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CONCERNING THE REDUCTION OF ALKYL HALIDES BY $LiAlH_4$. EVIDENCE THAT AlH_3 PRODUCED IN SITU IS THE ONE ELECTRON TRANSFER AGENT.

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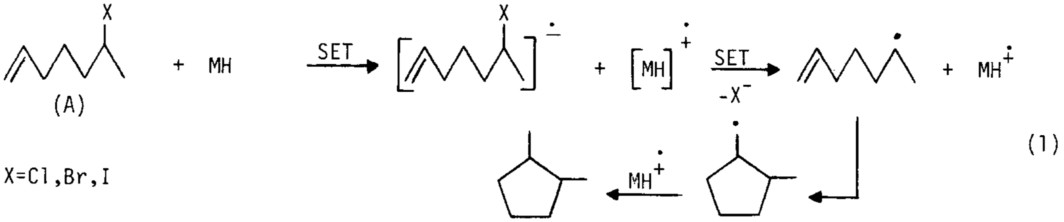
Abstract: The reduction of 1^0 and 2^0 alkyl iodides by $LiAlH_4$ has been shown to involve a radical intermediate formed by the reaction of the alkyl iodide with the AlH_3 and LiI produced in situ in conjunction with $LiAlH_4$ rather than by $LiAlH_4$ alone, as evidenced by cyclized products in the reduction of 6-iodo-1-heptene, by the trapping of the radical and by stereochemical studies of the 2-halooctanes.

Main group metal hydrides have been considered to react as nucleophilic reagents toward substrates such as organic halides.[1-3] Recently Brown and co-workers presented rate-structure profile studies for a series of reactions of alkyl halides with metal hydrides and proposed a S_N2 mechanism to describe the mechanistic pathway.[4] More recently we, and others, have presented evidence for a radical intermediate in the reduction of aryl, vinyl and alkyl halides by $LiAlH_4$.[5]

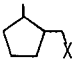
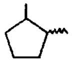
Our method of choice to establish the radical nature of the intermediate formed on reaction of $LiAlH_4$ with primary alkyl halides has involved the use of cyclizable probes.[5] In the present study, the reduction of secondary alkyl halides (6-halo-1-heptenes) A, was examined with the objective of detecting radical intermediates in a secondary halide system (eq. 1). Additionally, the method of Kuivila[6] (use of DCPH) was used to trap the intermediate radical and sterochemical studies were carried out with optically active halides in order to determine if the reaction proceeds with the intermediate formation of radicals.



(1)

The results of the reactions of metal hydrides with the 6-halo-1-heptene are given in Table I. Note that the order or reactivity as a function of leaving group is I>Br>Cl. More importantly, the major product of reduction when X=I is 1,2 dimethylcyclopentane (mixture of cis and trans); however, only small amounts (5% or less) of cyclic product are formed when X=Br and none is formed when X=Cl.

TABLE I. Reduction of 6-Halo-1-heptenes by Metal Hydrides in THF.

Exp.	X in	Hydride	Time (hrs)	PER CENT YIELD			
							
1	Cl	LiAlH$_4$ [a]	48	98	0.0	2.5	0.0
2	Br	LiAlH$_4$	96	2.0	0.0	91	2.2
3	Br	LiAlD$_4$, DCPH [b]	48	0.0	0.0	91(100%d$_1$)	2.8
4	Br	AlH$_3$	96	31	0.0	65	5.2
5	I	LiAH$_4$	4.0	0.0	0.0	42	53
6	I	LiAlD$_4$	4.0	0.0	0.0	42(96%d$_1$)	53(92%d$_1$)
7	I	LiAlD$_4$, DCPH [b]	4.0	0.0	0.0	56(11%d$_1$)	44
8	I	LiAlH$_4$	0.17	78	0.0	18	0.0
9	I	LiAlH$_4$	0.50	56	0.0	42	0.0
10	I	LiAlH$_4$	1.0	34	0.0	59	4.0
11	I	LiAlH$_4$	4.0	0.0	0.0	66	35
12	I	AlH$_3$	0.5	77	15	5	0
13	I	AlH$_3$	1.0	60	32	5	1
14	I	AlH$_3$	4.0	4	83	5	8
15	I	LiAlH$_4$ + AlH$_3$ + LiI	0.5	19	40	32	4

[a] Reactions were conducted at room temperature in the dark using 0.1M concentration of reagents. Hydride reagents were analyzed as described previously.[4] Deuterium incorp. was determined by g.c. - m.s. Yields were determined by g.l.c. analyses using internal standards. [b] A ten-fold molar excess of DCPH was added to the alkyl halide prior to the addition of the hydride.

Since Kuivila[6] has shown that dicyclohexylphospine (DCPH) is an effective agent for trapping alkyl radicals via hydrogen atom transfer, several reductions of 6-iodo-1-heptene by LiAlD$_4$ in the presence of DCPH were conducted. Appropriate control experiments demonstrated that DCPH in THF was unreactive to either LiAlD$_4$ or 6-iodo-1-heptene. From the data given (exps. 6-7 of Table I), it is clear that DCPH is indeed efficiently trapping intermediate radicals, as evidenced by the decrease in deuterium incorporation in both the straight chain and cyclized hydrocarbon products and the increased amount of straight chain hydrocarbon formed when DCPH is present in the reaction mixture. Thus, it is clear that an intermediate radical is produced in the reduction of A (X=I) by LiAlH$_4$ and that even the 1-heptene product, to a large extent, is formed by an electron transfer pathway since added DCPH caused a reduction in deuterium incorporation from 96%-d$_1$ to 11%-d$_1$ (exps. 6-7). On the other hand, reduction of 6-bromo-1-heptene by LiAlH$_4$ gave a 2.2% yield of cyclic hydrocarbon (exp. 2) indicating a small amount of radical involvement when X=Br. Furthermore, reaction of the bromide with LiAlD$_4$ and DCPH (exp. 3) produced 1-heptene with 100%-d$_1$ content, indicating that, unlike the iodide, none of the straight chain hydrocarbon is produced via a radical process.

A detailed reaction profile for the reduction of A(X=I) by LiAlH$_4$ (exps. 8-11) produced a most interesting result. It is clear that during the reduction of A(X=I) by LiAlH$_4$, the cyclic hydrocarbon is formed only during the latter half of the reaction. Thus, the data suggests that AlH$_3$ and/or LiI, produced in situ, is responsible for the observed electron transfer characteristics of the reduction of A(X=I). When AlH$_3$ alone was allowed to react with A(X=I), a substantial amount of the cyclized iodo compound (exps. 12-14) was formed and, furthermore, reduction of A(X=I) by LiAlH$_4$ to which was previously added AlH$_3$ and/or LiI produced immediate and rapid formation of the cyclized iodo compound (compare exps. 9 and 15).

These results further substantiate that it is not $LiAlH_4$ that is the one electron donor, but rather AlH_3, or $LiAlH_4$ in some way coordinated with AlH_3 and/or LiI.

The reduction of the optically active 2-halooctanes by $LiAlD_4$ was examined and the results are given in Table II. Since the configuration and maximum rotation of optically pure 2-deuterooctane are not available, one can only compare the corrected rotations of the 2-deuterooctane as a function of the leaving group. From exps. 1-3 of Table II, it is seen that the value of the corrected specific rotation for the deuterooctane varies from -0.85° for the (-)-tosylate to -0.89° for the (+) chloride to +0.95° for the (+) bromide; however, these values are essentially within experimental error. Thus, it has been shown that for X=OTs, Cl, and Br, the reduction of the 2-halooctanes by $LiAlD_4$ proceeds with the same degree of sterospecificity. However, the corrected specific rotation for the product of the (+)-iodide reduction is +0.14° and, hence, the reduction of (+)-2-iodooctane proceeds with substantially less stereospecificity than the reduction of the other 2-halooctanes. These studies indicate that the reduction of secondary iodides by $LiAlD_4$ proceeds predominantly by a process which involves radical intermediates that proceed to product with substantial loss of stereochemical integrity.

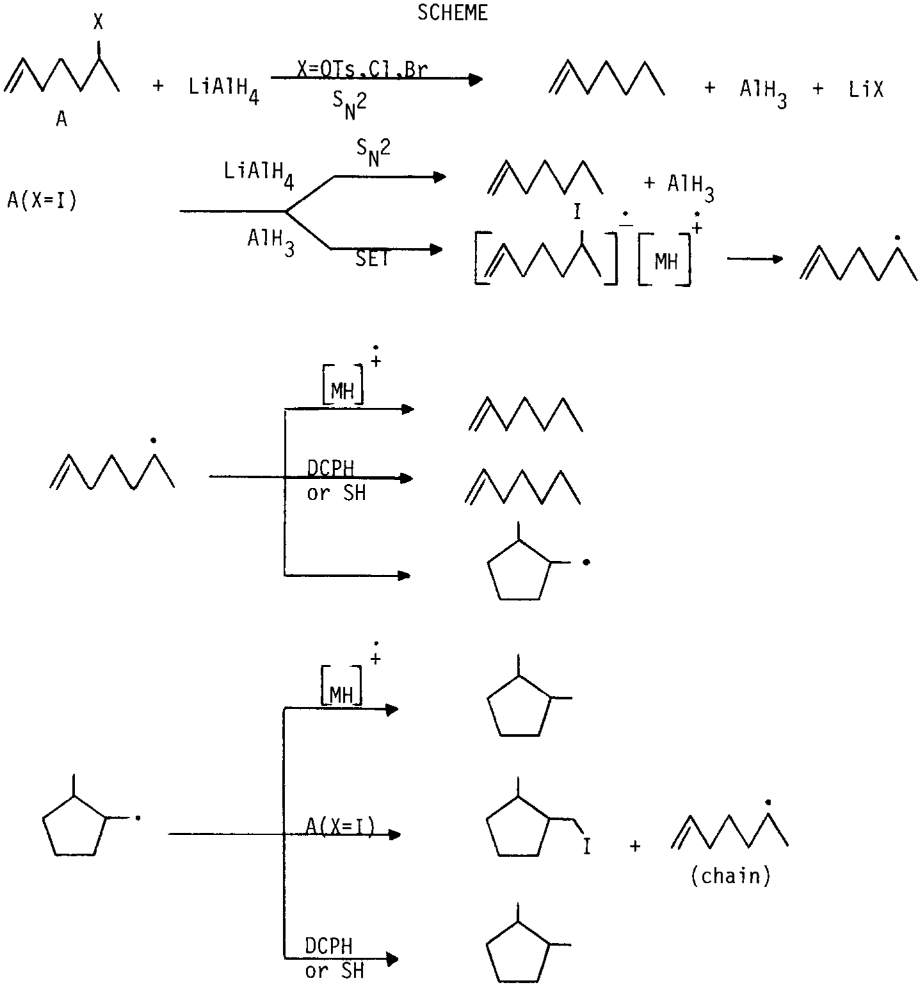
TABLE II. Reduction of 2-Halooctanes by $LiAlD_4$ in THF.

Experiment	Substrate [a] (% Opt Purity)	Temp (°C)	Time (hrs)	Yield [b] (%)	2-Deuterooctane [c] obs. $[\alpha]_D^{25}$	corr. $[\alpha]_D^{25}$
1	(-)-OTs, (77.1)	25	240	73	-0.66°	-0.85°
2	(+)-Cl, (97.4)	50	720	52	+0.78°	+0.89°
3	(+)-Br, (73.1)	25	48	85	+0.78°	+0.93°
4	(+)-I, (14.0)	25	24	98	+0.020°	+0.14°

[a] The 2-halooctanes were prepared by a known procedure.[7] [b] Yields were determined by g.l.c. In each case the isolated 2-deuterooctane exhibited complete deuterium incorporation, as determined by mass spec. [c] In exps. 1-3 rotations were determined using cyclopentane solutions, but in exp. 4 a neat sample was used. Limits of precision are ± 5%. Under identical conditions, (+)-Cl and (+)-Br were racemized by 0.5 equivs. of LiCl and LiBr, respectively, to the extents of 1.5% and 1.8%. After exposure of (+)-I to $LiAlD_4$ for 30 mins. (48% reduction) unreacted (+)-I was 37% racemized; however, (+)-I was 10% racemized by 0.5 equivs. of LiI in THF after four hrs. (92% reduction over the same time period).

In conclusion, it is clear that the reduction of secondary iodides by reagents such as $LiAlH_4$ or AlH_3 proceeds by a mechanism involving radicals, as shown in the Scheme. However, the data presented herein indicate that in the reduction of secondary alkyl iodides by $LiAlH_4$, the AlH_3 and LiI produced in situ, in conjunction with $LiAlH_4$, is the actual electron transfer agent. Also, the formation of cyclized iodo compound in the reduction of A(X=I) by AlH_3 is evidence of a radical chain process. On the other hand, the reduction of secondary chlorides, bromides and tosylates by $LiAlH_4$ may be described as predominantly an S_N2 process.

SCHEME



MH = $LiAlH_4$ or AlH_3

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