

On Electron Transfer in Aliphatic Nucleophilic Substitution

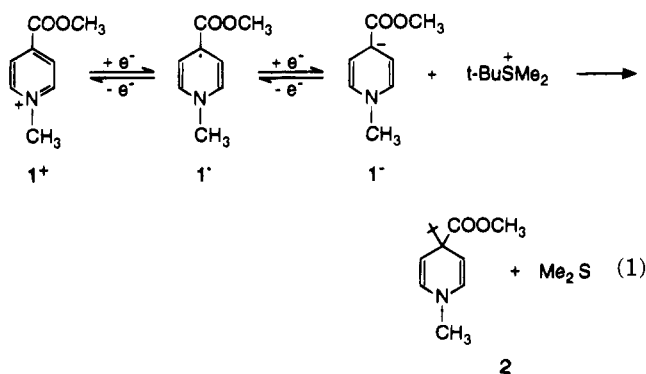
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Aliphatic nucleophilic substitution is one of the most investigated reactions in organic chemistry. In textbooks on organic chemistry, mechanisms are described for this reaction ranging from limiting S_N1 involving symmetrically solvated carbocations through intimate and solvent-separated ion pairs to the classical S_N2 reaction, implying that there is gradual transition between the different mechanisms described.¹ More recently several groups have considered an electron transfer (ET) mechanism; most of the aliphatic nucleophilic substitutions involving electron transfer have involved benzylic derivatives and have been reported to proceed through a chain reaction² initiated by light or otherwise; several accounts and reviews of $S_{RN}1$ and related reactions have been published.²

In 1979 it was found³ that the enolate ion 1^- , obtained by two successive one-electron reductions of 1-methyl-4-(methoxycarbonyl)pyridinium iodide (1^+), was an excellent electron donor and reacted without light initiation with *tert*-butyldimethylsulfonium iodide or *tert*-butyl bromide in *N,N*-dimethylformamide, DMF, with formation in good yield of 4-*tert*-butyl-1,4-dihydro-4-(methoxycarbonyl)-1-methylpyridine (**2**) as the only detectable product (eq 1).



An S_N1 reaction is unlikely under these conditions as *tert*-butyl bromide does not react with the large excess of tetrabutylammonium iodide used as supporting electrolyte; no *tert*-butyl iodide is formed. An

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S_N2 reaction is not occurring, as any well-behaved nucleophile reacting according to an S_N2 scheme would attack one of the methyl groups in the *tert*-butyldimethylsulfonium ion rather than the *tert*-butyl group. A reaction between the *tert*-butyl radical and 1^- in an $S_{RN}1$ -like fashion is highly unlikely as the steady state concentration of the nucleophile 1^- is negligible. The argument is that the 1^- formed at the electrode during the electrolysis reacts fast (rate constant about $10^2 \text{ M}^{-1} \text{ s}^{-1}$) with *tert*-butyl bromide. It was therefore suggested that the enolate anion 1^- had transferred an electron to the substrate, which cleaved immediately to a *tert*-butyl radical and a leaving group, and that the radical 1^* and the *tert*-butyl radical had coupled. It was also proposed that there might be found reactions with transition states (TS) ranging from the classical S_N2 TS, with an approximately equal bonding of the central carbon to both the incoming nucleophile and the leaving group, to an ET TS, in which there is negligible bonding (less than 1 kcal mol^{-1}) 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 an S_N2 TS and the nucleophile would not need to attack along the C–X axis. The reaction between 1^- and *tert*-butyl bromide could thus be described by eq 2.



Ashby later independently proposed a mechanism similar to eq 2 for the reaction of alkyl iodides with NaSnMe_3 ^{4a} and for the reaction of triphenylmethyl bromide with lithium diisopropylamide.^{4b}

The possible involvement of ET in a number of organic reactions^{5a–d} has been discussed on the basis of the Marcus equation,^{5e} and product studies of

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several nucleophilic reactions have been used as arguments for single electron transfer in such reactions.⁶

In most textbooks the S_N2 reaction has been described as an attack of the electron pair of the nucleophile on the substrate, but as Pross and Shaik⁷ have pointed out, the net result of the S_N2 reaction is the transfer of one electron from the nucleophile to the leaving group; in order to distinguish the formal movement of an electron from the classical ET, they introduced the term "electron shift". The question then arises, can this formal "electron shift" in some systems be a nonchain outer-sphere electron transfer where the transfer of an electron is the rate-determining step? This Account discusses some aspects of this question.

Many textbooks use the S_N1 and S_N2 reactions to introduce the students to the idea of reaction mechanism in organic chemistry, and the treatment implicitly suggests that it is a full description of the possible reaction paths of the aliphatic nucleophilic substitution reaction. It was therefore felt especially important that the proposal of ET in this reaction was supported by different kinds of experimental approaches, besides preparative results, and three types of experiments were made.

1. Kinetic Test. The idea behind the kinetic test is to compare the rate constant (k_{SUB}) of the substitution of a nucleophile (e.g., I⁻) 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. In an outer-sphere ET the bonding between the donor and the acceptor in the TS is less than 1 kcal mol⁻¹.⁸ The ratio $k_{\text{SUB}}/k_{\text{ET}}$ is a measure of the difference in the activation energy between the substitution reaction and the outer-sphere ET TS. If $k_{\text{SUB}}/k_{\text{ET}} \sim 1$, that is, if the rate of the substitution and the rate expected for an ET are the same, 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.⁹

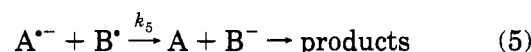
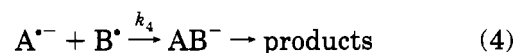
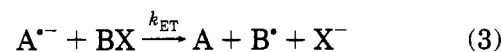
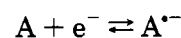
2. Stereochemical Probes. A classical S_N2 reaction would result in an inversion of the configuration at the central carbon, whereas in a radical reaction a stereochemical equilibration would be expected, although it has been argued that an inversion does not exclude a radical reaction.⁶ Under all circumstances a racemization would exclude an S_N2 mechanism.

3. Activation Parameters. An S_N2 reaction would be expected to have, compared with an ET reaction, a relatively low enthalpy of activation due to the bonding stabilization in TS, but a relatively more negative entropy of activation. The S_N2 TS is tighter than the ET TS, and it is generally assumed that strict stereochemical requirements in the TS result in a more negative ΔS^\ddagger .

Kinetic Test for Electron Transfer

Radical anions of aromatic hydrocarbons and heteroaromatic compounds were chosen as one-electron donors;⁹ they are stable in the absence of proton donors, and they have a relatively low reorganization energy connected with the electron transfer; alternatively certain metal complexes may be used as electron donors.¹⁰ In the reactions with alkyl halides, radical anions could, in principle, react either as electron transfer agents or as nucleophiles; evidence from the reactions between sodium salts of aromatic radical anions and alkyl halides strongly suggested that they reacted as electron donors rather than as nucleophiles.¹¹

In the middle of the 1970s a revival of the use of indirect electrolysis¹²⁻¹⁴ in organic chemistry occurred, especially concerning the reduction of aromatic^{12a} and aliphatic^{12c,13} halides by radical anions of aromatic and heteroaromatic compounds. In an indirect electrochemical reduction the electrode transfers an electron to a mediator, which then transfers the electron to the substrate. The occurrence of a competition between coupling (eq 4) and reduction (eq 5) in the reaction between aromatic radical anions and aliphatic radicals, produced by reduction of alkyl halides, was established,^{12c} and the following scheme was suggested for the reaction between an aromatic radical anion A^{*-} and an alkyl halide BX (eqs 3-5).



The reaction between aromatic radical anions and an acceptor including the parent aromatic compound has been suggested not to be outer-sphere ET, but to have an inner-sphere component.¹⁵ The generally accepted definition of an inner-sphere ET is an ET in which there is a bonding (stronger than 1 kcal mol⁻¹, but not necessarily much stronger) through a ligand between the donor and the acceptor. The inner-sphere TS has thus a lower enthalpy than the outer-sphere ET TS; the concept does not imply that there is an energy minimum on the reaction path. An S_N2 reaction may be described as an inner-sphere ET, in which the central carbon is the ligand. In the S_N2 reaction the ligand is transferred from the leaving group to the nucleophile.

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has been questioned,¹⁶ until convincing evidence of inner-sphere ET for such reactions is presented, we are still treating our data for the sterically hindered alkyl halides with the assumption that aromatic radical anions are outer-sphere electron donors. A small inner-sphere component would be of no consequence for our arguments. In this connection it is of interest that the reaction between anthracene radical anion and butyl bromide produced the same product mixture as the photochemical reaction of tetramethylammonium butyltriphenylborate with anthracene in which anthracene radical anion and butyl radical are formed.¹⁷ In the reaction between radical anions and methyl halides (and possibly also to a limited extent some primary alkyl halides, but not sterically hindered alkyl halides) there might be a certain inner-sphere component, most significant in the reaction with methyl chloride; the inner-sphere component becomes smaller when the driving force becomes larger.¹⁸

The quantitative aspects of the kinetics of the reaction between radical anions and aryl halides were later developed mainly by the Paris group,¹⁹ and the synthetic possibilities of the coupling reaction were explored by the Aarhus group and others.²⁰⁻²² Electron transfer to electrophiles other than monohalides, such as 1,2-dihalides,^{20a,c} 1,3-dihalides,^{20a,c} activated olefins,^{20a} carbon dioxide,^{20i,22} and anhydrides,^{20h,21} was demonstrated. It was also shown that dianions of aromatic compounds^{20a,m} and photoexcited anion radicals^{20j} were excellent electron donors.

The rate of electron transfer from aromatic radical anions to the substrate has been measured by different electrochemical techniques such as cyclic voltammetry,²³ linear sweep voltammetry,²³ double potential step chronoamperometry,²⁴ and homogeneous kinetic measurements using a rotating disk electrode or an ultra-microelectrode²⁵ to monitor the reaction. By these methods second-order rate constants from about 10^{-3} to $10^6 \text{ M}^{-1} \text{ s}^{-1}$ may be measured. The measured rate constants higher than $10^6 \text{ M}^{-1} \text{ s}^{-1}$ have been

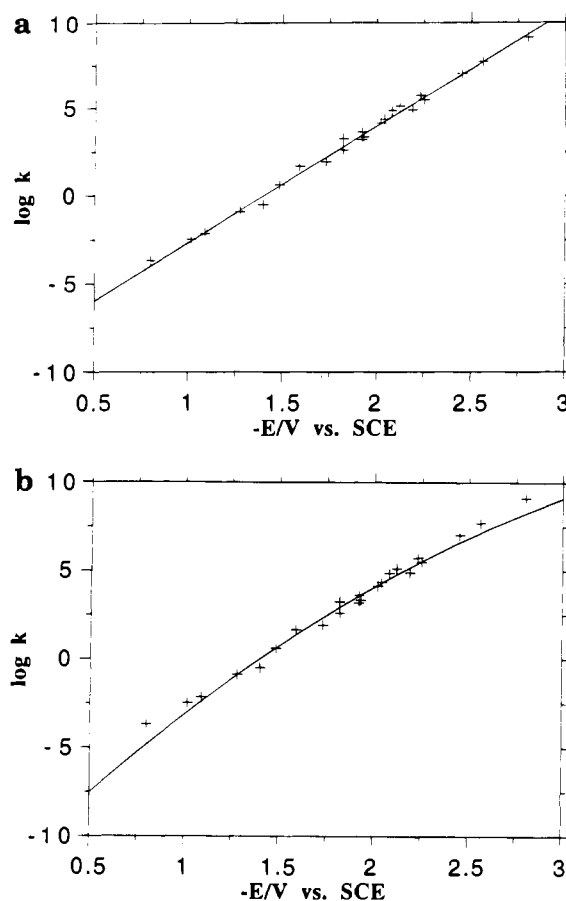


Figure 1. Logarithm of the rate constant (k_{ET}) of the reaction between *t*-BuBr and different aromatic radical anions (+) vs the reduction potential of the radical anions ($-E_A^o$ vs SCE); in plot b a parabola corresponding to $\lambda = 90 \text{ kcal mol}^{-1}$ is drawn.

obtained by pulse radiolysis. The lack of knowledge of E^o of the alkyl halides prevents the making of a usual Marcus plot, so the results are depicted in a plot with the driving force (proportional to the standard potential of the aromatic compound, E_A^o) as abscissa and the logarithm of the second-order rate constant of ET as ordinate.

The reaction between aromatic radical anions and alkyl halides involves a dissociative electron transfer, which means that the electron transfer to the alkyl halide and the cleavage of the C-X bond are concerted. The usual theory for outer-sphere electron transfer (Marcus theory)⁸ is not directly applicable for such reactions, and a theory for dissociative ET has been developed.²⁶ According to this theory the rate constant is, among other things, dependent on the C-X bond strength, which is the main contributor to the reorganization energy λ for the reaction; it retains from the Marcus theory, however, the quadratic dependence of the energy of activation on the driving force.

In Figure 1 the dependence of $\log k_{ET}$ of the reaction between aromatic radical anions and *t*-BuBr on the driving force is shown;²⁷ the fastest reactions ($k_{ET} > 10^6 \text{ M}^{-1} \text{ s}^{-1}$) have been measured by pulse radiolysis.²⁸ In Figure 1a a linear dependence is assumed, whereas in Figure 1b the theoretical parabola²⁶ calculated with

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the use of the parameters suggested^{16a} (the standard potential $E^{\circ}_{\text{BX}} = -0.92$ V vs SCE, the reorganization energy $\lambda = 90$ kcal mol⁻¹, and the pre-exponential factor 5×10^{12} M⁻¹ s⁻¹) is drawn. Together the range of rate constants spans 13 orders of magnitude, and as seen from Figure 1 the points seem best represented by a straight line.

We fail to see²⁹ how the rate constants measured for the slow reactions could be 1 or 2 orders of magnitude too high, as suggested in ref 16a to explain that a straight line rather than a parabola is obtained experimentally, so we think one has to accept the experimental results which point to a linear dependence of $\log k_{\text{ET}}$ on the driving force rather than a quadratic one or, alternatively, that λ is considerably larger than is usually assumed. Possibly an inner-sphere component becomes more significant when the ET becomes more endergonic and thus the reaction gradually develops more S_N2 character.

The reaction between *t*-BuBr and radical anions is, so far, the only reaction for which we have measured the rate constants in a range spanning 13 orders of magnitude. In most cases the rate of the reaction has been measured through 5–7 orders of magnitude, and in such a range the data do not allow a clear distinction between a linear or quadratic dependence when λ is very large (≈ 100 kcal mol⁻¹); the larger the λ the “flatter” the parabola, and the difference between a straight line and a parabola thus becomes smaller.

The reactions between nucleophiles and alkyl halides have been followed with methods similar to those for the radical anions, and the rate constant of the substitution reaction, k_{SUB} , has been measured. The logarithm of the ratio of the rate constants, $k_{\text{SUB}}/k_{\text{ET}}$, where k_{ET} is the rate constant of ET expected for an electron donor with the same oxidation potential and λ as the nucleophile, is a measure of the activation energy of the substitution reaction compared with that of the outer-sphere ET and is thus taken as an indication of the inner-sphere stabilization of the transition state.^{9,30}

In Figure 2 the crosses represent rate constants for the ET reaction of aromatic radical anions with isobornyl bromide (**3**), and the tilted square represents the rate constant for the substitution reaction of 1⁻ with **3**. As the k_{SUB} of 1⁻ falls on the straight line through the points for k_{ET} , $k_{\text{SUB}}/k_{\text{ET}}$ is approximately 1 in this case, and we assume therefore the rate-determining step for this aliphatic nucleophilic substitution to be the transfer of an electron.

In Figure 3 similar data are presented for the reaction of 1⁻ with 2-bromobutane (**4**). The ratio, $k_{\text{SUB}}/k_{\text{ET}}$, for **4** is 170 whereas for ethyl bromide (**5**) it is 2500. These numbers may indicate some bonding stabilization in the transition state compared to the outer-sphere ET reaction, or they may be interpreted as a result of a competition between two reaction

(29) In a recent paper it was suggested^{16a} that the rate constant measured by us²⁷ for the slow reactions depicted in Figure 1 ($k_{\text{ET}} \sim 10^{-3}$ M⁻¹ s⁻¹) were too large due to “reactions with electrophilic and reducible impurities”, and this was one of the reasons for the failure to observe a quadratic $\log k_{\text{ET}}$ vs $-E^{\circ}_{\text{A}}$ relation. The reactions were made by electrochemically generated anion radicals; when the oxidation current of the anion radical measured by a rotating disk electrode was constant, freshly distilled *t*-BuBr was added and the decay in the concentration of the anion radical was followed. Any “electrophilic and reducible impurities” would thus have reacted before the alkyl halide was added; the reactions were run at least three times.

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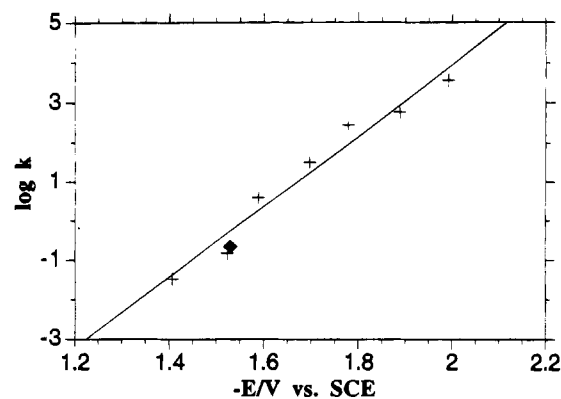


Figure 2. Logarithm of the rate constant (k_{ET}) of the reaction between isobornyl bromide and different aromatic radical anions (+) or 1⁻ (k_{SUB}) (◆) vs the reduction potential ($-E^{\circ}_{\text{A}}$) of the radical anions. The potentials are measured against SCE.

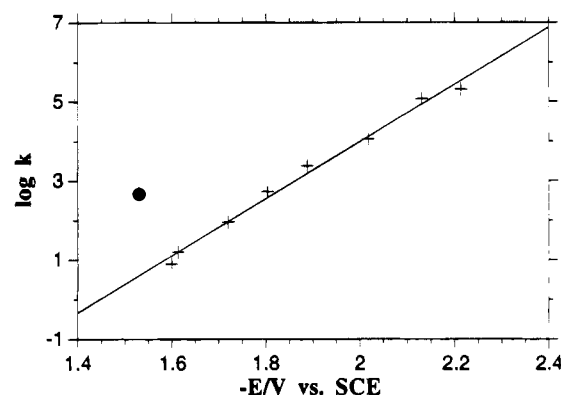


Figure 3. Logarithm of the rate constant (k_{ET}) of the reaction between 2-bromobutane and different aromatic radical anions (+) or 1⁻ (k_{SUB}) (◆) vs the reduction potential ($-E^{\circ}_{\text{A}}$) of the radical anions. The potentials are measured against SCE.

paths, outer-sphere ET and classical S_N2. We prefer the former point of view, but there is no compelling experimental evidence either way.

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 20–30 kcal mol⁻¹ compared with the outer-sphere ET TS), are extremes and that there exist in between them transition states with different bonding stabilizations (in a way somewhat similar to that often advocated for the S_N1–S_N2 reactions), then the reactions between 1⁻ and **4** and **5** have transition states relatively close to the ET transition state with a rather low bonding stabilization (2–5 kcal mol⁻¹). A similar interpretation has been made on basis of the valence bond configuration mixing model (VB-CM).⁷

In our investigations the standard nucleophile has been 1⁻, but other easily oxidizable, delocalized anions, such as 2,4,6-triphenylthiopyran anion, 1,4-dihydro-1-methyl-2,4,6-triphenylpyridine anion, and 4-benzoyl-1,4-dihydro-1-methylpyridine anion, which give stable radicals on oxidation, behave similarly²⁰ⁿ in reactions with alkyl halides, and similar $k_{\text{SUB}}/k_{\text{ET}}$ values are obtained. Examples have also been found that dianions^{20m} of aromatic compounds and neutral nucleophiles^{9d} may react with alkyl halides with ET, and similar values for $k_{\text{SUB}}/k_{\text{ET}}$ are found.

It would be of interest to use nucleophiles other than 1⁻ (and similar compounds) to better bridge the gap

between ET TS and a classical S_N2 TS. Superoxide, $O_2^{\cdot-}$, may react as a nucleophile and an electron donor. The rate of the reaction between $O_2^{\cdot-}$ and alkyl halides³¹ can be measured with the usual electrochemical techniques, but the interpretation of the k_{SUB}/k_{ET} values obtained is more difficult due to the lack of consistent data for the self-exchange reorganization energy $\lambda(0)$ for $O_2^{\cdot-}$; a value of about 45 kcal mol⁻¹ is probably the most reliable.³² The directly measured values for k_{SUB}/k_{ET} for the reaction between $O_2^{\cdot-}$ and some alkyl halides span a range from less than 0.6 for 1-iodoadamantane to 10⁹ for butyl chloride; these k_{SUB}/k_{ET} values may have to be multiplied by a factor of ~500 due to the difference in the self-exchange reorganization energies between $O_2^{\cdot-}$ and the other ET donors. If so, the corresponding stabilization energies compared to an outer-sphere ET range from below 4 kcal mol⁻¹ to 17 kcal mol⁻¹. The results illustrate that the same nucleophile/electron donor may react mainly as an electron donor toward sterically very hindered alkyl halides and as a typical nucleophile with sterically less hindered electrophiles.

Some evidence has been presented that for a given series of alkyl halides the importance of ET would be greatest for the alkyl iodide and smallest for the alkyl chloride.⁶ On the other hand, it has been argued³³ that there is no general justification for the frequent assumption that the best acceptor among a group of alkyl halides reacts with the highest degree of ET. We have investigated a number of alkyl chlorides, bromides, and iodides and find³⁴ that k_{SUB}/k_{ET} grows slightly on going from RI to RBr to RCl, but that the steric hindrance in the TS is much more important for the value of k_{SUB}/k_{ET} than the type of halogen; for benzyl chlorides, however, no clear trend was found.^{9d}

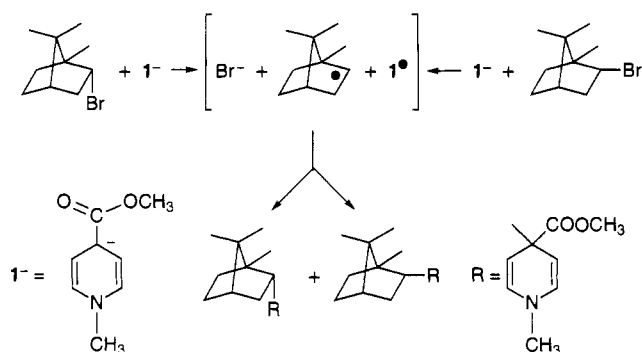
Stereochemical Investigations

As is well-known, the typical S_N2 reaction gives inversion at the central carbon atom. The reaction of lithium anthracene radical anion with optically active 2-octyl halides in diethyl ether gave substitution products with some inversion, depending on the leaving groups, with RCl giving 11–14%, RBr 5–6% and the mesylate 25–40% inversion.^{35a} A later investigation with electrochemically generated anthracene radical anion in DMF and optically active 2-octyl halides gave similar results with predominant racemization.^{35b}

Reduction of anthracene in DMF in the presence of bornyl and isobornyl bromide³⁶ gave the same 1:1 mixture of 9-(*exo*-2-bornyl)-9,10-dihydroanthracene and 9-(*endo*-2-bornyl)-9,10-dihydroanthracene. Curiously enough it happened to be a 1:1 mixture of *exo* and *endo* product; a certain preference for *exo*-substitution would have been expected. Small amounts of 1- and 2-substituted bornyldihydroanthracenes were detected by ¹H-NMR and GC-MS.

The steric results indicate that, in the reaction between anthracene radical anion and bornyl and

Scheme 1



isobornyl bromide, the stereochemical information of the substrate is lost during the reaction. This finding together with the evidence presented above further 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.

A racemization in an aliphatic nucleophilic substitution with 1^- would be expected only in the cases for which $k_{SUB}/k_{ET} \sim 1$, and the synthetic difficulties of making an optically pure chiral tertiary halide and establishing the degree of chirality in the substitution product made us turn to the *exo/endo* relation of the bornyl system.

Electrochemical reduction of 1^+ to 1^- in the presence of bornyl bromide in DMF gave two substitution products, **A** and **B**, in the proportion 1.4:1,³⁷ when isobornyl bromide and 1^- reacted, the same substitution products were found in approximately the same ratio, **A**:**B** = 1:1.3. The results are explainable if it is assumed that the 2-bornyl radical is a common intermediate in the reaction of 1^- with both bornyl and isobornyl bromide, Scheme 1. These results suggest that when the kinetic results indicate that $k_{SUB}/k_{ET} \sim 1$, it may be expected that a predominant racemization takes place during the substitution.

Reaction between isobornyl bromide and 1^- gave the same mixture of **A** and **B** at 25 and 50 °C, but on lowering the temperature to -40 °C the reaction gave a greater difference between the two stereoisomers **A** and **B** than at higher temperatures; isolation of the major isomer, hydrogenation of the dihydropyridine ring to a piperidine ring, and quaternization of the nitrogen with methyl iodide 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.³⁸

When *cis*- or *trans*-2-bromo-1-methoxycyclohexane (**6**) reacted with aromatic radical anions (from anthracene or quinoxaline), the ratio of *trans/cis* isomers of the 2-substituted methoxycyclohexanes was 5:1; when 1^- reacted with *trans*-**6**, the ratio was 3:1, close to that found in the ET reaction, whereas in the reaction with *cis*-**6** a ratio of 200:1 was found, which is nearly a complete inversion. For *trans*-**6** k_{SUB}/k_{ET} was 1, whereas for *cis*-**6** it was about 100. This indicates a close connection between k_{SUB}/k_{ET} and the stereochemical results.³⁹

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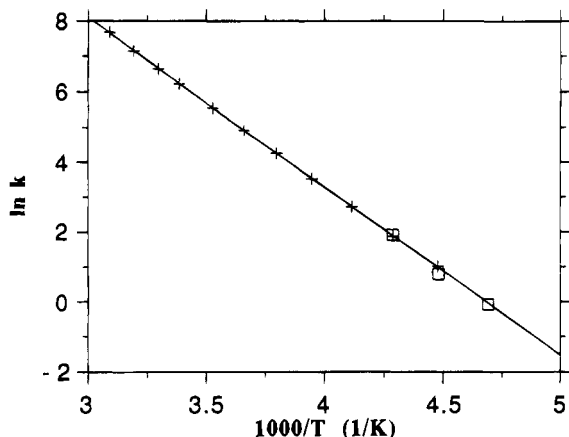


Figure 4. Temperature dependence of the rate constants of the reaction between anthracene radical anion and 1-bromobutane in DMF/TBABF₄ measured by CV (+) and a potentiostatic method using a rotating disk electrode (□).

Activation Parameters

The activation parameters of the S_N2/ET reactions has been studied, because they should be different for the S_N2 and the S_{ET} reactions. 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. We think that the distance in the ET TS between the incoming nucleophile and the central carbon is greater than in the S_N2 TS and that the initial approach of the nucleophile does not need to closely follow the C–X axis. It is generally assumed that strict stereochemical requirements in the TS result in a more negative ΔS[‡]. 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.

In Figure 4 the results obtained by us for the reaction between the radical anion of anthracene and butyl bromide in the interval –50 to 50 °C is shown.²⁷ The measurements have been made very carefully and several times, and when possible two different techniques have been applied to ensure as well as we could that the experimental results were correct. A previous report suggested a break in the curve which was interpreted as a change in reaction mechanism,^{40a} these results have been cited in the literature.⁴¹ In our group we obtained, as shown,²⁷ a straight line for the dependence of ln *k* on T⁻¹ for this reaction and for all of the about 100 other reactions between different radical anions and alkyl halides that we have investigated in this way. This we interpret to show that in the temperature interval investigated (–50 to 50 °C) there is no change detectable in this way in the mechanism of the reaction between aromatic radical anions and alkyl bromides. This seems now to be generally accepted; the original finding of a break in the Arrhenius plot was recently reported to be caused

by problems with the base line in the electrochemical measurements.^{40b}

From the Arrhenius plots the entropy and enthalpy of activation may be extracted.²⁷ In Table 1 some values of entropy of activation ΔS[‡]₂₉₈ for the reaction between radical anions and some alkyl halides together with corresponding values for the reaction between 1⁻ and the same alkyl halides are presented. The ΔS[‡]₂₉₈ values of a given alkyl halide in the reaction with radical anions is an average value of a number of reactions of different radical anions with the given alkyl halide.

In the reactions between radical anions and sterically hindered alkyl halides including *t*-BuBr, approximately the same ΔS[‡]₂₉₈ is found, and this value, ΔS[‡]_{298,ou} = –9 cal mol⁻¹ K⁻¹, is taken as the standard value of ΔS[‡]₂₉₈ for an outer-sphere dissociative ET. The values for ΔS[‡]₂₉₈ for primary and secondary alkyl halides are somewhat more negative than ΔS[‡]_{298,ou}, which could be due to a bonding interaction in the TS, but other interpretations may be possible.

In the reaction with the enolate anion 1⁻, only the most sterically hindered alkyl halides, 1-bromoadamantane and bornyl bromide, have the same values for ΔS[‡]₂₉₈ as ΔS[‡]_{298,ou}. This is in accordance with the above mentioned stereochemical results and the *k*_{SUB}/*k*_{ET} ~ 1 and indicates that for these sterically very hindered (against backside S_N2 attack) alkyl halides the substitution reaction may be described as an outer-sphere dissociative ET followed by a radical coupling. The less sterically hindered alkyl halides, even *t*-BuBr and *exo*-norbornyl bromide, show a more negative ΔS[‡]₂₉₈ than ΔS[‡]_{298,ou}, which may be interpreted as a slightly more S_N2-like TS. In the fourth column the difference between the values of the reaction with an outer-sphere electron donor (ΔS[‡]_{298,ou} = –9 cal mol⁻¹ K⁻¹) and with 1⁻ is translated into differences in activation energy due to the entropy effect, ΔΔG[‡]_{ΔS} = T(ΔS[‡]_{298,ou} – ΔS[‡]_{298,1⁻}).

The ΔH[‡]_{298,A⁻} value given in Table 1 for each alkyl halide is the one expected for a radical anion with the same standard potential as 1⁻; this enthalpy value is obtained from extrapolation of a plot of ΔG[‡]₂₉₈ vs E^o_A to the standard potential of 1⁻ and using the average values of ΔS[‡]₂₉₈. In Table 1 also are given the values for the enthalpy of activation, ΔH[‡]_{298,1⁻}, for the reaction between 1⁻ and the alkyl halides.²⁷ In the seventh column is given the difference ΔΔH[‡]_{298,A⁻,1⁻} between the values in columns 5 and 6, and in the last column are tabulated the *k*_{SUB}/*k*_{ET} values. As expected, the primary and secondary alkyl halides have the highest values of ΔΔH[‡]_{298,A⁻,1⁻} indicating the higher stabilization of the TS in their reactions with 1⁻. Again, only bornyl bromide and 1-bromoadamantane have the same enthalpy of activation in their reactions with 1⁻ and with radical anions. A comparison of the numbers in columns 7 and 8 indicates the close connection between the two; as expected, a linear dependence between ΔΔH[‡]₂₉₈ and log(*k*_{SUB}/*k*_{ET}) is found; it suggests that *k*_{SUB}/*k*_{ET} is a good parameter to characterize the S_{ET}/S_N2 spectrum.

The results from the measurements of the activation parameters as well as those from kinetic (*k*_{SUB}/*k*_{ET}) and stereochemical investigation 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 is caused by the competition between two distinct reaction

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Table 1. Some Activation Parameters from the Reactions between Aromatic Radical Anions or 1⁻ with Alkyl Halides^a

alkyl halide	$\Delta S^{\ddagger}_{298, A^{\cdot-}}$	$\Delta S^{\ddagger}_{298, 1^-}$	$\Delta\Delta G^{\ddagger}_{\Delta S}$	$\Delta H^{\ddagger}_{298, A^{\cdot-}}$	$\Delta H^{\ddagger}_{298, 1^-}$	$\Delta\Delta H^{\ddagger}_{298, A^{\cdot-}, 1^-}$	k_{SUB}/k_{ET}
butyl bromide	-16.4	-22.2	4.0	12.0	6.3	5.7	400
sec-butyl bromide	-16.5	-21.2	3.7	11.6	7.4	4.2	170
tert-butyl bromide	-8.4	-15.8	2.2	13.4	11.1	2.3	2.5
exo-norbornyl bromide	-10.8	-16.2	1.6	15.4	13.2	2.2	1.7
1-bromoadamantane	-7.6	-9.4	0.5	18.2	17.6	0.6	0.3
bornyl bromide	-8.7	-8.9	0.1	17.7	17.2	0.5	0.2

^a ΔS^{\ddagger} in cal mol⁻¹ K⁻¹ and ΔH^{\ddagger} and $\Delta\Delta G^{\ddagger}_{\Delta S} = 298(\Delta S^{\ddagger}_{298, ou} - \Delta S^{\ddagger}_{298, 1^-})$ in kcal mol⁻¹. $\Delta S^{\ddagger}_{298, ou} = -9$ cal mol⁻¹ K⁻¹, see text.

routes, ET and S_N2, with only two types of TS, (a) an outer-sphere dissociative ET followed by a radical coupling or (b) a classical S_N2 TS; an alternative explanation is that there are transition states with structures with varying degrees of inner-sphere (bonding) stabilization compared to the outer-sphere ET TS ranging from the outer-sphere ET TS to the classical S_N2 TS. Although there is no definite experimental evidence either way, the fact that we find a linear dependence of ln *k* vs *T*⁻¹ for all the substitution reactions we have investigated suggests that there is no shift in the reaction path in this interval. The observed difference in activation parameters (Table 1) would indicate that a break in the Arrhenius plot should be observed.

If one defines any TS which is not a pure outer-sphere ET TS as an S_N2 TS, then nearly all the reactions discussed here are S_N2 reactions. In analogy with the S_N2–S_N1 and E1–E2–E1cb types of reaction, it seems useful to have a special designation (e.g., S_{ET}/S_N2 hybrid) for reactions in the “gray” area between an outer-sphere ET TS and an S_N2 TS in which the TS has characteristics of both model reactions. A description of criteria to place a given reaction in a suitable category could be to use *k*_{SUB}/*k*_{ET}, or activation parameters, or reactions with some racemization as a characteristic for the “gray area”, or something else; the most convenient criterion for an S_{ET}/S_N2 hybrid would probably be *k*_{SUB}/*k*_{ET}.

The reductive elimination of *vic*-dihalides to alkenes has been investigated in a similar manner, and examples of outer-sphere ET from nucleophiles as 1⁻ or metal complexes to *vic*-dihalides have been found.^{42,43} It remains to be seen which other nucleophilic reactions may show examples of outer-sphere ET.

The results described above give hints on some of the important parameters which determine whether an ET, S_N2, or S_N1 type of reaction is likely to be favored. Besides the parameters, steric properties, and standard potentials of the reaction partners discussed herein, other properties of the system influence the reaction route. Our results suggest the following with regard to potentials and steric properties:⁴⁴

(a) Whenever the steric hindrance in the TS does not prohibit an approach of the reagents to a distance

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at which some bonding stabilization can occur and the difference between the standard potential of the nucleophile and the reduction potential of the electrophile BX, ΔE , is not too positive, then an S_N2-type reaction is likely to proceed.

(b) If the steric conditions prevent a bonding stabilization in the transition state and $\Delta E \leq 0$ V, then the ET reaction is likely to occur; the ET reaction is favored by a delocalized HOMO of the donor.

(c) In the cases where steric factors inhibit the S_N2 reaction and ΔE is too positive to allow ET to proceed with a reasonable rate, then the classical S_N1 reaction may come into play by creating a planar carbocation B⁺ with less steric hindrance than BX and which also is a much better electron acceptor than BX; this facilitates the bonding to the donor/nucleophile. Even then, if the nucleophile is very difficult to oxidize, the equivalent of being a very poor electron donor, the S_N1 may fail to occur; e.g., in aqueous solution anions such as perchlorate or tetrafluoroborate are practically unreactive in an S_N1 reaction.

Conclusion

The results of the investigations seem to indicate that there is, besides the classical S_N1 and S_N2, a reaction path in the aliphatic nucleophilic substitution involving a nonchain electron transfer and that this transfer of an electron may be the rate-determining step, when the nucleophile is a good electron donor and steric hindrance in the transition state excludes a classical S_N2. In certain cases an outer-sphere electron transfer takes place whereas in other cases the reaction has some characteristics of an ET and some of an S_N2. This can be interpreted as a competition between two different reaction paths, outer-sphere ET and classical S_N2; or it can be interpreted by an assumption that there exists a spectrum of different transition states, with an outer-sphere electron transfer as the one extreme and the classical S_N2 with an equal degree of bonding to the attacking nucleophile and the leaving group as the other extreme, and with transition states with varying degrees of bond stabilization compared to the outer-sphere ET TS of the attacking nucleophile in between (inner-sphere ET). We have no proof either way, but our experimental results in the form of a great number of linear Arrhenius plots and no examples of breaks in such lines have convinced us that the latter interpretation is the most likely one.

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