J Solid State Electrochem (2011) 15:1733–1751
DOI 10.1007/s10008-010-1265-8

REVIEW

From synthetic organic chemistry to electrochemistry

Henning Lund

Received: 27 October 2010 / Revised: 23 November 2010 / Accepted: 28 November 2010 / Published online: 22 December 2010

Abstract The paper describes the change of the author's research from synthetic organic chemistry to electrochemistry and the advantages and disadvantages of having been trained in organic synthesis rather than in electrochemistry. The described research in electrochemistry includes, among other projects, oxidations in non-aqueous solvents, reduction of azomethine derivatives and heterocyclic compounds, synthesis of heterocyclic compounds, reduction of graphite, electrocatalytic reductions, electron transfer in nucleophilic substitutions and additions, determination of redox potentials of short-lived radicals, and electrochemical formation of Grignard compounds having reducible groups. At the end, some considerations after 60 years of research are included.

Keywords Oxidations · Azomethine compounds · Heterocycles · Electrocatalysis · Electron transfer · Potentials of radicals

H. Lund (✉)
Department of Chemistry, University of Aarhus,
Langelandsgade 140,
8000 Aarhus C, Denmark
e-mail: hlund@chem.au.dk

Introduction

When I got an invitation to write a contribution to this special issue, I first thought of writing a chapter covering the development of organic electrochemistry since the book of Fichter [1] in 1942, but as I rather recently had written a paper on "A Century of Organic Electrochemistry" [2], I rejected that. Inspired by the title of this issue, I decided to write about how a chemist trained in organic synthesis and without any knowledge whatsoever of electrochemistry ended up as an electrochemist and which advantages and disadvantages that background had. I shall also try to describe how some of the new ideas came and the research that was the result of these ideas. I hope also to illustrate the advantage for a researcher to continue doing experimental research himself.

I finished as a chemical engineer from the Danish Technical University in 1952 and began at "Leo Pharma" where I got to work on a project on oxidation of one of three hydroxyl groups in a steroid. I had, in 1951, published a paper [3] "On Quinone as Oxidizing Agent in the Oppenauer Oxidation", so from that, came the idea that perhaps a quinone with a suitable oxidation potential could selectively oxidize one of the hydroxyl groups in the steroid and that afterwards the quinone could be regenerated by electrolysis. I suggested it to the head of the laboratory, and although he probably not was convinced that the idea would work, he said OK (possibly because he knew that I was drafted to begin in the army 3 months later).

The 3 months did not give the desired results so I had to join the army. Fortunately, I spent the latter half of my compulsory time in the research laboratory of the army doing synthetic projects. Afterwards, I returned to Leo Pharma and worked on the synthesis of different compounds, but was still interested in the possibility of using

preparative electrochemistry at controlled potential for oxidations in a similar way as Lingane [4] had done for a reduction.

In 1954–1955, I was a research fellow at Harvard University in the laboratory of Louis F. Fieser at the department of organic chemistry; he had, among many other things, studied quinones and their reduction potentials. There, I had a laboratory for the synthetic part of the research. The analytical department was headed by James J. Lingane, who was kind enough to let me work with a polarograph in the analytical department. His book "Electroanalytical Chemistry" (1953) [5] was valuable for my start of electrochemical experiments and the design of cells for electrolysis.

The first problem of the electrochemical part of the project was to find a suitable solvent. It should be difficult to oxidize, have a reasonably high dielectric constant, be able to dissolve a salt, which was difficult to oxidize, and it should easily be purified. Oppenauer oxidations are usually made in benzene or toluene (or without solvent) which did not seem useful for electrochemistry. Water and primary and secondary alcohols were, for several reasons, not suitable, and tertiary butanol had a low dielectric constant and could eliminate water under influence of protons formed during an oxidation. Furthermore, the solubility of inorganic salts was poor.

The choice finally fell on acetonitrile which has a comparatively high dielectric constant (about 35) and a suitable boiling point (81.6 °C), and it could easily be purified by distillation and dried by treatment with phosphorous pentoxide followed by distillation. Sodium perchlorate, which is rather resistant towards oxidation, is very soluble in acetonitrile. Silver perchlorate used in the silver/silver ion reference electrode would not disturb the voltammetric curves, if some diffused into the anode chamber. Apparently, no electrochemical oxidation had previously been made in acetonitrile.

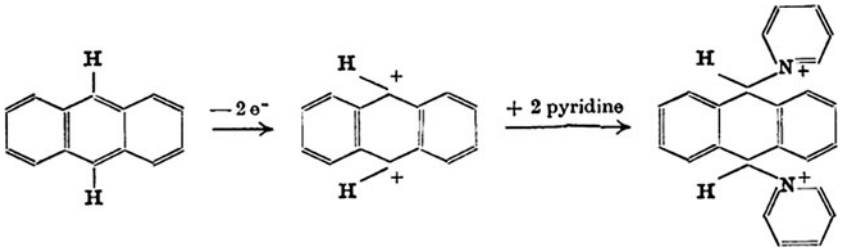
Anode material was a lesser problem as rather few metals are resistant towards oxidation, and a suitable form of carbon for microelectrodes was not available, so the choice was platinum. Attempts to find the oxidation potential of alcohols by manually making current–voltage curves were not successful. Electrochemical oxidation of alcohols of the type which reacted fast in the Oppenauer oxidation resulted in a current which rapidly fell to zero. The electrode became covered by a black insulating layer; the layer was chemically very stable and had to be burned to regenerate the surface of the electrode. I had no possibility to investigate the layer, so I do not know how it was compared with the surface layers which were produced by reducing aryldiazonium compounds about 40 years later [6, 7].

The polarograph in Lingane's laboratory was a photographic recording Sargent-Heyrovsky Model XII which measured the current with a mirror galvanometer, and the light beam was recorded on photographic paper. Before making the experiment, the potentials were marked on the photographic paper. The results became visible when the photographic paper was developed. It was thus difficult to realize during the experiment whether it was a success or a failure, so as the voltage change of the polarograph and the development of the paper were slow, longer time was used for an experiment.

Many different alcohols were tried without positive results, but after many failures, some substituted aromatic alcohols were found to give nice voltammetric curves showing the oxidation potential of the alcohol and a second oxidation at the potential of the aldehyde [8] at a more positive potential than the alcohol. Preparative electrochemical oxidation of an alcohol gave poor results, but in the presence of pyridine to accept the protons formed during the oxidation, high yields of the aldehydes were obtained. That an aldehyde was more difficult to oxidize than the corresponding alcohol made me wonder for some time, as aldehydes are usually easier to oxidize chemically than the alcohols. However, being an organic chemist, I realized that an aldehyde group is known to make an aromatic nucleus more electron deficient than an alcohol group, so I wondered whether it actually was the aromatic system which initially lost electrons during the electrochemical oxidation and this, thus, determined the oxidation potential.

Experiments with aromatic hydrocarbons showed in many cases nice oxidation curves in accordance with the assumption. The potentials of the aromatic hydrocarbons turned out to be linearly correlated to the wave numbers of the *p* bands in their UV spectra indicating that the electrochemical oxidation of aromatic hydrocarbons under these conditions was a direct transfer of electrons from the molecule to the electrode. This was the first time electrochemical oxidation was shown to be a direct electron transfer, previously oxidation products of the solvent or of the anode was assumed to make a "chemical" oxidation of the substrate.

For preparative oxidations, a proton acceptor was needed; aliphatic and aromatic amines are oxidized at too low potentials, but pyridine is difficult to react in electrophilic substitution and is resistant to oxidation. Oxidation of anthracene in the presence of pyridine gave high yield of 9,10-dipyridinium-9,10-dihydroanthracene diperchlorate which on treatment with cold base gave 9-pyridiniumanthracene perchlorate [9]. At that stage, the details of the reaction were less important than the result that such anodic syntheses were possible.



Returning to Leo Pharma, I got a position with the job to develop analyses for new compounds and to improve old analyses. If I had more time, I could work with my electrochemical experiments. I borrowed a Radiometer Type PO 3a recording polarograph from the research laboratory of the army so I could finish the work done at Harvard and continue doing electrochemical research. I have always been grateful to Leo Pharma that I got that freedom.

I doubt that this would be possible nowadays in industry and at many universities.

In connection with the development of some analytical methods at Leo Pharma, it was of interest to get some indication of the steps in the four-electron electrochemical reduction of the protonated oximes and phenylhydrazones. The first uptake of two electrons of an oxime could either result in a substituted hydroxylamine or in an imine so I prepared these intermediates. As the hydroxylamine was not further reducible at the applied potential, it was concluded that the first step in the electrochemical reduction of the protonated compounds of the type RR′C=N−Y (Y=O or N) was a cleavage of the N–Y bond, leaving a reducible imine for further reduction (1)–(3). So this would be the reduction route in acidic to neutral medium for oximes, N-oxides, arylhydrazones, azines and for most semicarbazones [10]. A few years later, I found examples of electrochemical reduction of some oximes to stable ketimines [11].

$$RR'C = N - Y + H^+ \rightleftarrows (RR'C = N - Y)H^+ \quad (1)$$

$$(RR'C = N - Y)H^+ + 2e^- + 2H^+ \rightarrow RR'C = NH_2{}^+ + HY \quad (2)$$

$$RR'C = NH_2^+ + 2\,e^- + 2H^+ \rightarrow RR'CH - NH_3^+ \quad (3)$$

About 40 years later, reductions of oximes were investigated in aprotic media (N,N-dimethylformamide (DMF)); (*Z*)- and (*E*)-benzaldoxime gave, in cyclic voltammetry, a small irreversible peak followed by a larger reversible one as shown on Fig. 1a. The first peak is due to the irreversible reduction of the oxime, whereas the reversible system is caused by benzonitrile. The reaction was proposed to follow the scheme (4)–(6) [12, 13].

$$PhCH = NOH + e^- \rightarrow PhCH = NOH^-\cdot \rightarrow PhCH = N^{\cdot} + OH^- \quad (4)$$

$$PhCH = N^{\cdot} + OH^- \rightarrow PhCN^-\cdot + H_2O \quad (5)$$

$$PhCN^-\cdot + PhCH = NOH \rightarrow PhCN + PhCH = NOH^-\cdot \quad (6)$$

Simulations of the cyclic voltammograms (CVs) using reasonable rate constants for the reactions in the scheme gave a curve close to the experimental one (Fig. 1b).

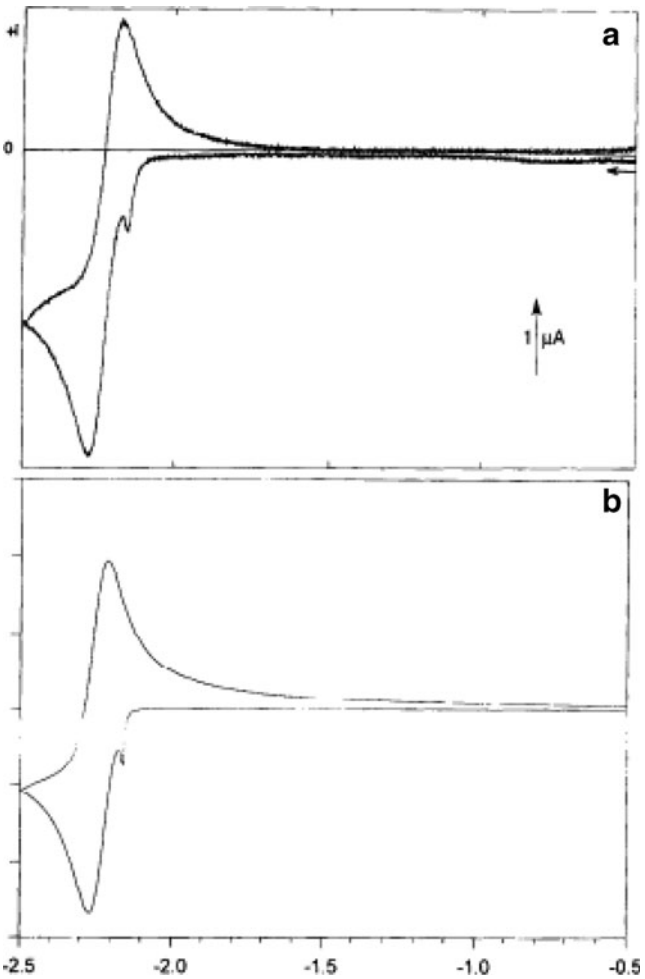
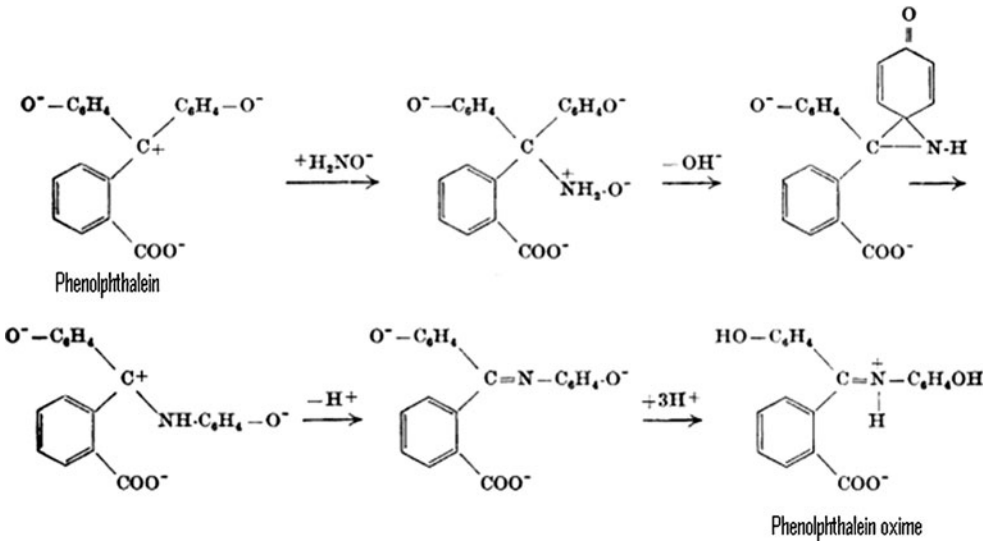


Fig. 1 **a** CV at a gold electrode of a (*E*)−benzaldoxime solution in DMF/0.1 M $TBABF_4$ at 0.1 V s^{-1} **b** Simulated CV

During the investigation of oximes, a compound called "phenolphthalein oxime" was of interest, as phenolphthalein was not expected to form an oxime. It was first prepared in 1893, and six different formulas had since been proposed in the literature. Which of them was right? By using IR spectra, polarography and controlled potential electrolysis, I got evidence for a seventh structure which is now accepted [14]. Its formation involved a new rearrangement akin to the Lossen rearrangement. Similar compounds were obtained in the reaction between hydroxylamine and fluorescein and hydroquinonephthalein [15].



An investigation of ketones of the general formula Ar–CO–CRR′X by polarography and macroscale electrochemical reduction at controlled potential indicated that, in most cases, both the polarographic and the macroscale reductions showed a two electron reduction of the C–X bond to the ketone which was reducible at a more negative potential. However, some of the compounds, e.g. 2-thiocyanato*iso*butyrophenone, showed only one two-electron polarographic wave, whereas a preparative reduction resulted in the further reducible *iso*butyrophenone. This seems to be the first reported examples of differences found between polarographic and preparative electrochemical results [16]. Further examples of this were given at the XIX International Congress of Pure and Applied Chemistry, London 1963.

A manuscript for a book *Elektrodereaktioner i organisk polarografi og voltammetri* together with a number of publications were sent in March 1960 to the University of Copenhagen for obtaining the degree of Doctor of Science. The manuscript was written in Danish as I wanted to have Danish words for the different phenomena. Today, I can see that it was a mistake.

In 1960, I got a position at the University of Aarhus, and my research was for about 10 years mostly directed at the electrochemistry of heterocyclic compounds. Especially during that period, the background in organic synthesis was very valuable. Rather few heterocyclic compounds were commercially available, and the money at hand for buying chemicals was short. So I just prepared most of the compounds I wanted, and for the isolation and structure determination of the products, familiar methods could be used.

Electrolysis of heterocyclic compounds

Much research has been made of the electrochemistry of heterocyclic compounds. Here, what will mainly be discussed is the work done in Aarhus; a fuller account on the subject can be found in the references given [17–24]. First, what will be described are some of the works on the influence of addition of water to substituents and to the heterocyclic nucleus, then reductions of heterocyclic compounds followed by electrochemical preparations of heterocyclic compounds.

Hydration of heterocyclic compounds

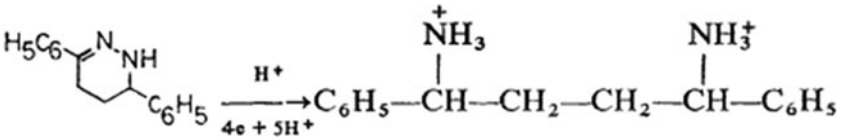
The first subject was the reduction of isonicotinic acid and its derivatives. The electrode reactions responsible for the polarographic results had not been suggested. It is known that aldehyde groups in compounds with strongly electron-attracting groups are highly hydrated and that the hydrated aldehyde would not be expected to be reducible; however, the unhydrated aldehyde group would be reducible at a less negative potential than the carboxylic acid group. A polarographic investigation of pyridine aldehydes had been made by Volke [25–26].

Preparative electrochemical reduction of isonicotinic acid at pH about 3 gave pyridine-4-aldehyde in fair to good yield, depending on pH and the temperature; low temperature which made the dehydration of the primarily formed hydrated aldehyde to the reducible free aldehyde slower raised the yield. This was the first example of an electrochemical reduction of a carboxylic acid to the corresponding aldehyde [27]. Isonicotinic amide is reduced similarly in mineral acid, but in acetate buffer, the reduction of the compound results in formation of the alcohol [28]. Isonicotinic hydrazide is on reduction in acid solution reduced first with two electrons to the amide and then further at a more negative potential to the hydrated aldehyde [29]. Some of the carboxylic acids of imidazole [30] and thiazole [30] showed a similar behaviour with reduction to the hydrated aldehyde.

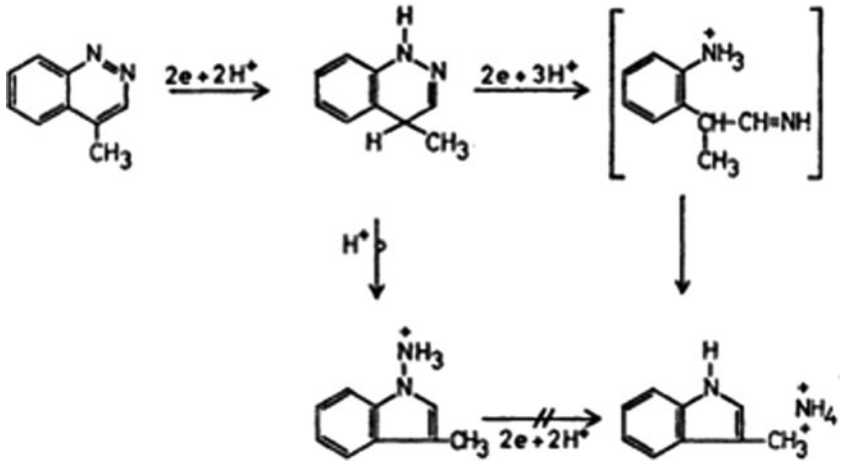
The mono-cation of quinazoline had been reported [31] to be hydrated in the nucleus, and a polarographic investigation [32] showed, in accordance with that, a minimum in the polarographic current at pH 1–2. Preparative electrochemical reduction both in acid and alkaline media gave a mixture of a dimeric dihydroquinazoline and 3,4-dihydroquinazoline; at low concentration, the latter predominated. At a more negative potential, the dihydroquinazoline could be further reduced to the tetrahydroquinazoline.

Reduction of heterocyclic compounds

A number of heterocyclic compounds having two neighbouring nitrogen atoms are reduced quite similarly to their non-cyclic analogues [10]. Thus, a compound like 3,6-diphenyl-2,3,4,5-tetrahydropyridazine may be regarded as a substituted hydrazone, and a reduction of the compound in acidic solution follows a similar path as a hydrazone; a four-electron reduction with a primary two-electron cleavage of the nitrogen–nitrogen bond followed by a two-electron reduction of the carbon–nitrogen double bond gave 1,4-diphenyl-1,4-diaminobutane [33].



In the reduction of some fully aromatic heterocycles with two neighbouring nitrogen atoms, the first uptake of two electrons produces a dihydro derivative which is analogous to a hydrazone. The 4-methylcinnoline is first reduced to 1,4-dihydro-4-methylcinnoline in two one-electron reductions or one two-electron reduction, depending on the acidity. The dihydro derivative is in acid solution further reduced to 2-(2′-imino-2′-methylethyl)aniline [34] which cyclized to 3-methylindol. The 1,4-dihydro-4-methylcinnoline is probably formed through the 1,2-dihydrocinnoline, as 4-methylcinnoline in DMF in the presence of acetic anhydride forms 1,2-diacetyl-1,2-dihydro-4-methylcinnoline [35].

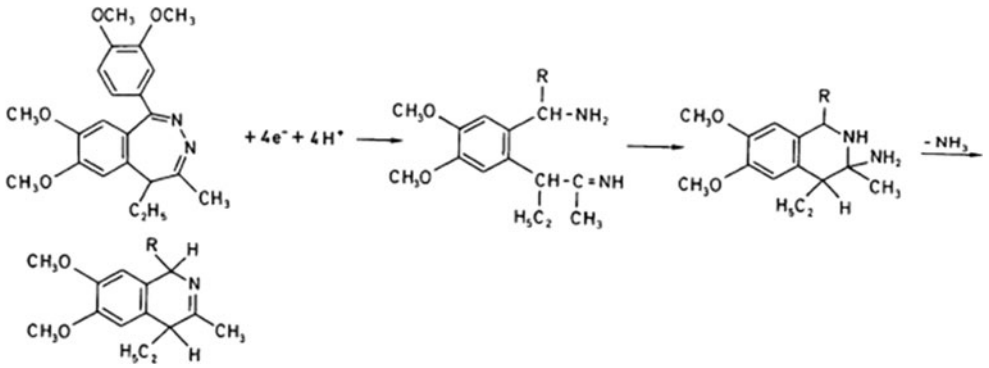


Tofisopam® is a 5-H-2,3-benzodiazepine; it can be determined polarographically in slightly acidic solution; the electrode reaction consumes four electrons, and the product has been suggested [36] to be a 1,2,3,4-tetrahydroderivative of Tofisopam®.

A 2,3-benzodiazepine may be regarded as an unsymmetrical azine of a derivative of benzophenone and an aliphatic ketone. As has been mentioned, it is generally found that compounds of the type RR′C=N–Y, where Y is a heteroatom, is reduced in aqueous acidic solution after

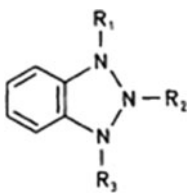
protonation with an initial cleavage of the N–Y bond. The electrode reaction suggested [36] for Tofisopam® would be an exception from the general behaviour of such compounds.

A model compound benzophenone cyclohexanone azine was reduced in a cold acetate buffer, and the products were benzhydrylamine and cyclohexanone in accordance with the general scheme. Tofisopam® was reduced in 0.2 M hydrochloric acid with n=4.3. The reduced solution was oxidized with an excess of potassium hexacyanoferrate; a possible tetrahydro derivative would be oxidized to starting material and any dihydro heterocyclic compound to the aromatic derivatives. The product was shown to be an isoquinoline derivative so the reduction followed the usual route [37].



In a few cases, another type of reduction is observed, where a carbon–nitrogen double bond is reduced before the nitrogen–nitrogen single bond in a "hydrazone-like" compound. So 4-methyl-1(2H)-phthalazinone forms 4-methyl-3,4-dihydro-1(2H)-phthalazinone on reduction. In acid solution at a more negative potential, the nitrogen–nitrogen bond is cleaved, and the amino group attacks the amide group with formation of 3-methylphthalimidine [38].

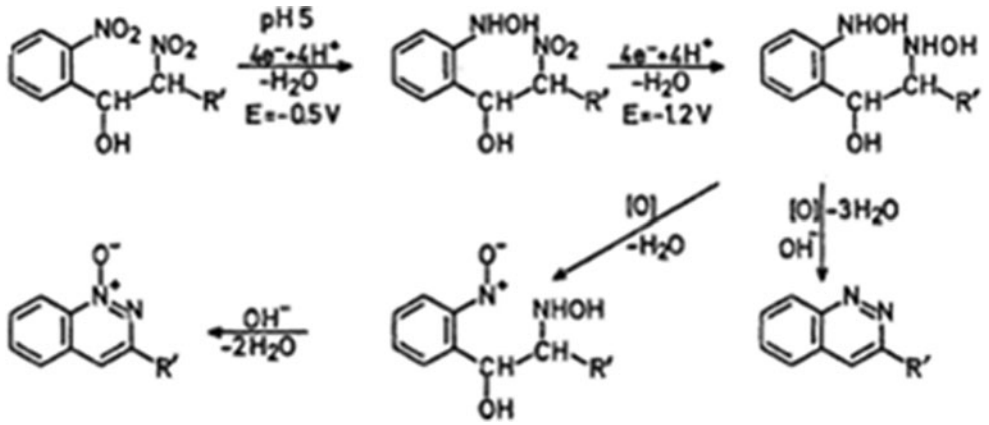
Benzotriazole is in hydrochloric acid reduced to 2-aminophenylhydrazine in a four-electron reduction. 2-Methylbenzotriazole exhibited a reversible voltammogram in DMF; on addition of an excess of phenol, a two-electron product was formed, but it was reoxidized to starting material during workup. Reduction of benzotriazole in DMF in the presence of acetic anhydride gave 1,2,3-triacetyldihydrobenzotriazole (R_1,R_2, R_3=CH_3CO) [39] which, together with 1,3-dihydro-1,3-dihydroxy-2-phenylbenzotriazole [40], seems to be the only stable derivatives of dihydrobenzotriazole isolated so far.



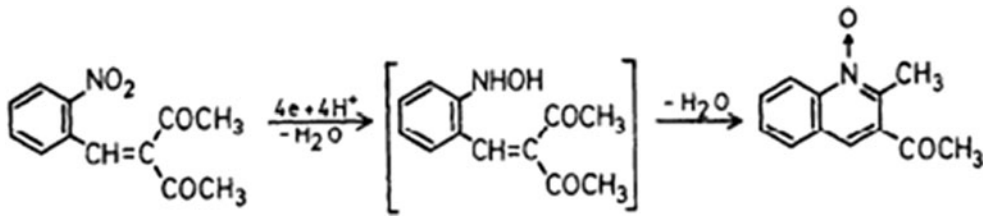
Besides the mentioned reactions, the reduction and voltammetry of a number of different heterocyclic compounds such as diazirines [41], cinnolines [34], pyridazines [42], benzotriazoles [43], oxaziridines [44], phthalazines [45], quinazolines [46], purines [47], pteridines [48], and pyrimidines [49] were investigated in protic solvents.

Synthesis of heterocyclic compounds

Cinnoline and some of its derivatives may be prepared by electrochemical reduction of a dinitro alcohol formed by a Henry addition of a 2-nitrobenzaldehyde with a primary nitroalkane. Thus, when 1-(2′-nitrophenyl)-2-nitroethanol formed from 2-nitrobenzaldehyde and nitromethane is reduced at a mercury electrode in an acetate buffer at the potential of the second polarographic wave, a dihydroxylamine was formed. After the reduction, the solution was made alkaline and allowed to stand in contact with air overnight with formation of cinnoline. When nitroethane was used in the condensation, a mixture of *erythro* and *threo* compounds results. There is only a small difference in the electrochemical behaviour of the two isomers and in their yields of 3-methylcinnoline. The yields of cinnolines are 50–70%, with 5–10% anthranil as a side product, formed by reversal of the Henry reaction. Compared to other syntheses of cinnoline, the electrochemical one is probably the easiest one as the starting materials are available and the yields acceptable [50].

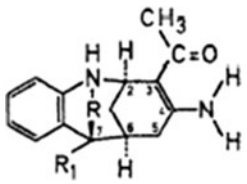


A ring closure to a quinoline-N-oxide can be made when a 2-substituted nitrobenzene is reduced to the hydroxylamine and a suitable group in the 2-substituent can react with the hydroxylamine. In 2-nitrobenzylidene acetylacetone a carbonyl group is situated, so by rotation of the side chain it can come close to the hydroxylamine group formed by reduction. The formed quinoline-N-oxide has three groups which are further reducible, the N-oxide, the carbonyl group in the 3-position of the quinoline ring, and the quinoline ring itself, so a suitable control of the reduction potential is necessary [51].



Benzo-1,2,4-triazine may be synthesized by different methods and an easy one is the electrochemical reduction of 2-nitrophenylazo phenylnitromethane, which gives, at pH 5, two 6-electron polarographic waves. Controlled potential reduction at a mercury electrode at the potential of the second reduction in an acetate buffer in 50% DMF consumed 12 F/mole and resulted in 1,4-dihydro-3-phenylbenzo-1,2,4-triazine. On oxidation with molecular oxygen, 3-phenylbenzo-1,2,4-triazine was obtained in 85–96% yield [52]. The 1,4-dihydro-3-phenylbenzo-1,2,4-triazine gives an anodic voltammetric wave, and anodic oxidation of the compound gives the aromatic triazine which, with the dihydro derivative, forms a reversible redox system. If the reduction of the starting material was done at the first wave of the reduction, the reaction consumed four electrons to an oxime hydrazone which, under preparative conditions, was hydrolyzed rapidly [52].

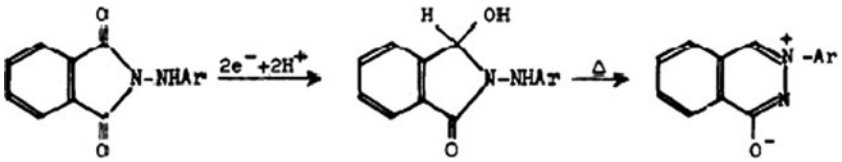
Reduction of 3-methylanthranil in acidic solution produced 2-aminoacetophenone. Reduction of this compound at pH 13 gave a mixture of the expected alcohol, the two isomeric pinacols, and about 60% of two compounds with the same elementary analysis as the pinacols. The formulae, thus, suggested that the compounds were formed from the same two radicals which produced the pinacols, but that the coupling had occurred in another way than that leading to the pinacols. It was not investigated whether other acetophenones with a nucleophilic substituent in the 2-position gave similar compounds [53].



From the ^{1}H-NMR of the two isomers, their triacetates and some other derivatives, and their IR spectra, the compounds were suggested to be stereoisomers of 3-acetyl-4-amino-7-hydroxy-2,6-dimethano-2,5,6,7-tetrahydro-1(1H)-benzazonine. The compounds have three asymmetric centres.

As shown, there are many examples that heterocyclic compounds on reduction form another heterocyclic derivative by ring contraction. An example of a ring

expansion is the electrochemical reduction in acid solution of *N*-arylaminophthalimides to *N*-arylamino-3-hydroxyphthalimides, which, on heating or boiling in water, give 3-aryl-ψ-phthalazinones. Electrochemical reduction in acid solution of 3-phenyl-ψ-phthalazinone-1 gives 3,4-dihydro-3-phenyl-1(2H)-phthalazinone, whereas the similar two-electron reduction of 2-phenyl-1-phthalazinone gave 3,4-dihydro-2-phenylphthalazinone [54].



Graphite

The product from the reduction of graphite in DMF with a tetraalkylammonium salt as supporting electrolyte depends on which tetraalkylammonium salt is used. With relatively small ions such as tetramethylammonium or tetraethylammonium a graphite electrode was found to be able to accept reversibly a rather large charge in a way somewhat akin to the formation of anion radicals and ion pairs of polycondensed aromatic hydrocarbons. The charged graphite may be used as an insoluble chemical reducing agent.

The smaller tetraalkylammonium ions seem to enter the graphite crystal between the layers of graphite akin to potassium graphite. However, when graphite was reduced at a mercury electrode in DMF with tetraoctylammonium bromide as supporting electrolyte, the distance between the graphite layers was not large enough to accommodate the tetraoctylammonium ions and the layers separated (Fig. 2) [55]. We had no equipment to investigate whether the graphite was separated into single layers (now called graphene) or just a few layers. At that time (1977), we did not know that graphene many years later would be of much interest (and giving a Nobel Prize in physics), but apparently nobody has, since our work investigated whether the reduction of graphite in DMF with tetraoctylammonium ions might be an easy way to obtain graphene.

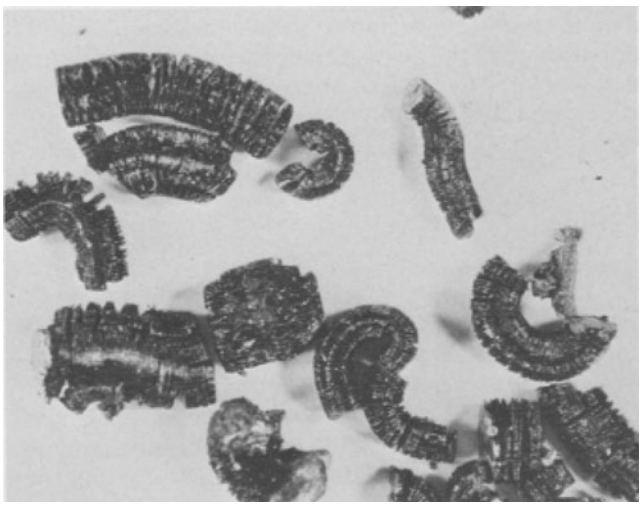


Fig. 2 Graphite crystals reduced at a stirred mercury electrode at −1.9 V (Ag/AgI, 0.1 M I^-) in DMF containing 0.1 M tetraoctylammonium bromide

Electron transfer

In 1973, one of Jacques Simonet's Ph.D. students had written her thesis, and I was an external examiner. In the thesis, there were some results which I did not find properly explained. During my talk, I suggested that the reaction might involve electron transfer in solution followed by a rapid follow-up reaction and that it was a catalytic reaction. I probably used more time on the subject and its implications than an examiner usually would do. At the end, I suggested some experiments to test the proposition, and when the exam was finished, we went to the laboratory and did the proposed experiments, and they worked as suggested. The experiment was polarography of an aromatic hydrocarbon to which an aromatic halide reducible at a more negative potential was added in an increasing amount, and an increase in the limiting current of the hydrocarbon was observed in accordance with a catalytic reaction [55–58]. It was later shown that also the dianion of an aromatic hydrocarbon could reduce an aromatic halide in a catalytic reaction [59].

Whereas the aromatic halides did not couple with the aromatic radical anion, the aliphatic halides could couple and the ratio of coupling to reduction depended on the constitution of the halide. The coupling influenced the cyclic voltammograms (CVs) by eventually making the limiting current independent on further addition of the halide. CV of benzyl chloride (Fig. 3) seems not to show a coupling with the radical anion,

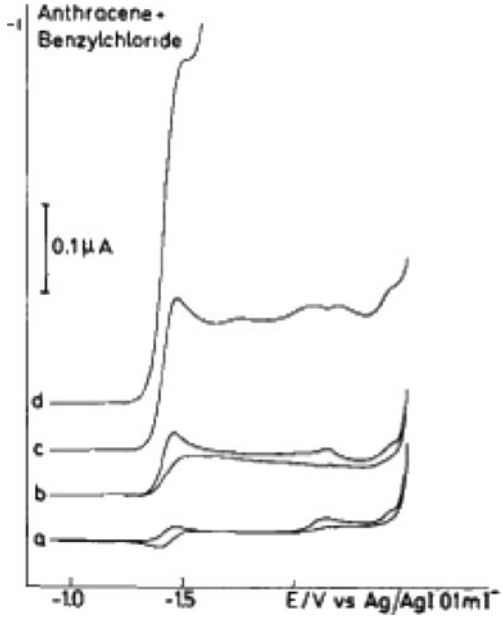


Fig. 3 CV of anthracene in DMF/0.1 M TBAI in the presence of different concentrations of benzyl chloride

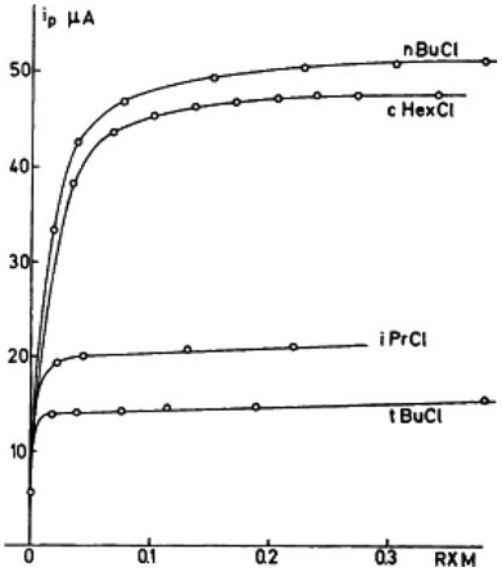


Fig. 5 Variation of the peak-height in CVs of naphthalene at a stationary mercury electrode in dependence of the concentration of various halides, medium DMF/0.1 M TBAI, v=10 mV/s [55–57]

cyclohexyl chloride and *n*-butyl bromide (Fig. 4) gave, in CV, a catalytic wave which stopped to grow after a certain concentration of the halide, whereas t-butyl chloride gave only a little enhancement of the wave and isopropyl chloride behaved in between (Fig. 5). This showed that *t*-butyl chloride is coupled more easily with the radical anion than the primary and secondary halides.

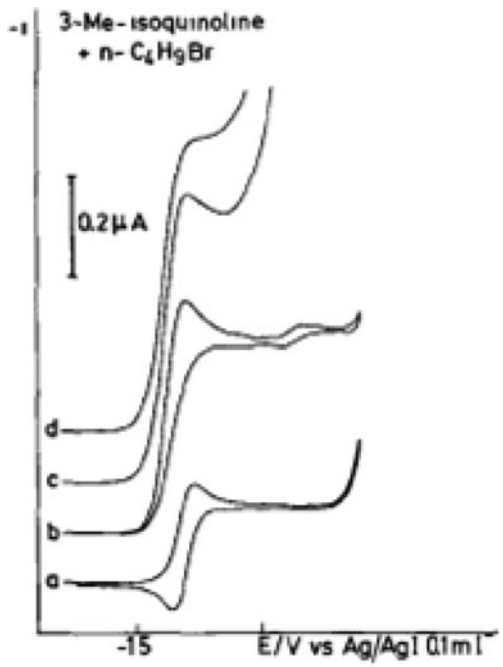


Fig. 4 CV of 3-methylisoquinoline in DMF/0.1 M TBAI in the presence of different concentrations of butyl bromide

The competition between the catalytic and the coupling reactions was proposed to follow the equations [59]

$$A + e^- \rightleftarrows A^{-\cdot} \tag{7}$$

$$A^{-\cdot} + BX \rightleftarrows A + (BX)^{-\cdot} \rightarrow A + B^{\cdot} + X^- \tag{8}$$

$$A^{-\cdot} + B^{\cdot} \rightarrow A + B^- \xrightarrow{H^+} A + BH \tag{9}$$

$$A^{-\cdot} + B^{\cdot} \rightarrow AB^- \xrightarrow{H^+} ABH \tag{10}$$

where (8) and (9) regenerate A which are the reactions responsible for the catalytic increase of the limiting current, whereas (10) results in the coupling reaction which stops the catalytic reaction.

This was the beginning of a series of publications, not only of electron transfer in catalytic reactions, but also on electron transfer in nucleophilic substitutions, on investigations of stereoisomerism of some radicals during nucleophilic substitutions and on the competition between electron transfer and coupling for the estimation of potentials of radicals.

Catalytic polarographic currents involving inorganic species were well known, and a theory for the connection between the ratio of the limiting current to the diffusion controlled current and the rate constant of the catalyzing reaction had been developed. Approximately at the same

time, a paper on catalytic transfer involving the reduction of the carbon–chlorine bond was published [60].

Cathodic reduction of pyrene [61] in the presence of *t*-butyl chloride yields 1-*t*-butylpyrene in good yield after reoxidation of the primarily formed dihydro derivative and minor amounts of other isomers. The EPR spectrum of the pyrene radical anion shows the highest electron density at C-1, which could suggest that the *t*-butyl radical attacked preferentially the position with the highest electron density. A similar *t*-butylation of 3-methylisoquinoline yields as main product 6-t-butyl-5,6-dihydro-3-methylisoquinoline [62], and as the highest electron density in the radical anion according to the EPR spectrum is at C-1 and the *t*-butylation gave only 17% yield of the 1-isomer, the electron density of the radical anion seems, thus, not to be a reliable guide.

Reduction of anthracene in the presence of 1,2-dichloroethane gave 9,10-dihydro-9,10-ethanoanthracene [63]. This is by far the most convenient way to prepare this compound. The reaction is probably that the intermediately formed negative charge which would mainly be at C-10 would attack the 2-chloroethyl group in the 9-position in a classical S_N2 reaction. Activated olefins may also be reductively alkylated; the *t*-butylation of ethyl cinnamate gives *t*-butylation at both C-2 and C-3 [64]. The reaction of ethyl cinnamate with *t*-butylmagnesium chloride [65] gave nearly the same yields of addition products as the electrochemical method. This could substantiate the suggestion that the Grignard reaction in this case involves a single electron transfer.

Other types of electrophiles may react in a similar way. Thus, reduction of anthracene in DMF in the presence of acetic anhydride produces the enol acetate of 9-acetyl-9,10-dihydroanthracene [66]. A similar acetylation of quinoxaline gives 1,4-diacetyl-1,4-dihydroquinoxaline a stable derivative of the very elusive compound 1,4-dihydroquinoxaline. This method provides a general way to isolate unstable reduction products. Reduction of ethyl cinnamate in the presence of acetic anhydride produces ethyl 3-phenyl-4-oxopentanoate [67]. Similar results were at the same time obtained by Shono et al. [68].

An $S_{RN}1$ reaction may also proceed intramolecularly; thus, injection of a small charge (<0.1 F mol^{-1}) into an aprotic solution of *S*,*S*-diarylbenzene-1,2-dicarbothiolate leads after some time to a 3,3-bis(arylthio)phthalide in almost quantitative yield. CV curves of the solution taken immediately after injection of the charge shows only the curve of starting material, but curves taken at different times after the injection show a gradually diminishing of this curve and the grows of the curve of the 3,3-bis(arylthio)phthalide [69] (Fig. 6).

Reduction of an aromatic or heteroaromatic compound with two electrons produces, in truly aprotic medium, the

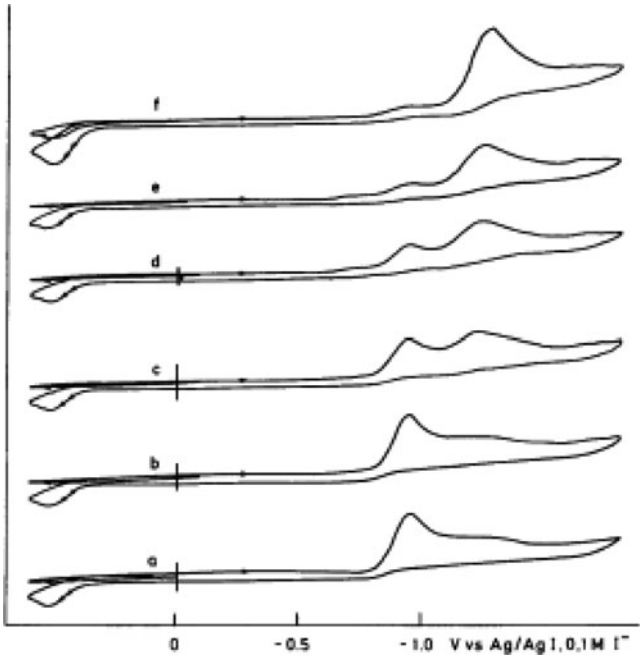


Fig. 6 CV of *S*,*S*-diphenyl benzene-1,2-dicarbothionate at a Pt-electrode before and after a short electrolysis; *a* before electrolysis, *b* immediately after, *c* after 30 min, *e* after 2 h, *f* solution *e* to which some starting material is added

dianion of the dihydro derivative. Fig. 7 shows the CV of perylene in DMF at two sweep rates, alone and in the presence of 1,4-dichlorobenzene. The first peak is unaffected by the addition of 1,4-dichlorobenzene,

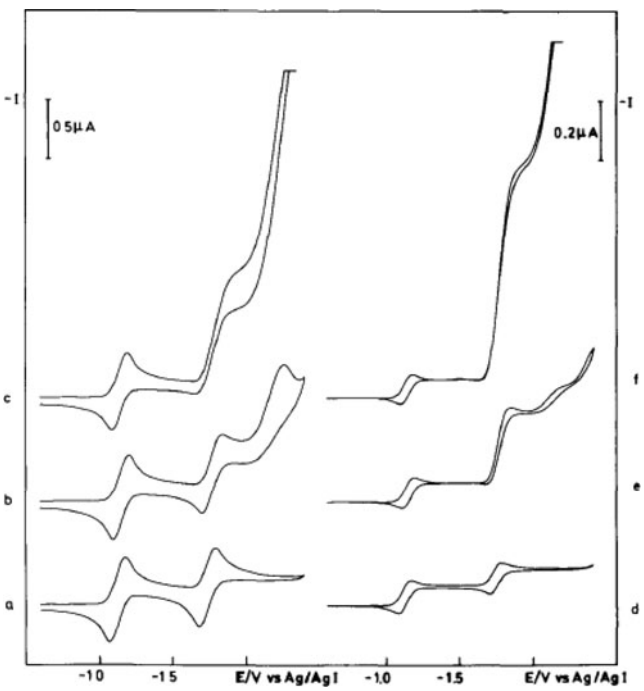


Fig. 7 CV of perylene in DMF/0.1 M TBAI at different sweep rates (10 and 400 mV s^{-1}) in the presence of different concentrations of 1,4-dichlorobenzene

whereas the second peak grows on this addition and becomes irreversible [59].

Radicals may be produced by indirect reduction of a compound which cleaves to a good hydrogen atom acceptor; this acceptor may abstract a hydrogen atom from a donor, and the radical thus formed may couple with the mediator. Thus, on reduction of 1,4-dicyanobenzene in the presence of iodobenzene and cyclohexane, 4-cyclohexylbenzonitrile was formed in fair yield [70, 71].

Photoexcited radical ions

As discussed above, relatively stable radical anions and dianions could transfer electrons to compounds with more negative reduction potentials if the radical anions of these dissociated rapidly. The question was then, could photoexcited radical anions or dianions transfer electrons to compounds to which the ground state of the radical anions or dianions could not?

The question was attempted solved by using light of a suitable wave length from a laser. It was expected that the light would cause some heating of the solvent close to the electrode which would influence the voltammetric curves. The heating turned up to be about 10 °C. To separate the effect of the heating and of the electron transfer from the photoexcited state on the voltammetric wave one of the experiments used was CVs of a solution of dimethyl terephthalate and chlorobenzene without and with illumination by the laser.

Without light, the voltammogram showed two reversible waves with no electron transfer to the chlorobenzene; when light was turned on, the height of the first wave increased by about 20% due to the heating, whereas the height of the second wave increased by a factor 5 (Fig 8) . This was

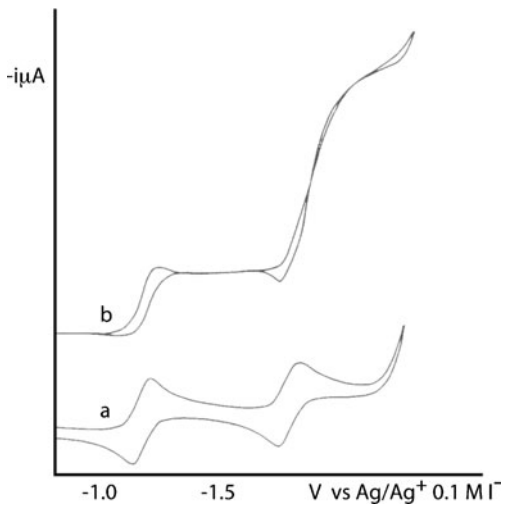


Fig. 8 CV of a solution of dimethyl terephthalate and chlorobenzene in DMF/TBAI; *a* without illumination, *b* with illumination

interpreted in a similar way as discussed above for the ground states as an electron transfer from the excited state of the dianion of dimethyl terephthalate to chlorobenzene and a rapidly cleavage of radical anion of chlorobenzene resulting in a catalytic wave [72].

The photoreduction of ketones by alcohols is one of the most studied photochemical reactions. The reaction is illustrated in most textbooks by the photoreduction of benzophenone by 2-propanol, in which reaction benzophenone pinacol and acetone are formed. The first step in the reaction is the transfer of a hydrogen atom from the alcohol to the triplet excited state of the ketone. This is followed by the transfer of a hydrogen atom from the substituted hydroxymethyl radical to the ground state ketone (12) and dimerization of the radical (13).

$$Ph_2CO^* + RR'CHOH \rightarrow Ph_2C^{\cdot}(OH) + RR'C^{\cdot}(OH) \quad (11)$$

$$Ph_2CO + RR'C^{\cdot}(OH) \rightarrow Ph_2C^{\cdot}(OH) + RR'CO \quad (12)$$

$$2Ph_2C^{\cdot}(OH) \rightarrow Ph_2C(OH) - C(OH)Ph_2 \quad (13)$$

But why is the cross-coupled product, the mixed pinacol $Ph_2C(OH)$-$C(OH)(RR')$, not observed? Even if the radicals are formed as a triplet pair some coupling could occur after spin inversion.

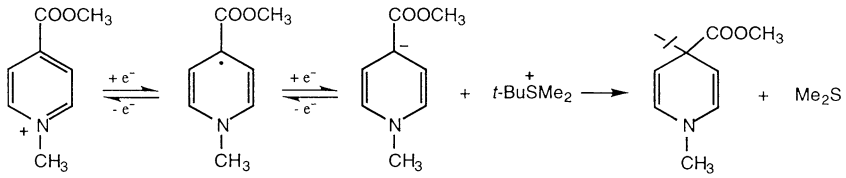
In the photoreduction of benzophenone by toluene, a statistical ratio (1:2:1) of bibenzyl, the cross-coupled product ($Ph_2C(OH)$-CH_2Ph) and benzopinacol, is obtained. How can this difference in coupling behaviour of the radical $Me_2C^{\bullet}OH$ and benzyl radical with $Ph_2C^{\bullet}OH$ be explained? Furthermore, in the photoreduction of acetone by benzhydrol, the mixed pinacol $Ph_2C(OH)C(OH)(CH_3)_2$ is observed.

The general problem with regard to the mixed pinacol formation is the rate of the electron transfer from the hydrogen atom donor radical $RR'C^{\bullet}(OH)$ to the ketone. Apparently, the electron exchange reaction is fast between $Me_2C^{\bullet}OH$ and benzophenone and slow in the reaction between the benzyl radical and benzophenone and in the reaction between $Ph_2C^{\bullet}(OH)$ and acetone compared with the coupling reactions. Although the reduction potentials of all the radicals used in the investigation are not known, the known values and a reasonable estimation of the unknown values support the idea that the redox potentials of the compounds and radicals involved are important factors in the determination of the product distribution [73].

Reactions of anions

As is well known, anions may act as bases towards protons, as nucleophiles in nucleophilic substitutions and additions, and as electron donors. Here, what will first be discussed are examples of solution electron transfer (ET) from electrogenerated anions to some substrates. The anion used is obtained by electrochemical reduction of 1-ethyl-4-methoxycarbonylpyridinium iodide (1^+) at the potential of the second wave. In Fig. 9, CVs of 1^+ and of 1,2-dichloro-1,2-diphenylethane (9a) and of the compounds together in dry DMF are shown. 1^+ exhibits two reversible one-electron waves, whereas 9a shows an irreversible wave followed by a reversible one due to the stilbene formed by reductive elimination of the chlorines. Both waves of the chloro compound are found at potentials more negative than the second wave of 1^+ in which the anion 1^- is formed. Addition of 9a to a solution of 1^+ results (Fig. 9 c) in an enhancement of the second wave of 1^+ and the disappearance of the first peak of 9a. The anion 1^- transfers electrons to 9a with reductive elimination of chloride and the formation of stilbene and of the radical $1^\bullet$; $1^\bullet$ is then reduced to 1^- giving rise to the increase of the current of the second wave of 1^+.

CV of 1^+ in the presence of *t*-butyl bromide shows a reversible wave followed by an irreversible one which is not influenced by further addition of *t*-butyl bromide. Preparative reduction of 1^+ at the potential of the second wave in the presence of *t*-butyl bromide yielded 4-*t*-butyl-1,4-dihydro-1-ethyl-4-methoxycarbonylpyridine as the only isolated product [74].



1^+ $1^\cdot$ 1^- 2 3

Our interest in the aliphatic nucleophilic substitution came from the observation that *t*-butyl bromide and dimethyl(*t*-butyl)sulfonium iodide reacted in DMF with the electrogenerated anion of 4-benzoyl-1-methylpyridinium perchlorate ($1'^-$) to 4-*t*-butyl-4-benzoyl-1-methyl-1,4-dihydropyridine [74]. The reaction could not be a classical S_N2 reaction for steric reasons, since one of the methyl groups in dimethyl(*t*-butyl)sulfonium would be attacked rather than the *t*-butyl group, and an S_N1 reaction is unlikely, as the *t*-butyl bromide did not form *t*-butyl iodide in DMF in the presence of a large excess of tetrabutylammonium iodide. An $S_{RN}1$ reaction is unlikely as the steady-state concentration of the nucleophile 1^- is negligible under the reaction conditions. Electron transfer has been shown to be involved in aliphatic nucleophilic substitution in some cases; derivatives of p-nitrobenzyl halides and 2-(4-nitrophenyl)-2-nitropropane react with certain nucleophiles in an $S_{RN}1$ reaction [75–77].

It was therefore suggested [74] that the enolate ion $1'^-$ had transferred an electron to the dimethyl(*t*-butyl)sulfonium iodide which cleaved to a *t*-butyl radical and the leaving group, and the radical $1^\bullet$ and the *t*-butyl radical coupled to give the product. It was also proposed that there might be found transition states (TS) ranging from the classical S_N2 TS with an approximately equal bonding of the central carbon atom to both the incoming nucleophile and the leaving group to an ET TS, in which there is

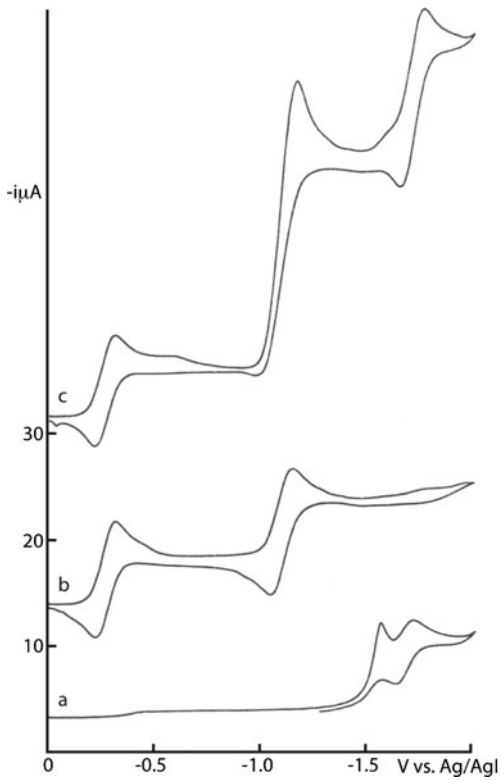


Fig. 9 CV at a Pt-electrode in DMF/0.1 M TBAI; *a* 1,2-dichloro-1,2-diphenylethane, *b* 1-ethyl-4-methoxycarbonylpyridinium iodide, *c* a mixture of *a* and *b*

a negligible bonding between the nucleophile and the central carbon. In such a TS, the distance between the nucleophile and the central carbon would be greater than in the classical S_N2 TS.

Radical anions of aromatic and heteroaromatic compounds have been suggested to react with alkyl halides through initial transfer of a single electron [78–80]. It has also been suggested that in both S_N2 and ET mechanisms, a single electron shift occurs. The ET pathway should involve first a transfer of an electron followed by bond formation, whereas the S_N2 reaction should involve a synchronous shift of a single electron and bond formation [81, 82].

The products of the reactions between 1^- and *t*-butyl bromide and dimethyl(*t*-butyl)sulfonium iodide suggested a mechanism involving ET, but in order to have other arguments than product studies, three types of experiments were carried out—kinetic measurements, stereochemical studies and determination of thermodynamic parameters.

Kinetic measurements

Radical anions of aromatic hydrocarbons and heteroaromatic compounds were used as one-electron donors [83–88]; they are stable in the absence of proton donors, and they have a relatively low reorganization energy connected with the electron transfer. Evidence from the reactions between sodium salts of aromatic radical anions and alkyl halides suggested that they reacted as electron donors rather than as nucleophiles [78–80].

The idea behind the kinetic test is to compare the rate constant (k_{SUB}) of the substitution of the nucleophile on a certain alkyl halide with the rate constant of electron transfer (k_{ET}) from an outer-sphere electron donor with the same standard potential and reorganization energy λ as the nucleophile to the same alkyl halide. A condition for the following arguments is that the generally accepted assumption that radical anions of aromatic and heteroaromatic compounds react with alkyl halides by outer-sphere electron transfer is correct. The ratio k_{SUB}/k_{ET} is a measure of the difference in the activation energy between the substitution reaction and the outer-sphere ET TS. If k_{SUB}/k_{ET} is ~1, then the rate-determining step is assumed to be the transfer of an electron from the nucleophile to the alkyl halide for this aliphatic nucleophilic substitution [89–92].

In Fig. 10, the logarithm of the rate constant (k_{ET}) of the reaction between isobornyl bromide and different aromatic radical anions (plus sign) or 1^- (k_{SUB}) (diamond) is plotted versus the reduction potentials of the compounds. The rate of substitution of 1^- on isobornyl bromide has the same value as the rate of electron transfer, so in this substitution, the rate of electron transfer is the rate-determining step. In

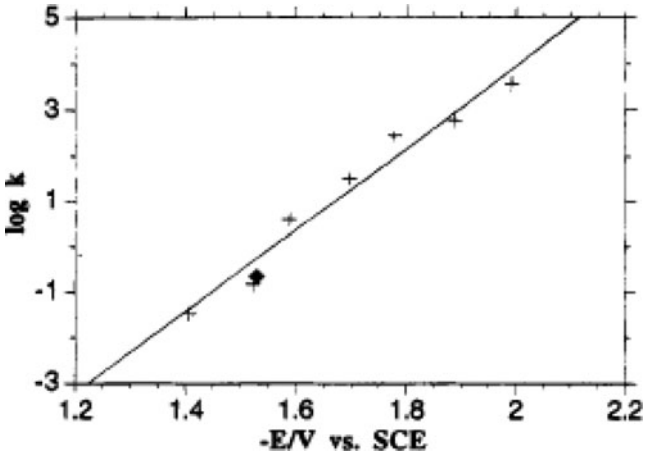


Fig. 10 Logarithm of the rate constant (k_{ET}) of the reaction between isobornyl bromide and different radical anion (*plus sign*) or 1^- (k_{SUB}) (*diamond*) vs the reduction potentials ($-E^o_A$) of the radical anions

Fig. 11, a similar curve with k_{SUB} for 2-bromobutane is shown. It can be seen that the substitution of 1^- on 2-bromobutane is approximately 170 times faster than the electron transfer from a radical anion to 2-bromobutane; for ethyl bromide, the value is approximately 2,500.

If one accepts the model that the outer-sphere ET TS and the classical S_N2 TS, the latter with a significant bonding to both the incoming group and the leaving group in the TS (thus, a stabilization energy of the order of 20–30 kcal mol^{-1} compared with the outer-sphere ET TS) are extremes and that there exist in between them TS with different bonding stabilizations (in a way somewhat similar to that often advocated for the S_N1 - S_N2 reactions), then the reaction between 1^- and 2-bromobutane has a transition state close to the ET TS with a low bonding stabilization of 2–3 kcal mol^{-1}.

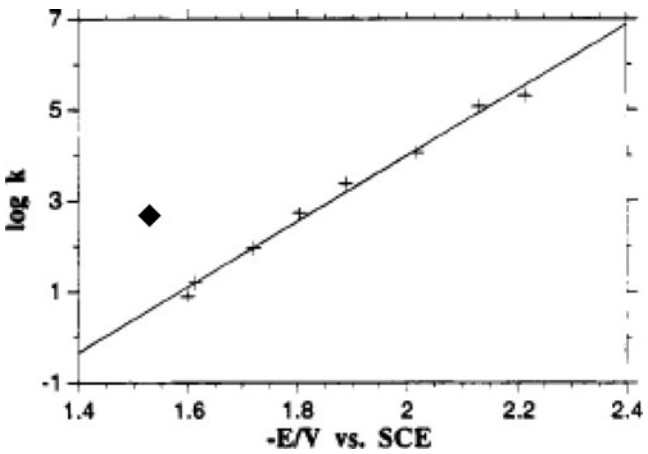


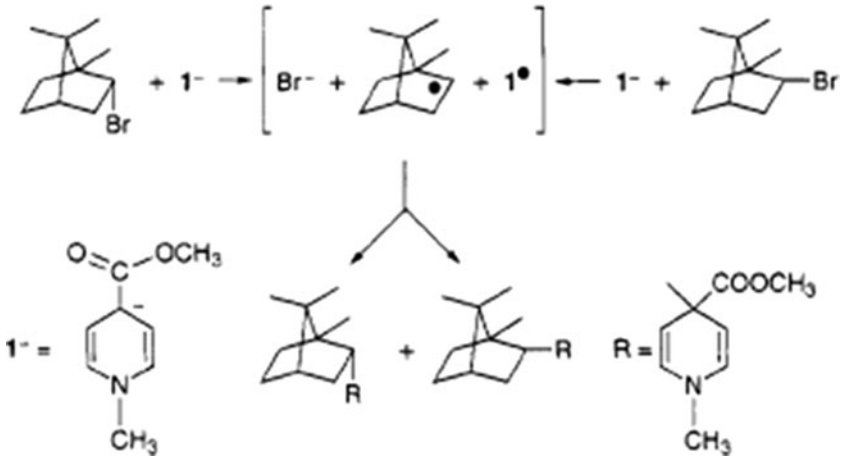
Fig. 11 Logarithm of the rate constant (k_{ET}) of the reaction between 2-bromobutane and different radical anions (*plus sign*) or 1^- (k_{SUB}) (*diamond*) vs the reduction potentials of the radical anions

Stereochemical probes

Racemization in an aliphatic nucleophilic substitution with 1^- would be expected only in cases when k_{SUB}/k_{ET} is ~1, and the synthetic difficulties of making an optically pure chiral tertiary halide and to establish the degree of chirality in the substitution product made us turn to the *exo*/*endo* relation of the bornyl system.

As is well known, the typical S_N2 reaction leads to inversion at the central carbon atom. Reduction of anthracene in DMF in the presence of bornyl or isobornyl bromide gave the same mixture of 9-(*exo*-2-bornyl)-9,10-dihydroanthracene and 9-(*endo*-2-bornyl)-9,10-dihydroanthracene. The steric results show that in the reaction between anthracene radical anion and bornyl and isobornyl bromide, the stereochemical information of the substrate is lost during the reaction and that the reaction is an outer-sphere ET. This indicates that some aliphatic nucleophilic substitutions with aromatic radical anions may proceed through outer-sphere ET and that the stabilization in the transition state is very small. In reactions with less sterically hindered alkyl halides, an inner-sphere ET component may influence the stereochemical results [93, 94].

Electrochemical reduction of 1^+ to 1^- in the presence of bornyl bromide gave two substitution products A and B in the proportion 1.4:1; when isobornyl bromide and 1^- reacted, the same substitution products A:B=1:1.3 were found. The results are explicable if it is assumed that 2-bornyl radical is a common intermediate in the reaction of 1^- with both bornyl and isobornyl bromide. This suggests that when the kinetic results indicate that k_{SUB}/k_{ET} is ~1, it may be expected that a predominant racemization takes place during the substitution.



The reaction between isobornyl bromide and 1^- gave the same mixture of stereoisomers at 25 and 50 °C, but on lowering the temperature to −40 °C, the reaction gave a greater difference between the two isomers than at higher temperatures. Isolation of the major isomer, hydrogenation of the dihydropyridine ring to a piperidine ring, quaternization of the nitrogen gave a compound the perchlorate of which gave crystals suitable for an X-ray structure determination. It turned out that the major isomer was formed by inversion [93, 94].

Activation parameters

The entropy of activation for the S_N2 reaction should be more negative than that of the ET reaction. This is, among other things, caused by the strict geometrical requirements and associative character of the S_N2 TS. On the other hand, the enthalpy of activation of the S_N2 reaction would be expected to be smaller than that of the ET reaction due to the bonding stabilization in the TS. To obtain these parameters, the dependence of the rate of reaction on the temperature was measured. For a "well-behaved" reaction, a linear connection between ln k and T^{-1} is expected from the Arrhenius equation.

From the results for the reaction between the radical anion of anthracene and butyl bromide in the interval −50 to 50 °C and for all the other about 100 reactions between different radical anions and alkyl bromides, a straight line was obtained. This we have interpreted to show that in the temperature interval investigated (−50 to 50 °C), there is no change detectable by this method in the reaction between aromatic radical anions and alkyl bromides [89–92], (Fig. 12).

From the Arrhenius plots, the entropy and enthalpy of activation may be extracted. In the reactions between radical anions and sterically hindered alkyl halides including *t*-butyl bromide, approximately the same value for $\Delta S^{\ddagger}_{298}$ is found, and this value (−9 cal mol^{-1} K^{-1}) is taken

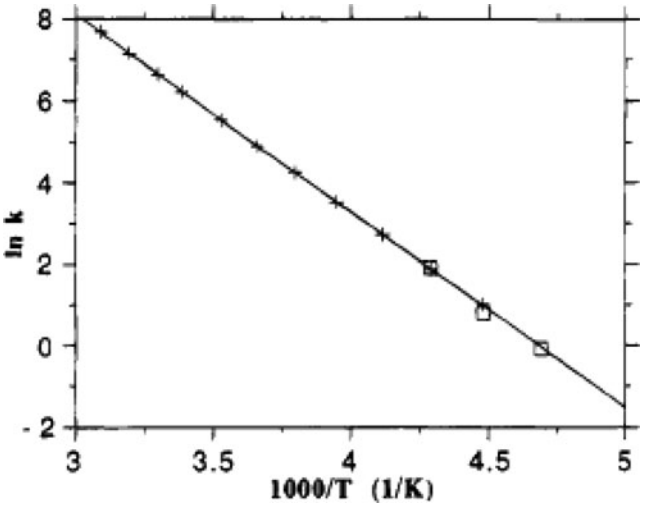


Fig. 12 Temperature dependence of the rate constants of the reaction between anthracene radical anion and 1-bromobutane in DMF/$TBABF_4$ measured by CV (*plus sign*) and a potentiometric method using a rotating disc electrode (*square*)

as a standard value for $\Delta S^{\ddagger}_{298}$ for an outer-sphere dissociative ET. The somewhat more negative $\Delta S^{\ddagger}_{298}$ for primary and secondary alkyl halides might be due to a bonding interaction in the TS or something else.

In the reaction with 1^{-}, only the most sterically hindered alkyl halides, 1-bromoadamantane and bornyl bromide, have the same values for $\Delta S^{\ddagger}_{298}$ as the radical anions. This is in accordance with the stereochemical results and the $k_{SUB}/k_{ET} \sim 1$ which indicates that for these sterically very hindered (against back-side S_N2 attack) alkyl halides, the substitution may be described as an outer-sphere dissociative ET followed by a radical coupling. The sterically less hindered alkyl halides, even *t*-BuBr and *exo*-norbornyl bromide, show a more negative $\Delta S_{298}^{\ddagger}$ which may be interpreted as a slightly more S_N2-like TS.

The results from the measurements of the activation parameters as well as those from the kinetic (k_{SUB}/k_{ET}) and the stereochemical investigations show that there is a gradual change from the characteristics of a pure ET reaction to those of a classical S_N2 reaction. This may be interpreted in two ways; the observation may be caused by the competition between two distinct reaction routes, ET and S_N2, with only two types of TS, an outer-sphere dissociative ET followed by a radical coupling or a classical S_N2 TS; an alternative explanation is that there are TS with structures with varying degrees of inner-sphere (bonding) stabilization ranging from pure ET TS to the classical S_N2 TS. Although there is no definite evidence either way, the fact that we find a linear dependence of ln *k* vs. T^{-1} for all the substitutions we have investigated suggests that there is no shift in the reaction path in this interval.

How are the possibilities to predict the ET–S_N2 TS from a knowledge of structure and potentials of the reactants? Shaik and Pross have proposed a valence bond configuration mixing (VBCM) model [81, 82] according to which all nucleophilic reactions proceed through an initial shift of one electron. If the interaction between $Nu^{\bullet}$ and $R^{\bullet}$ in the transition state is very weak, the mechanism can be classified as an outer-sphere ET mechanism. The VBCM model predicts that if the steric hindrance of R in RX is increased the ET character of the TS will increase, and this is found in most cases by the experiments. It is also predicted that when the electron-donating power of the nucleophile is increased or the electron-accepting ability of the substrate is increased, then the activation energy will decrease. Again, it is correct for many, but not for all of the experiments. It is also predicted from the VBCM model to expect a decrease in k_{SUB}/k_{SET} when the electron-donating power of the nucleophile increases. This seems to be the case for the reactions with alkyl bromides, but not with benzyl bromides. However, it must be remembered that all the experiments in our work [83–88] are much closer to the ET TS than to the S_N2 TS.

Outer-sphere/inner-sphere in other reactions

Whether a reaction follows an outer-sphere electron transfer or goes via formation of an intermediate adduct can be difficult to establish. Substitution–inert complexes such as $Fe(CN)_6^{4-}$ are usually considered to react by ET with most acceptors. It was thus concluded previously [95] that the reaction between $Fe(CN)_6^{4-}$ and aryl diazonium ions, $ZC_6H_4N_2^{+}$, where Z denotes a substituent on the benzene ring, was an outer-sphere ET. However, kinetic studies and identification of products from 4-nitro- and 4-methoxybenzenediazonium with an excess of $Fe(CN)_6^{4-}$ showed that the reactions go via the formation of an adduct, a diazoisocyanide complex, according to (14)

$$ZC_6H_4N_2^{+} + Fe(CN)_6^{4-} \rightarrow ZC_6H_4N_2(NC)Fe(CN)_5^{3-} \qquad (14)$$

The diazoisocyanide complex decomposes by expulsion of nitrogen to form mainly (~85%) an isocyanide complex, $ZC_6H_4(NC)Fe(CN)_5^{3-}$ and some substituted benzonitrile. The observation that a short-lived diazoisocyanide complex and an isocyanide complex are formed is in accordance with an inner-sphere mechanism. Further support of this conclusion comes from the observation that the slope of the activation–free energy plot for the reactions of $NO_2C_6H_4N_2^{+}$ and $MeOC_6H_4N_2^{+}$ with $Fe(CN)_6^{4-}$ is higher than that expected for an outer-sphere mechanism [96].

Potentials of radicals

Several methods have been used to determine redox potentials of radicals [97]. Here the "competition method" will be discussed. It rests on the competition between coupling of a radical with a radical anion and the reduction

of the radical by the same radical anion as shown in the scheme [98–103].

$$A + e^- \rightleftarrows A^{-\cdot} \quad (15)$$

$$A^{-\cdot} + RX \rightarrow A + R^{\cdot} + X^- \quad (16)$$

$$R^{\cdot} + A^{-\cdot} \rightarrow RA^- \quad (17)$$

$$R^{\cdot} + A^{-\cdot} \rightarrow R^- + A \quad (18)$$

$$R^-,\ AR^- + H^+ \rightarrow RH,\ ARH \quad (19)$$

In the scheme, A is an aromatic or heteroaromatic compound which by electron uptake forms a radical anion stable on the time scale of the experiment. RX is a derivative of the radical $R^{\bullet}$, usually an alkyl halide, which should be reduced in a dissociative electron transfer. The anions formed R^- and AR^- are finally protonated. Reaction (18) is regarded as an outer-sphere electron transfer and its rate is assumed to follow the Marcus activation-driving force relationship, $\Delta G^{\#} = (\lambda/4)\{1 + [F(E^{\circ}_{A} - E^{\circ}_{R\bullet})]/\lambda\}^2$. Accordingly, the rate of reaction is dependent on the redox potential of the radical ($E^{\circ}_{R\bullet}$) and A (E°_{A}) and the reorganization energy associated with the electron transfer λ.

The rate of the competing reaction (17) is close to diffusion control. If the rate of the coupling reaction can be assumed to be constant for all the different radicals and radical anions employed, a competition parameter $q = k_{18}/(k_{17}+k_{18})$ can be introduced from which information on k_{18} can be extracted. When q is plotted against E°_{A}, an S-shaped curve is obtained (Fig 13) and, at the mid-point of the curve, a reduction potential can be found. The uncertainty of $E^{q}_{\frac{1}{2}}$ is estimated to be about 50 mV.

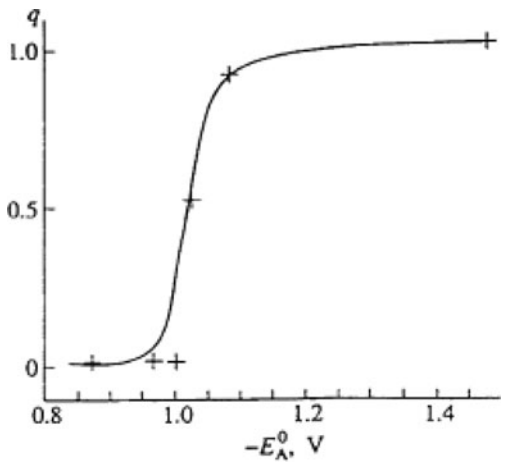


Fig. 13 q-Values for benzyl chloride vs the redox potential of some radical anions in DMF/$TBABF_4$

A crucial point for the competition method is thus that the rate of the coupling reaction is reasonably constant. Three approaches have been employed to investigate the problem, the use of radical clocks, the competition between the coupling reaction and another second order reaction, the addition of a radical to an olefin, and the third method was a competition between the coupling reaction and the reaction between the radical $R^{\bullet}$ and a hydrogen atom donor, benzenethiol. All three approaches for most radicals have given similar results for k_{17} ($\approx 10^9$ mol^{-1} l s^{-1}) [98–103], so the competition method seems reliable for the determination of the potential at which the chemistry changes from radical to ionic reactions for a carbon-centred radical, i.e. $E^{q}_{\frac{1}{2}}$.

Bases

Electrochemical reductions often are combined with the uptake of protons and thus at the same time with the formation of a deprotonated compound, a base. In the Aarhus group, several aspects of electrochemically formed bases have been investigated, including electron transfer from such bases.

Our interest in this area was inspired by a paper by T. Shono [104] in which phosphonium ylides were prepared by electrolytic reduction of phosphonium halides. The electrolysis was carried out at a carbon electrode at 15–50 V, and the carbonyl compound in the Wittig reaction was used as solvent. The reaction was formulated as a one-electron reduction of the phosphonium compound forming an ylide plus a hydrogen atom.

The published conditions did not indicate which compounds received the electrons, so we decided to separate the redox reaction from the acid–base reaction. The easily reducible azobenzene was chosen as the electron acceptor, benzyltriphenylphosphonium bromide as the proton donor and benzaldehyde as the other component in the Wittig reaction; DMF was the solvent with dry lithium chloride as the salt. By using controlled potential reduction, it was made certain that only azobenzene took up electrons and the reduction product, the hydrazobenzene anion, the only base. The only proton donor was the phosphonium bromide and the ylide formed on the protonation of the hydrazobenzene anion. The isolated yield of this form for Wittig reaction was 98% of stilbene with a cis/trans ratio of 3:2 [105].

The electrolytic method of generating bases has several advantages. The amount of base formed is easily measured by a coulometer, and any desired concentration of base can

be maintained by controlling the current. Side reactions caused by the addition of a conventional, strong base, such as butyl lithium, might be avoided.

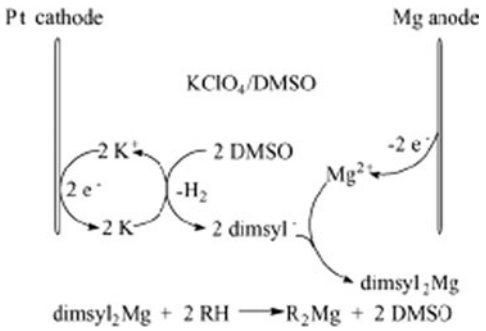
Reactions of aromatic compounds with hydroxide or alkoxide ions induce in some cases reductions although a direct electron transfer involving these basic species is excluded for energetic reasons. The reaction between hydroxide ion and nitrosobenzene to yield as a main product azoxybenzene was first made for more than 100 years ago. Since then, several authors have proposed a scheme for the reactions.

In our hands, a 2-day reaction at ambient temperature of a deaerated suspension of finely powdered nitrosobenzene in 1 M potassium hydroxide in water or 30% acetonitrile under vacuum gave azoxybenzene and 4-nitrosophenol. In the first step, an addition of a hydroxide ion is suggested to take place either at the nitroso group or at the aromatic ring. Whereas the addition to the nitroso group may proceed as a reversible process, the addition to the ring is more likely to become irreversible due to a loss of a proton from the introduced hydroxyl group. On the assumption that the hydroxyl group of 4-hydroxycyclohexa-2,5-dien-1-one oxime is deprotonated fast at high pH, the so-formed dianion may transfer a hydride ion to nitrosobenzene yielding the anion of phenylhydroxylamine. Subsequently, this anion reacts with nitrosobenzene to afford azoxybenzene [106].

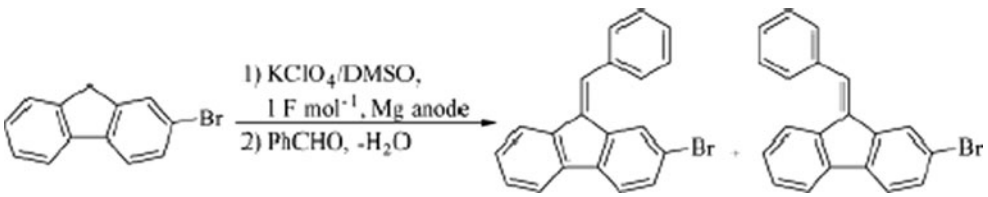
Grignard reagents

Grignard reagents have for many years been important species employed in organic synthesis. In the classical approach, the reagent is formed in a reaction between an organic halide and magnesium in an inert solvent, generally an ether. Although extremely useful, this approach has some limitations, as it prohibits the presence of other reactive or reducible functional groups in the same molecule; thus, carbonyl, nitro and cyano groups along with acidic groups must be avoided because of their high reactivity towards the Grignard functionality. Some methods of preparing the reagents in a way which avoids some of these limitations have previously been described [106–109].

The usual formation of the Grignard reagents consists of two steps, the reduction of the halogen compound and the coordination of magnesium with the reduction product. The first step in the method described here consists of an electrochemical generation of the strong dimsyl base through a reduction of a potassium salt to potassium metal in dimethyl sulfoxide. The electrolysis is carried out in an undivided cell with a magnesium sacrificial anode, and the dimsyl base is ion-paired (and stabilized) with magnesium. In the second non-electrochemical step, the dimsyl base is used to deprotonate a weakly acidic substrate, thereby generating the target Grignard molecule R_2Mg. The great advantage of this procedure is that it allows the formation of R_2Mg reagents containing electrophilic substituents such as halogen, carbonyl and cyano [110].



The yields were good (phenylacetonitrile+benzaldehyde to (Z)-2,3-diphenylacrylonitrile, 92%) to medium (fluorene+4-(*N*,*N*-dimethylamino)-benzaldehyde to 9-(4′-*N*,*N*-dimethylaminobenzylidene)fluorene, 42%). If 2-bromofluorene and benzaldehyde were reacted with $dimsyl_2Mg$, a mixture of the (*E*)- and (*Z*)-benzylidene-2-bromofluorene resulted, of which the constitution of the (*E*) isomer was determined by X-ray analysis.



Sandbjerg meetings

When discussing the research in Aarhus, the Sandbjerg meetings ought to be mentioned. Sandbjerg is a small castle which was given to the University of Aarhus and, during the years, developed to a modern conference centre. The first meetings were small Scandinavian conferences, but later they became international meetings. From 1969 to

2001, I organized 21 meetings; as UNESCO had asked me to organize collaboration between organic electrochemists from the East and the West, Sandbjerg meetings had participants from both sides and from all continents. The meetings were rather informal; they had five to six main lectures by international known scientists and 20–25 shorter contributions mostly by Ph.D. students or postdoctoral researchers; for many of the young participants, it was their first experience to present their work for an international audience.

Conclusion

Above has been presented some of the research my collaborators and I have published since 1951, but it should also be mentioned that the work in organic electrochemistry of our group is being continued by two groups of my collaborators, one headed by K. Daasbjerg and S.U. Pedersen at the University of Aarhus and the other one headed by T. Lund at the University of Roskilde.

And what is the conclusion after 60 years of experience of research mainly in organic electrochemistry? An obvious advantage has been to be able to combine knowledge from different fields. As mentioned previously that my background in synthetic organic chemistry was to a high degree determining my electrochemical research for a number of years and even when research on electron transfer became dominating, the wish to explore the details of the reaction mechanisms was the driving force for the work.

A disadvantage of having been mainly trained in organic synthesis and the industrial use of it was that I had no knowledge of organic electrochemistry and there was no expertise at the universities in Denmark of that kind of electrochemistry, so I had to get the basic elements from books and papers. However, the lack of conventional knowledge of how to do electrochemical research made me do unusual experiments, and sometimes, the results turned out to be better than I had hoped for. So much of the new results were obtained partly because I had no adviser to tell me what to do.

I also think that it is an advantage that the group leader does experiments himself. When I suggested/discussed a project with a student/collaborator, I had always made experiments related to the project to make sure that suitable results could be obtained. It also was an advantage to do that if something unexpected turned up during these preliminary experiments. I would notice it and possibly find that these unexpected results might be as interesting as those expected from the original proposal. It is not certain that a student would notice the unexpected results or he might just disregard them as irrelevant.

But what about electrochemistry in the years to come? As the saying goes, it is difficult to make predictions, especially about the future. What specialists have said about how the economical and political situation would develop has not been impressive. In electrochemistry, the research on modification of surfaces and the study of ionic solvents will be hot subjects for some years. I hope that some breakthrough will come for the storage of energy and a high yield cheap utilization of solar energy, and I believe that electrochemistry will play an important role in this development.

We live in an age where science for many of the money-deciding authorities is justified only by the economic value of the products build on the scientific results, so ideal science from that point of view has a short path from experiment to product. Most of the money is given to large groups working on similar projects as many other large groups around the world. It is difficult for somebody with a new, “wild” idea to get economic support; some of such ideas fail, but the money used for new ideas is not lost, as long as just some of them can be further developed. New science is made by someone who has got an idea and has a burning desire to develop that and to understand its possibilities. Such an idea gets into your gut and makes you work in another way than if you feel that your experiments could just as well be done by somebody else in an industrial laboratory.

References

1. Fichter F (1942) Organische Elektrochemie. Theodor Steinkopff, Dresden und Leipzig
2. Lund H (2002) J Electrochem Soc 149:S21–S33
3. Lund H (1951) Acta Chem Scand 5:1394–1395
4. Lingane JJ, Swain CG, Fields M (1943) J Am Chem Soc 65:1348–1353
5. Lingane JJ (1953) Electroanalytical Chemistry. Interscience, New York
6. Allongue P, Delamar M, Desbat B, Fagebaume R, Hitmi R, Pinson J, Savéant JM (1997) J Am Chem Soc 119:201–207
7. Pinson J, Podvorica F (2005) Chem Soc Rev 34:429–439
8. Lund H (1957) Acta Chem Scand 11:491–498
9. Lund H (1957) Acta Chem Scand 11:1323–1330
10. Lund H (1959) Acta Chem Scand 13:249–267
11. Lund H (1964) Acta Chem Scand 18:563–565
12. Soucaze-Guillous B, Lund H (1997) J Electroanal Chem 423:109–114
13. Soucaze-Guillous B, Lund H (1998) Acta Chem Scand 53:417–424
14. Lund H (1960) Acta Chem Scand 14:359–378
15. Lund H, Lunde P, Kaufmann F (1966) Acta Chem Scand 20:1631–1644
16. Lund H (1960) Acta Chem Scand 14:1927–1938

17. Lund H (1970) In: Katritzky AR, Bouloton AJ (eds) Advances in heterocyclic chemistry, vol 12. Academic Press, New York, pp 213–316
18. Lund H, Tabakovic I (1984) In: Katritzky AR, Boulton AJ (eds) Advances in heterocyclic chemistry, vol 36. Academic Press, New York, pp 235–341
19. Toomey JE (1984) In: Katritzky AR, Boulton AJ (eds) Advances in heterocyclic chemistry, vol 37. Academic Press, New York, p 167
20. Armand J, Pinson J (1984) In: Gupta RR (ed) Physical methods in heterocyclic chemistry, vol 7. Academic Press, New York, p 427
21. Baumgärtel H, Retslav KJ (1984) In: Bard AJ, Lund H (eds) Encyclopedia of electrochemistry of the elements, vol 15. Dekker, New York, pp 168–315
22. Richter HP, Pfegel P (1985) Pharmazie 40:81
23. Moeller KD (1997) Curr Top Chem 185:49
24. Lund H (2001) In: Lund H, Hammerich O (eds) Organic Electrochemistry. Dekker, New York, pp 669–724
25. Volke J (1957) Experientia 13:274–275
26. Volke J (1958) Coll Czech Chem Comm 23:1486–1495
27. Lund H (1963) Acta Chem Scand 17:972–978
28. Lund H (1963) Acta Chem Scand 17:2325–2340
29. Lund H (1963) Acta Chem Scand 17:1077–1086
30. Iversen PE, Lund H (1967) Acta Chem Scand 21:279–285, 389–396
31. Albert A, Armarego WLF, Spinner E (1961) J Chem Soc 2689–2696
32. Lund H (1964) Acta Chem Scand 18:1984–1995
33. Lund H (1967) Oesterr Chem Z 68:43–53, 152–163
34. Lund H (1967) Acta Chem Scand 21:2525–2543
35. Lund H, Simonet J (1973) C R Acad Sci Paris 277:1387–1389
36. Oelschläger H, Volke J, Bresch C (1985) Arch Pharm (Weinheim, Ger) 318:271–276
37. Fuhlendorff R, Lund H (1988) Acta Chem Scand B42:52–54
38. Lund H (1965) Coll Czech Chem Commun 30:4237–4249
39. Pedersen SU, Lund H (1988) Acta Chem Scand B 42:319–322
40. Studnickova M, Flerov VN, Fischer O, Potacek M (1985) J Electroanal Chem 187:297–306
41. Lund H (1966) Coll Czech Chem Commun 31:4175–4177
42. Lund H, Lunde P (1967) Acta Chem Scand 21:1067–1080
43. Kwee S, Lund H (1968) Acta Chem Scand 22:2879–2889
44. Lund H (1969) Acta Chem Scand 23:563–566
45. Lund H, Jensen ET (1970) Acta Chem Scand 24:1867–1877
46. Kwee S, Lund H (1971) Experimentia Suppl 18:387–394
47. Kwee S, Lund H (1972) Acta Chem Scand 26:1195–1200
48. Kwee S, Lund H (1973) Biochem Biophys Acta 297:285–296
49. Martigny AP, Lund H (1979) Acta Chem Scand B33:575–579
50. Lund H, Nilsson NH (1976) Acta Chem Scand B 30:5–11
51. Lund H, Feoktistov LG (1969) Acta Chem Scand 23:3482–3492
52. Kwee S, Lund H (1969) Acta Chem Scand 23:2711–2716
53. Lund H, Thomsen AD (1969) Acta Chem Scand 23:3567–3576, 3582
54. Lund H (1965) Tetrahedron Lett 6:3973–3976
55. Simonet J, Lund H (1977) J Electroanal Chem 75:719–730
56. Lund H, Michel M-A, Simonet J (1974) Acta Chem Scand B 28:900–904
57. Lund H, Michel M-A, Simonet J (1975) Acta Chem Scand B29:217–220
58. Simonet J, Michel M-A, Lund H (1975) Acta Chem Scand B 29:489–498
59. Lund H, Simonet J (1975) J Electroanal Chem 65:205–218
60. Sease JW, Reed RC (1975) Tetrahedron Lett 16:393–396
61. Hansen PE, Berg A, Lund H (1976) Acta Chem Scand B30:267–270
62. Degrand C, Lund H (1977) Acta Chem Scand B31:593–598
63. Hobolth E, Lund H (1977) Acta Chem Scand B31:395–398
64. Degrand C, Lund H (1977) Nouveau J Chim 1:35–39
65. Crossland I (1975) Acta Chem Scand B29:468–470
66. Lund H (1977) Acta Chem Scand B 31:424–425
67. Lund H, Degrand C (1977) Tetrahedron Lett 18:3593–3594
68. Shono T, Nishiguchi I, Ohmizu H (1977) J Am Chem Soc 99:7396–7397
69. Praefcke K, Weichsel C, Falsig M, Lund H (1980) Acta Chem Scand B 34:403–407
70. Kjær NT, Lund H (1997) Electrochim Acta 42:2041–2047
71. Kjær NT, Lund H (1995) Acta Chem Scand 49:848–852
72. Carlson HS, Lund H (1980) Acta Chem Scand B 34:409–412
73. Lund T, Lundgren B, Lund H (1995) Acta Chem Scand 49:755–761
74. Lund H, Kristensen LH (1979) Acta Chem Scand B 33:495–498
75. Kornblum N (1975) Angew Chem Int ed 14:734–745
76. Russell GA, Danen WC (1966) J Am Chem Soc 88:5663–5665
77. Bunnett JF (1978) Acc Chem Res 11:413–420
78. Sargent GD, Lux GA (1968) J Am Chem Soc 90:7160–7162
79. Garst JF (1971) Acc Chem Res 4:400–406
80. Ashby EC (1988) Acc Chem Res 21:414–421
81. Pross A, Shaik SS (1983) Acc Chem Res 16:363–370
82. Pross A (1985) Acc Chem Res 18:212–219
83. Lund T, Lund H (1986) Tetrahedron Lett 27:95–98
84. Lund T, Lund H (1986) Acta Chem Scand B 40:470–485
85. Lund T, Lund H (1987) Acta Chem Scand B 41:93–102
86. Lund T, Lund H (1988) Acta Chem Scand B 42:269–279
87. Lund H (1986) J Mol Catal 38:203–226
88. Daasbjerg K, Pedersen SU, Lund H (1989) Acta Chem Scand 43:876–881
89. Daasbjerg K, Pedersen SU, Lund H (1991) Acta Chem Scand 45:424–430
90. Lund H, Daasbjerg K, Lund T, Pedersen SU (1995) Acc Chem Res 28:313–319
91. Lund H, Daasbjerg K, Lund T, Occhialini D, Pedersen SU (1997) Acta Chem Scand 51:135–144
92. Lund H, Daasbjerg K, Lund T, Pedersen SU (1998) Macromol Symp 134:73–82
93. Daasbjerg K, Hansen JN, Lund H (1990) Acta Chem Scand 44:711–714
94. Daasbjerg K, Lund H (1996) Acta Chem Scand 50:299–302
95. Doyle MP, Guy JK, Brown KC, Mahapatro SN, VanZyl CM, Pladziewicz JR (1987) J Am Chem Soc 109:1536–1540
96. Kläning U, Lund T, Lund H, Pedersen SU Daasbjerg K (2010) J Phys Chem A 114:6575–6585
97. Daasbjerg K, Pedersen SU, Lund H (1999) In: Alfassi ZB (ed) General aspects of the chemistry of radicals. Wiley, Chichester, pp 385–427
98. Fuhlendorff R, Occhialini D, Pedersen SU, Lund H (1989) Acta Chem Scand 43:803–806
99. Occhialini D, Pedersen SU, Lund H (1990) Acta Chem Scand 44:715–719
100. Occhialini D, Kristensen JS, Daasbjerg K, Lund H (1992) Acta Chem Scand 46:474–481
101. Occhialini D, Daasbjerg K, Lund H (1993) Acta Chem Scand 47:1100–1106
102. Lund H, Daasbjerg K, Occhialini D, Pedersen SU (1995) Russ J Electrochem 31:865–873
103. Lund H, Skov K, Pedersen SU, Lund T, Daasbjerg K (2000) Coll Czech Chem Commun 65:829–843
104. Shono T, Mitani M (1968) J Am Chem Soc 90:2728–2729
105. Iversen PE, Lund H (1969) Tetrahedron Lett 10:3523–3524
106. Lund H, Pedersen JA, Larsen JB, Daasbjerg K (2000) Proc Electrochem Soc 15:64–68
107. Burns TP, Rieke RD (1987) J Org Chem 52:3674–3680
108. Sapountzis I, Knochel P (2002) Angew Chem Int Ed 41:1610–1611
109. Ren H, Krasovsliy A, Knochel P (2004) Org Lett 6:4215–4217
110. Lund H, Svith H, Pedersen SU, Daasbjerg K (2005) Electrochim Acta 51:655–664