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The Question of the Validity of Using Radical Probes for Determining SET. The Reaction of Alkyl Halides with $LiAlH_4$.

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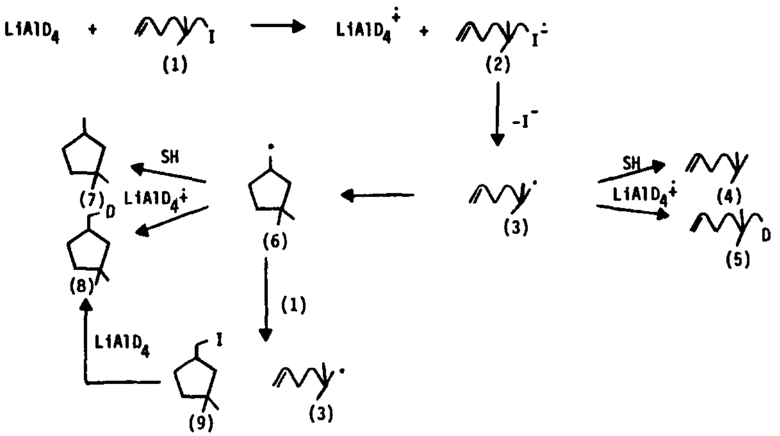
Abstract The validity of using a cyclizable alkyl iodide as a radical probe on reaction with $LiAlH_4$ and other nucleophiles has been recently questioned. Both previously presented data as well as new data presented here makes it clear that the cyclized products formed in the reactions studied are indeed formed to a significant extent via an electron transfer process involving a radical precursor.

Cyclizable alkyl halide radical probes have been used widely as a tool to detect radical intermediates in reactions of alkyl halides with nucleophiles or metal hydrides.[1,2] In such studies the formation of a radical intermediate results not only in the formation of a product with the same skeletal backbone, but also a cyclized product. Thus the observation of cyclized products has been interpreted to mean that (1) the mechanistic pathway involves a radical intermediate and (2) the radical intermediate is produced by single electron transfer from the nucleophile or metal hydride to the alkyl halide.

As early as 1983, we proposed a mechanism consistent with all of the data we had collected concerning the reaction of alkyl halide radical probes with $LiAlH_4$ (Scheme 1).[2b-d] We monitored the formation 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 direct reduction of the cyclized halide (**9**) with $LiAlH_4$, it was clear that much of the cyclized product (**7**, **8**) was formed by the reaction of the radical intermediate (**6**) with a hydrogen source other than $LiAlH_4$. Our major reason for this conclusion was based on the fact that the formation of (**5**) and (**8**) from the reaction of (**1**) with $LiAlD_4$ was 5.5% (69% d_1) and 89% (59% d_1) respectively.[2c] These data show that 41% of cyclized product (**7**, **8**) has a radical precursor which is abstracting hydrogen from a source other than $LiAlD_4$. In an attempt to establish that the radical intermediate is a result of electron transfer from $LiAlH_4$ and not impurities in the $LiAlH_4$, we fractionally recrystallized the $LiAlH_4$ from ultra pure THF (atomic absorption analysis could detect no transition metal impurities in the recrystallized $LiAlH_4$) and found that reactions with this $LiAlH_4$ or $LiAlH_4$ doped with transition metal impurities produced the same results as reported earlier.[2c] Additionally we have reported that $LiAlH_4$ behaves as a one electron donor toward polynuclear hydrocarbons forming the corresponding radical anions[3] and reacts with trityl chloride to form the trityl radical.[4]

Scheme 1. Mechanism of Reaction of (1) with $LiAlD_4$.

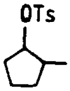
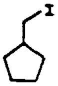
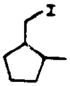
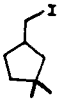


Recently, Curran[5] has claimed that observation of cyclized products (**7**, **8**) in the above reaction is not indicative of the process described in scheme 1 in which intermediate (**6**) proceeds to (**7**) and (**8**), but rather a polar reaction of the cyclized iodide (**9**) with $LiAlH_4$. It appeared to us that we had already discussed the importance of halogen atom exchange in the above reactions in our previous studies.[2c,d] These studies clearly show that straight chain and cyclized products are produced not only from the cyclized iodide (**9**), but also from the cyclized radical (**6**). In addition, these studies show that cyclized product must have a radical precursor since the product is so high in protium indicating radical abstraction of hydrogen from the solvent or the alkyl iodide.

Nevertheless we would like to report further studies to establish even stronger evidence that iodine atom abstraction from (**1**) by (**6**) to form (**9**) is not the sole precursor of cyclized product (**7**, **8**). Even if it were then why is it assumed that (**9**) is not reduced to (**8**) via an electron transfer process? The results of the present studies show that a significant amount of cyclized hydrocarbon (**7**, **8**) is formed directly from its radical precursor (**6**) by hydrogen atom abstraction from a source other than $LiAlH_4$ and that at least some of the cyclized iodide (**9**) that is formed in the reaction is reduced by $LiAlD_4$ also by an electron transfer process.

Reference to the Table (exps 1-4) show that (1) cyclized hydrocarbon is produced in the reduction of four different alkyl iodide radical probes and (2) that the low deuterium contents of the cyclized hydrocarbons indicates that the precursor is the cyclized radical (**6**). The cyclized radical (**6**) can react with the solvent (SH), the alkyl iodide or $LiAlD_4^+$ and the results show that both hydrogen and deuterium abstraction take place. The very low deuterium content observed for the cyclized product of exp. 4 indicates that most (83%) of the cyclized product must have as its precursor the radical equivalent to (**6**).

Table. Reduction of Alkyl Iodides with $LiAlD_4$

Exp.	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)

The question as to whether cyclized iodide (**9**) can be reduced by $LiAlD_4$ via intermediate radical (**6**) is answered by exps. 5-8. The tosylate (exp. 5) shows a product with 100% deuteruim 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 by product in these reactions and since we have shown earlier[2b] that this by-product 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 exps. 1-3 (94, 88 and 59) with the deuterium incorporation of the cyclized hydrocarbons produced in exps. 6-8 (90, 95, 98). If the cyclized hydrocarbons produced in exps. 1-3 arise from reduction of (**9**) by $LiAlD_4$, then shouldn't the deuterium values for exps. 1-3 compared to those from exps. 6-8 be the same? The reason they aren't the same is because the intermediate (**6**) doesn't just abstract an iodine atom from (**1**), but also abstracts hydrogen from a source other than $LiAlD_4$.

In this defense the main conclusion of our earlier work is almost forgotten; namely, that reduction of alkyl iodides and to some extent bromides by $LiAlH_4$ is not a polar process as originally thought, but involves radical intermediates. The use of radical probes was never meant to quantify radical formation, but simply show that radicals are present in the reaction.[6]

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6. Since this paper was submitted, Newcomb[7] has also published a report questioning the validity of using radical probes as an indication of electron transfer. We showed earlier that halogen atom exchange to form cyclized halide (**9**) is important and we specifically pointed out some of those cases.[2c,d] However, we also reported some reactions in which halogen atom exchange is not important. In the reaction of the radical probe 6-iodo-1-heptene with Me_3Sn^-, the ratio of straight chain to cyclized product is constant throughout the entirety of the reaction, thus demonstrating that halogen atom transfer is not at all important in this reaction. These data are inconsistent with Newcomb's sweeping conclusion that, "radical clocks....are poor for qualitative evaluation of whether or not an electron transfer process occurred in a reaction of a nucleophile with an alkyl halide."

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