

SINGLE ELECTRON-TRANSFER AS RATE-DETERMINING STEP IN AN ALIPHATIC NUCLEOPHILIC SUBSTITUTION

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Abstract - The rate of the reaction between the anion of 1,4-dihydro-4-methoxycarbonyl-1-methylpyridine (1^-) and sterically hindered alkyl halides, and between the perylene dianion (Pe^{2-}) and *t*-butyl chloride and *sec*-butyl bromide has been measured by electrochemical techniques. The rate was found to be close to the rate of single electron-transfer (SET) from anion radicals ($A^{\cdot-}$) with the same standard potential as $1^-/1^{\cdot-}$, resp. Pe^-/Pe^{2-} to the corresponding alkyl halides. The kinetic results strongly suggest that a SET mechanism is the rate-determining step in these nucleophilic substitutions.

Single electron-transfer (SET) has been suggested to play a role in the aliphatic nucleophilic substitution in several cases, e.g. derivatives of *p*-nitrobenzyl, α -nitrohalides, and *gem*-dinitro compounds may react with certain nucleophiles in an $S_{RN}1$ or related reaction;¹ the lithium salt of some alkynes reacts with 2-X-2-nitropropane (X = Cl, NO₂) in what is considered to be an $S_{ET}2$ -reaction;² evidence has been presented for an SET-component in the reaction between PhS^- and 1- and 2-X-butane (X = leaving group);³ CIDNP has been used^{4,5} to establish the presence of radicals during the reaction between RLi and RX; a "radical clock" has been used as argument for the involvement of radicals in the reaction between lithium diisopropylamide and 2,2-dimethyl-1-iodo-5-hexene,⁶ and EPR-spectra and the unusual substitution product in the reaction between potassium *tert*-butoxide and trityl bromide have been taken as evidence of a SET-mechanism.⁶ This reaction has later been suggested to follow an S_N2' -mechanism rather than an SET-mechanism.⁷

It is well recognized that the occurrence of radicals during a reaction does not necessarily mean that the observed substitution product is formed through a SET-mechanism; some of the reactions have been questioned or rejected as candidates for a true SET-mechanism on the grounds that the rate constant for a SET, calculated according to Marcus' theory for SET from thermodynamic data and an estimate of the reorganization energy, was too low compared to the observed reaction rate.⁸

Below is reported on the aliphatic nucleophilic substitutions of an enolate anion, the anion of 1,4-dihydro-4-methoxycarbonyl-1-methylpyridine, on 1-bromoadamantane, neopentyl bromide, and *t*-butyl bromide, and of the perylenedianion (Pe^{2-}) on *t*-butyl chloride and *sec*-butyl bromide.

In these cases the rate of the reaction was found to be compatible with a SET as the rate-determining step.

It has previously been shown⁹ that the anion of 1,4-dihydro-4-methoxycarbonyl-1-methylpyridine (1^-) reacted with *t*-BuBr in high yield to 4-*tert*-butyl-1,4-dihydro-4-methoxycarbonyl-1-methylpyridine as the only detectable product, that 1^- was a good SET-reagent toward 1,2-dichloro-1,2-diphenylethane, and that the anion of 4-benzoyl-1,4-dihydro-1-methylpyridine was *tert*-butylated rather than methylated by *tert*-butyl dimethylsulfonium iodide. Reaction of 1^- with chiral 2-bromo-octane gave predominantly racemization together with a small, but detectable chirality, probably caused by inversion.¹⁰

Anion radicals of aromatic and heteroaromatic compounds have been shown to react with alkyl halides through an initial transfer of a single electron.¹¹ The single electron rate constants k_{SET} from electrochemically generated anion radicals to a number of alkyl halides in *N,N*-dimethylformamide (DMF) have now been measured by cyclic voltammetry,¹² assuming the following reaction scheme. Here A is an aromatic compound and BX an alkyl halide. k_2 and $k_3 \gg k_{\text{SET}}$, and k_2 is 4-30 times larger than k_3 for the compounds investigated here. In Fig. 1 the plot of $\log k_{\text{SET}}$ vs. E_A of the aromatic systems is shown for BX = *sec*-BuBr. Similar plots obtained for the other alkyl halides studied in this work are used to calculate k_{SET} for these alkyl halides.

The anion 1^- can be produced electrochemically in two one-electron steps from a 4-methoxycarbonyl-1-methylpyridinium (1^+) salt through the stable radical 1^\cdot . The reaction of 1^- with alkyl halides BX can be formulated as:

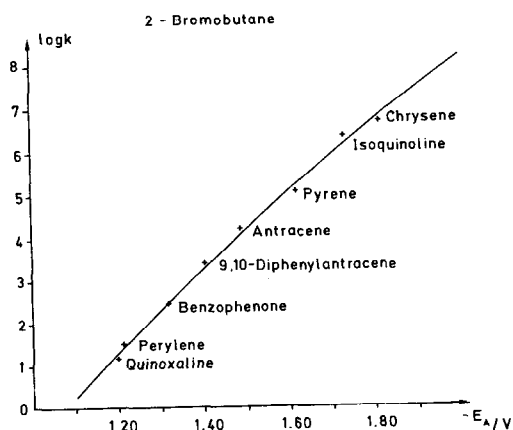
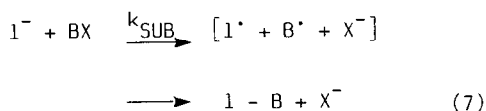
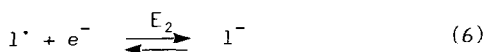
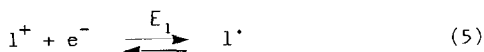
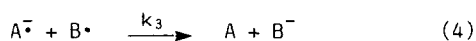
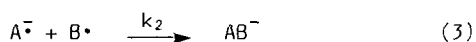
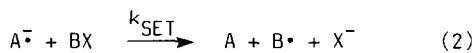


Fig. 1. Rate (k_{SET}) of electron transfer from different aromatic anion radicals (A^-) to *sec*-BuBr; reference electrode: Ag/AgI, 0.1 M I^- ; $t = 25.0$ °C; solvent: DMF.



where $E_1 = -0.30$ V and $E_2 = -1.13$ V (vs. Ag/AgI, 0.1 M I^-). (6) + (7) can be described as an EC-reaction (electrochemical-chemical). Table 1 shows the rate of substitution k_{SUB} of 1^- and six alkyl halides together with the expected rate constants k_{SET} for the transfer of an electron from A^- ($E_A = E_2$) to BX. The

k_{SET} values are obtained from the $-E_A$, $\log k_{SET}$ curves.

For the sterically hindered alkyl halides 1-bromoadamantane, neopentyl bromide, and *t*-BuBr the k_{SUB} is approximately equal to k_{SET} , which strongly suggests that the rate-determining step in the nucleophilic substitution of I^- on these alkyl halides is the transfer of a single electron from I^- to these alkyl halides.

Table 1. The Substitution Rate between I^- and Some Alkyl Halides

A	BX	$E_2^0/V^a)$	$k_{SUB}/M^{-1}\cdot s^{-1}$	$k_{SET}/M^{-1}\cdot s^{-1}$	k_{SUB}/k_{SET}
1-Methyl-4-methoxy-carbonylpyridinium iodide	1-Bromoadamantane	-1.13	$1.5\cdot 10^{-2}$ b)	$1.9\cdot 10^{-2}$	0.80
"	1-Bromo-2,2-dimethylpropane	"	$2.9\cdot 10^{-2}$ b)	$2.3\cdot 10^{-2}$	1.3
"	<i>t</i> -BuBr	"	30 c)	12	2.5
"	<i>sec</i> -BuBr	"	480 c)	2.8	170
"	<i>n</i> -BuBr	"	1420 c)	3.5	400
"	CH_3CH_2Br	"	3052 c)	1.2	2500

a) Measured against the Ag/AgI, $I^- = 0.10$ M reference electrode.

b) Obtained by polarography.

c) Obtained by cyclic voltammetry.

The rate constants k_{SET} for the SET from aromatic anion radicals to *t*-BuBr, *s*-BuBr, and *n*-BuBr are of the same order of magnitude; this is not true for k_{SUB} ; $k_{SET} \sim k_{SUB} (t\text{-BuBr}) < k_{SUB} (s\text{-BuBr}) < k_{SUB} (n\text{-BuBr})$, with $k_{SUB} (n\text{-BuBr}) \sim 400 k_{SET}$. This may be explained by participation of an increasing part of the classical S_N2 reaction path on going from *t*-BuBr through *s*-BuBr to *n*-BuBr. The question is, however, whether two competing pathways (S_N2 , SET) are operating or whether it is a single pathway with the transition state (TS) at different points along the reaction coordinate (RC) and with different overlap between the HOMO of the anion and LUMO of the alkyl halide. The point on RC of the transition state would be expected to be dependent on the oxidation potential of the nucleophile, the reduction potential of the electrophile, the steric crowding in the TS, the stability of any radicals involved, and the reorganization energy for an electron transfer.

In the reaction between I^- and *t*-BuBr the *t*-Bu-radical and I^- are reasonably stable and ET takes place with negligible bonding between I^- and *t*-BuBr; *t*-BuBr dissociates irreversibly almost immediately on accepting an electron, and I^- and *t*-Bu \cdot combine to product, probably before leaving the solvent cage. In the reaction between I^- and *s*-BuBr the steric crowding in TS is smaller, and a somewhat stronger overlap may exist, which lowers the energy of TS; the bonding may not be strong enough to make inversion the preferred pathway. The *n*-Bu-radical would be the least stabilized one, the steric crowding the smallest, and the energy of SET may be lowered by a more extensive overlap between HOMO of the anion and LUMO of *n*-BuBr bond formation in TS.

The reversible oxidation potential of l^- can be obtained from CV, but this is not the case for most anions; voltammetric peak or half-wave potentials have been reported for many anions,^{13,14} but the relation between them and the thermodynamic potentials is uncertain. Generally, "soft" anions may be candidates for electron transfer reactions, and further investigations with such anions are in progress.

Dianions of aromatic hydrocarbons have been shown to be good electron donors toward aryl halides.¹⁵ The reaction of such a dianion with an alkyl halide might also be a SET-reaction; the reaction would then be described by: $A + e^- \rightleftharpoons A^{\cdot-}$ $E_1 = -1.21$ V (8)

In Table 2 are given the rate constants k_{10} of the reaction between the $A^{\cdot-} + e^- \rightleftharpoons A^{2-}$ $E_2 = -1.80$ V (9)

dianion of perylene and *t*-BuCl, resp. $A^{2-} + BX \xrightarrow{k_{SUB}} [A^{\cdot-} + B^{\cdot} + X^-] \rightarrow AB^- + X^-$ (10)

sec-BuBr, together with the expected

k_{SET} for $E_A = E_2$. The ratio k_{10}/k_{SET} is close to 1 which again strongly suggests that the rate-determining step in the substitution reaction (10) of the perylene dianion on *t*-BuCl and *sec*-BuBr is the transfer of a single electron.

Table 2. The Rate of the Substitution Reaction between the Dianion of Perylene (Pe^{2-}) and Alkyl Halides

A	BX	$E_2/V^a)$	$k_{SUB}/M^{-1}\cdot s^{-1}$	$k_{SET}/M^{-1}\cdot s^{-1}$	k_{SUB}/k_{SET}
Perylene	<i>t</i> -BuCl	-1.80	171 ^{b)}	141	1.21
Perylene	<i>sec</i> -BuCl	-1.80	400×10^3 ^{b)}	282×10^3	1.42

a) Measured against Ag/AgI, $I^- = 0.10$ M. b) Obtained by cyclic voltammetry.

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