Electron-transfer Chain Catalysis of Substitution Reactions

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Summary The opportunities for electron-transfer chain catalysis of organic substitution reactions are discussed, and it is proposed that, in addition to the known $S_{RN}1$ mechanism, $S_{OE}1$, $S_{RE}2$, and $S_{ON}2$ processes should be observable

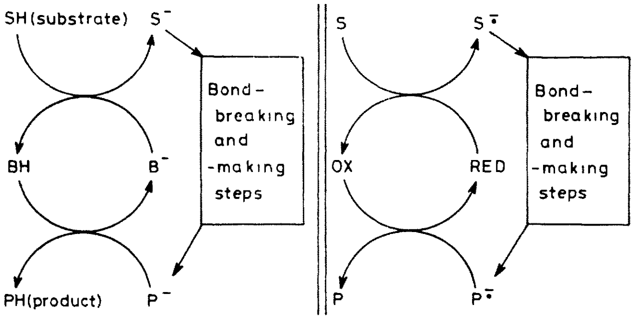
The $S_{\mathrm{RN}}1$ mechanism [1–4] is a unimolecular mechanism for nucleophilic substitution in which the bond-breaking and bond-making steps occur in the one-electron reduced substrate (its radical anion). At its simplest the propagation cycle is as represented by equations (1)—(4).

$$[\mathrm{RX}]^{\cdot-} \rightarrow \mathrm{R}^{\cdot} + \mathrm{X}^- \qquad (1)$$

$$\mathrm{R}^{\cdot} + \mathrm{Y}^- \rightarrow [\mathrm{RY}]^{\cdot-} \qquad (2)$$

$$[\mathrm{RY}]^{\cdot-} + \mathrm{RX} \rightarrow \mathrm{RY} + [\mathrm{RX}]^{\cdot-} \qquad (3)$$

$$\text{Result:} \quad \mathrm{RX} + \mathrm{Y}^- \rightarrow \mathrm{RY} + \mathrm{X}^- \qquad (4)$$



Scheme.

This mechanism can be seen as one example of a potentially general phenomenon, electron-transfer (or redox) catalysis,[4a] in which a transformation which is not overall an oxidation or reduction is accelerated *via* a mechanism involving electron-transfer steps. It is useful to draw analogy with acid–base (proton-transfer) catalysis, where a transformation which does not consume acid or base is accelerated *via* a mechanism involving proton-transfer steps (Scheme). Whereas, in acid–base catalysis, protonation or deprotonation of the substrate activates[5] it for the bond-breaking or -making steps, in electron-transfer catalysis, this is done by oxidation or reduction. Proton transfers are commonly intrinsically rapid processes and this is undoubtedly important for the ubiquitous nature of acid catalysis.† For electron-transfer catalysis to be efficient, the electron (or hole) must be handed on from product to substrate as in the last step of the $S_{\mathrm{RN}}1$ mechanism shown above. It is indeed encouraging that electron transfer is also often an intrinsically rapid process.[6] Whether the electron-transfer occurs directly, or *via* a pool of otherwise unreactive oxidising or reducing species (including an electrode or metal surface) is not immediately important,[3c] but it is significant that a chain process is involved, and one can usefully speak of electron-transfer chain catalysis (E.T.C. catalysis). It is plain that E.T.C. catalysis is fundamentally different from mechanisms such as those proposed[7] for aromatic substitution, equations (5) and (6), where the electron transfer is immediately obliterated in the bond-formation step. Finally, just as one commonly performs, *e.g.*, base catalysis with buffer solutions at a pH well below the pK_a of the substrate, it should be possible to operate E.T.C. catalysis at a potential well below that required for full reduction (or oxidation) of the substrate. Indeed Kornblum[2] speaks of the surprising effectiveness of such a 'low-pressure' source of electrons as the conjugate base of 2-nitropropane in promoting $S_{\mathrm{RN}}1$ reactions.

$$\begin{tikzcd} \mathrm{ArH} + \mathrm{NO_2}^+ \arrow[r] & {[\mathrm{ArH}]^{\cdot+} + \mathrm{NO_2}^{\cdot}} \arrow[dl] & (5) \\ {[\mathrm{ArHNO_2}]^+} \arrow[r] & \mathrm{ArNO_2} + \mathrm{H}^+ & (6) \end{tikzcd}$$

In acid–base catalysis, it is the chemical properties of the protonated (or deprotonated) substrate which are of importance. For electron-transfer catalysis, the reactivity of the reduced (radical anion) or oxidised (radical cation) substrate must be considered.[8,9] In this paper, I consider electrophilic and nucleophilic substitutions where the reactions of radical anions and radical cations involving the loss or gain of normal, even-electron, electrophiles and nucleophiles are of crucial concern. Radical anions are electron-rich and can (i) dissociate into radicals and anions and (ii) add electrophiles; in particular they are readily protonated. The first behaviour forms the basis for the $S_{\mathrm{RN}}1$ mechanism, the catalysis resulting from the ready dissociation of, say, $[\mathrm{PhI}]^{\cdot-}$, compared with the reluctance of PhI to ionise to Ph^+ and I^-. The second behaviour can form the basis of a bimolecular (associative) mechanism for electrophilic substitution (hydrogen–deuterium exchange), *via* one-electron reduction of the substrate, $S_{\mathrm{RE}}2$ [equations (7)—(9)]. (In Bunnett's[3a] definition of $S_{\mathrm{RN}}1$ the R stands for radical; *for the purposes of this paper only* R will indicate a mechanism involving one-electron *reduction* of the substrate, and the subscript O will indicate a mechanism proceeding *via* one-electron *oxidation*).

$$[\mathrm{RH}]^{\cdot-} + \mathrm{BD} \rightarrow [\mathrm{RHD}]^{\cdot} + \mathrm{B}^- \rightarrow [\mathrm{RD}]^{\cdot-} + \mathrm{BH} \qquad (7)$$

$$[\mathrm{RD}]^{\cdot-} + \mathrm{RH} \rightarrow \mathrm{RD} + [\mathrm{RH}]^{\cdot-} \qquad (8)$$

$$\text{Result:} \quad \mathrm{RH} + \mathrm{BD} \rightarrow \mathrm{RD} + \mathrm{BH} \qquad (9)$$

No clearcut examples of this process appear to be known. Since it depends on the reversibility of the radical anion protonation step, it is most likely to be observed where well stabilised radical anions are found, *i.e.* with easily reducible substrates. Aromatic nitro-compounds react with bases in many ways.[10] Amongst these, radical-anion formation and the exchange of nuclear hydrogen occur under similar conditions. A mechanism which is essentially $S_{\mathrm{RE}}2$ was considered but discounted for *ortho*-hydrogen exchange in nitrobenzene,[11] and exchange is generally taken to occur *via* inductively stabilised phenyl anions. However, an $S_{\mathrm{RE}}2$ mechanism may account for the 40-fold enhancement in the rate of exchange at C-9 in anthracene with lithium cyclohexylamide in the presence of 20 mol % anthracene radical anion.[12]

Radical cations are electron-poor species which (i) capture nucleophiles and (ii) lose protons. These properties should form the basis for $S_{\mathrm{ON}}2$ and $S_{\mathrm{OE}}1$ mechanisms respectively. $S_{\mathrm{ON}}2$ is a bimolecular (associative) mechan-

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† Methylation of substrates could provide similar activation to protonation but since methyl cation transfers *via* $S_{\mathrm{N}}2$ reactions have high barriers, methyl cation transfer catalysis is unlikely to be efficient.

ism for nucleophilic substitution *via* one-electron oxidation of the substrate [equations (10)—(12)] Some possible

$$[RX]^{\cdot+} + Y^- \rightarrow [RXY]^{\cdot} \rightarrow [RY]^{\cdot+} + X^- \quad (10)$$

$$[RY]^{\cdot+} + RX \rightarrow RY + [RX]^{\cdot+} \quad (11)$$

$$\text{Result} \quad RX + Y^- \rightarrow RY + X^- \quad (12)$$

examples of $S_{ON}2$ mechanisms are discussed in the accompanying paper [13]

The final mechanism, $S_{OE}1$, is a unimolecular, dissociative, process for electrophilic substitution *via* one-electron oxidation of the substrate [equations (13)—(16)]

$$[RH]^{\cdot+} + B \rightarrow R^{\cdot} + BH^+ \quad (13)$$

$$R^{\cdot} + BD^+ \rightarrow [RD]^{\cdot+} + B \quad (14)$$

$$[RD]^{\cdot+} + RH \rightarrow RD + [RH]^{\cdot+} \quad (15)$$

$$\text{Result} \quad RH + BD^+ \rightarrow RD + BH^+ \quad (16)$$

Tertiary amine radical cations are known[14] to deprotonate from an α-carbon forming $R_2\dot{C}\ddot{N}R_2$ radicals If conditions can be found where reprotonation at carbon occurs, hydrogen–deuterium exchange at the carbon α to nitrogen in a tertiary amine could be accomplished by an $S_{OE}1$ mechanism This is precisely what Gardini and Bargon have recently observed[15] when tertiary amines and naphthalene (an electron acceptor) are irradiated in the presence of proton donors

It should be apparent from the discussion above that while $S_{RN}1$, $S_{RE}2$, $S_{ON}2$, and $S_{OE}1$ defined as above are viable mechanisms, $S_{RN}2$, $S_{RE}1$, $S_{OE}2$, and $S_{ON}1$ are not chemically reasonable (thus $S_{RN}2$ requires bimolecular reaction between two electron-rich species, a radical anion and a nucleophile, while $S_{ON}1$ would require a nucleophile to depart from an electron-deficient radical cation) Evidence against an $S_{RN}2$ mechanism has recently been produced,[16] but another paper[17] proposes a mechanism called $S_{RN}2$ for displacements from 1-alkylpyridinium ions by carbanions However, the mechanism proposed was not a chain process

There is no *logical* reason why electron-transfer chain catalysis should not be as general as acid-base catalysis E T C -catalysed additions,[18] eliminations,[19] and rearrangements are conceivable and likely examples can be selected by consideration of the properties of radical ions E T C catalysis is already known in the reactions of transition-metal compounds [20] Finally it should be noted that the chemospecificity and regiospecificity of the reactions of radical ions are quite distinct from those of their even-electron counterparts (*e g* protonated species) Thus, although the examples cited above may seem trivial from the point of view of organic synthesis E T C catalysis can in principle, lead to unique transformations and the reversal of normal reactivity patterns

Added in proof Since the submission of this manuscript, an important review of chemical reactions by electrodes has appeared J -M Saveant, *Acc Chem Res* , 1980, **18**, 223

I thank Professor Lennart Eberson for bringing likely examples of $S_{ON}2$ reactions to my notice

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[5] Stewart has introduced the illuminating concept of the proton activating factor, R Stewart and R Srinivasan, *Acc Chem Res* , 1978, **11**, 271

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[11] R D Guthrie and D P Wesley, *J Am Chem Soc* , 1970, **92**, 4057

[12] A Streitwieser, Jr and R G Lawler, *J Am Chem Soc* , 1965, **87**, 5388

[13] L Eberson and L Jonsson, following communication

[14] S F Nelsen and C R Kessel, *J Chem Soc , Chem Commun* , 1977, 490, R P Kelly and J R Lindsay-Smith, *ibid* , 1978, 329

[15] G P Gardini and J Bargon, *J Chem Soc , Chem Commun* , 1980, 757 It seems likely that an $S_{OE}1$ sequence is also involved in the extensive deuteriation α to nitrogen observed during the oxidant-promoted formation of inside-protonated 1,6-diazabicyclo-[4 4 4]tetradecane in D_2SO_4/D_2O (R W Alder, A Casson, and R B Sessions, *J Am Chem Soc* , 1979, **101**, 3652) In 85% w/w D_2SO_4/D_2O > 90% complete α-deuterium exchange can be observed, but the inside hydrogen is *still* a proton

[16] C Galli and J F Bunnett, *J Am Chem Soc* , 1979, **101**, 6137

[17] A R Katritzky, G Z de Ville, and R C Patel, *Tetrahedron Lett* , 1980, 1723

[18] Several examples of [2 + 2] cyclo-dimerisations of electron-rich olefins have been reported (see ref 9, pp 251—252) in which olefin radical cation attacks olefin and which can be classified as E T C -catalysed cycloadditions, the E T C -catalysed tetramerisation of *N*-benzylaziridine has just been reported, R Kossai J Simonet, and G Dauphin *Tetrahedron Lett* 1980 3575

[19] Norris and his co-workers have identified an elimination mechanism, which they call $E_{RC}1$, which is in some respects the eliminative counterpart of $S_{RN}1$, but which is an overall reduction and therefore not an example of E T C catalysis, R K Norris and R J Smyth-King, *Aust J Chem* , 1979, **32**, 1949, and references therein

[20] Some examples are discussed in K F Purcell and J C Kotz, 'Inorganic Chemistry,' Saunders, Philadelphia, 1977, p 684