Single-Electron Transfer, a Major Reaction Pathway in Organic Chemistry. An Answer to Recent Criticisms

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The development of what has become known today as single-electron-transfer (SET) chemistry has resulted in a most exciting time in the history of organic chemistry. As early as 1966 Kornblum[1] and Russell[2] independently provided details of the $S_{RN}1$ pathway for the specific reactions that they were studying, and in 1970 Bunnett[3] discovered that such a pathway was also in effect in some cases of nucleophilic aromatic substitution (Scheme I). Step i involves SET from the nucleophile (Y^-) to the substrate (RX). In step ii the radical anion ($RX^{\bullet -}$) dissociates very rapidly to the radical ($R^\bullet$), which then reacts with Y^- in step iii to form the product radical anion ($RY^{\bullet -}$), which in step iv serves as the one-electron donor in the radical chain process.

Scheme I

$S_{RN}1$ Mechanistic Pathway

$$RX + Y^- \rightarrow RX^{\bullet -} + Y^\bullet \quad \text{(i)}$$

$$RX^{\bullet -} \rightarrow R^\bullet + X^- \quad \text{(ii)}$$

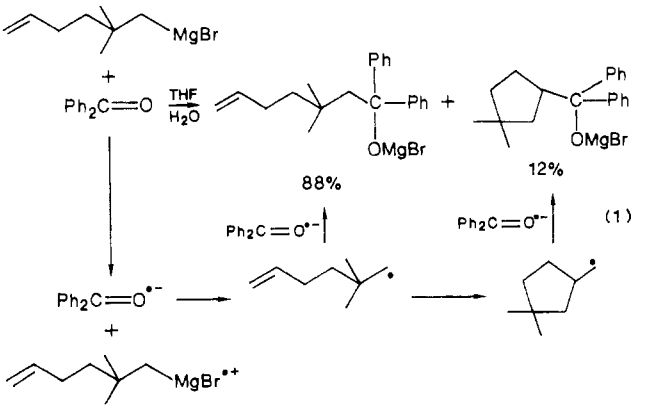
$$R^\bullet + Y^- \rightarrow RY^{\bullet -} \quad \text{(iii)}$$

$$RY^{\bullet -} + RX \rightarrow RY + RX^{\bullet -} \quad \text{(iv)}$$

We define a SET reaction as one that is initiated by single-electron transfer from the nucleophile to the substrate producing a radical intermediate. The fate of the resulting radical intermediate can then be involved in any number of events, one of which is described in the $S_{RN}1$ mechanistic pathway. Our own contributions in this area have been to provide evidence that many classic organic reactions heretofore classified as polar reactions actually involve radical intermediates formed by a process initiated by SET from the nucleophile to the substrate. We believe that SET is just as major a reaction pathway in organic reactions as the S_N2 pathway, but is even more extensive because it describes not only reactions of nucleophiles with alkyl halides but also reactions of nucleophiles with carbonyl compounds. Furthermore, we believe that it is no longer valid to assign a specific reaction mechanism for a specific name reaction because the mechanism can change from polar to SET within a reaction type depending on whether the reaction with the nucleophile is carried out with an aliphatic or an aromatic ketone or whether the alkyl halide involved is an iodide or a chloride. The above positions are rationalized on the basis that (1) an aromatic ketone has a more favorable reduction potential than an aliphatic ketone and therefore is much more susceptible to one-electron transfer and (2) an alkyl iodide has a more favorable reduction potential than the corresponding chloride.

We have not tried to quantify the extent of SET in a specific reaction, but only to detect the presence of radical intermediates. When we began our studies in 1975, the question was not quantification; the question was "is it possible to get *any evidence whatsoever* that typical nucleophilic aliphatic substitution reactions involve radical intermediates, no matter what the amount?" Indeed in 1975 SET was considered a unique reaction pathway that was only operative for certain select reactions under certain conditions. The possibility of SET being involved in a broad sense in typical nucleophilic aliphatic substitution and carbonyl addition reactions was not a matter of discussion at that time.

In 1975 we suggested that the reaction of "CH_3MgBr" with 2-methylbenzophenone involved a radical intermediate.[4] In 1980 we tested this hypothesis further by using a cyclizable radical probe that resulted in the formation of cyclized product as well as straight-chain product (eq 1).[5] We had worked 14 years on the



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mechanism of this reaction without definitive evidence of a radical intermediate until a cyclizable radical probe was used.[6] Today much more is known about the radical nature of this reaction not only due to our own efforts but particularly due to the efforts of Holm,[7] who provided the first substantive evidence of the radical nature of the reaction of Grignard reagents with ketones from Hammett studies.

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After the Grignard–ketone study, we immediately began to wonder if other reagents might also be one-electron donors toward ketones. In 1980 we reported evidence that SET was involved in the reduction of a benzophenone derivative with AlH_3 (eq 2).[8] The reaction of AlH_3 with dimesityl ketone produced a violet solution within a few minutes that exhibited a well-resolved ESR spectrum. The disappearance of the paramagnetic intermediate was found to have a rate constant within experimental error of the rate constant describing the appearance of the product; thus the credibility of relating the product to the intermediate was established.

$$AlH_3 + Ar_2C{=}O \underset{\text{fast}}{\overset{k_1}{\rightleftharpoons}} [AlH_3^{\bullet+}][Ar_2C{=}O^{\bullet-}] \xrightarrow[\text{slow}]{k_2} Ar_2C(H)OAlH_2 \xrightarrow{H_2O} Ar_2C(H)OH \quad (2)$$

Since 1980 we have attempted to extend the investigation of SET in reactions of nucleophiles with ketones[9] to other well-known reactions and also to extend our studies to reactions of nucleophiles with alkyl halides.[10] We have done this and the results have been far beyond our initial expectations. In this report we describe the methodology that we have used to study the reactions of nucleophiles with ketones and with alkyl halides and report the results and conclusions of such studies. Second, we address recent criticisms[11,12] concerning the use of cyclizable radical probes as indications of SET in reactions of nucleophiles with alkyl halides.

Methodology

The methodology that we have used to provide evidence for SET in a particular reaction falls into two categories. One category involves the reaction of a nucleophile with a ketone, and the other involves the reaction of a nucleophile with an alkyl halide. In both cases we believe that the possibility of SET depends mainly on the one-electron-donor ability of the nucleophile (oxidation potential), the electron-acceptor ability of the ketone or alkyl halide (reduction potential), and, to a lesser extent, the polarity of the solvent. We have studied reactions in which the nucleophiles RMgX, $LiAlH_4$, AlH_3, R_3Sn^-, R_2P^-, RS^-, OH^-, OR^-, RLi, enolates, and $LiCuR_2$ show evidence as one-electron donors toward either alkyl halides or ketones or both.[9,10] In our studies we have found the following order of nucleophiles as one-electron donors: $Me_3Sn^- > Me_2P^- > {}^iPrS^- > {}^iPrO^-$. We have also shown that only aromatic ketones are sufficiently good electron acceptors to exhibit evidence of reaction with nucleophiles to form ketyls[9] and that the order of electron-acceptor ability of alkyl halides (RX) is X = I > Br > Cl > OTs.

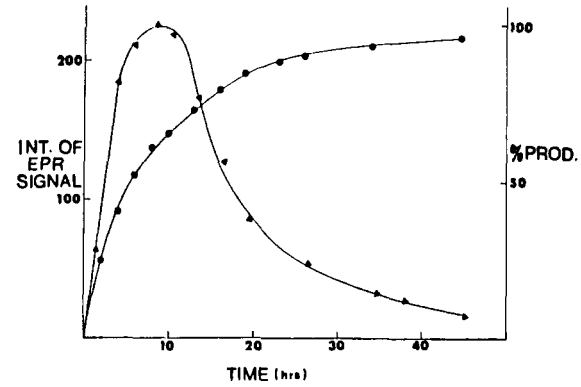
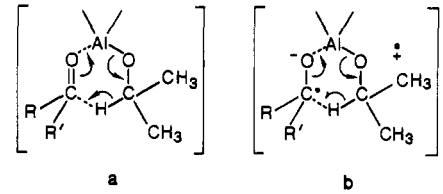


Figure 1. Reaction of benzophenone (0.076 M) with lithium isopropoxide in THF: (▲) intensity of EPR signal (mm) vs time (h), where 1 mm = 0.01% radical; (●) reduction product (%) vs time (h).

The evidence for a SET pathway in the reaction of a nucleophile with a carbonyl compound involves the observation of a paramagnetic intermediate and kinetic data establishing that the rate constant for the disappearance of the paramagnetic intermediate is within experimental error of the rate constant for the appearance of the product. This methodology was used to provide evidence that aromatic ketones, aldehydes, and esters can react with the following electron donors by SET: (1) aromatic ketones with AlH_3 (discussed earlier),[8] alkoxides (Meerwein–Pondorff–Verley reduction),[9b] and hydroxide ion or enolate (aldol condensation),[9a] (2) aromatic aldehydes with OH^- (Cannizzaro reaction),[9c] and (3) aromatic esters with enolates (Claisen condensation).[9d] In order to demonstrate the methodology of studying the reaction of an aromatic ketone with a nucleophile, we have selected the reaction of benzophenone with $LiOPr^i$ as the example to be described in some detail.

Reaction of Nucleophiles with Carbonyl Compounds. Meerwein–Pondorff–Verley Reduction of Aromatic Ketones by Alkoxides.[9b] The Meerwein–Pondorff–Verley reduction of ketones is normally carried out with $Al(OPr^i)_3$, and by means of deuterium labeling has been shown to involve the β-hydrogen of the alkoxide. Although a six-center polar transition state (a) has been used to represent the mechanistic



a b

pathway taken by this reaction, it is also possible to envision the reaction taking place via a radical transition state (b). We were able to show that not only aluminum alkoxides but also lithium, sodium, potassium, and magnesium alkoxides reduce ketones. However, since alkali-metal alkoxides are such strong bases and therefore will enolize aliphatic ketones readily, aluminum alkoxides were chosen as the preferred reducing agent. However, when nonenolizable aromatic

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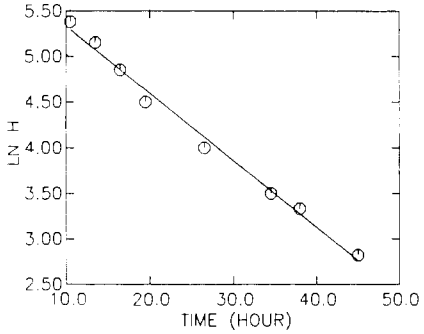


Figure 2. Plot of ln H vs time for the first-order decay of radical intermediate in the reaction of benzophenone with lithium isopropoxide.

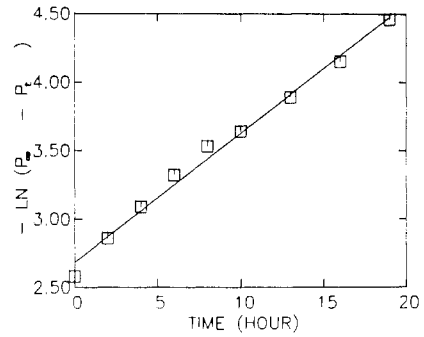
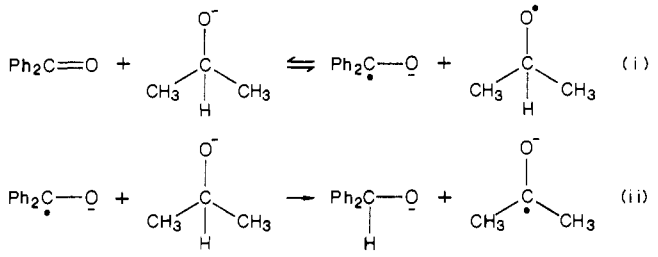


Figure 3. Plot of ln $(P_\infty - P_t)$ vs time for the pseudo-first-order formation of benzhydrol in the reaction of benzophenone with lithium isopropoxide.

Scheme II



ketones are to be reduced, LiOPr^i is also a very effective reducing reagent.

When benzophenone was allowed to react with LiOPr^i in THF, a blue solution formed, and the reaction mixture was shown to be ESR active. Figure 1 shows that the product formed during the same time period that the paramagnetic intermediate disappeared. The paramagnetic intermediate was shown to be benzophenone ketyl, and Figure 2 shows that the ketyl disappeared in a first-order fashion. Furthermore, the rate constant describing the rate of disappearance of the ketyl is within experimental error of the pseudo-first-order rate constant for the appearance of product (Figure 3). The proposed mechanism (Scheme II) involves two key steps: step i, electron transfer from the alkoxide to the ketone, and step ii, reaction of the resulting ketyl with the alkoxide. Evidence for step i is convincing in that an alkoxide such as $^-OBu^t$, which contains no β-hydrogen for reduction, nevertheless does react with benzophenone to produce the corresponding ketyl. In order to test the notion that the product is formed from the reaction of the alkoxide with the ketyl (step ii), benzophenone ketyl was prepared independently and observed to react with LiOPr^i (Figure 4). The rate constant for the disappearance of the ketyl was

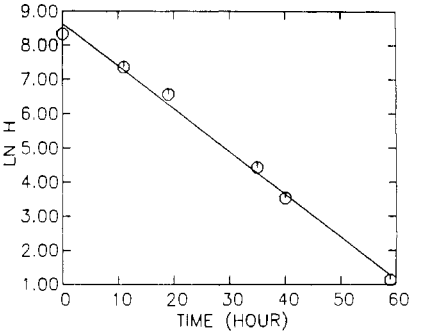
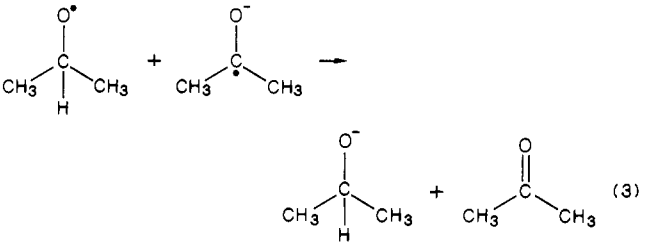


Figure 4. Plot of ln H vs time for the first-order decay of benzophenone ketyl in the reaction of the ketyl with lithium isopropoxide.

within experimental error of the rate constant obtained for the reaction of benzophenone with LiOPr^i. These results are consistent with a mechanism in which the rate-determining step involves the reaction of the ketyl intermediate with LiOPr^i. As for the aliphatic byproducts in steps i and ii, there are at least three ways that they can react to account for the stoichiometry of the reaction. One way is to suggest that the two aliphatic byproducts react according to eq 3.



There is no evidence to support SET in Meerwein–Pondorff–Verley reductions when the ketone is aliphatic. Similar studies using the same methodology directed to aldol condensation,[9a] Claisen condensation,[9d] the Cannizzaro reaction,[9c] and reduction of aromatic ketones with AlH_3[8] produced similar evidence consistent with a SET pathway. The mechanism presented (Scheme II) is consistent with all observations; however, the recurring dichotomy that formation of an intermediate can be a dead-end step that does not lead to the product (eq 4) cannot be rigorously excluded.

$$P \leftarrow A + B \rightleftharpoons I \rightarrow P \qquad (4)$$

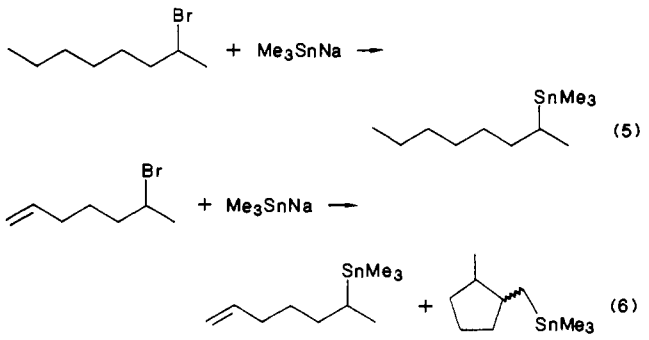
Reaction of Nucleophiles with Alkyl Halides. Mechanism of Nucleophilic Aliphatic Substitution. Stereochemical Considerations. Nucleophilic aliphatic substitution involving reactions of nucleophiles with alkyl halides is one of the most fundamental reactions in organic chemistry. It is becoming increasingly clear that some reactions, heretofore considered to be classic S_N2 processes because of their exhibited characteristic of inversion of configuration of the reaction center, involve the presence of radical intermediates. We believe that reactions considered to be classic S_N2 processes that do not proceed with 100% inversion of configuration give evidence of either an exclusive or competing alternate pathway. The suggestion is that one of the alternate pathways is a one-electron-transfer process involving transfer of an electron from the nucleophile to the backside (σ^* orbital) of the substrate. When a substrate is difficult to reduce (large negative reduction potential), a S_N2 pathway should predominate; however, when the substrate is easy to reduce

Table I
Reactions of 2-Halooctanes with Nucleophiles in DMF at Room Temperature

expt	Nuc	R*X	% inversion	expt	Nuc	R*X	% inversion
1	LiSPh	OTs	100.0	12	$LiPPh_2$	OTs	100.0
2	LiSPh	Cl	99.5	13	$LiPPh_2$	Cl	100.0
3	LiSPh	Br	99.6	14	$LiPPh_2$	Br	93.8
4	LiSPh	I	88.6	15	$LiPPh_2$	I	94.0
5	$LiSPr^i$	OTs	100.0	16	$NaSnMe_3$	OTs	100.0
6	$LiSPr^i$	Cl	99.8	17	$NaSnMe_3$	Cl	89.0
7	$LiSPr^i$	Br	85.7	18	$NaSnMe_3$	Br	77.2
8	$LiSPr^i$	I	85.1	19	$NaSnMe_3$	I	81.1
9	LiCN	OTs	100.0	20	$LiAlD_4$	OTs	100.0
10	LiCN	Br	83.6	21	$LiAlD_4$	Cl	100.0
11	LiCN	I	82.9	22	$LiAlD_4$	Br	100.0
				23	$LiAlD_4$	I	75.8

(small negative reduction potential), a one-electron-transfer pathway should be favored.

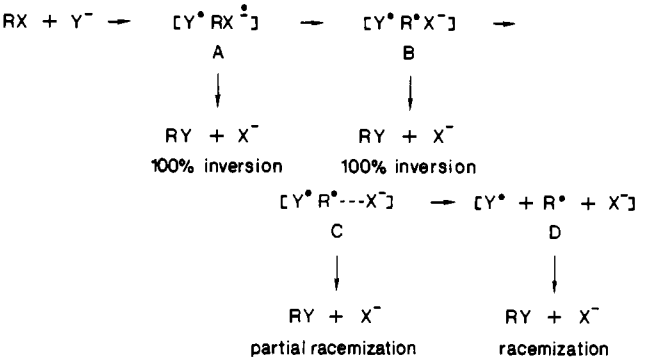
We have described studies of the reactions of alkyl halides with RLi, $LiAlH_4$, $LiCuMe_2$, enolates, Me_3Sn^-, SR^-, and OR^- and in each case have reported evidence for single-electron transfer (SET) and radical intermediates when the halide is iodide.[10] When the nucleophile is a super one-electron donor, such as Me_3Sn^-, we have found strong evidence for SET even when the halide is bromide or chloride.[10g] 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. For example, the reaction of Me_3Sn^- with (+)-2-bromooctane resulted in 77% inversion of configuration in the substitution product (eq 5), and yet a similar reaction involving



6-bromo-1-heptene produced a 70% yield of cyclized substitution product (eq 6).[10g] Thus, evidence has been provided that a reaction that exhibits substantial radical character can proceed with predominant inversion of configuration. We were also able to demonstrate that the reaction of (+)-2-iodooctane and 6-iodo-1-heptene with $LiAlH_4$ 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.

We suggest that observation of cyclized substitution product in a reaction such as represented by eq 6 is evidence for a radical intermediate; however, the absence of cyclized product should not be interpreted as evidence for the absence of a radical intermediate. Since cyclized substitution product results only after diffusion of the radical from the solvent cage, rapid geminate coupling of radicals inside the solvent cage should give no evidence of a radical intermediate using a cyclizable radical probe. On the other hand, a chiral

Scheme III



center should lose its stereochemical integrity inside the solvent cage at a rate at least competive with that of geminate coupling. Therefore, the loss of stereochemical integrity should be an indication of radical formation in the solvent cage. Thus, a method exists for detecting 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 (Table I). The reactants and products were monitored throughout the reactions with no evidence of racemization during or after the reaction.

Since RX compounds are more easily reduced in the order X = I > Br > Cl > OTs, reactions of tosylates are more likely to take place by an S_N2 pathway whereas reactions of iodides are more likely to take place by SET. Thus, in expt 1 (Table I), when LiSPh was allowed to react with (−)-2-octyl tosylate in DMF at room temperature, (+)-2-(thiophenoxy)octane was obtained.[13] Because of the unfavorable reduction potential of tosylates, reactions with typical nucleophiles should proceed with 100% inversion of configuration. Thus it is clear from the optical purities of the products that the reactions of LiSPh in expt 1–4 proceed with inversion of configuration, decreasing according to the trend OTs, Cl, Br, and I as expected for electron transfer and not for an S_N2 pathway. The results for the other nucleophiles show the same trend.

Although more detailed studies of the reactions of nucleophiles with alkyl halides are needed to provide a complete description of a SET pathway in these reactions, a reasonable suggestion (Scheme III) is pres-

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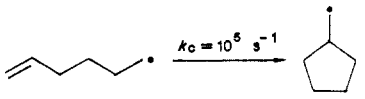
ented to account for the inversion of configuration process that involves SET and radical intermediates. It is suggested that the nucleophile approaches the σ^* orbital at the backside of the C–X bond followed by electron transfer. Within the solvent cage, the leaving group (X^-) protects the front side of the α carbon of $RX^{\bullet-}$ (A) from attack by $Y^\bullet$, leading to the observed 100% inversion of configuration. Further along the reaction coordinate A dissociates to B (a tight radical anion pair). Since $Y^\bullet$ should still be at the backside of $R^\bullet X^-$ and the front side is still protected by X^-, attack by $Y^\bullet$ should produce 100% inversion of configuration. However, when there is significant separation of $R^\bullet$ and X^- (C), some racemization of the probe can occur in the solvent cage prior to coupling since attack of $Y^\bullet$ can take place to some extent at the front side of $R^\bullet$. Of course, when the radical anion pair dissociates (D) and the radical is kinetically free, a completely racemic product should form.

When N_3^- and $^tBuS^-$ were allowed to react with the substrate, products were produced with 100% inversion of configuration when X = OTs, Cl, Br, and I. This is evidence that a carbonium ion is not formed in any of the reactions with the other nucleophiles since carbonium ion formation is independent of the nucleophile. Similar reactions in THF gave similar results.

Use of Cyclizable Radical Probes. Arai[14] first reported the cyclization of the 5-hexenyl radical to the methylcyclopentyl radical (eq 7). Since that time,



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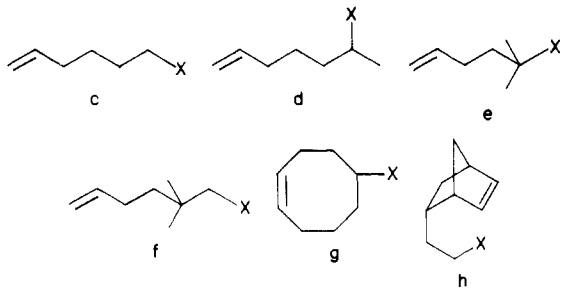
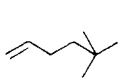
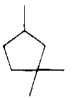
Brace,[15] Lamb,[16] Walling,[17] Julia,[18] Beckwith,[19] Garst,[20] and others have employed this cyclization either for synthetic or for mechanistic purposes. Ingold[21] has described the use of this and similar cyclizations as "radical clocks" based on the determined rates of cyclization. In 1980 we used compounds c–f in our studies



involving Grignard reagent addition to ketones[5] and later used these probes, as well as g,[10a,c,h] and h,[10b] as cyclizable probes for the study of other reactions. Compound h cyclizes over 100 times faster than c and shows cyclization products in cases where probe c did not. This is because cyclization is always in competition with other pathways, and if the probe does not cyclize fast enough, even though a radical intermediate may be present, no cyclized product may be formed. Comparable carbonium ions and carbanions can also cyclize, although much more slowly; therefore in those cases where these kinds of intermediates are possible, they must be excluded before evidence for a radical intermediate can be proposed.

Table II
Reduction of 5,5-Dimethyl-6-halo-1-hexenes by $LiAlH_4$ in THF at Room Temperature

RX	% yield of product (% d_1)	
		
ROTs	1.8	0
RCl	0	0
RBr	9.8	7.5
RI	2.5	96
RI ($LiAlD_4$)	5.5 (69% d_1)	89 (59% d_1)

Reaction of Alkyl Halides with $LiAlH_4$

Mechanism of Reaction. Since hydrides are electron-rich reducing agents, it is not unreasonable to think of them as one-electron donors, especially in light of theoretical considerations presented by Eberson.[22] We had found earlier that $LiAlH_4$ reacts with polynuclear hydrocarbons to form the corresponding radical anion (eq 8);[23] thus we suspected that $LiAlH_4$ might also act

$$\text{perylene} + LiAlH_4 \rightarrow [\text{perylene}]^{\bullet-} \quad (8)$$

$$Ph_3CBr + LiAlD_4 \rightarrow Ph_3CBr^{\bullet-} \rightarrow Ph_3C^\bullet \rightarrow Ph_3CD \quad (9)$$

as a one-electron donor toward other compounds with similar reduction potentials. On reaction of $LiAlD_4$ with trityl bromide in THF, we observed a high concentration of the trityl radical by ESR and proposed a SET process to describe the pathway (eq 9).[24]

We also studied the reactions of alkyl halides with $LiAlH_4$ by using a variety of radical probes c–h, where X = OTs, Cl, Br, and I. Although no evidence of a radical intermediate was found in THF with the nonsterically hindered primary alkyl halide probe c, evidence for a radical intermediate was observed in both ether and THF solvents in the cases of probes d, f, g, and h, where X = I. The data obtained for the sterically hindered primary alkyl halide probe f is summarized in Table II.[10i] The data establish the intermediacy of radicals in the reaction of $LiAlH_4$ with the radical probe f, and furthermore, probes d, g, and h gave similar results. It is indicated from the data that the extent of formation of cyclized hydrocarbon follows the order RI > RBr > RCl > ROTs, which is consistent with a SET pathway. The results of the reaction of the alkyl iodide with $LiAlD_4$ show that the products have a substantial protium content, indicating a radical precursor. The mechanism in Scheme IV was proposed in 1984 based on ESR spectra, radical probe, radical trapping, and stereochemical studies for the reduction of hindered

(14) Arai, S.; Sato, S.; Shida, S. *J. Chem. Phys.* **1960**, *33*, 1277.
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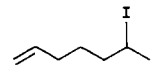
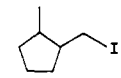
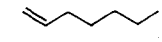
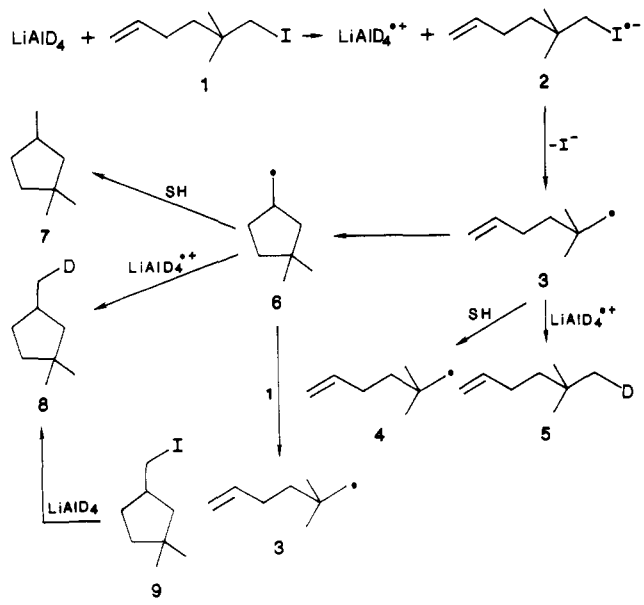
(19) Beckwith, A. L. J.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613.
(20) Garst, J. F.; Smith, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 1520.
(21) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.
(22) Eberson, L. *Adv. Phys. Org. Chem.* **1982**, *18*, 79.
(23) Ashby, E. C.; Goel, A. B. *J. Am. Chem. Soc.* **1981**, *103*, 973.
(24) Ashby, E. C.; Goel, A. B.; DePriest, R. *Tetrahedron Lett.* **1981**, *22*, 3729.

Table III
Rate Profile Studies of the Reaction of 6-Iodo-1-heptene (1a) with $LiAlH_4$ and AlH_3 in THF at Room Temperature

			% yield			
						
expt	reagent	time, min		cis/trans		cis/trans
1	$LiAlH_4$	10	48	28 (5.8)	16	6 (2.1)
		20	19	40 (7.2)	19	18 (2.0)
		60	1	27 (8.7)	18	44 (2.5)
		120	0	9	20	67 (2.8)
		260	0	<1	19	80 (3.5)
2	AlH_3	10	70	28 (3.7)	<1	<1
		20	50	41 (4.1)	<1	3.5
		60	21	61 (3.9)	<1	11 (4.2)
		240	<1	69 (3.8)	<1	21 (4.2)

Scheme IV



primary iodides and secondary alkyl iodides.[10i]

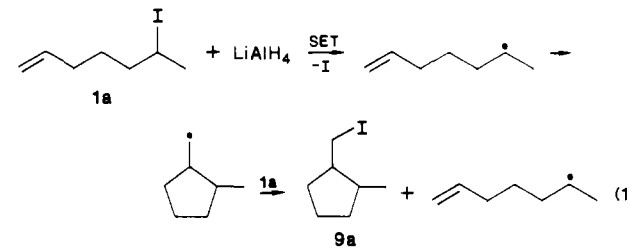
Validity of the Use of Cyclizable Radical Probes. Recently, Newcomb[11] and Curran[12] claimed that observation of cyclized products (**7**, **8**) in the above reaction is not indicative of the process described in Scheme IV in which intermediate **6** proceeds to **7** and **8** directly and via intermediate **9**, but rather exclusively via a polar reaction of the cyclized iodide **9** with $LiAlH_4$. As to how radical **3** is proposed to initiate the chain, Newcomb suggests that it is formed from adventitious impurities.[11b]

We had the impression on reading the reports by Newcomb and Curran that the reader was being alerted for the first time that halogen exchange (**6** ⇄ **9**) had been overlooked by ourselves and that the polar reduction of **9** is the exclusive route to **7** and **8**. Curran reports,[12] "Reactions assumed to proceed via a polar mechanism have been proposed to have a significant electron-transfer component.[10i] However, this deceptively simple analysis neglects the atom-transfer cyclization." We will address both of these points: (1) the implication that halogen atom exchange had been overlooked and (2) that radical **3**, needed to initiate the radical chain process, is not formed by SET, but by adventitious impurities. In 1984,[10i] 3 years prior to the Newcomb and Curran reports, we proposed the above mechanism, supported with extensive data from a variety of experiments. We monitored the appearance of cyclized halide (**9**) formed by a radical chain process during the reaction and showed that although some of the cyclized product (**7**, **8**) was formed by reduction of the cyclized halide (**9**) with $LiAlH_4$, it was also clear that some of the cyclized product was formed by the direct reaction of the radical intermediate **6** with a hydrogen source other than $LiAlH_4$. In addition to **1**, other probes (d,[10i] g,[10c] and h,[25] where X = I) were also shown to involve halogen exchange. In each case the intermediate comparable to **9** was monitored throughout the reaction.

In order to establish that halogen exchange **6** ⇄ **9** had been discussed in depth by ourselves 3 years prior to the Newcomb and Curran reports, we present the following excerpts from our report in 1984.[10i] (Table, compound, and equation numbers have been changed to correspond to the sequence in the present report.)

"Table III provides data on the reduction of 6-iodo-1-heptene (**1a**) with both $LiAlH_4$ and AlH_3 in THF. The purpose of these studies was to provide a reaction profile of the reactions with particular emphasis on the cis/trans ratio of the cyclized hydrocarbon (1,2-dimethylcyclopentane) formed in the reaction. It was our surprise to find that the starting iodide (**1a**) cyclized rapidly to (2-methylcyclopentyl)methyl iodide (**9a**) during the reactions with both $LiAlH_4$ and AlH_3, and *therefore much of the product formed was a result of direct reduction of the cyclized iodide.*"

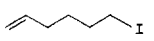
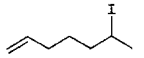
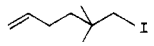
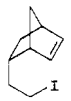
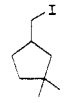
"The isomerization of **1a** to its cyclic isomer **9a** can be visualized as a radical chain process that is initiated by SET from $LiAlH_4$ or AlH_3, as in eq 10."



We would now like to continue this discussion to show that in spite of the halogen atom, radical chain process just mentioned, even the cyclized iodide **9** reacts with $LiAlH_4$ by a SET process. Reference to Table IV (expt 1–4) shows (1) that cyclized hydrocarbon is produced in the reduction of four different alkyl iodide radical probes and (2) that the low deuterium contents of the straight-chain and cyclized hydrocarbons indicate

(25) Ashby, E. C.; Pham, T., unpublished results.

Table IV
Reduction of Alkyl Iodides with $LiAlD_4$

expt	alkyl iodide	solvent	% straight-chain hydrocarbon	% cyclized hydrocarbon
1		Et_2O	95 (100% d_1)	2.5 (94% d_1)
2		THF	32 (100% d_1)	65 (88% d_1)
3		THF	5.5 (69.0% d_1)	89 (59% d_1)
4		Et_2O	86 (97.3% d_1)	11 (17% d_1)
5		THF	$LiAlD_4$	100 (100% d_1)
6		THF	$LiAlD_4$ AlD_3	98 (90% d_1) 100 (77% d_1)
7		THF	$LiAlD_4$ AlD_3	99 (95% d_1) 98 (74% d_1)
8		THF	$LiAlD_4$ AlD_3	99 (98% d_1) 98 (68% d_1)

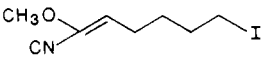
that the precursors are the radicals **3** and **6**.[26] These radicals can react with the solvent (SH), $LiAlD_4$, or $LiAlD_4^{\bullet+}$, and the results show that both hydrogen abstraction and deuterium abstraction take place.

Furthermore, the results of expt 5–8 clearly show that even when cyclized iodide **9** is an intermediate, reduction with $LiAlD_4$ involves an electron-transfer pathway. The tosylate (expt 5) shows a product with 100% deuterium incorporation whereas the cyclized iodides show some protium incorporation from reaction of the radical intermediate **6** with a hydrogen source other than $LiAlD_4$. Since AlD_3 is a byproduct in these reactions and since we have shown earlier that this byproduct also participates in the cyclization of **1** to **9**, these data show that reduction of **9** and other cyclized iodides by $LiAlD_4$ and AlD_3 to hydrocarbon must involve the radical intermediate **6** since protium incorporation in the product is so high.

A final point involves a comparison of the deuterium incorporation in the cyclized hydrocarbons produced in expt 1–3 (94, 88, and 59%) with the deuterium incorporation of the corresponding cyclized hydrocarbons produced in expt 6–8 (90, 95, and 98%). If the cyclized hydrocarbons produced in expt 1–3 arise from reduction of **9** by $LiAlD_4$, then the deuterium values for expt 1–3 compared to those from expt 6–8 should be the same. The reason they are not is that intermediate **6** not only abstracts an iodine atom from **1** but also abstracts hydrogen from a source other than $LiAlD_4$.

Newcomb's suggestion that the initial electron transfer is due to adventitious impurities[11b] was made with the knowledge of our 1984 report,[10i] which stated that the halide substrate was distilled and found to contain no other components as determined by GLC, that the $LiAlH_4$ was doubly recrystallized from distilled THF–benzene (no transition-metal impurities in the $LiAlH_4$ were detected by atomic absorption analysis), and that all solvents were distilled over sodium benzophenone ketyl or $NaAlH_4$. Furthermore, doping experiments of $LiAlH_4$ with $FeCl_3$ gave the same results as with pure $LiAlH_4$. Since painstaking care was employed to exclude impurities, the burden of proof that adventitious impurities act as a catalyst for initial radical formation lies with the suggester. These reactions were carried out under conditions of rigorous exclusion of oxygen. When oxygen was purposely added, it retarded the reaction rate.

In a more recent report questioning the validity of cyclizable radical probes as evidence for SET in the reaction of $LiAlH_4$ with alkyl halides, Newcomb has reported that the reaction of **1b** with $LiAlH_4$ does not result in the formation of cyclized product.[11b]



1b

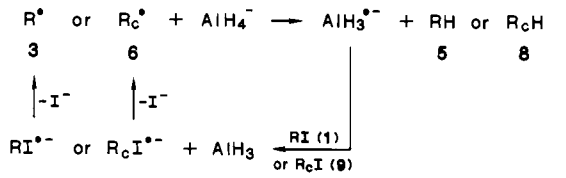
The reason given for the lack of cyclization product is that radical **6b** because of its stability should not participate in rapid halogen exchange with **1b** to produce **9b**, since this involves converting a more stable radical (**6b**) to a less stable radical (**3b**), therefore eliminating what he claims to be the only route to cyclized product. He concludes that when halogen atom exchange does not take place, cyclized product is not produced and hence when other probes used by ourselves and others resulted in cyclization, all cyclized product was a result of reduction of **9a** by a "conventional two-electron nucleophilic displacement".

First, to claim that SET does not happen in all of the previous systems studied because it does not happen in a special case that he studied is not sound logic. We can show (1)[27] that probe **1b** studied by Newcomb *does* show evidence of a radical intermediate even though no cyclized product was found, (2) why **1b** is an invalid probe, and (3) that the results of a study using a *valid* probe to test the exclusivity of halogen atom exchange as the sole route to cyclized product do indicate a SET pathway. Our conclusions are based on the following facts: (1) When halide **1b** was allowed to react with $LiAlD_4$ in THF in the presence of the hydrogen atom donor 1,4-cyclohexadiene, the deuterium incorporation of the product **5b** was only 92–95%, indicating that at least 5–8% of the alkyl halide produced a radical intermediate that was trapped by the hydrogen atom donor. As we have shown, 100% deuterium incorporation is observed in those cases where a two-electron-transfer process is expected. (2) In the studies involving **1b**, the integrity of the double bond was not monitored during the course of the reaction. We found **1b** to have an E/Z ratio of 62/38; however, the E/Z ratio of the product changed to 84/16. This is not unexpected since the α,β-unsaturated nitrile would be expected to have a considerably lower reduction potential than a compound such as **1** that does not have a cyano group. In addition, when the cyano group is not present, such double-bond isomerization does not take place. There is no question from these data that the double bond is involved in this reaction (probably in the formation of the radical anion of the α,β-unsaturated nitrile), thus providing a possible reason for the inhibition of cyclization of **3b** to **6b**. (3) In order to determine the uni-

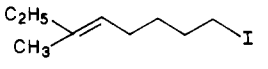
(26) Ashby, E. C.; Pham, T. *Tetrahedron Lett.* **1987**, *28*, 3197.

(27) Ashby, E. C.; Pham, T.; Amrollah Madjdabadi, A., manuscript submitted.

Scheme V



queness of **1b** as an invalid probe, we reacted $LiAlH_4$ with 8-iodo-3-methyl-3-octene (**1c**), thus replacing the



1c

methoxy and cyano groups with methyl and ethyl groups, which do not affect the reduction potential of the double bond as would be expected for **1b**. We found that the E/Z ratio of the product does not change from that of the reactant, indicating that the double bond is not affected by these groups. Importantly, when **1c** was reduced with $LiAlH_4$ in ether, cyclized product **7c** was formed in 9.6% yield and when **1c** was reduced with $LiAlD_4$, cyclized product **8c** was formed in 18.4% yield.

Since cyclized product would not be expected to come from cyclized iodide **9c**, it must come from radical **6c**. Additional convincing evidence comes from the reduction of **1c** by $LiAlD_4$ in ether. There is significant protium content not only in the cyclized product (11%) but also in the straight-chain product (5%). All of these data are clearly compatible with the mechanism shown in Scheme IV that we proposed in 1984.

Recently, in addition to the halogen atom radical chain process $6 \rightleftarrows 9$, which accounts for some of the cyclized products (**7**, **8**), we have found evidence to support a hydrogen atom radical chain process to account for the conversion of $3 \rightarrow 5$, $6 \rightarrow 8$, and $9 \rightarrow 8$ by reaction of radicals R$^\bullet$ (**3**) and $R_c^\bullet$ (**6**) with $LiAlH_4$ (Scheme V). Support for the hydrogen atom radical chain process is based on (1) the increased amount of **5** formed (3.3% to 9.4% to 15.2%) as the $LiAlH_4$:1 ratio is increased from 0.1:1 to 1:1 to 1:5, showing that radical **3** is quenched with $LiAlH_4$ at a faster rate in competition with reaction with SH, $LiAlH_4^{\bullet+}$, and the cyclization of $3 \rightarrow 6$ and (2) the results of an entrainment experiment that shows that although the corresponding chloride of **1**, which does not react with $LiAlH_4$ in THF for 48 or 92 h, 28% reaction does take place over the same period of time in the presence of an equivalent amount of iodide (**1**). It has been shown that chloride is not converted to **1** by reaction with I^-. Both of these studies are consistent with a hydrogen atom radical chain process.

In conclusion, we believe that SET is indeed a major reaction pathway in organic chemistry and that even reactions heretofore thought to be classic S_N2 processes proceed, at least to some extent, via a SET pathway. This pathway is particularly important when X = I, but even when X = Br and Cl when a super one-electron donor such as Me_3Sn^- is involved. Evidence has also been presented to support SET as a major reaction pathway in the reactions of aromatic ketones with certain nucleophiles. We continue to believe that the use of alkyl halide cyclizable radical probes does provide important information concerning the radical nature of reactions classified as nucleophilic aliphatic substitution.

We are indebted to the National Science Foundation (Grant No. CHE 8403024) for support of our work.

Organometallic Chemistry of Electrophilic Transition and Lanthanide Metal Ions. The Dominant Pathways for Reactions Involving C=C, C–C, and C–H Bonds

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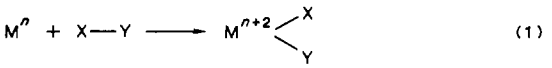
The chemistry of electron-rich transition-metal centers has been studied extensively in recent years, and many of the characteristic reactions are, by now, well understood. The one reaction that appears to dominate this chemistry is oxidative addition (eq 1),[1] and the propensity to undergo this reaction *increases* with *increasing* electron density on the metal. In contrast, with the important exceptions of (a) reactions involving nucleophilic attack on π-complexes[2] and (b) reactions involving early transition, lanthanide, and actinide metal hydrocarbyls,[3] the mechanistic aspects of the



(1)

common examples: X, Y = hydrocarbyls, H, and halogens

Ayusman Sen received his early education in India and holds a Ph.D. in chemistry from the University of Chicago. Following a year of sunbathing at the California Institute of Technology, he joined The Pennsylvania State University, where he is now an Associate Professor of Chemistry. He is a recipient of the Alfred P. Sloan Research Fellowship and the Paul J. Flory Award from IBM.

(1) Review: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; p 279.
(2) Review: ref 1, p 409.
(3) Leading references for "four-center" electrophilic activation of hydrocarbons by early transition metal, lanthanide, and actinide complexes: (a) Bunel, E.; Burger, B. J.; Bercaw, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 976. (b) Thompson, M. E.; Baxter, S. M.; Bulls, A. R.; Burger, B. J.; Nolan, M. C.; Santasiero, B. D.; Schaefer, W. P.; Bercaw, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 203. (c) Watson, P. L. *J. Am. Chem. Soc.* **1983**, *105*, 6491. (d) Teuben, J. H. In *Fundamentals and Technological Aspects of Organo-f-Element Chemistry*; Marks, T. J., Fragala, I. L., Eds.; NATO ASI Series; D. Reidel: Boston, 1985; p 195. (e) Smith, G. M.; Carpenter, J. D.; Marks, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 6805.

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