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S_N2 and Single-Electron-Transfer Mechanisms. The Distinction and Relationship[1]

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Abstract: Single-electron-transfer (SET) mechanisms for substitution reactions encounter a logical obstacle for S_N2 reactions, especially methyl transfers, the rates of which are found to follow the Marcus equation. This relates the rate to the rates of identity reactions and the thermodynamics only. The obstacle is that plausible SET mechanisms for identity reactions are incompatible with the principle of microscopic reversibility. We conclude that the mechanisms of the identity reactions (which are one-step S_N2 reactions and cannot be multiple-step SET mechanisms) carry over to all substitutions covered by the Marcus equation. The limits of the range of the Marcus equation in S_N2 reactions have not been reached. Nevertheless, a number of highly reducing nucleophiles do show reactions, such as with *tert*-alkyl halides, not characteristic of the S_N2 process; they have been shown convincingly to be initiated by single-electron transfer. The clear distinction of the two processes is emphasized: they are different and only rarely competitive.

The S_N2 reaction was identified by Ingold in the 1930s[2] and has been a fundamental part of mechanistic organic chemistry ever since. For many years, the thrust of much research was concerned with the other Ingold mechanism, S_N1, and the structural effects, solvent effects, stereochemical course, accompanying rearrangements, details of intermediates between the reagent, the mostly separated ions, and the ultimate products were studied intensively. The S_N2 reaction was largely neglected; it had been shown early to lead to inversion of configuration, no rearrangements, and understandable steric effects. The rates with different nucleophiles could be described using the Swain–Scott nucleophilic parameters[3] or a longer closely related list.[4]

Several newer features of the S_N2 reaction became of interest more recently. In one area, the role of solvent became more clear as the very large rate effects on going to the dipolar aprotic solvents were uncovered by Parker.[5] An extreme has been the observation of very fast reactions with no solvent at all in the gas phase.[6] The rates of many methyl transfers have been shown to be predictable by the Marcus equation, relating the rate only to the rates of identity reactions and the equilibrium constant.[7,8] The extension to all S_N2 reactions in all solvents has been suggested but not experimentally demonstrated. The use of the Marcus equation for methyl transfers well removed from its original theoretically derived application to electron transfers has been justified by Murdoch.[9]

The possibility of free radicals contributing to the S_N2 reaction in any way was not seriously considered until later. A seminal paper by Bank and Noyd[10] in 1973 described the reaction of *sec*-butyl *p*-nitrobenzenesulfonate with thiophenoxide ion. An apparently straightforward S_N2 reaction, yielding the inverted phenyl *sec*-butyl sulfide, in the presence of a nitrone gave a trapped radical identified by ESR as the corresponding *sec*-butyl nitroxyl radical. The PhS• radical was also trapped in the presence of styrene as a telomer. Furthermore, the ratio of rates of primary to secondary butyl *p*-nitrobenzenesulfonate was smaller than with other sulfonates or halides as leaving groups. They suggested that the radicals arose in the group-transfer reaction by a single-electron-transfer reaction

$$X^- + RY \rightarrow X^\bullet + RY^{\bullet -} \quad (1)$$

$$RY^{\bullet -} \rightarrow R^\bullet\ Y^- \quad (2)$$

The suggestion that RX, the S_N2 product, actually arose from the combination of R and X• (eq 3) was made, but a more rigorous conclusion was that the S_N2 reaction had considerable SET

$$R^\bullet + X^\bullet \rightarrow RX \quad (3)$$

character, possibly only with respect to the transition state. The detection of trapped radicals by sensitive methods does not demonstrate that they are involved with the major substitution reaction. Nevertheless, this often cited paper has initiated consideration of SET mechanisms for nucleophilic substitution.

The possibility of the general mechanism for S_N2 reactions 1 and 2 or with most leaving groups, reaction 4 followed by reaction 3, has not been widely accepted, because the radicals X• and R•

$$X^- + RY \rightarrow X^\bullet + R^\bullet + Y^- \quad (4)$$

free in solution would be expected to show other reactions such as dimerization or hydrogen abstraction from most solvents, which are not usually observed. This difficulty is avoided by confining all the species in a solvent cage, thus allowing reaction 3 to occur at a rate greater than that of diffusion control. Thus, to some extent, these problems of "free" radicals are avoided.

A result similar to Bank and Noyd's with detected radicals was obtained by Flesia[11] and co-workers using the reaction of thiophenoxide with benzyl halides. They state that the only distinction between the S_N2 reaction and this SET formation of detected radicals is the extent to which the radical pair escapes from the solvent cage.

The solvent cage has been interpreted by some as enforcing the inversion of configuration, but some have suggested that loss of stereospecificity may occur while the species are still "caged".[12] The stereochemical consequences of this cage radical combination are not yet clear.

In contrast to these views, Kornblum,[13] who (along with Russell and Bunnett)[14] has been influential in establishing the "S_RN"

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[1] A part of this paper was presented at the Southwest Regional Meeting of the American Chemical Society, Corpus Christi, TX, Dec 1988.

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radical chain mechanism for effecting nucleophilic substitution, said that "It would be incorrect to regard S_N2 reactions as electron transfer processes. The S_N2 reaction is distinct and different." This view is not universally shared. Lund and Lund[15] support the suggestion that SET and S_N2 are extremes of a continuous mechanism. Similarly, Ashby[12] has found a number of net substitution reactions which give evidence of SET steps but believes that SET net substitution reactions give rise variously to partially or completely racemic products from secondary alkyl reagents.

Savéant and co-workers[16] have studied the reactions of a number of electrochemically produced nucleophiles with alkyl halides. They conclude that separate and distinguishable SET and S_N2 reactions can be identified. An outer-sphere electron transfer from X^- to RY, coupled with cleavage of the RY band as in reaction 4, has a rate predictable by Marcus theory (modified to allow for the instability of $RY^{\bullet-}$).[17] When a measured reaction rate is in agreement with this calculated rate, an electron-transfer mechanism is assigned. When the reaction is substantially faster than this, an S_N2 mechanism is assigned.[18] The assignment is confirmed by the temperature dependence, the S_N2 is characterized by relatively low $\Delta H^{\ddagger}$ and substantially negative $\Delta S^{\ddagger}$, and the SET has a higher $\Delta H^{\ddagger}$ and a near zero $\Delta S^{\ddagger}$. In accordance with well-established ideas, the S_N2 reaction does not occur on *tert*-butyl bromide; *sec*-butyl bromide with anthracene anion radical shows a mixed behavior and a non-linear Arrhenius plot. *n*-Butyl bromide shows S_N2 behavior with all unhindered reduced porphyrin derivatives, but with the anthracene anion radical, it shows (from the Arrhenius plot) clear S_N2 behavior at low (< −15 °C) temperatures ($\Delta S^{\ddagger} = -19$) and clear SET behavior at higher temperatures ($\Delta S^{\ddagger} = +5$).[16]

Two features are of special relevance for consideration of possible SET mechanisms. Fast second-order reactions of highly reduced nucleophiles with tertiary halides are certainly SET processes, which sometimes but not always lead to substitution products. Similarly, Kornblum has pointed out that net substitution on a tertiary halide cannot be an S_N2 process.[13] Secondary compounds can react by either mechanism, nearly all primary halides except neopentyl types show S_N2 reactivity. The near zero activation entropy of the identified SET process suggests that the approach of the reagents does not have to lie on a severely restricted path and therefore is unlikely to lead to a quantitative inversion of configuration, a conclusion also evident from the reactions of bridgehead halides.[16]

The purpose of this paper is to show that the class of S_N2 reactions with rates following the Marcus equation cannot go by a discreet SET mechanism. This class specifically includes methyl transfers in water described by Albery and Kreevoy,[7] and those in sulfolane described by the Rice group.[8] In most of the cases studied, but not necessarily all cases, the rate constant $k_{(YX)}$ for reaction 5 is given by the very simple eq 6, in which the often small

$$X^- + MeY \xrightarrow{k_{YX}} XMe + Y^- \qquad (5)$$

$$\log k_{YX} = \tfrac{1}{2}(\log k_{YY} + \log k_{XX}) + \tfrac{1}{2}\log K_{YX} \qquad (6)$$

quadratic term of the Marcus equation is neglected.[8a,c,f] where k_{YY} is the rate constant for the attack of Y^- on MeY, k_{XX} is the corresponding identity rate constant for the X^- + MeX reaction, and K_{YX} is the equilibrium constant for reaction 5. If $\log K_{YX}$ is a very large positive or negative number and the identity rates are both very fast, the quadratic term of the Marcus equation may no longer be negligible. There are so far not enough such cases to confirm the quadratic form.

Equation 6 has been found applicable over a wide range of rates, probably within the precision of determination of identity rates and equilibrium constants. The first part of our argument about the S_N2–SET distinction is that reactions following the Marcus equation, whether in complete form or by eq 6, must have the same mechanism as the two identity reactions. The application of the Marcus equation would otherwise be a wild coincidence. The equilibrium constant K_{YX} is of course mechanism independent.

If we now focus on the identity reaction 7 and write for it the SET mechanism of (4a), followed by (3a), the forward rate and the reverse rate must be equal, and each step must be reversible.

$$X^- + MeX \rightleftarrows XMe + X^- \qquad (7)$$

$$X^- + MeX \rightleftarrows X^\bullet + Me^\bullet + X^- \qquad (4a)$$

$$X^\bullet + Me^\bullet \rightleftarrows XMe \qquad (3a)$$

However, the reverse of (3a) is the homolysis of XMe, an unlikely step for any familiar X (for example, the MeI bond energy is about 56 kcal/mol,[19] the lower limit of the activation energy for the reverse of (3a)). Furthermore, the principle of microscopic reversibility requires that, if this is indeed the reverse mechanism, then it must contribute exactly as much as (4a). A more plausible mechanism for identity reactions is one with either a symmetrical transition state or a symmetrical intermediate. A few such reactions are shown below, all starting with the electron transfer (1). They are shown for clarity with the leaving group Y, although for the identity reaction Y = X.

mechanism A

$$X^- + MeY \rightleftarrows X^\bullet + MeY^{\bullet-} \qquad (1)$$

$$X^\bullet + MeY^{\bullet-} \rightleftarrows XMe^{\bullet-} + Y^\bullet$$

$$Y^\bullet + XMe^{\bullet-} \rightleftarrows Y^- + XMe$$

This mechanism is unlikely for several reasons. First it assumes $MeY^{\bullet-}$ and $XMe^{\bullet-}$ are stable species; second the central radical displacement reaction has no analogy in ordinary radical chemistry.

mechanism B

$$X^- + MeY \rightleftarrows X^\bullet + MeY^{\bullet-}$$

$$MeY^{\bullet-} \rightleftarrows Me^- + Y^\bullet$$

$$X^\bullet + Me^- \rightleftarrows MeX^{\bullet-}$$

$$XMe^{\bullet-} + Y^\bullet \rightleftarrows XMe + Y^-$$

This requires $MeY^{\bullet-}$ and $MeX^{\bullet-}$ to be stable and decompose in an unusual direction. All of the original MeY and the product MeX bonds are gone at the intermediate stages.

mechanism C

$$X^- + MeY \rightleftarrows X^\bullet + Me\text{-}Y^{\bullet-}$$

$$X^\bullet + MeY^{\bullet-} \rightleftarrows X\text{-}M^-\text{-}Y$$

$$X\text{-}Me^-\text{-}Y \rightleftarrows XMe^{\bullet-} + {}^\bullet Y$$

$$XMe^{\bullet-} + {}^\bullet Y \rightleftarrows XMe + Y^-$$

In this, there is a high-energy hypervalent anion, and the participation of the electron transfer steps seems forced.

mechanism D

$$X^- + MeY \rightleftarrows X^\bullet + Me^\bullet + Y^-$$

$$X^\bullet + Y^- \rightleftarrows X^- + Y^\bullet$$

$$X^- + Me^\bullet + Y^\bullet \rightleftarrows XMe + Y^-$$

This, like B, suffers from loss of all the bonds; it has termolecular steps but does not require a stable $MeY^{\bullet-}$ or $MeX^{\bullet-}$.

Each of these four mechanisms has a reverse identical to the forward process when X = Y, each starts with the electron transfer step, but none appears energetically acceptable. The inversion of configuration also does not appear to be required. Nevertheless, they have central intermediates or transition states reminiscent

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of the various contributions to the transition state for the one-step S_N2.[7]

If these mechanisms are indeed unacceptable, and the simplest SET mechanism of (1) (2), and (3), or (4) and (3) is impossible for identity reactions, then we are forced to conclude that the mechanisms are also impossible for all methyl transfers, the rates of which fit the Marcus equation. Familiar S_N2 reactions on other primary and some secondary alkyl groups with other leaving groups probably also fit eq 6, but SET, sometimes leading to net substitution, can be expected when the structure is such as to make the S_N2 very slow. These include tertiary, neopentyl, and aryl halides and are, of course, only found with nucleophiles of very low oxidation potentials.

Correlation of second-order rate constants with oxidation potential of the nucleophile has often been observed.[20] Such a correlation does not require SET mechanisms; it can be attributed to important contributions of the (electron paired) structure $X^{\bullet}G^{-\bullet}Y$ to the S_N2 transition state. Even powerfully reducing unhindered nucleophiles such as iron(0) porphyrins still can react by ordinary S_N2 reactions[16] with primary halides.

SET reactions are also promoted by favorable electron affinity of RY, as in the *p*-nitrobenzenesulfonate ester of Bank and Noyd[10] or with the cationic *N*-alkyl-2,4,6-triphenylpyridinium salts of Katritzky.[21] In this case, the nucleophile piperidine appears to react by S_N2, but with the nucleophile $Me_2CNO_2^-$, an SET mechanism is implicated. The evidence is that isopropyl is transferred faster than methyl to the nitronate ion, but not to piperidine, that the C-alkylated nitro compound results, rather than the O-alkylated material characteristic of S_N2 processes with other alkylating agents, and that even a *p*-tolyl group is transferred. In these cases, the instant decomposition of the electron recipient with loss of the leaving group analogous to reaction 4 is not demonstrated, nor is it likely.

The intermediacy of radicals in SET reactions of some low oxidential potential nucleophiles with certain alkyl halides has been shown by Ashby[12] by the formation of extensively racemized products from optically active halides and the formation of cyclized products from 6-bromo-1-hexene derivatives. Many of Ashby's cases use 6-bromo-5,5-dimethyl-1-hexene as both the RY and the radical detector. The radical from this, as he points out, cyclizes somewhat faster than the parent radical and thus makes radical detection more sensitive. However, the starting bromide also, by virtue of its neopentyl-like structure, strongly discourages the ordinary S_N2.

A further aspect of this problem remains. In an interesting series of papers on organic reactions, Shaik and Pross[22] have modeled the S_N2 reaction by their configuration mixing (CM) model, in which the reaction coordinate is described by the interaction, and avoided crossing of a curve corresponding to X^-RY with one describing $X^{\bullet} + RY^{\bullet-}$ as the reaction proceeds.

Although this has been described as a single-electron shift, it must not be confused with the SET mechanism such as that starting with eq 1 or 4. The Shaik and Pross model[22] is a model for a one-step reaction from $X^- + RY$ to $XR + Y^-$, i.e., the classic S_N2 mechanism. Their transition state, however modeled, is a method of treating the single S_N2 transition state. The model, as ordinarily written, does not accommodate the microscopic reversibility feature but is readily modified to handle identity reactions.[23] Pross comments[24] on the S_N2–SET relation using this model are entirely in keeping with other views, and the many qualitative conclusions of the CM model are most valuable.

The view of the S_N2 as an SET process can be made compatible with microscopic reversibility by describing the S_N2 as an inner-sphere electron transfer, that is, one in which the electron transfer is facilitated by a bond-making process. This may sometimes be an excellent description, but it describes the course of the reaction on the way to the transition state. It suffices for most purposes to describe only real intermediates in potential energy minima and the transition states connecting them, not the intervening pathways. The only mechanism excluded by the arguments here is that with discrete intermediates.

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