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Selective Reductions. 31. Lithium Triethylborohydride as an Exceptionally Powerful Nucleophile. A New and Remarkably Rapid Methodology for the Hydrogenolysis of Alkyl Halides under Mild Conditions

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Lithium triethylborohydride exhibits enormous nucleophilic power in S_N2 displacement reactions with alkyl halides, far more powerful than the other common nucleophiles, such as *n*-butyl mercaptide (14 times), thiophenoxide (20 times), borohydride (10^4 times), and nitrate (10^7 times). The reaction follows second-order kinetics and exhibits typical characteristics of a nucleophilic substitution of the S_N2 type. In addition to being the best nucleophile, it is the most powerful nucleophilic reducing agent available for the reduction of alkyl halides, far more powerful and cleaner than lithium aluminum hydride and lithium borohydride. Even hindered alkyl halides, such as cyclohexyl bromide, neopentyl bromide, and *exo*-norbornyl bromide, undergo facile reduction to the corresponding alkanes in >96% yield with this reagent. Consequently, the new reagent provides a highly useful and simple means as a probe for studying S_N2 displacement reactions and also for the facile dehalogenation of hindered alkyl halides where this is required in synthetic transformations. The corresponding deuterated derivative, lithium triethylborodeuteride, conveniently synthesized from lithium deuteride and triethylborane, is useful for the stereospecific introduction of deuterium in the molecule.

Hydrogenolysis of carbon–halogen bonds is an important and frequently encountered synthetic transformation in organic synthesis.[2] A number of catalytic hydrogenation procedures have been developed toward this goal. A majority of these procedures are applicable for aryl–halogen bonds rather than alkyl–halogen bonds. A number of hydride reagents have evolved for the reduction of organic halides.[3] Recently we have examined the applicability of a number of complex metal hydrides and metal hydrides for the hydrogenolysis of alkyl halides.[4] This evaluation study led to the identification of two promising hydride reducing agents for the rapid hydrogenolysis of alkyl–halogen bonds. Recently we explored in detail one of the promising reagents, lithium aluminum hydride, for this transformation.[5]

However, the study clearly indicated lithium triethylborohydride to be the most effective reagent for the rapid reduction of alkyl halides. This study[5] also revealed that for such reductions, lithium triethylborohydride ($LiEt_3BH$) is far more effective and powerful than the conventional reagent, lithium aluminum hydride ($LiAlH_4$). Recently, lithium triethylborohydride has emerged as an exceedingly powerful, yet highly selective nucleophilic reducing agent for the reduction of organic functional groups.[6] Further, preliminary exploration of lithium triethylborohydride has clearly indicated it to be the most powerful, simple nucleophile available to the organic chemist for substitution reactions.[7]

Accordingly, it was desirable to explore in detail the reaction of lithium triethylborohydride with organic halides of different structural features, its effectiveness as a nucleophile, and the applicability of the reagent for the hydrodehalogenation. The results of these investigations are reported in this paper.

Results and Discussion

Preparation of Lithium Triethylborohydride and Lithium Triethylborodeuteride Solutions. Solutions of lithium triethylborohydride in tetrahydrofuran (THF) were conveniently prepared by stirring at 25 °C under nitrogen triethylborane (Et_3B) with finely divided lithium hydride (in moderate excess) for approximately 24 h. Filtration removed the excess lithium hydride and gave crystal clear solutions, stable under nitrogen for long periods of time. The THF solution of lithium triethylborohydride is characterized by a strong broad absorption in the infrared at 4.83 μm.[8]

A solution of lithium triethylborodeuteride ($LiEt_3BD$) in THF was prepared by stirring triethylborane and lithium deuteride for 1 h at 65 °C. The usual filtration resulted in a crystal clear solution of lithium triethylborodeuteride in quantitative yield.

In all of the reactions, clear solutions of these reagents in THF were employed.

Stoichiometry of the Reaction. Choice of the Reaction Condition. For studies of the major characteristics of the reaction, the possibility of utilizing solutions 0.25 M in the reagent and the substrate was explored. The solutions were maintained at 25 °C and the rate of reaction was monitored by GLC at appropriate intervals of time for residual halide and hydrocarbon. Thus, the reaction of *n*-octyl chloride proceeds quite rapidly at 25 °C in the initial phases of the reaction up to 50%. However, after 50% of reaction, the rate of reaction decreases rapidly.[4,9]

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Table I. Reaction of Representative Alkyl Halides with Lithium Triethylborohydride, Lithium Aluminum Hydride, and Lithium Borohydride in Tetrahydrofuran at 25 °C[a]

compound	reagent	time, h	reaction products	yield,[b] %
n-octyl chloride	$LiEt_3BH$	3	*n*-octane	100
	$LiAlH_4$	24	*n*-octane	92
	$LiBH_4$	24	*n*-octane	1.5
			n-octyl chloride	97
cyclohexyl bromide	$LiEt_3BH$	24	cyclohexane	64
			cyclohexyl bromide	34
	$LiAlH_4$	24	cyclohexane	8
	$LiBH_4$	24	cyclohexane	0
			cyclohexyl bromide	100

[a] In all cases the solutions were 0.25 M in compound and 0.5 M in complex metal hydride. [b] All yields reported were determined by GLC using a suitable internal standard and authentic synthetic mixtures.

Further reduction is relatively slow. It is clearly evident from this result that in the slow stage of the reaction lithium triethylborohydride (eq 1–3) is deactivated by the reaction product, Et_3B.

$$n\text{-}C_8H_{17}Cl + LiEt_3BH \xrightarrow{k_2} n\text{-}C_8H_{18} + Et_3B + LiCl \quad (1)$$

$$LiEt_3BH + Et_3B \xrightarrow{k_2'} Li^+[Et_3B\text{--}H\text{--}BEt_3]^- \quad (2)$$

$$n\text{-}C_8H_{17}Cl + 2LiEt_3BH \rightarrow n\text{-}C_8H_{18} + Li(Et_3B)_2H + LiCl \quad (3)$$

Further reduction of *n*-octyl chloride by the species lithium hexaethyldiborohydride, $Li(Et_3B)_2H$, is very slow. Indeed, a 1:1 molar mixture of $LiEt_3BH$ and Et_3B has been found to reduce *n*-octyl chloride sluggishly (eq 4). Further,

$$Li[Et_3B\text{--}H\text{--}BEt_3] + n\text{-}C_8H_{17}Cl \xrightarrow{k_2''} n\text{-}C_8H_{18} + 2Et_3B + LiCl \quad (4)$$

^{11}B NMR study has clearly revealed the formation of a relatively stable 2:1 addition compound between lithium hydride and triethylborane in THF.[9,10] The results are summarized in Figure 1.

Consequently, in order to avoid these complications, it was decided to increase the concentration of lithium triethylborohydride to 0.5 M. Thus, solutions 0.5 M in lithium triethylborohydride and 0.25 M in substrate in THF were utilized at 25 °C for the rate studies.

Procedure for Rate Studies and Product Analysis. The procedure adopted was to add 5 mmol of the alkyl halide to 10 mmol of lithium triethylborohydride and 5 mmol of a suitable internal standard in sufficient THF to give 20 mL of solution. This makes the reaction mixture 0.5 M in reagent and 0.25 M in the compound under examination. The solution was maintained at 25 °C and examined periodically by GLC for the formation of hydrocarbon and the residual halide. A similar procedure was employed for reductions involving lithium aluminum hydride and lithium borohydride ($LiBH_4$).

In most cases, the same reaction mixture was utilized for product analysis. In a few cases, separate runs on a 5-mmol scale were conducted.

Comparison of Lithium Triethylborohydride with Other Complex Metal Hydrides. Before any detailed study, it was desirable to compare the reactivity of lithium triethylborohydride in displacement reactions with the conventional reagents, lithium aluminum hydride and lithium borohydride, under standard conditions (0.5 M in reagent, 0.25 M in RX, 25 °C, THF). Accordingly, the reductions of *n*-octyl chloride and cyclohexyl bromide were examined with the three reagents lithium triethylborohydride, lithium aluminum hydride, and lithium borohydride. The results clearly reveal the superiority of lithium triethylborohydride over the other two conventional reagents with respect to the rate of reaction as well as the cleanliness of the products. The great speed of these reactions, far greater than those involving lithium aluminum hydride and lithium borohydride, is indicated by the results for the reduction of *n*-octyl chloride summarized graphically in Figure 2. Similarly, the reduction of cyclohexyl bromide proceeds quite well at 25 °C. The results are summarized in Table I.

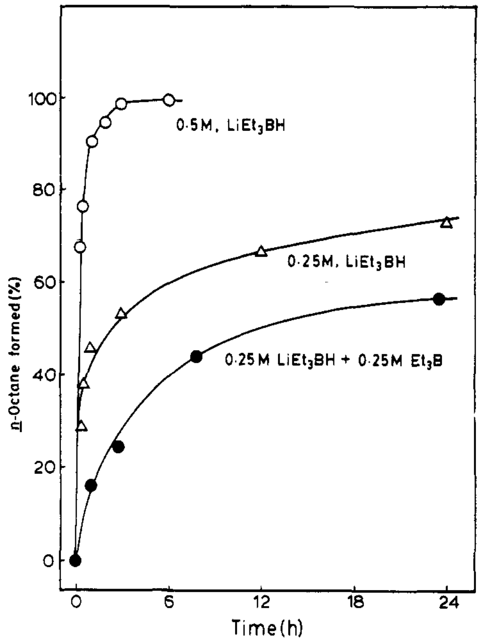

Figure 1. Rates of reduction of *n*-octyl chloride (0.25 M) with lithium triethylborohydride in tetrahydrofuran at 25 °C.

Comparison of Lithium Triethylborohydride to Other Nucleophiles. The superior reactivity of lithium triethylborohydride toward *n*-octyl chloride persuaded us to undertake a quantitative comparison of the rates of lithium triethylborohydride and sodium thiophenoxide in S_N2 substitution reactions. Accordingly, the rates of reaction of *n*-octyl chloride with these two reagents were compared in THF solvent under identical conditions. For the triethylborohydride reaction, second-order rate constant was calculated from the rate equation, $k_2 = 2.303/at \log [(a - x)/(a - 2x)]$, where a = initial concentration of RX and reagent and x = concentration of product at t (min). This was derived based on stoichiometric eq 1–4. The results clearly reveal that the reaction involving lithium triethylborohydride is far faster (Table II). By employing the rate expression derived for lithium triethylborohydride, the second-order rate constant for the

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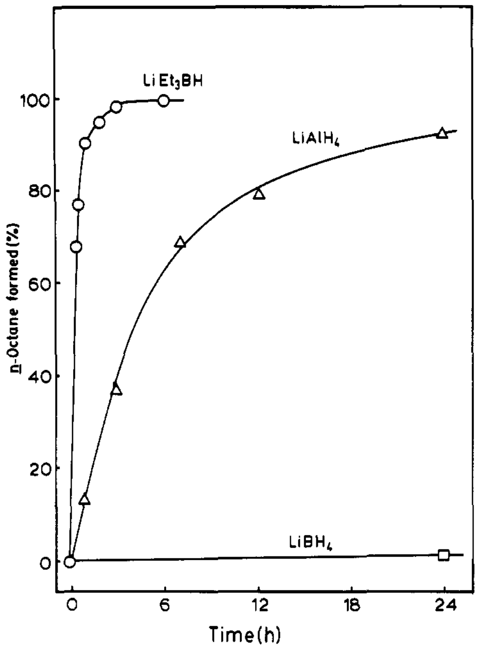


Figure 2. Rates of reduction of *n*-octyl chloride (0.25 M) with representative complex metal hydrides (0.5 M) in tetrahydrofuran at 25 °C.

Table II. Second-Order Rate Constants for the Reaction of *n*-Octyl Chloride with Lithium Triethylborohydride and Sodium Thiophenoxide in Tetrahydrofuran at 25.00 ± 0.01 °C[a]

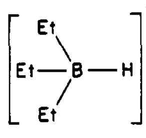
reagent	nucleophile	k_2, L mol^{-1} min^{-1}
lithium triethylborohydride	Et_3BH^-	2.02×10^{-1}
sodium thiophenoxide	$C_6H_5S^-$	1.05×10^{-2}

[a] All reactions were carried out in a thermostated bath under dry nitrogen and the kinetics were followed by measuring the disappearance of *n*-octyl chloride or the appearance of *n*-octane with time by GLC using an internal standard. Reactions were conducted in duplicate and gave excellent second-order plots

reaction of *n*-octyl chloride with lithium aluminum hydride is calculated to be 5×10^{-3} L mol^{-1} min^{-1} and that for lithium borohydride 2.11×10^{-5} L mol^{-1} min^{-1}.

From these results, we calculate the nucleophilic reactivity of other nucleophiles, using Streitwieser's nucleophilicity data:[11] Et_3BH^-, 9 400 000; $n\text{-}C_4H_9S^-$, 680 000; $C_6H_5S^-$, 470 000; AlH_4^-, 230 000; I^-, 3700; $C_2H_5O^-$, 1000; BH_4^-, 940; Br^-, 500; $C_6H_5O^-$, 400; NO_3^-, 1.00. These results reveal that triethylborohydride is the most powerful, simple nucleophile available for S_N2 displacement reactions.

Thus, replacement of three of the four hydrogen atoms in $LiBH_4$ by ethyl groups enhances the nucleophilicity by a factor of 10 000! The enormously enhanced nucleophilic power of $LiEt_3BH$ presumably arises from the greater ease of transferring hydride ion from the weaker Lewis acid, triethylborane (1), than from the stronger Lewis acid, borane (2).



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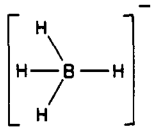

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Lithium Triethylborohydride as a Convenient Probe in the Displacement Reactions of Alkyl Halides. Encouraged by these results, we examined representative alkyl halides (0.25 M) with lithium triethylborohydride (0.5 M) in THF at 25 °C in order to establish its effectiveness as a probe in nucleophilic substitution reactions. Approximate rate constants are computed from the second-order kinetic expression, $k_2 = x/[(2a(a - x)t]$ derived for this reaction where a = initial concentration of RX, x = concentration of RH at time t. A series of reductions were carried on *n*-octyl derivatives. The results clearly reveal that the rate of the reaction markedly decreases from the iodide to the bromide to the tosylate to the chloride, revealing that the reactivity varies in the order I > Br > OTs > Cl. Increasing alkyl substitution at the reacting carbon results in a substantial decrease in the rate of reduction. Accordingly, the rate of reduction decreases markedly from *n*-octyl bromide to *sec*-octyl bromide to the 2-bromo-2-methylpentane (tertiary), revealing the order primary > secondary > tertiary, observed in common S_N2 substitution reactions. The reaction of the tertiary bromide, 2-bromo-2-methylpentane, is very slow and it reacts mostly by elimination, possibly with lithium triethylborohydride functioning as the base.

Introduction of methyl substituents on the β-carbon decreases markedly the rate of reduction. Thus, the rate of reduction drastically drops from the *n*-octyl bromide to 1-bromo-2-methylpentane to neopentyl bromide: primary > isopentyl > neopentyl. Benzyl bromide and allyl bromide are reduced very rapidly, almost instantaneously.

A series of representative cycloalkyl bromides were examined toward lithium triethylborohydride under standard conditions. The influence of the ring size on the reactivity varies in the order cyclopentyl bromide > 2-bromooctane > cycloheptyl bromide > cyclooctyl bromide > cyclohexyl bromide, which is also the order observed for S_N2 halide substitution of cycloalkyl halides.[12,13]

Under standard conditions, the reduction of *exo*-norbornyl bromide was very slow, even slower than the rate of reduction of neopentyl bromide.[15]

Unlike lithium aluminum hydride,[14] lithium triethylborohydride shows very little reactivity toward aromatic halogen. Thus, under standard conditions, 1-bromonaphthalene is completely inert to this reagent.

Temperature has a marked influence of the rate of reduction. The rate of reduction of neopentyl bromide with lithium triethylborohydride was examined at 25 °C and 65 °C in refluxing THF. The results indicate that 95% of the reduction is over in 3 h at 65 °C, whereas at 25 °C, only 86% of the reduction is over in 24 h. The results are summarized in Table III.

Synthetic Applicability. The great speed of these reactions, far greater than those involving lithium aluminum hydride and lithium borohydride, indicate that this reagent should provide a new, rapid, facile means for the nucleophilic reduction of alkyl halides where this is required in synthetic operations. In order to establish the synthetic utility, product studies for the reduction of representative alkyl halides were carried out. In most cases, even the standard conditions (0.5 M in $LiEt_3BH$ and 0.25 M in substrate at 25 °C in THF) were sufficient to

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[11] For a detailed review and discussions on the subject of nucleophilic reactivity, see (a) Bunnett, J. F. *Annu. Rev. Phys. Chem.* **1963**, *14*, 271. (b) Streitwieser, A., Jr. "Solvolytic Displacement Reactions"; McGraw-Hill: New York. (c) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16. (d) Pearson, R. G.; Sobel, H.; Songstad, J. *Ibid.* **1972**, *94*, 1750.

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Table III. Rates of Reactions of Lithium Triethylborohydride with Representative Alkyl Halides in Tetrahydrofuran at 25 °C[a]

	reduction,[b] %										
compound	1 min	2 min	5 min	15 min	30 min	1 h	3 h	6 h	12 h	24 h	k_2, L mol^{-1} min^{-1}
benzyl bromide	100										very fast (>200)
allyl bromide[c]				95	96	96					very fast (>200)
n-octyl iodide		100									very fast (>200)
n-octyl bromide		100									198.00
n-octyl tosylate			96	97							9.60
n-octyl chloride				68	77	91	100				2.23×10^{-1}
1-bromo-2-methylpentane		90	98	98							9.00
neopentyl bromide							36	60	69	86	6.25×10^{-3}
2-bromooctane				58	71	82	98				1.84×10^{-1}
2-bromo-2-methylpentane										2	*d*
cyclohexyl iodide							85		92		6.3×10^{-2}
cyclohexyl bromide							15	30	41	63	2.4×10^{-3}
cyclohexyl chloride										1	$<1.4 \times 10^{-5}$
cyclopentyl bromide				87	95	99					8.9×10^{-1}
cycloheptyl bromide					65	75	99				1.2×10^{-1}
cyclooctyl bromide					18	35	64	69	89	95	3.6×10^{-2}
exo-norbornyl bromide									4	12	1.2×10^{-4}
1-bromonaphthalene										1	1.4×10^{-5}

[a] In all cases solutions were 0.25 M in compound and 0.5 M in $LiEt_3BH$. [b] Rates of reduction were monitored by GLC for the production of hydrocarbon and the disappearance of the alkyl halide using a suitable internal standard and authentic synthetic mixtures. [c] Rate of reduction was followed by the analysis for residual "hydride." [d] Accompanied by elimination $k_{\text{elim.}} >> k_{\text{subst.}}$.

Table IV. Products of the Reaction of Lithium Triethylborohydride with Representative Alkyl Halides in Tetrahydrofuran[a]

		time		reaction products,[b,c] %		
compound	temp, °C	h	min	RX	RH	other
benzyl bromide	25		1		100	
n-octyl iodide	25		2		100	
n-octyl bromide	25		2		100	
n-octyl tosylate	25		10	(4)[d]	96	ROH
n-octyl chloride	25	1		9	91	
	25	3			100	
1-bromo-2-methylpentane	25		5		98	
neopentyl bromide	25	24		14	86	
	65	3		5	96	
2-bromooctane	25	3			98	
2-bromo-2-methylpentane	25	24		8	<2	84, olefins[e]
cyclohexyl iodide	25	12			92	2, olefin
cyclohexyl bromide	25	24		34	64	
	65	6		4	88	2, olefin
cyclohexyl chloride	25	24		99	1	
	65	48		58	34	
cyclopentyl bromide	25	1			99	
cycloheptyl bromide	25	3			99	
cyclooctyl bromide	25	24			95	
exo-norbornyl bromide	25	24		84	12	
	65	12		40	59	
	65	72		4	96	
1-bromonaphthalene	25	24		99	<1	
	65	24		88	10	

[a] In all cases solutions were 0.25 M in compound and 0.5 M in $LiEt_3BH$. [b] All yields reported were determined by GLC using a suitable internal standard and authentic synthetic mixtures. [c] Except where indicated, no olefins were detected. [d] Not analyzed for. [e] Mixture of 17% 2-methyl-1-pentene and 67% of 2-methyl-2-pentene.

bring about rapid hydrogenolysis. In few cases, the temperature of the reaction mixture was raised to 65 °C (refluxing THF) to decrease the reaction time. The results are summarized in Table IV.

Benzyl bromide is converted to toluene in 100% yield in 1 min under standard conditions! *n*-Octyl iodide and bromide are reduced to *n*-octane in 100% yield in 2 min (eq 5 and 6).

$$C_6H_5CH_2Br \xrightarrow[25\,°C,\ <1\ \text{min}]{LiEt_3BH,\ THF} \underset{100\%}{C_6H_5CH_3} \qquad (5)$$

$$n\text{-}CH_3(CH_2)_6CH_2Br \xrightarrow[25\ °C,\ <2\ \text{min}]{LiEt_3BH,\ THF} \underset{100\%}{n\text{-}C_8H_{18}} \qquad (6)$$

n-Octyl tosylate is reduced in 10 min to 96% *n*-octane, with both 1-octene and 1-octanol being completely absent. *n*-Octyl chloride is reduced to 91% *n*-octane in 1 h with this reagent, whereas under identical conditions, lithium aluminum hydride requires 24 h.

Similarly, 1-bromo-2-methylpentane and 2-bromooctane are cleanly reduced to their corresponding hydrocarbons in quantitative yield (eq 7). The tertiary halide 2-bromo-2-methylpentane predominantly yields olefinic products (eq 8).

$$CH_3(CH_2)_5CHBrCH_3 \xrightarrow[25\ °C,\ 3\ h]{LiEt_3BH,\ THF} \underset{98\%}{n\text{-}C_8H_{18}} \qquad (7)$$

$$CH_3CH_2CH_2CBr(CH_3)_2 \xrightarrow[25\ ^\circ C,\ 24\ h]{LiEt_3BH,\ THF} \underset{<2\%}{CH_3CH_2CH_2CH(CH_3)_2} + \underset{67\%}{CH_3CH_2CH{=}C(CH_3)_2} + \underset{17\%}{CH_3CH_2CH_2(CH_3)C{=}CH_2} \tag{8}$$

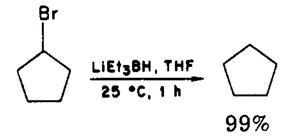
One of the most important applications of this reagent is the facile S_N2 substitution at neopentyl carbon without rearrangement. Very few bimolecular substitution reactions proceed at a measurable rate with neopentyl derivatives.[16]

Thus, under standard conditions, neopentyl bromide is reduced to the extent of 86% in 24 h. Under reflux conditions, the reduction is essentially complete in 3 h. the product, neopentane, is realized in 96% yield, free completely of isomeric alkanes (eq 9).

$$(CH_3)_3CCH_2Br \xrightarrow[65\ ^\circ C,\ 3\ h]{LiEt_3BH,\ THF} \underset{96\%}{C(CH_3)_4} \tag{9}$$

The clean reduction of neopentyl halides to their corresponding hydrocarbons without any alkyl migration should provide an excellent method for the reduction of such structures. There have been many instances recorded in the literature where reduction with lithium aluminum hydride gives very poor yields of the desired hydrocarbon. One such typical reduction reported is the reduction of 1-(hydroxymethyl)adamantane tosylate to 1-methyladamantane in 25% yield by lithium aluminum hydride.[17] Lithium triethylborohydride has proved highly useful for such reductions.[18]

Cycloalkyl bromides undergo facile and clean reduction to their corresponding cycloalkanes in essentially quantitative yield. Thus, under standard conditions, cyclopentyl, cycloheptyl, and cyclooctyl bromides are converted to their corresponding cycloalkanes in excellent yields (eq 10 and 11).



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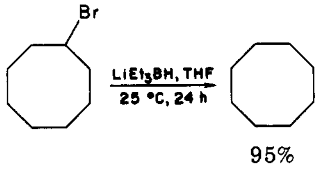

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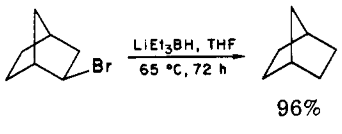
The reduction of cyclohexyl iodide and bromide proceeds quite well, even at room temperature.

exo-Norbornyl bromide undergoes clean reduction to norbornane in refluxing THF (eq 12).



(12)

Aromatic halides are far more stable to this reagent than they are to lithium aluminum hydride.[14] The reverse is true for aliphatic halides. Thus, it becomes easier to achieve the selective reduction of aliphatic halogen without simultaneous hydrogenolysis of aromatic halogen.

Table V. Reduction of Alkyl Halides by Lithium Hydride in the Presence of Catalytic Quantities of Triethylborane in Refluxing Tetrahydrofuran[a]

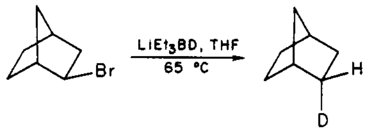
compound	time, h	reaction products[b]	yield, %
n-octyl bromide	0.25	*n*-octane	99
n-octyl chloride	3.5	*n*-octane	96
2-bromooctane	0.5	*n*-octane	99
cyclohexyl bromide	5.0	cyclohexane	95
		cyclohexene	4
cycloheptyl bromide	0.5	cycloheptane	99
cyclooctyl bromide	1.0	cyclooctane	98

[a] In all cases solutions were 1.5 M in LiH, 1.0 M in RX, and 0.2 M in Et_3B. [b] Reactions were followed by GLC utilizing a suitable internal standard. Unless otherwise indicated, no other side products were detected on gas chromatography.

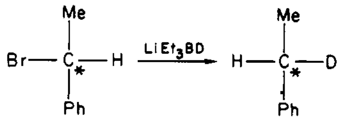
Finally, lithium triethylborodeuteride is highly useful for the specific introduction of deuterium in the molecule where this is required in synthetic operations. Thus, 2-bromooctane is reduced with $LiEt_3BD$ under standard conditions to 92% octane-2-*d* in 4 h. Deuterium incorporation was found to be 96% by mass spectral analysis (eq 13). Further, $LiEt_3BD$ provides a simple means of

$$CH_3(CH_2)_5CHBrCH_3 + 2\ LiEt_3BD \xrightarrow{THF} \underset{92\%\ (96\%\ D\ incorporation)}{CH_3(CH_2)_5CHDCH_3} \tag{13}$$

introducing deuterium into systems with stereochemical inversion at the substitution center (eq 14 and 15).[15b,19,20]



(14)



(15)

Reduction of Alkyl Halides by Lithium Hydride in the Presence of Catalytic Quantities of Triethylborane. In the reduction of alkyl halides and related derivatives by lithium triethylborohydride, triethylborane is regenerated as one of the products of the reaction (eq 16). Consequently, it should be possible to achieve hydrogenolysis of alkyl halides with lithium hydride in the presence of catalytic quantities of triethylborane, the reaction proceeding through the intermediate formation of lithium triethylborohydride (eq 17–19). After certain preliminary experiments, the following reaction conditions were selected: 1.5 M in lithium hydride, 1.0 M in substrate,

$$LiEt_3BH + RX \rightarrow RH + Et_3B + LiX \tag{16}$$

$$LiH + \underset{(catalytic)}{Et_3B} \rightarrow LiEt_3BH \tag{17}$$

$$LiEt_3BH + RX \rightarrow RH + Et_3B + LiX \tag{18}$$

$$Et_3B + LiH \rightarrow LiEt_3BH \xrightarrow{RX} \rightarrow \text{etc. to completion} \tag{19}$$

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(16) Marshall, J. A.; Ruden, R. A. *J. Org. Chem.* **1971**, *36*, 594.

(17) Stelter, H.; Schwarz, M.; Hirschhorn, A. *Chem. Ber.* **1959**, *92*, 1629.

(18) (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064. (b) Krishnamurthy, S. *J. Organomet. Chem.* **1978**, *156*, 171.

(19) The product was identified as the pure endo-*d* isomer by measuring the decrease in the intensity of the ^1H NMR signal at δ 1.13 (endo protons) using the intensity of the bridgehead tertiary hydrogens (2.28 δ) as the standard. While the relative intensity of exo protons (1.43 δe to the bridgehead protons remained unchanged (2), as in the case of norbornane, the intensity of the signal due to the endo protons at δ 1.13 diminished by an amount corresponding to one proton in the deuterated product.

(20) Hutchins, R. O.; Masilamani, D.; Maryanoff, C. A. "Abstracts of Papers", 168th National Meeting of the American Chemical Society, Atlantic City, NJ, Sept 1974; American Chemical Society: Washington, DC, 1974; ORGN 21.

and 0.2 M in triethylborane (20 mol %) in refluxing THF.

Indeed, a fast reduction of alkyl halides was achieved. The generality of this procedure was tested by utilizing a wide variety of alkyl derivatives. In all cases excellent yields were realized. Consequently, this should serve as a convenient and simple preparative procedure. The results are summarized in Table V.

Conclusions

Reaction of alkyl halides with lithium triethylborohydride and other active nucleophiles such as thiophenoxide has been examined. The results clearly reveal that lithium triethylborohydride is the most powerful simple nucleophile available to the organic chemist. The rate of reaction of alkyl halides with lithium triethylborohydride are far greater than those involving conventional reagents—lithium aluminum hydride and lithium borohydride. The product alkane is clean and formed essentially in quantitative yield. Even highly hindered halides such as neopentyl, cycloalkyl, and bicyclic halides undergo smooth reduction to their corresponding alkanes. The ready availability of lithium triethylborodeuteride offers promise for the stereospecific introduction of deuterium in the molecule via hydrogen displacement.

Experimental Section

Materials. All glassware was thoroughly dried in the oven and cooled under a dry stream of nitrogen just before using. Hypodermic syringes were used to transfer solutions. Tetrahydrofuran was dried and distilled (bp 65 °C) over lithium aluminum hydride and kept under dry nitrogen. Lithium hydride was from Alfa Inorganics. Lithium deuteride (98.2% deuterium) was from the Metal Hydrides Inc. Triethylborane used was from the Callery Chemical Co. Most of the olefins and alkanes used as authentic samples were from Phillips 66 Petroleum Co., >99 mol% pure and free of any isomers. Most of the alkyl halides used as substrates were the same collections utilized in the previous study.[5] They were further purified by fractional distillation or recrystallization when necessary before use. 2-Bromo-2-methylpentane was prepared in 72% yield by stirring a mixture of 2-methyl-1-pentene and 48% hydrobromic acid (10% excess) at room temperature for 6 h; bp 51 °C (52 mm); n^{20}_{D} 1.4447 [lit.[13] bp 47 °C (30 mm); n^{20}_{D} 1.4442]. GLC analysis on 5% Carbowax 20M, 12 ft × 0.125 in. column, and the ^{1}H NMR spectrum in CCl_4 indicated the compound to be >98% pure.

Spectra. ^{1}H NMR spectra were recorded on Varian T-60 and Varian XL-100 spectrometers. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6A mass spectrometer with ionization voltage of 75 eV.

Gas Chromatographic Analysis. All reaction mixtures were analyzed by GLC on a Varian 1200 series temperature-programmed gas chromatograph equipped with a flame ionization detector with controllable injector and detector temperatures.

Preparation of Lithium Triethylborohydride Solution in Tetrahydrofuran and Standardization. A 500-mL flask, oven-dried, equipped with a sidearm fitted with a Teflon stopcock and a silicone rubber stopple, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler was cooled to room temperature under a stream of dry nitrogen. In the flask were placed 4 g (0.5 mol) of finely divided lithium hydride and 215 mL of THF. Then 35 mL (0.25 mol) of triethylborane was introduced and the resulting mixture was vigorously stirred under nitrogen for 24 h at 25 °C. Analysis of an aliquot of the reaction mixture by quenching with a known amount of *n*-octyl iodide and measuring the *n*-octane formed by GLC revealed the presence of 100% lithium triethylborohydride. The resulting solution was filtered under slight positive pressure of nitrogen to remove excess lithium hydride through a 1-in. bed of tightly packed Celite prepared on a sintered-glass disk, previously sealed into a large cylinder for enclosing the solution. The clear filtered solution was stored under dry nitrogen in a 500-mL flask with a sidearm closed with a rubber stopple for removing aliquots. The solution was standardized by removing a known aliquot with a hypodermic syringe, hydrolyzing with a THF–water–glycerin mixture (1:1:1), and measuring the hydrogen evolved. The concentration was found to be 1.0 M in $LiEt_3BH$ (100% yield) which is also the expected concentration based on the stoichiometric equation. The THF solution of lithium triethylborohydride is characterized by a strong, broad absorption in the infrared at 4.83 μm (B–H). Maintained under dry nitrogen, these solutions were stable for long periods of time.

Preparation of Lithium Triethylborodeuteride in Tetrahydrofuran.[21] The apparatus was the same as in the previous experiment. Finely divided lithium deuteride (1.44 g, 160 mmol) was placed in a 200-mL reaction flask. Then 68.6 mL of THF was injected. After the mixture was brought to constant reflux, 11.4 mL (80 mmol) of triethylborane was introduced into the reaction flask and vigorously stirred. Analysis of an aliquot of the reaction mixture after 1 h by quenching with a known amount of *n*-octyl iodide revealed the presence of 100% lithium triethylborohydride. After another additional hour of stirring, the mixture was cooled and filtered, resulting in crystal clear solution of lithium triethylborodeuteride in THF, stable under nitrogen for long periods of time. The concentration was found to be 1.0 M (100% yield) by hydrolysis.

Kinetic Procedure. Reaction of Lithium Triethylborohydride with *n*-Octyl Chloride at 25.00 + 0.01 °C. Reactions were carried out in long-necked flasks to avoid any effect due to temperature gradient and the mixtures were stirred by using air-driven stirrers. The reactants were thermostated for at least 2 h prior to mixing.

Into a 50-mL flask with a long neck and a sidearm, equipped with a magnetic stirring bar and connected to a mercury bubbler, 11 mL of THF was introduced, followed by 5 mL (5 mmol) of a 1.0 M solution of $LiEt_3BH$ in THF and 2 mL (5 mmol) of 2.5 M solution of *n*-nonane (internal standard). The flask was immersed in the thermostat maintained at 25.00 ± 0.01 °C. After 2 h, 2.0 mL (5 mmol) of a 2.5 M solution of *n*-octyl chloride in THF was introduced with vigorous stirring. When half the syringe was empty, a stopwatch was started. At appropriate intervals, 0.5 mL of the reaction mixture was quenched with water, extracted with ether, and analyzed by GLC on a 5% SE-30 column, 6 ft × 0.125 in. Each sample was analyzed at least two times and the reproducibility was ±1.0%. A plot of $\log (a - x)/(a - 2x)$ vs. t in minutes gave a good straight line. A duplicate was conducted under identical conditions.

Procedure for Rate Studies and Product Analysis. All reactions were carried out under a dry nitrogen atmosphere. Reductions of cycloheptyl bromide and 2-bromo-2-methylpentane are representative of the procedures employed.

Reduction of Cycloheptyl Bromide. An oven-dried, 100-mL flask, equipped with a sidearm, silicone rubber stopple, magnetic stirring bar, and reflux condenser connected to a mercury bubbler, was cooled to room temperature under dry nitrogen. The flask was immersed in a water bath at 25 °C. Then 10 mL of a 1.0 M solution in THF of lithium triethylborohydride (10 mmol) was injected into the reaction flask, followed by 5 mL of a 1.0 M solution in THF of *n*-nonane (5 mmol) to serve as the internal standard. Finally, 5 mL of a 1.0 M solution in THF of cycloheptyl bromide (5 mmole was introduced. The reaction mixture was stirred vigorously, and after 30 min, 1 mL of the reaction mixture was withdrawn by a syringe, quenched with water, extracted with ether, and analyzed by GLC on a 5% SE-30, 12 ft × 0.125 in. column. The analysis revealed the presence of 65% cycloheptane. Similarly, the reaction was followed at 1 h, 2 h, and 3 h. At the end of 3 h, analysis revealed the presence of 99% cycloheptane and the complete absence of cycloheptyl bromide and cycloheptene.

Reduction of 2-Bromo-2-methylpentane. The experimental setup was the same as in the previous experiments. A 1.0 M solution in THF of lithium triethylborohydride (10 mL, 10 mmol) was injected into the reaction flask maintained at 25 °C, followed by 5 mL of a 1.0 M solution in THF of *n*-octane (5 mmol) to serve as the internal standard. Finally, 5 mL of a 1.0 M solution in THF of 2-bromo-2-methylpentane was injected. The mixture was

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(21) Lithium triethylborohydride (Super-Hydride) and lithium triethylborodeuteride (Super-Deuteride) are now commercially available as a 1 M solution in THF from the Aldrich Chemical Co., Milwaukee, WI 53201.

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stirred vigorously and monitored by GLC for the disappearance of the alkyl bromide, maintaining the injector temperature at 100 °C. (It was established independently that at 100 °C injection temperature, the tertiary bromide passes through the column without any decomposition.) In 24 h, 93% of the bromide had disappeared.

Another run of this reaction was conducted exactly as above on a 5-mmol scale and allowed to stir for 24 h at 25 °C. Then excess hydride was destroyed, ether was added, and the ethereal layer was subjected to gas chromatographic examination on a 5% SE-30 column, 18 ft × 0.125 in. This revealed a <2% yield of 2-methylpentane, 17% of 2-methyl-1-pentene, 67% of 2-methyl-2-pentene, and 8% of unreacted 2-bromo-2-methylpentane.

Reduction of Cyclooctyl Bromide by Lithium Hydride in the Presence of a Catalytic Quantity of Triethylborane. The apparatus was the same as in the previous experiments. In the flask was placed 0.24 g of finely divided lithium hydride (30 mmol) and 12.4 mL of THF. The mixture was heated under reflux under nitrogen for 30 min. Then 0.56 mL of triethylborane (4 mmol) (as catalyst), 3.9 mL of *n*-decane (20 mmol) (internal standard), and 3.12 mL of cyclooctyl bromide (20 mmol) were introduced. The reaction mixture was stirred vigorously. As the reaction proceeds, the reaction mixture approaches clarity, due to conversion of the suspended lithium hydride to soluble lithium bromide and soluble lithium triethylborohydride. After 0.5 h, 0.5 mL of the reaction mixture was withdrawn by a syringe, quenched with water, extracted with ether, and analyzed by GLC on a 5% SE-30 column, 12 ft × 0.125 in. This revealed the presence of 77% cyclooctane and 23% of unreacted cyclooctyl bromide. After 1 h, GLC analysis revealed the presence of 98% cyclooctane and traces of cyclooctyl bromide. No cyclooctene was detected.

Reduction of 2-Bromooctane with Lithium Triethylborodeuteride. A typical reaction setup was assembled. Into the reaction flask maintained at 25 °C 10 mL of a 1.0 M solution of lithium triethylborodeuteride (10 mmol) was injected into the reaction flask, followed by 5 mL of a 1.0 M solution in THF of *n*-nonane (5 mmol) to serve as the internal standard. The reaction was monitored by GLC on a 5% SE-30 column, 12 ft × 0.125 in.; 92% of the reduction was over in 4 h. This reveals that the rate of reaction is slightly slower than the corresponding reaction involving $LiEt_3BH$. A small quantity of octane-2-*d* was separated from the reaction mixture by preparative GLC on a 10% SE-30 column, 12 ft × 0.5 in., and subjected to mass spectral analysis. Six individual scans were made. The percentage of deuterium incorporation was computed as follows: let M be the intensity of the peak at m/e 114 (due to unlabeled *n*-octane) and $M + 1$ be the intensity of the peak at m/e 115. Correcting for the contributions of the unlabeled species to the peak at m/e 115, the intensity of this peak due to octane-2-*d* alone is given by $(M + 1)_{cor} = (M + 1) - M \times 0.067$. The percentage of deuterium incorporated is given by

$$\frac{(M + 1)_{cor} \times 100}{(M + 1)_{cor} + M}$$

This was found to be 94 ± 1%; after correction for the isotopic purity of the starting lithium deuteride used (98.2%), the actual deuterium incorporation is 96 ± 1%.

Acknowledgment. Financial support of this study by the U.S. Army Research Office through grant DA 31-124-(AROCD)453 is gratefully acknowledged.

Registry No. $LiEt_3BH$, 22560-16-3; $LiAlH_4$, 16853-85-3; $LiBH_4$, 16949-15-8; *n*-octyl chloride, 111-85-3; cyclohexyl bromide, 108-85-0; benzyl bromide, 100-39-0; allyl bromide, 106-95-6; *n*-octyl iodide, 629-27-6; *n*-octyl bromide, 111-83-1; *n*-octyl tosylate, 3386-35-4; 1-bromo-2-methylpentane, 25346-33-2; neopentyl bromide, 630-17-1; 2-bromooctane, 557-35-7; 2-bromo-2-methylpentane, 4283-80-1; cyclohexyl iodide, 626-62-0; cyclohexyl chloride, 542-18-7; cyclopentyl bromide, 137-43-9; cycloheptyl bromide, 2404-35-5; cyclooctyl bromide, 1556-09-8; *exo*-norbornyl bromide, 2534-77-2; 1-bromonaphthalene, 90-11-9; lithium triethylborodeuteride, 74540-86-6; *n*-butyl mercaptide, 20733-16-8; thiophenoxide, 13133-62-5; borohydride, 16971-29-2; nitrate, 14797-55-8.

Selective Reductions. 32. Structural Effects on the Reduction of Epoxides by Lithium Triethylborohydride. A Kinetic Study

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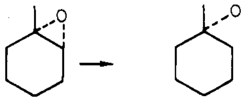
An analytical procedure for the estimation of lithium triethylborohydride utilizing iodimetry has been developed. The rates of reduction of a number of epoxides are studied. The reaction exhibits second-order kinetics, first order with respect to each reactant. Methyl substitution decreases the reactivity of the epoxide by a factor of 8–10. In the case of aliphatic derivatives, the cis epoxide reacts 12 times faster than the trans. On the other hand, *cis*- and *trans*-β-methylstyrene oxides exhibit the opposite trend. A remarkable change in the regioselectivity of reduction of these two epoxides was observed. A possible explanation is presented. The kinetic isotope effect has been established both by rate studies and by determination, by mass spectrometry, of the deuterium incorporation in a competitive reaction between $LiEt_3BH$, $LiEt_3BD$, and the epoxide. A value of $k_H/k_D \approx 1.4–1.5$ is obtained by both methods. A mechanism is proposed to account for these results.

Reduction of epoxides by lithium triethylborohydride (Super-Hydride, Aldrich) is quite facile and highly regiospecific, yielding exclusively the Markovnikov alcohol.[1] Thus, 1,2-epoxybutane gives 2-butanol and 1-methylcyclohexene oxide gives 1-methylcyclohexanol exclusively (eq 1). Even the reduction of styrene oxide produces 97% of 1-phenylethanol. This remarkable regioselectivity prompted us to use this reaction as a model for a projected study of the asymmetric reduction of epoxides using optically active trialkylborohydrides, such as lithium *B*-iso-



(1)

(100% tertiary)

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[1] Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* 1980, *45*, 1.

0022-3263/83/1948-3091$01.50/0 © 1983 American Chemical Society