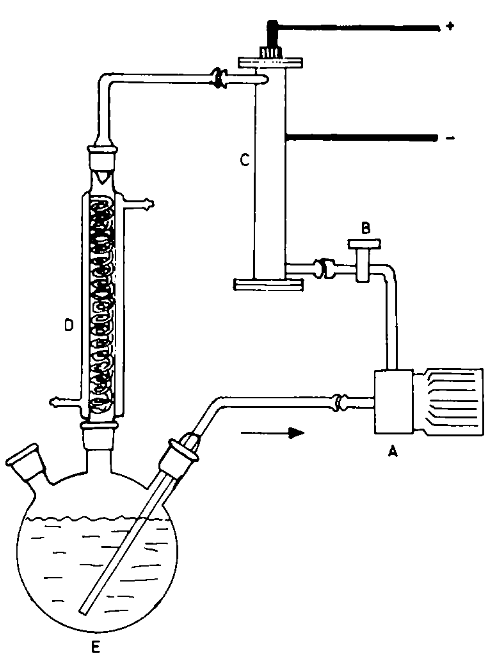


Fig. 10. Schematic picture of large-scale cell (Fig. 9) flow system. A, pump; B, valve; C, cell; D, heat exchanger; E, electrolyte reservoir.

(3) The construction should be as simple as possible in order for the cell to be useful for organic chemists.

(4) The cell should be convertible to a divided one.

The concentric capillary gap cell (Figs. 9 and 10) meets these criteria reasonably well. It has now been used with good results for acetoxylations, alkoxylations and couplings (examples, see Table 3). In laboratory practice, we have not aimed at running the reactions at as low an E_{app} as possible, but instead tried to keep the supporting electrolyte concentration low (0.01 M or lower), of course due to the rather peculiar arrangement for financial support at university laboratories; electricity is free but chemicals not. It is just as easy to invert these aims or to optimize with respect to both, as one really should do. The cell has been built in two versions, with anode areas of 800 and 3000 cm^2, respectively. In the latter one, runs at 350 A have been successfully performed. A divided version of the smaller cell has been built (a Nafion® membrane as cell divider) but the membrane problem in nonaqueous media has hitherto prevented its use for reactions other than chemically trivial test reactions.

Another approach to eliminate the disadvantages of low-conductance electrolyte systems has been to use emulsion electrolysis[80] which holds promise to be the method of choice for many cases of large-scale electrolysis. The idea behind is illustrated in Fig. 11, where aqueous sodium cyanide is the continuous phase and dichloromethane-substrate the dispersed one. In order to bring cyanide ion into the organic phase, a small amount of a phase transfer agent is added, e.g. tetrabutylammonium sulfate. Anodic oxidation of an emulsified system of this type gives good yields of cyanation products (Table 4 for examples) in contrast to the low yields obtained in homogeneous media.[35,81] Besides, E_{app} is reduced by a factor of 4–18 as compared to a homogeneous dichloromethane electrolyte.

Emulsion electrolysis has also been applied to acetoxylation and works well, if one provides for ion pair extraction of acetate ion not as such, but as AcO^-HOAc, by adding an equivalent amount of the free carboxylic acid to the system.[82] Thus acetoxylation of anisole occurs

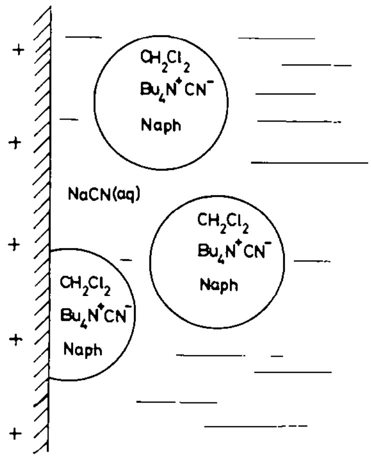


Fig. 11. Principle of emulsion cyanation. Droplets of dichloromethane containing substrate (naph = naphthalene) and tetrabutylammonium cyanide are produced by agitation, using aqueous sodium cyanide as the continuous phase. Anodic oxidation in the organic phase produces cyanonaphthalene, and the used cyanide is constantly replenished by ion-pair extraction from the aqueous phase.

Table 4. Anodic cyanation in different systems[35,80,81] (Pt anode)

System	Substrate	Material yield of cyanation product	Ratio of *o*/*p* or *α*/*β*
Emulsion[a]	Anisole	71	30/70
MeOH/NaCN (1.6M)	Anisole	7	38/62
MeCN/Et_4NCN (0.5M)	Anisole	5	51/49
Emulsion[a]	Naphthalene	69	88/12
MeOH/NaCN (1.0M)	Naphthalene	17	100/0[b]

[a] Aqueous sodium cyanide (3.0M) dichloromethane-substrate (0.5M) with tricaprylylmethylammonium ion as the phase transfer agent.

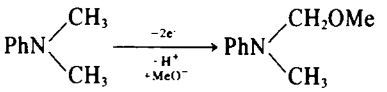
[b] Another investigation in the same system gave a ratio of 90/10.

with 45% current yield in aqueous sodium acetate/dichloromethane-acetic acid with tetrabutylammonium ion as the phase transfer agent.

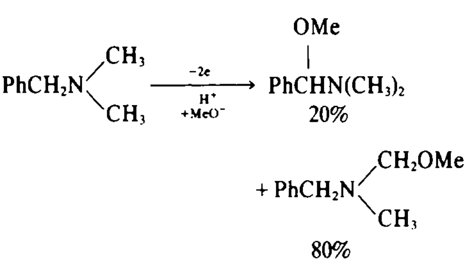
11. APPLICATIONS OF ANODIC ADDITION AND SUBSTITUTION REACTIONS

11.1 *General*. The purpose of this section is to illustrate the synthetic uses of anodic addition and substitution reactions, especially those with represent C–O, C–N and C–C bond formation. Fluorinations via cationic species have already discussed in Section 8 (Table 1). Since literally thousands of anodic substitutions and additions have been described, we must limit ourselves to the most promising synthetic applications.

11.1 *Alkoxylation*. Anodic alkoxylation can be performed either in strongly basic systems, such as alcohol/alkoxide, or in neutral ones, e.g. alcohol/tetraalkylammonium tetrafluoroborate.[8,9] The most commonly employed alcohol is methanol. In the basic system, the synthetic use of methoxylation is limited to easily oxidizable compounds since methoxide ion is oxidized already at about 0.9 V. Thus substrates like N,N-dimethylaniline[83] ($E_{1/2}$ 1.20 V) and N,N-dimethylbenzylamine[65,84] ($E_{1/2}$ 0.92 V) are methoxylated in 90 and 60% material yield, respectively (eqns 46 and 47),



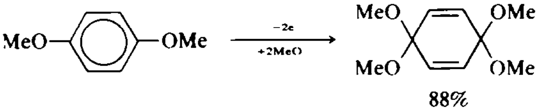
$$\mathrm{PhN}\left\langle\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\right. \xrightarrow[\substack{-\mathrm{H^+}\\ +\mathrm{MeO^-}}]{-2e^-} \mathrm{PhN}\left\langle\begin{matrix}\mathrm{CH_2OMe}\\ \mathrm{CH_3}\end{matrix}\right. \qquad (46)$$



$$\mathrm{PhCH_2N}\left\langle\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\right. \xrightarrow[\substack{\mathrm{H^+}\\ +\mathrm{MeO^-}}]{-2e} \underset{20\%}{\mathrm{PhC}\overset{\mathrm{OMe}}{\overset{|}{\mathrm{H}}}\mathrm{N(CH_3)_2}} + \underset{80\%}{\mathrm{PhCH_2N}\left\langle\begin{matrix}\mathrm{CH_2OMe}\\ \mathrm{CH_3}\end{matrix}\right.} \qquad (47)$$

whereas tetralin ($E_{1/2}$ estimated at about 1.9 V) gives *α*-methoxytetralin in 13% yield only.[85] Nuclear substitution of aromatic compounds takes place to a very low extent in basic electrolytes,[8] presumably because of *α* proton abstraction when possible (or possibly addition; see below).

Anodic reactions of the methoxylation type sometimes permit unusual reaction pathways due to the fact that carbocations are generated in strongly nucleophilic/basic media. Thus, the Wheland intermediate can be trapped to give the anodic addition product from an aromatic derivative, as for example with 1,4- and 1,2-dimethoxybenzene[86] (eqns 48 and 49). The tetraketal from the latter reaction is opened oxidatively to give hexamethyl *cis,cis*-orthomuconate in 77% yield. Anodic additive methoxylation has had some interesting synthetic applications, as for example shown in eqn (50).[87] Furans have long been known to undergo anodic 1,4-bisalkoxylation (eqn 51) with high yields of synthetically useful intermediates.[88] In benzofurans, 1,2-addition takes place across the olefinic bond.[89]



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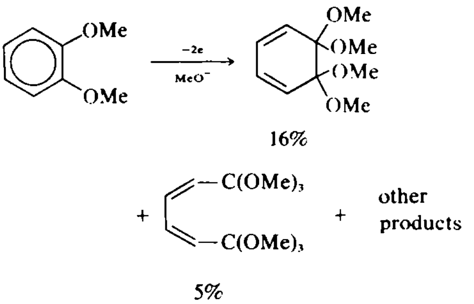

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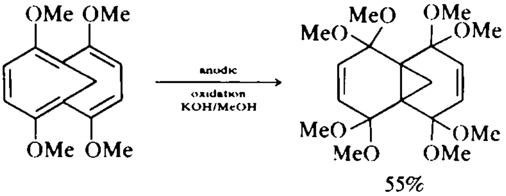

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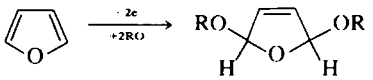
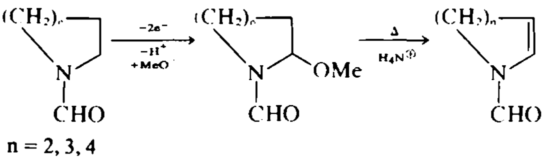


(51)

N,N-Dialkylamides, mostly derived from formic acid, are excellent substrates for methoxylation[79] (for examples, see Table 3). *α*-Methoxyamides are formed in almost quantitative yield; they are intermediates for the synthesis of otherwise very difficultly accessible enamides[90] (eqn 52) and amidoalkylation of aromatic compounds (eqn 53).



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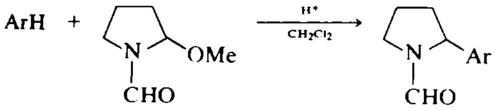
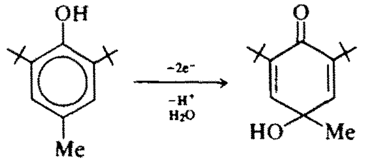


(53)

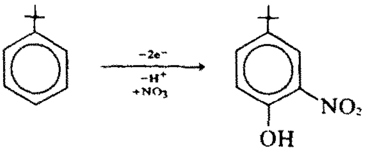
The latter reaction in principle allows for *ω*-functionalization of aromatic compounds via a hydrogenation step. Also carbamates[91] can be anodically alkoxylated α to nitrogen.

11.3 Anodic hydroxylation, although in principle a very attractive reaction type, has not found much use due to the inherent difficulty that products in many cases are much more easily oxidized than starting materials. Some α-hydroxylations of alkylarenes have been successfully run (e.g. isopropylbenzene[92] and hexamethylbenzene[68]) and, as mentioned above, some additive hydroxylations of furan derivatives[43] (eqn 30) have proved to be of great synthetic value. Certain hindered phenols have been hydroxylated to give hydroxycyclohexadienones,[93] again a reaction with some synthetic potential (eqn 54).



(54)

11.4 *Anodic nitratation* competes with acetoxylation during anodic oxidation of alkylarenes in acetic acid/ammonium nitrate[23-26] (eqns 4a and 4b). From alkylarenes, only α nitrates are formed; if no α position is available, o-nitrophenols, which probably are formed by rearrangement of nuclear nitrates, can be isolated in low yield[23] (eqn 55).



+ isomers (55)

11.5 *Anodic acyloxylation* is one of the most generally applicable substitution reactions.[19] It permits acyloxylation of alkanes,[64] olefins,[27,94] deactivated[95] and activated[96] aromatic compounds, and amides,[9] provided the carboxylate is chosen with care. For substrates that are difficult to oxidize (alkanes, deactivated aromatics) trifluoroacetate is the reagent of choice; for the rest acetate works satisfactorily. Formyloxylation and aroyloxylation have been performed occasionally but do not offer any advantages over the others.[9]

Anodic aromatic acyloxylation has been extensively studied because of its applicability to a wide range of aromatic compounds. Therefore, one can obtain a fairly large and homogeneous collection of data permitting comparison with theoretically estimated ones (see Figs. 6 and 7). Its characteristics as an aromatic substitution reaction is shown in Table 5 whereas the variation in the nuclear vs side-chain substitution ratio in acetic acid/sodium acetate is shown in Table 6. In neutral medium, i.e. with no acetate ion present, only side-chain substitution takes place. This allows for the ready preparation of benzylic acetates of different kinds,[79,97] in themselves useful intermediates for mild Friedel–Crafts reactions[98] (for an example, see eqn 56). Amides can be

Table 5. Anodic nuclear acyloxylation of aromatic compounds[69,95,96,100] at platinum (A = acetoxylation, T = trifluoroacetoxylation)

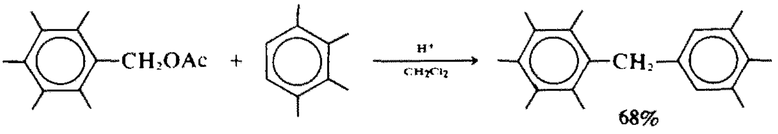
Compound	Isomer distribution *o*	*m*	*p*	Reaction type
Fluorobenzene	34	8	58	A
Chlorobenzene	37	6	57	A
Bromobenzene	30	4	66	A
Iodobenzene[a]	17	4	79	A
Toluene[b]	43	11	46	A
Ethylbenzene[c]	43	10	47	A
Isopropylbenzene[d]	44	17	39	A
t-Butylbenzene	35	22	43	A
Neopentylbenzene	No products formed			A
Diphenylmethane[e]	43	12	45	A
Anisole	67	4	29	A
Phenyl acetate	40	5	55	A
Diphenyl ether	40	—[f]	60	A
Biphenyl	31	1	68	A
Naphthalene	96(1)	4(2)		A
Nitrobenzene	22	59	19	T
Benzotrifluoride	35	47	18	T
Benzonitrile	45	35	25	T
Benzoic acid[g]	73	—[h]	27	T
Methyl benzoate	58	29	13	T
Ethyl benzoate[g]	69	—[h]	31	T
Acetophenone	59	32	14	T
	90[g]	—[h]	10[a]	T
Benzophenone	70	18	12	T

[a] The predominant product (90%) was formed by attack on iodine. [b] 29% α. [c] 50% α. [d] 47% α. [e] 19% α. [f] Not given. [g] In 2:1 methylene chloride-trifluoroacetic acid with 0.1 M tetrabutylammonium tetrafluoroborate as supporting electrolyte. [h] Yield not given.

Table 6. Nuclear *vs* side-chain (α) anodic acetoxylation of alkylarenes in CH_3COOH/CH_3COONa at platinum[69,74,79,96,97,100,101]

Compound	Nuclear substitution	Side-chain substitution
Toluene	71	29
Ethylbenzene	50	50
Isopropylbenzene	53	47
Neopentylbenzene	No reaction[a]	
Diphenylmethane	81	19
p-Methoxytoluene	4	96
p-Xylene	51	49
Indan	21	79
2-Methylindan	16	84
2,2-Dimethylindan[b]	2	98
2-t-Butylindan	17	83
Mesitylene[c]	81	19
Acenaphthene	11	89
1-t-Butylacenaphthene	11	89
Durene	<0.2	100
Pentamethylbenzene	<0.2	100

[a] In HOAc/Bu_4NBF_4 (0.1 M) the α acetate is formed. [b] On graphite the nuclear: α ratio was 15:84. [c] On graphite the nuclear: α ratio was 96:4.



(56)

acetoxylated in good yield,[9] N - acetoxymethyl - N - alkylamides being synthetically useful as amidoalkylating agents under very mild conditions.[41]

Additive acyloxylation is of some preparative interest, as for example shown in eqn (29). Only relatively easily oxidizable compounds undergo this reaction; if the substrate is not oxidized at the prevailing potential, alkyl radicals from the Kolbe oxidation of the carboxylate ion add to the double bond or system of double bonds, with rather complex mixtures as the result.[99]

11.6 *Anodic acetamidation*, first recognized and extensively studied in its Kolbe version[102–105] (eqn 2, $Nu^- = CH_3CN$, $E^+ = CO_2$) has turned out to be a widely applicable reaction for the substitution of C–H bonds,[68,77,106–110] especially non-activated ones.[77,107,109,110] It can also be performed with alkyl iodides[111] (in one case even a bromide[77]) but here it seems as if the initially postulated direct mechanism (eqn 57) at least partially must be supplemented by an indirect one (eqn 58), proceeding via an I(I) species.[112]

$$R{-}I \xrightarrow{-e} RI^{\dot{+}} \xrightarrow{CH_3CN} R\overset{+}{N}{\equiv}C{-}CH_3 + 1/2I_2 \qquad (57)$$

"Two-pot" reaction: $1/2I_2 \xrightarrow{-e^-} \text{“}I^+\text{”} \xrightarrow{RI} R^+ + I_2$

$$\xrightarrow{CH_3CN} R\overset{+}{N}{\equiv}CCH_3. \qquad (58)$$

We have already alluded to the fact that acetamidation must be run in a divided cell in order to avoid cathodic transformations of the initially formed nitrilium ion. In some cases undivided cell operation has been reported,[77] but yields of products are much lower.

Alkanes, from pentane upwards, can be oxidized to acetamido compounds in the presence of inert electrolytes like tetrabutylammonium tetrafluoroborate.[107] In acetonitrile, this supporting electrolyte allows for attaining very positive potentials, up to 3.2 V vs SCE. From alkanes a mixture of isomers is obtained, exemplified by the formation of 2-, 3- and 4-acetamido-octane in 15, 16 and 14% yield. No skeletal rearrangement is observed, and the product distribution is the statistically expected one (cf. trifluoroacetoxylation of decane).[64] At low temperature (−45°C) certain branched hydrocarbons are cleaved,[109] as for example in the case of 2,2,4-trimethylpentane (eqn 59). Adamantane and derivatives thereof is converted into 1-acetamido derivatives in very good yields.[77]

$$(CH_3)_3CCH_2CH(CH_3)_3 \xrightarrow[\substack{-45°C \\ CH_3CN}]{\substack{\text{Anodic} \\ \text{oxidation}}} (CH_3)_3CNHCOCH_3$$

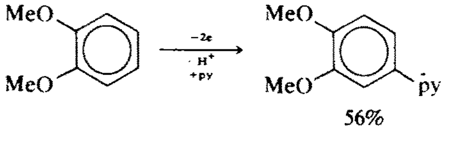
$$+ (CH_3)_2CHNHCOCH_3 + CH_3CH_2CH(CH_3)NHCOCH_3. \qquad (59)$$

A few aromatic compounds (benzoic acid, ethyl benzoate, aceto- and propiophenone, anthracene) have been acetamidated in the ring,[95b,113,114] but the scope of this reaction is far from explored. It has the potentiality of being a direct aromatic amination reaction, where the product is relatively difficult to oxidize, and should have great practical value. In methylarenes, the α position is substituted in fair yield[68] (undivided cell operation).

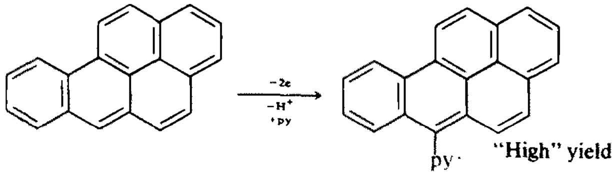
Of great interest are the (ω − 1) acetamidations that have been reported to occur with straight-chain aliphatic esters[110] and ketones.[109] Although the reaction is not more than moderately selective in most cases, it holds some promise for permitting unconventional synthetic steps.

11.7 *Anodic pyridination* is a little explored procedure that can take place either as substitution or addition. So far its main interest has been mechanistic; pyridine and its derivatives constitute a range of nucleophiles with conveniently variable electronic and steric properties and can thus be used for testing different aspects of electrode mechanisms.[115–119] They are very resistant toward oxidation ($E_{1/2} > 2.0$ V) and the products formed, pyridinium ions, even more so, so that preparative pyridinations normally proceed with very good yields (in a divided cell; pyridinium ions are easily reducible!).

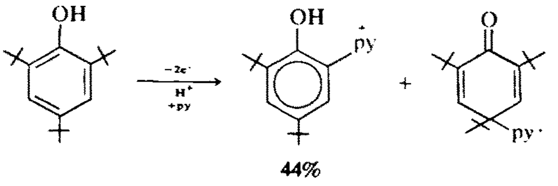
Substitutive pyridinations have been carried out with benzanilides,[120] Schiff's bases,[121] benzo[a]pyrene,[122] veratrole,[123] and t-butyl substituted phenol derivatives,[36] whereas the additive variety has been applied mostly to aryl olefins and anthracene derivatives.[115–119] Some examples are shown in eqns (60)–(62); note that t-butyl acts as a leaving group in eqn (62).



(60)



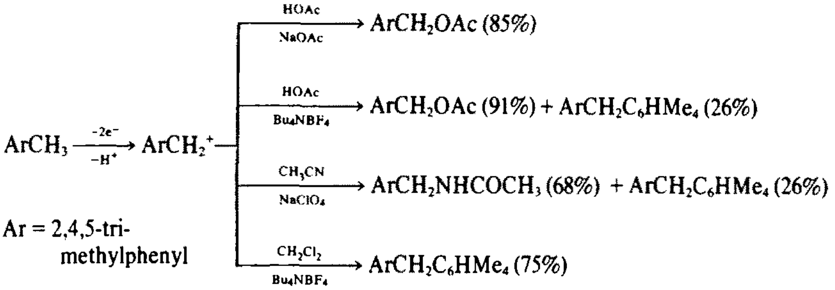
(61)



(62)

11.8 *Anodic isocyanation* is a rare reaction in the electrochemical literature. An example is the formation of 1-naphthyl isocyanate by anodic oxidation of naphthalene in molten ammonium cyanate.[124]

11.9 *Anodic dehydrodimerization or coupling* is an important reaction with many successful applications described.[9] The reason for this is obvious: The concentration profiles of substrate and intermediates set up at or near the electrode surface clearly must favor reactions between intermediates (e.g. coupling of two radicals) or between an intermediate and substrate (e.g. attack of radical cation upon substrate), provided the nucleophilicity of the other electrolyte components is weak or nonexisting. This is demonstrated by the anodic transformations of durene in electrolyte solutions of decreasing nucleophilicity[3] (eqn 63).



$$\mathrm{ArCH_3} \xrightarrow[-\mathrm{H}^+]{-2e^-} \mathrm{ArCH_2}^{+} \begin{cases} \xrightarrow[\mathrm{NaOAc}]{\mathrm{HOAc}} \mathrm{ArCH_2OAc}\ (85\%) \\ \xrightarrow[\mathrm{Bu_4NBF_4}]{\mathrm{HOAc}} \mathrm{ArCH_2OAc}\ (91\%) + \mathrm{ArCH_2C_6HMe_4}\ (26\%) \\ \xrightarrow[\mathrm{NaClO_4}]{\mathrm{CH_3CN}} \mathrm{ArCH_2NHCOCH_3}\ (68\%) + \mathrm{ArCH_2C_6HMe_4}\ (26\%) \\ \xrightarrow[\mathrm{Bu_4NBF_4}]{\mathrm{CH_2Cl_2}} \mathrm{ArCH_2C_6HMe_4}\ (75\%) \end{cases} \qquad (63)$$

Ar = 2,4,5-tri-
methylphenyl

Side-chain substitution takes place via the benzylic cation and only when all nucleophiles except durene itself are removed is the coupling process the favored one (as in dichloromethane-tetrabutylammonium tetrafluoroborate). One step further in decreasing nucleophilicity is to work in acidic electrolytes[125]—remember that a lot of classical organic electrochemistry was successfully performed in sulfuric acid containing media[51]—and here we encounter the recent brilliant work carried out by Parker *et al.* in trifluoroacetic acid,[59] a medium convening unusually high stability to radical cations and even dications. The full synthetic scope of acidic media is not known yet but should be wide-ranging.

The coupling mode in eqn (63), diphenylmethane coupling, is more strongly dependent upon medium nucleophilicity than the second possible aromatic dehydrodimerization reaction, biaryl coupling.[126–128] Thus coupling of mesitylene to give high yields of bimesityl takes place equally well in acetic acid, acetonitrile, and dichloromethane with tetrabutylammonium tetrafluoroborate as the supporting electrolyte. A third possibility, bibenzyl coupling, is in principle possible with alkylbenzenes,[68,129] but has so far been observed as a side-reaction only.

Intramolecular couplings have been performed in a few complex systems of great interest, e.g. alkaloid precursors.[130,131] Table 7 contains selected examples of synthetically useful coupling reactions of the inter- and intramolecular type (see also Table 3). Phenol and phenol ether couplings have also attracted a great deal of interest.[9]

11.10 *Anodic cyanation* is predominantly known as a substitution reaction with arenes and amines as substrates.[35,49,80,132–136] Additive cyanation is rare; only two cases of addition of two cyano groups are known (to 9,10-dialkylanthracenes[137] and pentaphenylpyrrole[138] with formation of a nitrileisonitrile and dinitrile adduct, respectively), whereas several cases of the anodic addition of one methoxy and one cyano group have been reported (furans,[139] thiophenes[140] and 1,4-dimethoxybenzene[141]). The reluctance toward addition of cyano groups is somewhat surprising since one would expect that trappling of a cation, e.g. a Wheland type intermediate, by the strongly nucleophilic cyanide ion would be a favored reaction.

Anodic aromatic cyanation has its peculiar features as compared to acetoxylation. Table 8 shows it to be a fairly selective aromatic substitution reaction; what does appear to be anomalous is the absence of side-chain substitution in alkylarenes. Only a slight hint about the feasibility of this reaction is to be found in the literature, in that *p*-methoxytoluene has been reported to give "traces of" *p*-methoxybenzyl cyanide.[136] And this should indeed be an extremely favorable case! Why should not cyanide ion abstract an α proton from an alkylarene radical cation at least as easily as acetate ion which gives 97% side-chain substitution[96] with *p*-methoxytoluene? To increase the complexity further, cyanide ion does abstract protons α to an amino function, as for example in N,N-dimethylbenzylamine[80] and methyldiphenylamine.[135]

Another rather unique feature of anodic aromatic cyanation is the possibility of displacing alkoxy groups bound to an aromatic ring.[49,80] Since aromatic ethers are easily available compounds, this reaction should be useful for synthetic purposes (see, e.g. eqn 26).[38]

12. OTHER TYPES OF OXIDATIVE SUBSTITUTION REACTIONS

We would not be typical representatives for our profession if we did not strive for finding alternative methods to electrolysis, simpler in operation but with the same synthetic scope. High-valence metal ions in different forms are the logical candidates as substitutes for the anode in eqn (2), Pb(IV), Co(III) and Mn(III) being known since long to act as electron transfer oxidants.[20,149,150] Thus acyloxylations and dehydrodimerization reactions can be performed with these agents.

We have been particularly interested in finding homogeneous counterparts to anodic substitution reactions in order to be able to compare results from heterogeneous and homogeneous reactions. In this connection anhydrous iron(III) chloride was found to dehydrodimerize alkylbenzenes in very much the same way as the anode does;[151] also cobalt(III) and manganese(III) trifluoroacetate can be used with success for dehydrodimerizations.[152] Acetoxylation can be performed with Pb(IV), Co(III) and Mn(III) acetate, but these reagents tend to favor side-chain acetoxylation.[150] In order to achieve nuclear acetoxylation, bis - (2,2′ - bipyridine) - silver(II) peroxydisulfate in acetic acid/sodium acetate (0.5 M) was found to act in a way very similar to anodic oxidation, giving good yields of aryl acetates.[153] Here Ag(II) can be used in catalytic amounts with peroxydisulfate as the ultimate oxidant; this reaction is a cheap and effective way of achieving acetoxylation of substrates which are not too difficult to oxidize.

Palladium(II) catalyzed dehydrodimerization and acetoxylation are other interesting possibilities that have been explored for synthetic purposes by us[154–156] and others.[150] The Pd(II) catalyzed acetoxylation of aromatic

Table 7. Selected examples of dehydrodimerization[79,130,142–148] (for others, see Table 3)

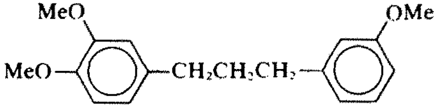
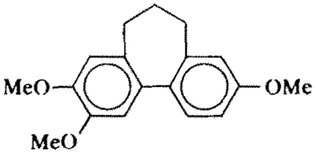
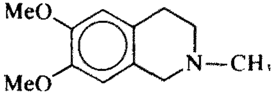
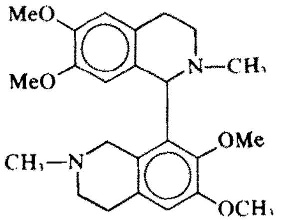
Substrate(s)	Electrolyte	Product(s)	Yield (%)
Pentamethylbenzene	CH_2Cl_2/Bu_4NBF_4	Decamethylbiphenyl, 2,3,4,5,2′,3′,4′,5′,6′-nonamethyldiphenylmethane (15:85)	24
Hexamethylbenzene, toluene	CH_2Cl_2–CH_3SO_3H/Bu_4NBF_4	Pentamethylbenzyltoluene (*o*:*p* 17:83)	81
Hexamethylbenzene, mesitylene	CH_2Cl_2–CF_3COOH/Bu_4NBF_4	Pentamethylbenzylmesitylene	66
Tetraphenylethylene	CH_3CN/Et_4NClO_4	9,10-Diphenylphenanthrene	100
α-Methylstyrene	CH_3OH/KOH	1,4-Dimethyl-1,4-diphenylbutadiene	45
1,2,4-Trimethoxybenzene	H_2O-acetone/H_2SO_4	2,4,5,2′,4′,5′-Hexamethoxybiphenyl	85
1,2-Dimethoxybenzene	CH_2Cl_2–CF_3COOH/Bu_4NBF_4	Hexamethoxytriphenylene	50
	$CH_2Cl_2/CF_3COOH/Bu_4NBF_4$		50–70
	CH_3CN–H_2O/Et_4NClO_4		80
(±)-Laudanosine	$CH_3CN/LiClO_4$ (solid Na_2CO_3)	*O*-Methylflavinantine	52
1-Benzyltetrahydroisoquinolines		Morphinanedienone alkaloids	40–80

Table 8. Nuclear[a] cyanation of aromatic compounds in $CH_3OH/NaCN$ (unless otherwise noted) at platinum[35,49,80,133–136]

Compound	Isomer distribution *o*	*m*	*p*
Chlorobenzene	50	0.5	50
Toluene	40	8	52
Ethylbenzene	30	10	57
Isopropylbenzene	36	14	50
t-Butylbenzene	41	13	46
Anisole	53	0.1	47
Anisole[b]	53	0.1	47
Anisole[c]	30	—	70
Diphenyl ether	—	35	65
Biphenyl	24	0.4	76
Diphenylamine	—	—	100
Diphenylacetylene	—	—	100
Naphthalene	90(1)	10(2)	
	86(1)	14(2)	

[a] Side-chain substitution has been detected in only one case, namely *p*-methoxytoluene, from which a trace amount of *p*-methoxybenzyl cyanide was isolated.[136] [b] In CH_3CN/Et_4NCN. [c] In CH_2Cl_2/Bu_4NBF_4.

compounds has been developed into a reasonably efficient method (up to 800% yield based upon catalyst, 80% based upon unrecovered substrate) provided that a cooxidant is added. Peroxydisulfate[154] and nitrate ion[155] have been successful in this respect, with the first-mentioned one the better choice (very few side-reactions). An additional bonus of the Pd(II) catalyzed acetoxylation reaction is its anomalous selectivity for the *meta* position in compounds that would be attacked predominantly *ortho-para* by electrophilic reagents.[157] Table 9 summarizes the substitution patterns of the different acetoxylation processes. From these data is is obvious that the Pd(II) catalyzed reaction must be mechanistically different from the two other reactions (presumably a metalation vs electron transfer oxidation mechanism.)[154]

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Table 9. Comparison of isomer distributions between anodic[a] (see Tables 5 and 6) and homogeneous[153,154] acetoxylation of aromatic compounds

	Anodic[a] *o*	*m*	*p*	*α*	$Pd(II)/S_2O_8^{2-}$ [b] *o*	*m*	*p*	*α*	$Ag(II)/S_2O_8^{2-}$ [c] *o*	*m*	*p*	*α*
Fluorobenzene	34	8	58		20	42	38					
Chlorobenzene	37	6	57		7	51	42					
Bromobenzene	30	4	66		8	55	37					
Iodobenzene	17	4	79									
Toluene[d]	43	11	46	29	6	59	35	10				
Ethylbenzene[d]	43	10	47	50								
Isopropylbenzene	44	17	39	47								
t-Butylbenzene	35	22	43		T[e]	56	44					
Diphenylmethane[d]	43	12	45	19	3	60	37					
Anisole	67	4	29		2	58	40		68	1	31	
Phenyl acetate	40	5	55		25	42	33					
Diphenyl ether	40		60									
Biphenyl	31	1	68		3	52	45		22		78	
Naphthalene	96	4	—		22	78	—		95	5		
Benzotrifluoride	No reaction				T[e]	73	27					
Methyl benzoate	No reaction				4	62	34					
Indan[d]	43	57	—	79	34	66	—					
Mesitylene	81	—	—	19	T[e]			99	70	—	—	30

[a] In HOAc/NaOAc at Pt. [b] In HOAc with bipyridine added. [c] Bis - (2,2′ - bipyridine) - silver(II) peroxydisulfate in HOAc/NaOAc. [d] Nuclear isomer distribution normalized to 100%. [e] Trace.

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