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Trapping the Single Electron Transfer Intermediate in an S_N2 Reaction

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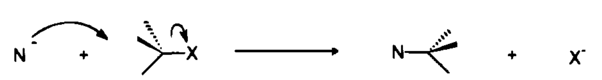
It has been suggested that the S_N2 reaction does not involve a simultaneous transfer of electron pairs as in Scheme 1, but rather a single electron shift synchronized to the bond rearrangement. When the the donor−acceptor relationship of the nucleophile and the substrate improves, the synchronicity can be disrupted, and the S_N2 reaction may occur in a stepwise mechanism via an SET step.[1,2] Scheme 2 shows a mechanism via such an SET pathway.

Even if an S_N2 reaction could be found in which the radicals and the radical anions shown in Scheme 2 were discrete intermediates, they would usually be expected to continue to the S_N2 products so quickly that their concentration would be too low for them to be trapped by a radical scavenger in detectable amounts or to be detected by a physical method. One way of obviating this difficulty would be if the S_N2 reaction in question were the identity reaction: $X^- + RX \rightarrow RX + X^-$. Under those conditions, even a minute extent of reaction with the radical scavenger might eventually build up to a detectable amount of trapped intermediate. This would be further favored if the scavenger were present in very large concentration, e.g., if it was a solvent such as cumene (Scheme 3).

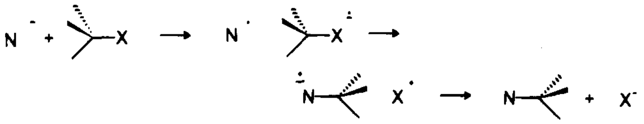
In Table 1 are shown the results of the identity S_N2 reaction of *p*-bromophenacyl bromide under various conditions. As can be seen, a 47% yield of the reduced substrate can be obtained by stiring the phenacyl bromide with bromide ion at 100 °C for 66 h. That this involves an S_N2 reaction is evident from the next three entries, which show that in the absence of any salt, in the presence of a non-nucleophilic salt, $(n\text{-}C_4H_9)_4NHSO_4$, or in the presence of a salt like LiBr, which is quite insoluble in cumene, the reactant is recovered unchanged.

Another conceivable mechanism for the reduction of phenacyl bromide in the presence of Br^- would be one involving nucleophilic substitution on halogen.[3] Such mechanisms have been proposed for I^- and RS^- nucleophiles.[3] This does not appear to be a better explanation for the reduction observed in run 1 for the following reasons. (1) The amount of reduced product declines as the solvent becomes a poorer hydrogen atom donor (runs 5 and 6). (2) The other products isolated in run 1, shown in Chart 1, are all descendants of the cumyl radical. (3) With I^- as the nucleophile, the reduction product is indeed observed (runs 7 and 8), but there seems to be no dependence on the H donor ability of the solvent. (4) With I^- as the nucleophile (runs 7 and 8), the cumyl radical-derived products observed in run 1 are absent.

Scheme 1



Scheme 2



Scheme 3

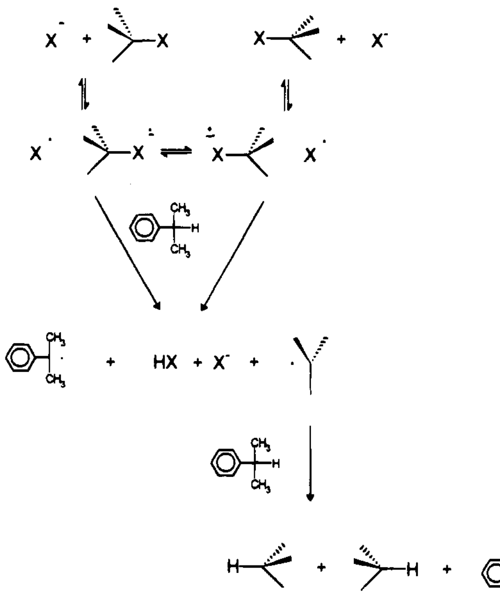


Table 1. Reaction[a] of $p\text{-}BrC_6H_4COCH_2Br$ with Various Salts at 100 °C for 66 h

run	solvent	salt	yield (%) $p\text{-}BrC_6H_4COCH_3$
1	cumene	$(n\text{-}C_4H_9)_4NBr$	47
2	cumene	none	0
3	cumene	$(n\text{-}C_4H_9)_4NHSO_4$	0
4	cumene	LiBr	0
5	toluene	$(n\text{-}C_4H_9)_4NBr$	3
6	anisole	$(n\text{-}C_4H_9)_4NBr$	0.7
7	cumene	$(n\text{-}C_4H_9)_4NI$	97
8	toluene	$(n\text{-}C_4H_9)_4NI$	68

[a] Each entry represents 2−4 runs, done under N_2, using 0.25−0.33 mmol of $p\text{-}BrC_6H_4COCH_2Br$ and 0.25 mmol of salt in 5 mL of solvent. All solvents were dried, and cumene was freshly distilled under N_2 before each run. Products were identified by GC/MS and by ^1H NMR of the GC-isolated product. Additional data for the reaction under different conditions are given in the supplementary material.

Another possibility that could be raised is that this is an S_{RN} reaction.[4] However, as Kornblum[4] has shown, the S_{RN} reaction, unlike the S_N2 reaction, is insensitive to steric effects. The present reaction, however, is highly sensitive to steric effects. The data in Table 2 show that as one slows the identity S_N2 reaction by introducing a bulky ortho substituent on the phenacyl halide, the product of the trapping reaction (the ketone) gradually vanishes.

Finally, the objection might be raised that even if a radical is shown to be present under the reaction conditions, it might not be on the pathway of the S_N2 reaction. However, if a mechanism exists which accounts for the observed facts (one

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[1] (a) Bank, S.; Noyd, D. A. *J. Am. Chem. Soc.* **1973,** *95,* 8203. However, see also: Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975,** 734. (b) Bordwell, F. G. *J. Am. Chem. Soc.* **1987,** *109,* 5470. (c) Ashby, E. C. *Acc. Chem. Res.* **1988,** *21,* 414. However, see also: Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988,** *21,* 206.

[2] (a) Shaik, S. *J. Am. Chem. Soc.* **1981,** *103,* 3692. (b) Pross, A. *Acc. Chem. Res.* **1985,** *18,* 212. (c) Shaik, S. *Acta Chem. Scand.* **1990,** *44,* 205.

[3] See the following review: Zefirov, N. S.; Makhonkov, D. I. X-Philic Reactions. *Chem. Rev.* **1982,** *82,* 615 and references cited therein.

[4] Kerber, R. C.; Urry, G. W.; Kornblum, N. *J. Am. Chem. Soc.* **1964,** *86,* 3904. Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975,** 734.

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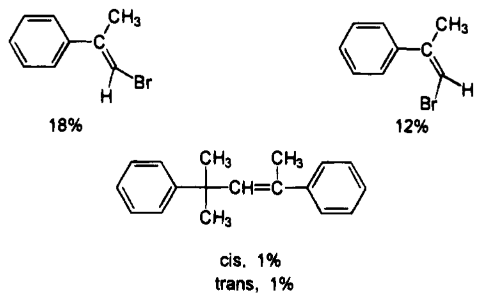
Table 2. Reaction[a] of Phenacyl Halides with $(n\text{-}C_4H_9)_4NBr$ in Cumene at 100 °C for 66 h

phenacyl halide	product	yield (%)
2,4-dimethylphenacyl bromide	2,4-dimethylacetophenone	41%
2,5-dimethyl-3,6-dichlorophenacyl chloride	2,5-dimethyl-3,6-dichloroacetophenone	18%
2,5-diethylphenacyl chloride	2,5-diethylacetophenone	3.2%
2,4-diisopropylphenacyl chloride	2,4-diisopropylacetophenone	1.6%

[a] Reactions were carried out under N_2, using 0.25−0.33 mmol of phenacyl halide and 0.25 mmol of salt in 5 mL solvent. Cumene was freshly distilled under N_2 before each run. Products were identified by GC/MS and by ^1H NMR of the GC-isolated product.

Chart 1. Other Products Obtained in Run 1



electron transfer, Scheme 2), then it is unnecessary to postulate another, parallel mechanism (pairwise electron transfer, Scheme 1), which is not required by any of the observed facts.

Supplementary Material Available: Table 3, giving data for the reaction of $p\text{-}BrC_6H_4COCH_2Br$ with various salts for 66 h under different solvent and temperature conditions (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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