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Evidence for Electron Transfer in Reactions of Nucleophiles with Optically Active Alkyl Halides. A Challenge to the S_N2 Transition State.

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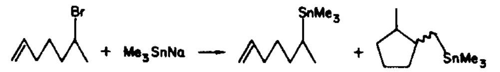
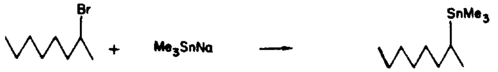
Abstract: A variety of nucleophiles have been used in a study of reactions with optically active 2-halooctanes in DMF in order to detect the occurrence of an electron transfer pathway.

Nucleophilic aliphatic substitution involving the reactions of nucleophiles with alkyl halides is one of the most fundamental reactions in organic chemistry.[1] It is becoming increasingly clear that some reactions heretofore considered to be classic S_N2 processes, because of their exhibited characteristic of inversion of the reaction center, are actually electron transfer processes involving radical intermediates.[2,5] It is the purpose of this report to show that reactions considered to be classic S_N2 reactions do not proceed with 100% inversion of configuration as required and therefore give evidence of an alternate reaction pathway. We believe the alternate pathway is a one electron transfer process from the nucleophile to the lowest lying anti-bonding orbital of the substrate. When a substrate is difficult to reduce (large negative reduction potential), a S_N2 pathway results, when the substrate is easy to reduce (smaller negative reduction potential), one electron transfer is favored.

This laboratory has been involved in the study of the reaction of alkyl halides with $LiAlH_4$,[2] cuprates,[3] enolates,[4] Me_3Sn^-,[5] and thiolates[6] and in each case has reported evidence for single electron transfer (SET). Involvement of a SET pathway in these reactions was demonstrated by spectroscopic studies (visible and EPR) as well as product studies using cyclizable radical probes. In addition, secondary optically active alkyl halides have been employed in some of the reactions mentioned above in order to compare the degree of racemization in a particular reaction with the degree of cyclization of a structurally similar radical probe in the same reaction.[2a,5a,b] For example, the reaction of Me_3Sn^- with (+)-2-bromooctane resulted in 77% inversion of configuration in the substitution product (eq. 1) and a similar reaction involving 6-bromo-1-heptene produced a 70% yield of cyclized substitution product (eq. 2).[5] Thus, evidence has been provided that a reaction that exhibits radical character can proceed with predominant inversion of configuration. Later we were able to demonstrate that the reaction of $LiAlH_4$ with (+)-2-iodooctane and 6-iodo-1-

heptene gave results similar to those reported for the reactions with Me_3Sn^-, i.e., evidence of a radical intermediate yet the observation of inversion of configuration.


(1)


(2)

Formation of cyclized substitution product in a reaction such as eq. 2 has been suggested as evidence for a radical intermediate and the absence of cyclized product has been erroneously interpreted as evidence for the absence of a radical intermediate. However, since cyclized substitution product results only after diffusion of the radical from the solvent cage, rapid geminate coupling of radicals inside the solvent cage gives no evidence of a radical intermediate. On the other hand, a chiral center should lose its stereochemical integrity inside the solvent cage at a rate much faster than that of geminate coupling. The extent of loss of stereochemical integrity should then be a measure of the extent of radical formation in the solvent cage. Thus, a method exists for determining the intermediate formation of radicals in a reaction even when the radicals are not detectable by cyclization, trapping or direct observation by esr. Using chirality as a probe, we have found six nucleophiles that react with optically active 2-substituted octanes resulting in a loss of optical activity of the product as the leaving group proceeds from tosylate to iodide (see Table).

Table. Reactions of 2-Halooctanes with Nucleophiles in DMF at Room Temperature.[a-b]

			Reactants		R*-Nuc Product[d]			
Exps	Nuc	R^*X	$[\alpha]_D$	opt. Purity	obs[c]$[\alpha]_D$	corr.$[\alpha]_D$	% opt. Purity	% Inversion[h]
1	LiSPh	OTs	-10.5°	90.5% ee	+ 5.11°	+ 5.65°	100.0[e]	100.0
2	"	Cl	+30.6°	96.8% ee	- 5.42°	- 5.60°	99.1	99.5
3	"	Br	+34.4°	78.9% ee	- 4.43°	- 5.61°	99.3	99.6
4	"	I	+20.6°	32.6% ee	- 1.42°	- 4.36°	77.2	88.6
5	LiSPr[i]	OTs	-10.5°	90.5% ee	+22.75°	+25.11°	100.0[f]	100.0
6	"	Cl	+30.6°	96.8% ee	-24.20°	-25.00°	99.6	99.8
7	"	Br	+34.4°	78.9% ee	-14.17°	-17.96°	71.5	85.7
8	"	I	+20.6°	32.6% ee	- 5.74°	-17.60°	70.1	85.1
9	LiCN	OTs	-10.5°	90.5% ee	+23.30°	+25.74°	100.0[g]	100.0
10	"	Br	+34.4°	78.9% ee	-13.65°	-17.30°	67.2	83.6
11	"	I	+20.6°	32.6% ee	- 5.52°	-16.93°	65.8	82.9
12	$LiPPh_2$	OTs	-10.5°	90.5% ee	+10.12°	+11.18°	100.0	100.0
13	"	Cl	+30.6°	96.8% ee	-10.89°	-11.25°	100.0	100.0
14	"	Br	+34.4°	78.9% ee	- 7.73°	- 9.80°	87.6	93.8
15	"	I	+20.6°	32.6% ee	- 2.03°	- 9.85°	88.1	94.0
16	$NaSnMe_3$	OTs	-10.5°	90.5% ee	+25.75°	+28.45°	100.0	100.0
17	"	Cl	+30.6°	96.8% ee	-21.52°	-22.23°	78.1	89.0
18	"	Br	+34.4°	78.9% ee	-12.23°	-15.50°	54.5	77.2
19	"	I	+20.6°	32.6% ee	- 5.77°	-17.69°	62.2	81.1
20	$LiAlD_4$[j]	OTs	-10.5°	90.5% ee	+ 0.86°	+ 0.95°	100.0	100.0
21	"	Cl	+30.6°	96.8% ee	- 0.96°	- 0.99°	100.0	100.0
22	"	Br	+34.4°	78.9% ee	- 0.77°	- 0.98°	100.0	100.0
23	"	I	+20.6°	32.6% ee	- 0.16°	- 0.49°	51.6	75.8

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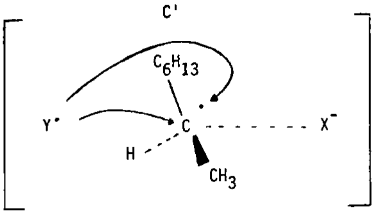
[a] All reactions carried out with an excess of nucleophile to halide (0.3 M to 0.1 M) for a period of 8h. [b] Racemization of (2), (3), and (4) (X = Cl, Br, I) by LiCl, LiBr and LiI, respectively, in DMF was negligible under similar conditions. [c] Limits of precision are ±5%. [d] Rotation measured in hexane solution. [e] Based on rotation of +5.65° for optically pure 2-(thiophenoxy)octane (5). [f] Based on rotation of +25.11° for optically pure 2-(thioisopropoxy)octane (6). [g] Based on rotation of +25.74° for optically pure 2-cyanooctane (7). [h] Calculated as % inversion = 100-[0.5(100 - % opt. purity)]. [j] Reactions carried out in THF.

Although inversion of configuration has normally been considered adequate indication of a S_N2 process,[7] it is now clear that inversion of configuration can also result from a SET process due to rapid geminate coupling of incipient radicals inside the solvent cage.[5b] Since RX compounds are more easily reduced in the order X = I>Br>Cl>OTs, reactions of tosylates are more likely to react by a S_N2 pathway whereas iodides are more likely to react by SET. Thus, in Exp. 1, when LiSPh was allowed to react with (-)-2-octyltosylate[8] in DMF at room temperature, (+)-2-(thiophenoxy)octane was obtained. Because of the unfavorable reduction potential of tosylates, such reactions are believed to proceed with 100% inversion of configuration.[9] Thus, the value of +5.65° was assumed to be the rotation of the optically pure product obtained from the tosylate since the maximum rotation of the product has not been reported.[9] From experiments 1-4 of the Table, it is seen that the value of Corr.$[\alpha]_D$ for 2-(thiophenoxy)octane varies from +5.65° (X=OTs) to -5.60° (X=Cl) to -5.61° (X=Br) to -4.36° (X=I). Thus it is clear, from the optical purities of the products, that the reactions of LiSPh in exps. 1-4 proceed with stereoselectivity decreasing according to the trend OTs ~ Cl ~ Br> I as expected for electron transfer. The results of the other five nucleophiles show the same trend.

Although more detailed studies of the reactions of nucleophiles with alkyl halides might be needed to provide a complete description of a SET pathway in these reactions, a reasonable suggestion (Scheme) is presented to account for the inversion of configuration observed in a process which involves SET and radical intermediates. It is suggested that the nucleophile approaches the backside of the C-X bond (σ* orbital) followed by electron transfer. Within the solvent cage, the leaving group (X^-) protects the front side of the alpha carbon of the radical anion $RX^{\overset{\cdot}{-}}$ (A) leading to the observed 100% inversion of configuration. When RX exists as a tight radical anion pair $R^{\cdot}X^-$(B), one should also observe 100% inversion of configuration. However, when there is separation of $R^{\cdot}$ and X^- (C), some racemization of the probe should occur in the solvent cage (prior to coupling) resulting in less than 100% inversion of configuration of the product; (C') is a more detailed representation of (C). Finally, when the radical anion pair dissociates (D) and the radical is kinetically free, then a completely racemic product should form. All of our data are consistent with this interpretation.

Scheme. Mechanism of Nucleophilic Aliphatic Substitution Involving a Radical Intermediate

$$\begin{tikzcd}
 & \text{(A)} & \text{(B)} & \text{(C)} & \text{(D)} \\
RX + Y^- \arrow[r] & {[Y^{\cdot}RX^{\overset{\cdot}{-}}]} \arrow[r] \arrow[d] & {[Y^{\cdot}R^{\cdot}X^-]} \arrow[r] \arrow[d] & {[Y^{\cdot}R^{\cdot}{-}{-}{-}X^-]} \arrow[r] \arrow[d] & {[Y^{\cdot} + R^{\cdot} + X^-]} \arrow[d] \\
 & RY + X^- & RY + X^- & RY + X^- & RY + X^- \\
 & \text{(100\% inversion)} & \text{(100\% inversion)} & \text{(partial racemization)} & \text{(racemization)}
\end{tikzcd}$$



In no case was racemization of the reactant or product observed during the course of any of the reactions. The fact that other nucleophiles such as N_3^- and t-BuS$^-$ produced product with 100% inversion of configuration when X = OTs, Cl, Br and I is evidence that carbonium ion formation is not involved, since carbonium ion formation is independent of the nucleophile and therefore partial racemization (at least with the alkyl iodide) would have been expected. In addition, the above reactions with added lithium salts produced the same results as those reactions in which no salt was added. Moreover, initial studies using THF as a solvent in the reaction of the 2-substituted octanes with i-PrS$^-$ show comparable results to those reported above in DMF. Thus, comparable results in a solvent of lower polarity (THF) in which carbonium ion formation is less favored than DMF, is further indication of the absence of carbonium ion intermediates in these reactions.

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