

수소화붕소리튬에 의한 선택환원. 수소화붕소리튬과 대표적 유기화합물과의 반응

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(1977. 1. 13 접수)

Selective Reduction with Lithium Borohydride. Reaction of Lithium Borohydride with Selected Organic Compounds Containing Representative Functional Groups

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(Received Jan. 13, 1977)

요 약. 수소화붕소리튬-테트라히드로푸란용액의 환원특성에 대한 계통적인 연구가 52가지의 대표적인 작용기를 가진 유기화합물을 가지고 표준조건 (0° , 테트라히드로 푸란)에서 대략의 반응속도 및 정량 관계를 알아봄으로써 이루어 졌다.

ABSTRACT. The approximate rates and stoichiometries of the reaction of lithium borohydride, with fifty two selected organic compounds containing representative functional groups under the standard condition (tetrahydrofuran, 0°), were studied. Among the active hydrogen compounds, primary alcohols and compounds containing an acidic proton liberated hydrogen relatively fast, but secondary and tertiary alcohols very sluggishly. All the carbonyl compounds examined were reduced rapidly within one hour. Especially, among the α, β -unsaturated carbonyl compounds tested, the aldehydes consumed one hydride cleanly, however the cyclic ketones consumed more than one hydride even at -20° . Carboxylic acids were reduced very slowly, showing about 60 % reduction in 6 days at 25° , however acyl chlorides reduced immediately within 30 minutes. On the other hand, the reductions of cyclic anhydrides proceeded moderately to the hydroxy acid stage, however the further reductions were very slow. Aromatic and aliphatic esters, with exception of the relatively moderate reduction of acetate, were reduced very slowly, however lactones were reduced at a moderate rate. Epoxides reacted slowly, but amides and nitriles as well as the nitro compounds were all inert to this reagent. And cyclohexanone oxime and phenyl isocyanate were reduced very sluggishly. Last of all, all sulfur compounds studied were inert to this hydride.

INTRODUCTION

Since sodium borohydride¹ and lithiumalu-

minum hydride² have been discovered, more selective reducing agents—various alkoxyaluminumhydrides³, aluminum hydride⁴, borane⁵,

alkyl boranes⁶, and other basic and/or neutral borohydrides⁶ — were introduced in order to increase or moderate the reducing capabilities. These new reducing agents have been subjected to the systematic studies in tetrahydrofuran at 0° with a standard list of compounds containing the representative organic functional groups.

Schlesinger and Brown synthesized the basic borohydride, lithium borohydride, by several methods⁷, but the most convenient and commercially available one is by metathesis from the sodium borohydride and lithium salt in isopropyl amine⁸ or diglyme⁸. So, we prepared *in situ* the THF solution of lithium borohydride, by refluxing a slurry of lithium chloride and sodium borohydride in THF. And we decided to carry out the systematic study of the reaction of lithium borohydride with the standard list of compounds under the standard condition in order to compare the reducing behavior with boranes, “acidic” reducing agents and lithium aluminum hydride, a strong “basic” reducing agent.

RESULTS AND DISCUSSION

In general, all the reaction was performed with a mixture of lithium borohydride (0.25 M, 1.00 M in hydride) and a compound (0.25 M) in the ratio of 4:1 in THF at 0°. However, in some cases of compounds consuming 4 hydrides per mole of compound, the concentration of compound was maintained constant, and the hydride concentration was increased to give a ratio of 6:1.

The hydrogen evolution from the addition of compound to the reagent was noted. After the indicated reaction period, the aliquot of the reaction mixture was hydrolyzed and the residual hydride was calculated. A blank experiment was performed under the identical condition, but without the compound. From the data of

hydrogen evolution, hydrolysis of aliquot, and blank experiment, the hydride utilized for reduction was calculated.

“Active Hydrogen” Compounds. The reaction of secondary and tertiary alcohols failed to liberate the theoretical quantity of hydrogen. However, the primary alcohols evolved hydrogen quantitatively at a sluggish pace. *n*-Hexylamine and 1-hexanethiol reacted only slightly, whereas phenol and beznenethiol, contained an acidic proton, reacted completely in 3.0 hours. In contrast to lithium borohydride, lithium aluminum hydride⁹ and borane⁵ liberated hydrogen rapidly and quantitatively.

In the reactions of alcohols and thiols, no additional hydride consumption was observed in our reaction condition, indicating that hydrogenolyses of C—O or C—S bond did not occur with this hydride under the standard condition. The results are summarized in Table 1.

Aldehydes and Ketones. All the aldehydes and ketones examined took up 1 equivalent of hydride very fast, without evolution of any significant quantity of hydrogen. Consequently, in these cases, the reduction goes cleanly to the corresponding alcohol stage.

In the case of borane, the rate of reduction of benzophenone was considerably slower than the other ketones, and attributed to a consequence of the combined steric and electronic effects of the phenyl groups. However, all the carbonyl compounds examined with this reagent did not show such phenomenon. According to the recent paper by Ashby and Boone¹⁰, lithium aluminum hydride is about ten times more reactive than sodium aluminum hydride which indicates the importance of the cation in the mechanism of the reaction. It is believed that borane reduction of carbonyl compounds proceed prior coordination of BH₃ to carbonyl oxygen, therefore it would be interesting to investigate

Table 1. Reaction of lithium borohydride with representative "active hydrogen" compounds in tetrahydrofuran at 0°.

Compound ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^c	Hydride used for reduction ^b
1-Hexanol	1.0	0.12	0.12	0.00
	3.0	0.23	0.23	0.00
	6.0	0.33	0.33	0.00
	24.0	0.65	0.65	0.00
	48.0	0.92	0.92	0.00
	72.0	0.97	0.97	0.00
	96.0	0.97	0.97	0.00
Benzyl alcohol	1.0	0.33	0.33	0.00
	3.0	0.68	0.68	0.00
	6.0	0.84	0.84	0.00
	24.0	0.94	0.94	0.00
	48.0	1.02	1.02	0.00
3-Hexanol	1.0	0.01	0.01	0.00
	6.0	0.02	0.02	0.00
	48.0	0.08	0.08	0.00
	96.0	0.13	0.13	0.00
3-Ethyl-3-pentanol	3.0	0.03	0.03	0.00
	6.0	0.04	0.04	0.00
	24.0	0.10	0.10	0.00
	120.0	0.20	0.20	0.00
Phenol	0.5	0.81	0.82	0.01
	1.0	0.95	0.97	0.02
	3.0	1.07	1.10	0.03
	6.0	1.07	1.10	0.03
<i>n</i> -Hexylamine	3.0	0.03	0.03	0.00
	6.0	0.05	0.05	0.00
	24.0	0.19	0.19	0.00
1-Hexanethiol	3.0	0.04	0.04	0.00
	6.0	0.07	0.07	0.00
	24.0	0.20	0.20	0.00
Benzenethiol	0.5	0.86	0.86	0.00
	1.0	0.94	0.94	0.00
	3.0	1.00	1.00	0.00
	6.0	1.00	1.00	0.00

^a 10.0 mmoles of compound, except where otherwise indicated, to 40.0 mmoles of hydride; ^b Millimoles/mmmole of compound; ^c White precipitate.

the role of lithium ion in the reduction of carbonyl compounds with borane. We are going to explore this shortly.

Cinnamaldehyde, α, β -unsaturated carbonyl compound, reacted immediately with 1 equivalent of hydride, and no further hydride

uptake was apparent even after 6 hrs. This means that lithium borohydride reduces the aldehyde group cleanly without affecting the double bond to produce cinnamyl alcohol. The results are summarized in Table 2a.

In order to test the generality of such a

Table 2a. Reaction of lithium borohydride with representative aldehydes and ketones in tetrahydrofuran at 0°.

Compound ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^b	Hydride used for reduction ^b
Caproaldehyde ^c	0.5	0.03	0.99	0.96
	1.0	0.03	1.03	1.00
	6.0	0.03	1.03	1.00
Benzaldehyde ^d	0.5	0.02	1.02	1.00
	6.0	0.02	1.02	1.00
2-Heptanone	0.5	0.01	1.00	0.99
	6.0	0.01	1.00	0.99
Norcamphor	0.5	0.04	0.97	0.93
	1.0	0.04	1.01	0.97
	3.0	0.04	1.05	1.01
	6.0	0.04	1.05	1.01
Acetophenone	0.5	0.00	1.00	1.00
	3.0	0.00	1.00	1.00
Benzophenone	0.5	0.01	1.00	0.99
	6.0	0.01	1.00	0.99
Cinnamaldehyde	0.5	0.06	1.06	1.00
	6.0	0.06	1.06	1.00

^{a, b} See corresponding footnotes in Table 1; ^c Exothermic reaction; ^d White precipitate.Table 2b. reaction of lithium borohydride with representative α, β -unsaturated carbonyl compounds in tetrahydrofuran at 0°.

Compound ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^b	Hydride used for reduction ^b
Crotonaldehyde	0.5	0.11	1.14	1.03
	3.0	0.11	1.14	1.03
	6.0	0.11	1.16	1.05
Isophorone	0.5	0.01	1.01	1.00
	1.0	0.01	1.31	1.30
	3.0	0.01	1.61	1.60
	6.0	0.01	1.73	1.72
	0.5 ^c	0.00	0.46	0.46
	1.0 ^c	0.00	0.76	0.76
	3.0 ^c	0.00	0.96	0.96
3-Methyl-2-cyclohexenone	6.0 ^c	0.00	1.33	1.33
	0.5	0.04	1.73	1.69
	3.0	0.04	1.91	1.87
	6.0	0.04	1.99	1.95

^{a, b} See corresponding footnotes in Table 1; ^c At -20°.

selective reduction of α, β -unsaturated carbonyl compound, we examined three more carbonyl compounds, namely crotonaldehyde, isophorone,

and 3-methyl-2-cyclohexenone. Crotonaldehyde, like cinnamaldehyde, consumed only one hydride cleanly, however the two α, β -

unsaturated ketones consumed more than one hydride even at -20° . It is noteworthy that Nystrom and his coworkers¹¹ obtained crotyl alcohol in a yield of 70 % from the reduction of crotonaldehyde with this hydride. Recently we have demonstrated that zinc borohydride¹² is excellent for this kind of selective reduction, therefore we did not explore further with lithium borohydride. These results are summarized in *Table 2b*.

Quinones. As pointed out earlier⁹, the reduction of a quinone to a hydroquinone should consume two equivalent of hydride, one for reduction and the other for hydrogen evolution. On the other hand, the reduction to the 1,4-dihydroxycyclohexadiene stage should require 2 moles of hydride for reduction, without hydrogen evolution. It is evident that the data in *Table 3* do not indicate that the reduction takes either of these possible courses exclusively. In the case of *p*-benzoquinone, the total uptake of hydride is almost exactly 2 moles within the limits of the experiment, and the hydrogen evolution is almost half a mole. Therefore, it is believed that the reduction of *p*-benzoquinone proceeded equally to hydroquinone and 1,4-dihydroxy-2,5-cyclohexadiene. On the other hand, anthraquinone was converted to 9,10-

dihydroxyanthracene and 9,10-dihydro-9,10-anthracenediol with a related 23:77 distribution. Recently we have studied the reaction of 9-BBN¹³ extensively. 9-BBN reacted with anthraquinone consuming two hydrides without hydrogen evolution, and 80 % yield of 9,10-dihydro-9,10-anthracenediol was obtained. This supports our interpretation of the experimental results. The results are summarized in *Table 3*.

Carboxylic Acids and Their Derivatives.

Carboxylic acids liberated 1 equivalent of hydrogen instantly and quantitatively; however, only the slight sign of reduction was observed at 0° , and there was no sign that the reduction rate was promoted in the case of reverse addition.¹⁴ Even at room temperature, partial reduction was observed in 6 days. This is a remarkable contrast to the facile reduction of carboxylic acids with borane⁵, an "acidic" hydride.

On the other hand, acid chlorides were reduced quantitatively with remarkable ease, in contrast to the slow reduction with borane⁵. Acid anhydrides consumed 2 equivalent of hydride at a relatively faster rate, but subsequent reduction proceeded very slowly. Thus, phthalic anhydride rapidly consumed two hydrides in 0.5 hour and the subsequent reduction to the diol stage

Table 3. Reaction of lithium borohydride with representative quinones in tetrahydrofuran at 0° .

Compound ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^b	Hydride used for reduction ^b
<i>p</i> -Benzoquinone ^c	0.5	0.45	1.71	1.26
	3.0	0.48	2.03	1.55
	6.0	0.48	2.03	1.55
Anthraquinone ^d	0.5	0.00	1.71	1.71
	3.0	0.07	1.85	1.78
	6.0	0.10	1.92	1.82
	48.0	0.23	2.22	1.99

^a, ^b See corresponding footnotes in *Table 1*; ^c Immediate dark-blue gelatinous precipitate; ^d The compound was added as solid, reverse addition (solution of reagent added to suspension of the quinone), immediate dark-brown precipitate.

Table 4. Reaction of lithium borohydride with representative carboxylic acids and acyl derivatives in tetrahydrofuran at 0°

Compound ^a	Time, hr	Hydrogen evolved ^b	Hydride used ^b	Hydride used for reduction ^b
Caproic acid	6.0	1.03	1.07	0.04
	24.0	1.03	1.10	0.07
	120.0	1.03	1.58	0.53
	6.0 ^c	1.01	1.52	0.51
	24.0 ^c	1.01	2.11	1.10
	144.0 ^c	1.01	2.33	1.37
Benzoic acid	6.0	1.03	1.11	0.08
	24.0	1.03	1.19	0.16
	120.0	1.03	1.79	0.76
	6.0 ^c	1.00	1.25	0.25
	24.0 ^c	1.00	1.40	0.40
	144.0 ^c	1.00	2.07	1.07
Acetic anhydride ^d	1.0	0.02	0.94	0.92
	6.0	0.02	1.59	1.57
	24.0	0.02	1.84	1.82
	48.0	0.02	2.07	2.05
	96.0	0.02	2.03	3.01
	216.0	0.02	3.98	3.96
Succinic anhydride ^{d,e}	0.5	0.08	1.10	1.02
	1.0	0.08	1.10	1.02
	6.0	0.08	1.15	1.07
	24.0	0.08	1.30	1.22
	1.0 ^c	0.05	1.52	1.47
	3.0 ^c	0.05	1.61	1.56
	24.0 ^c	0.05	1.71	1.66
	144.0 ^c	0.05	2.02	1.97
	168.0 ^c	0.05	2.03	1.98
Phthalic anhydride ^{d,f}	0.5	0.06	1.34	1.28
	1.0	0.06	1.42	1.36
	6.0	0.06	1.72	1.66
	24.0	0.06	2.02	1.96
	1.0 ^c	0.03	2.13	2.10
	3.0 ^c	0.03	2.26	2.23
	24.0 ^c	0.03	2.64	2.61
	240.0 ^c	0.03	4.00	3.97
Caproyl chloride	0.5	0.08	2.11	2.03
	6.0	0.08	2.11	2.03
Benzoyl chloride	0.5	0.02	2.03	2.01
	6.0	0.02	2.03	2.01

^{a,b} See corresponding footnotes in Table 1; ^c At room temperature (about 20°); ^d Hydride to anhydrides in the ratio of 6: 1, and exothermic reaction; ^e Reverse addition (solution of reagent added to suspension of the anhydride), and immediately white precipitate was observed; ^f To be turbid within 0.5 hr., and then white precipitate was deposited.

required 10 days at room temperature, whereas succinic anhydride was reduced slowly to the hydroxy acid stage in 6 to 7 days consumed only two hydrides slowly, reading a plateau in 7 days at room temperature, corresponding to the hydroxy acid stage. The experimental results are summarized in *Table 4*.

Esters and Lactones. Ethyl caproate and

ethyl benzoate were reduced very slowly at 0° and even at room temperature; however, phenyl acetate was reduced readily in about 20 hours. Brown and his coworkers⁸ reported that esters are reduced rapidly to the corresponding alcohols with sodium borohydride-lithium bromide in diglyme at 100° within 3 hours in yields of approximately 100 %.

Table 5. Reaction of lithium borohydride with representative esters and lactones in tetrahydrofuran at 0°.

Compound ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^b	Hydride used for reduction ^b
Ethyl caproate	6.0	0.00	0.26	0.26
	24.0	0.00	0.34	0.34
	120.0	0.00	1.02	1.02
	264.0	0.00	1.97	1.97
	6.0 ^c	0.02	0.50	0.48
	24.0 ^c	0.02	1.00	0.98
	48.0 ^c	0.02	1.29	1.27
Ethyl benzoate	6.0	0.00	0.09	0.09
	24.0	0.00	0.13	0.13
	168.0	0.00	0.98	0.98
	234.0	0.00	1.61	1.61
	336.0	0.00	1.96	1.96
	6.0 ^{c,e}	0.02	0.18	0.16
	24.0 ^{c,e}	0.02	0.53	0.51
γ -Butyrolactone ^{c,d}	48.0 ^{c,e}	0.02	0.62	0.60
	0.5	0.03	1.12	1.09
	6.0	0.06	1.78	1.72
	24.0	0.06	2.05	1.99
	48.0	0.06	2.07	2.01
Phthalide ^{c,f}	6.0	0.03	0.45	0.42
	24.0	0.03	0.83	0.80
	72.0	0.03	1.91	1.88
	96.0	0.03	2.07	2.04
Isopropenyl acetate	3.0	0.00	0.65	0.65
	6.0	0.00	1.15	1.15
	24.0 ^g	0.00	2.10	2.10
	52.0 ^g	0.00	2.42	2.42
	0.5 ^{c,d}	0.04	1.13	1.09
	3.0 ^{c,d}	0.04	2.04	2.00
	24.0 ^{c,d}	0.04	2.60	2.56
	72.0 ^{c,d}	0.04	2.74	2.70

^{a,b} See corresponding footnotes in *Table 1*; ^c At room temperature (about 21°); ^d To be turbid within 0.5 hr., but after 0.5 hr white precipitate was deposited; ^e Slightly turbid after 3.0 hr; ^f Gelatinous white precipitate was observed after about 72 hrs; ^g To be slightly turbid after about 24 hrs.

On the other hand, γ -butyrolactone was reduced at a moderate rate and phthalide slowly, to the glycol stages, but faster than the esters, probably because of their ring strain.

In the case of isopropenyl acetate, two moles of hydride was consumed fast, and another one very slowly even at room temperature. Presumably, the very slow consumption of the third hydride is due to the slow reduction of the enolate, similar to the reaction of lithium trimethoxyaluminumhydride⁴ and aluminum hydride¹⁵. The results are summarized in Table 5.

Epoxides. All the epoxides examined were reduced at a relatively slow rate, with the uptake of 1 equivalent of hydride per mole of epoxide.

As pointed out by Fuchs¹⁶, lithium ion may play a minor role in the lithium borohydride reduction of epoxides, and the reduction of unsymmetrical epoxides by this reagent appears to be highly selective, with transfer of the hydride occurring almost exclusively to the less substituted carbon atom. In the case of 1,2-butylene oxide, the reduction product is only 2-butanol, showing 100 % primary attack^{16,17}.

This indicates that the hydride attack occurred in typical S_N2 fashion. However, in the case of styrene oxide, an aromatic epoxide, primary alcohol is produced in a yield of 26 %¹⁶, presumably due to electronic effect. The results are summarized in Table 6.

Amides and Nitriles. All the amides examined—the primary, tertiary, and aliphatic or aromatic amides—were inert to this reagent, and no substantial hydrogen evolution was observed. It is particularly noteworthy that no hydrogen evolution and no reduction was observed in the reaction of amides, as in the case of sodium borohydride¹⁸.

In addition, nitriles did neither evolve hydrogen, nor undergo reduction. However, the amides and nitriles were reduced with lithium aluminum hydride⁹ readily, and with borane⁵ at a moderate rate.

These suggest that one could reduce the reactive groups selectively in the presence of amide and/or nitrile functional groups with this reagent. In fact, Stewart¹⁹ carried out the selective reduction of ester group in the presence of the amido and cyano groups at room temper-

Table 6. Reaction of lithium borohydride with representative epoxides in tetrahydrofuran at 0°.

Compound ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^b	Hydride used for reduction ^b
1,2-Butylene oxide	3.0	0.00	0.27	0.27
	24.0	0.00	0.80	0.80
	36.0	0.00	1.01	1.01
	48.0	0.00	1.01	1.01
Styrene oxide	3.0	0.00	0.18	0.18
	24.0	0.00	0.53	0.53
	48.0	0.00	0.83	0.83
	72.0	0.00	1.03	1.03
Cyclohexene oxide	3.0	0.00	0.17	0.17
	24.0	0.00	0.49	0.49
	48.0	0.00	0.79	0.79
	72.0	0.00	1.02	1.02

^{a, b} See corresponding footnotes in Table 1.

Table 7. Reaction of lithium borohydride with representative amides and nitriles in tetrahydrofuran at 0°.

Compound ^a	Time, hr	Hydrogen evolved ^b	Hydride used ^b	Hydride used for reduction ^b
Caproamide	3.0	0.08	0.08	0.00
	10.0	0.08	0.08	0.00
Benzamide	3.0	0.04	0.04	0.00
	10.0	0.04	0.04	0.00
<i>N,N</i> -Dimethyl benzamide	3.0	0.00	0.00	0.00
	48.0	0.00	0.01	0.01
Capronitrile	6.0	0.01	0.01	0.00
Benzonitrile	6.0	0.00	0.02	0.02

^{a, b} See corresponding footnotes in Table 1.

ature in a yield of 84 %. The experimental results are summarized in Table 7.

Nitro Compounds and Their Derivatives.

1-Nitropropane was reduced very slowly and no liberation of hydrogen was observed. However, nitrobenzene, azobenzene, and azoxybenzene were almost inert to this reagent even at room temperature. Also, Nystrom¹¹ reported that aromatic nitro groups were generally resistant to attack by this reagent, and even under prolonged refluxing they were only partially reduced. These suggest that one could reduce the reductive groups in the presence of nitro groups. In fact, Nystrom¹¹ carried out a selective reduction of *m*-nitroacetophenone with this reagent to α -(*m*-nitrophenyl)-ethanol in a yield of 93 %.

It is interesting to note that borane⁵ is similar to lithium borohydride toward nitro compounds, however azobenzene is reduced with borane moderately, in contrast to the inertness with lithium borohydride. The results are summarized in Table 8.

Other Nitrogen Compounds. Cyclohexanone oxime rapidly evolved 1 equivalent of hydrogen and was reduced very slowly; this reduction showed that one hydride was consumed in relatively faster rate, equivalent to the hydroxylamine stage, and another one slowly, equi-

valent to the amine stage.

Phenyl isocyanate utilized 2 equivalent of hydride for reduction, one hydride being consumed relatively fast in 3 to 6 hrs, and the second mole of hydride was consumed very slowly in 5 days. This corresponds to the formation of *N*-hydroxymethyl aniline as with zinc borohydride²⁰.

Pyridine consumed 0.41 hydride rapidly in 3 hours; however, no further reduction was observed over the period of 2 days. Pyridine-*N*-oxide was reduced very slowly at 0°, but at room temperature it slowly consumed more than one equivalent of hydride. Such unexpected reductions cannot be inferred until they are explored in greater detail. The results are summarized in Table 9.

Sulfur Compounds. Disulfide, sulfone, and sulfoxide appeared to be quite inert to this reagent under the standard condition. Both of the sulfonic acids tested evolved hydrogen instantly, but were not reduced. Last of all, cyclohexyl tosylate exhibited only traces of reaction in 48 hours. Consequently, the results indicate the possibility of achieving the selective reduction of the reactive functional groups in the presence of these relatively stable sulfur substituents. The results are summarized in Table 10.

Table 8. Reaction of lithium borohydride with representative nitro compounds and their derivatives in tetrahydrofuran at 0°.

Compound ^a	Time, hr	Hydrogen evolved ^b	Hydride used ^b	Hydride used for reduction ^b
1-Nitropropane	24.0	0.01	0.21	0.20
	72.0	0.01	0.71	0.70
	144.0	0.01	1.96	1.95
Nitrobenzene	24.0	0.00	0.16	0.16
	96.0	0.00	0.26	0.26
Azobenzene	24.0	0.00	0.21	0.21
	127.0	0.00	0.40	0.40
Azoxybenzene	24.0	0.00	0.00	0.00
	24.0 ^c	0.04	0.11	0.07
	144.0 ^c	0.07	0.51	0.44

^{a, b} See corresponding footnotes in Table I, ; ^cAt room temperature (about 21°).

Table 9. Reaction of lithium borohydride with representative other nitrogen compounds in tetrahydrofuran at 0°.

Compound ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^b	Hydride used for reduction ^b
Cyclohexanone oxime	3.0	0.15	0.31	0.16
	24.0	1.02	1.29	0.27
	48.0	1.04	1.53	0.49
	3.0 ^c	0.92	1.57	0.65
	6.0 ^c	1.05	1.81	0.76
	24.0 ^c	1.06	2.09	1.03
	144.0 ^c	1.06	2.54	1.48
Phenyl isocyanate	0.5	0.00	0.74	0.74
	6.0	0.00	1.07	1.07
	24.0	0.00	1.20	1.20
	144.0	0.00	2.04	2.04
Pyridine	1.0	0.00	0.08	0.08
	3.0	0.00	0.41	0.41
	48.0	0.00	0.41	0.41
Pyridine-N-oxide ^d	1.0	0.00	0.00	0.00
	3.0	0.00	0.15	0.15
	48.0	0.02	0.25	0.23
	1.0 ^c	0.03	0.24	0.21
	48.0 ^c	0.12	0.49	0.37
	96.0 ^c	0.27	1.07	0.80
	144.0 ^c	0.30	1.57	1.27

^{a, b} See corresponding footnotes in Table I; ^cAt room temperature (about 21°); ^d Immediate white precipitate.

CONCLUSION

Lithium borohydride and borane are much milder than lithium aluminum hydride or

aluminum hydride. However, the reducing characteristics of lithium borohydride are quite contrasted with those of borane as revealed in

this study.

Carboxylic acids are almost inert to lithium borohydride, but rapidly reduced with borane. On the other hand, acyl chlorides are rapidly reduced with lithium borohydride, but considerably slower with borane. Amides and nitriles are inert to lithium borohydride, but moderately reduced with borane.

These characteristics show that lithium borohydride is a "basic" type reducing agent, whereas borane is an "acidic" type reducing agent.

EXPERIMENTAL

General. All of the compounds used were commercial products of the highest purity available, with the exception of caproyl chloride which was synthesized. All of them were further purified, just before use.

Sodium borohydride (95+ % purity, Ventron) and lithium chloride (reagent grade, J. T. Baker Chemical Co.) were used without further purification, but tried to dry them out thoroughly by heating vacuum desiccator at 110° for 7 to 9 hours.

Tetrahydrofuran was distilled over slight excess lithium aluminum hydride while thoroughly protected from moisture. Then, the distilled THF was stored over a small quantity of molecular sieve, and a connection to a mercury seal. In order to exclude a small quantity of oxygen which could possibly be present in the nitrogen, nitrogen gas passed through an oxygen-exclusion apparatus (the column containing copper foil was heated to 450°), and the calcium chloride column as a drying agent.

Hypodermic syringes were used at all times to introduce and transfer materials. All glass apparatus was dried in a drying oven at 125° for more than 3 hours, assembled, and then cooled under a stream of dry nitrogen. Thus all reactions were carried out under the anhydrous nitrogen atmosphere. Since the reactions were carried out at 0°, the hydride solution, THF, and the THF solution of the compound to be tested were all cooled to 0° in an ice bath just before they were mixed.

Preparation of THF Solution of Lithium Borohydride Reagent. In a 500 ml hot flask,

Table 10. Reaction of lithium borohydride with representative sulfur derivatives in tetrahydrofuran at 0°.

Compound ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^b	Hydride used for reduction ^b
Di- <i>n</i> -butyl disulfide	6.0	0.00	0.00	0.00
	48.0	0.00	0.09	0.09
Dimethyl sulfoxide ^c	6.0	0.01	0.01	0.00
	36.0	0.01	0.01	0.00
Diphenyl sulfone	24.0	0.00	0.00	0.00
Methanesulfonic acid ^d	1.0	1.05	1.09	0.04
	24.0	1.05	1.06	0.01
<i>p</i> -Toluenesulfonic acid monohydrate ^e	0.5	3.02	3.03	0.01
	24.0	3.02	3.02	0.00
Cyclohexyl tosylate	6.0	0.02	0.03	0.01
	48.0	0.02	0.23	0.21

^{a, b} See corresponding footnotes in Table 1; ^c White precipitate was observed immediately; ^d Immediately white gelatinous precipitate was observed, and to be clear after about 6 hours; ^e Gelatinous white precipitate was deposited after 1 hour.

fitted with an inlet port and rubber syringe cap, were placed the pre-dried hot lithium chloride (6.3885 g, 150 mmoles) and 10 % excess over the stoichiometric amount of sodium borohydride (6.25 g, 165 mmoles), and then the flask was promptly equipped to the apparatus. Thereafter, the flask was cooled to room temperature with stirring under a stream of dry nitrogen, and 300 ml of freshly distilled THF was introduced to provide a solution of about 0.5 M in lithium borohydride, 2 M in hydride. The flask was heated at a rate sufficient to maintain a gentle reflux, for 4 days with continuous stirring. After 4 days, the standard reagent solution was cooled down to room temperature under the dry nitrogen, and allowed to stand to permit the sodium chloride and the unreacted sodium borohydride precipitate to settle. The hydride concentration was estimated by injecting aliquots from the clear supernatant solution into a 2 N sulfuric acid-THF mixture and measuring the hydrogen evolved. Thus we found the result to be 1.84 M in hydride, 0.46 M in lithium borohydride, a yield of 92 %. And the solution was stored under a slight positive nitrogen pressure with a connection to a mercury seal.

The hydride concentrations of the aliquots were also measured after 1, 2, and 3 days. Thus they were 0.6 M in 1 day, 1.22 M in 2 days, and 1.68 M in 3 days. They correspond to 30, 61, and 84 % reaction, respectively. The hydride concentration was practically constant for more than 1 month at room temperature. Throughout the experiments, a calculated quantity of the reagent was transferred from the clear supernatant, as needed.

The clear supernatant solution was also analyzed for lithium, by titration with standard acid using methyl red as an indicator, and boron by titration with standard base in the presence of mannitol using phenolphthalein.

The analysis showed Li: B: H⁻ being 1.00: 1.00: 3.93, indicating LiBH₄ solution.

Procedure. The reduction of caproaldehyde is illustrative of the procedure utilized here. An oven-dried 100 ml flask, fitted with a rubber cap, and a magnetic stirring bar, was connected to a reflux condenser. And the flask was cooled to 0° under a stream of dry nitrogen, and then there were added 40.0 mmoles of lithium borohydride solution in THF and enough extra solvent to make a total volume of 30.0 ml. The reduction was started by the dropwise addition of 10.0 ml. of 1.0 M pre-cooled caproaldehyde solution (10.0 mmoles, 2(1.002 g) with constant stirring. This makes the reaction mixture 0.25 M in lithium borohydride (i.e., 1.0 M in hydride) and 0.25 M in the aldehyde. When the solution of the compound was added, there was observed 4 ml. of hydrogen evolution and this corresponds to 0.15 mmole of hydrogen, and the hydrogen evolution did not continue. Since this was evolved from 5.0 mmoles of compound, 0.03 mmole of hydrogen was evolved per mmole of compound. After the appropriate reaction periods, each 4.0 ml aliquot of the reaction mixture was hydrolyzed to measure the residual hydride content.

The reverse addition method was adopted for the reaction with the compound (e.g., succinic anhydride) not dissolved in THF efficiently. When the reaction proceeded with the formation of precipitate, so that accurate transfer of aliquots with syringe was difficult (e.g., anthraquinone and dimethyl sulfoxide), the reactions for each time period were carried out separately and the whole reaction mixtures were hydrolyzed with 1:1 mixture of 2 N sulfuric acid-THF.

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