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Effect of Trialkylborane on the Stereochemistry of Ketone Reduction with Lithium Borohydride

Nung Min Yoon[1], Jin Soon Cha and Won Suh Park

Department of Chemistry, Sogang University, Seoul 121, Korea (*Received August 6, 1982*)

The effects of trialkylborane on the stereochemistry of ketone reduction with lithium borohydride were studied for the four representative ketones, namely 4-*t*-butylcyclohexanone, 2-methylcyclohexanone, norcamphor, and camphor. The presence of trialkylborane increased the yields of the less stable alcohols. For example, in the presence of tri-*s*-butylborane, 42 % yield of *cis*-4-*t*-butylcyclohexanol was observed whereas only 8 % yield with lithium borohydride alone in the reduction of 4-*t*-butylcyclohexanone. The *in situ* formation of lithium trialkylborohydride, by the hydride transfer from lithium trialkoxyborohydride to trialkylborane, was demonstrated as a possible mechanism for the catalytic effect of trialkylborane.

Introduction

The stereochemistry of the ketone reduction by metal hydride reagents has been extensively studied.[1-5] In the case of the rigid bicyclic ketones such as norcamphor and camphor, the attack of hydride from the reagents occurs predominantly at the less hindered side of the carbonyl group to provide the less stable isomer of the two possible alcohols as a major product. On the other hand, in the case of the less rigid monocyclic ketones such as 2-methylcyclohexanone and 4-*t*-butylcyclohexanone, the major reduction products are the more stable equatorial alcohol isomer.

There are many attempts and achievements to increase stereoselectivity toward the less stable alcohol isomer by modifying metal hydrides. Among them, some of the recently synthesized trialkylborohydrides possessing great steric requirements have shown excellent selectivities in the reduction of both cyclohexanones and bicyclic ketones.[6-9] Thus lithium tri-*s*-butylborohydride, a hindered trialkylborohydride, reduced 4-*t*-butylcyclohexanone and norcamphor to yield 93 % of *cis*-4-*t*-butylcyclohexanol and 99.6 % of *endo*-norborneol, the less stable isomers.

Recently, we have carried out a systematic study for the reaction of lithium borohydride with representative organic compounds.[10] In this study, lithium borohydride showed remarkable contrasts to borane in reducing characteristics, presumably due to its basic character compared to the acidic character of borane. And we have found that trialkylborane exhibits significant catalytic effects[11] on the reactions of alcohol, epoxide, and ester with lithium borohydride.

Therefore, it appeared desirable to explore the effect of trialkylborane on the stereochemistry of the ketone reductions with lithium borohydride. Accordingly, we selected a group of model ketones, 4-*t*-butylcyclohexanone, 2-methylcyclohexanone, norcamphor, and camphor, and subjected them to the reduction by lithium borohydride in the presence of trialkylboranes, under the standard condition (0°, THF).

Results and Discussion

In general, all reactions were carried out with a mixture of the compound (0.25 *M*), and various concentrations of the hydride reagents and trialkylboranes in THF at 0°.

After the appropriate time of reaction, the reaction mixture was hydrolyzed with water and oxidized with alkaline hydrogen peroxide. And then THF layer was separated by addition of anhydrous potassium carbonate, dried over anhydrous magnesium sulfate, and subjected to glpc analysis.

Effect of Trialkylborane on the Stereochemistry of Ketone Reduction with Lithium Borohydride. In order to examine the effect of trialkylborane on the stereochemistry of ketone reduction with lithium borohydride, representative ketones, namely 4-*t*-butylcyclohexanone, 2-methylcyclohexanone, norcamphor, and camphor, were reacted at 0° in THF with lithium borohydride itself and with lithium borohydride in the presence of equimolar amount of triethylborane or tri-*s*-butylborane. The total yields of alcohols and the normalized percentage of the less stable alcohols are summarized in Table 1.

As shown in Table 1, for the reaction of monocyclic ketones, as the size of alkyl substituents on boron increased, the per-

TABLE 1: Stereochemistry on the Ketone Reductions with Lithium Borohydride-Trialkylborane Systems in Tetrahydrofuran at 0°[a]

Hydride system	Ketone	4-*t*-Butylcyclohexanone			2-Methylcyclohexanone			Norcamphor			Camphor		
	Alcohol	4-*t*-Butylcyclohexanol			2-Methylcyclohexanol			Norborneol			Borneol		
	H/Compd[b]	*cis* (%)[c]	Yield (%)	Time (h)	*cis* (%)[c]	Yield (%)	Time (h)	*endo* (%)[c]	Yield (%)	Time (h)	*exo* (%)[c]	Yield (%)	Time (h)
$LiBH_4$	4/1	7	100	3.0	31	100	3.0	88	100	3.0	77	109	3.0
	1/1	8	100	3.0	32	100	3.0	91	100	3.0	77	29	3.0
$LiBH_4$-BEt_3 (1 : 1)[d]	1/1	20	100	3.0	36	100	3.0	93	100	3.0	81	18	24.0
$LiBH_4$-$B(s\text{-}Bu)_3$ (1 : 1)[d]	1/1	42	100	3.0	55	100	3.0	93	100	3.0	81	13	48.0

[a] All reactions were carried out 0.25 M in the compound; [b] Ratio of available hydride to ketone; [c] Glpc analysis and normalyzed percentage; [d] Molar ratio of reagents.

centage of the less stable alcohols were increased. Thus, in the case of 4-*t*-butylcyclohexanone, the percentage of *cis*-alcohol increased from 8 % with lithium borohydride itself to 20 % with the $LiBH_4$-BEt_3 (1:1) system and to 42% with the $LiBH_4$-$B(s\text{-}Bu)_3$ (1:1) system, and in the case of 2-methylcyclohexanone, the percentage of *cis*-alcohol increased from 32 % with $LiBH_4$ to 36 % with the $LiBH_4$-BEt_3 (1:1) system and to 55% with the $LiBH_4$-$B(s\text{-}Bu)_3$ (1:1) system. However, the effect of trialkylboranes was not significant in the case of the bicyclic ketones.

Since the effect of tri-*s*-butylborane was greater than that of triethylborane, and the effect of tri-*s*-butylborane was most remarkable in the reduction of 4-*t*-butylcyclohexanone, the reaction with tri-*s*-butylborane and 4-*t*-butylcyclohexanone was chosen for the more detailed study of the effect of trialkylborane on the stereochemistry of ketone reduction with lithium borohydride.

As shown in Table 2, in the absence of trialkylborane, 4-*t*-butylcyclohexanone was reduced to give only 7-8 % of the corresponding *cis*-alcohol, regardless of the amount of $LiBH_4$ (the equivalents of the available hydride to the ketone were 4:1 and 1:1). However, in the presence of tri-*s*-butylborane, the yields of the *cis*-alcohol increased to ca. 40 % and remained at nearly constant value even when the equivalents of tri-*s*-butylborane to the ketone were changed from one-tenth to two as listed in Table 2. And this 40 % yield of the *cis*-alcohol was not affected even by changing the reaction temperature (0°, 25°, and 65°).

TABLE 2: Stereochemistry on the Reduction of 4-*t*-Butylcyclohexanone with Lithium Borohydride-Tri-*s*-butylborane in Tetrahydrofuran[a]

Hydride system ($LiBH_4$:R_3B:Ketone)[b]	Temp. (0° C)	Time. (h)	*cis*-Alcohol (%)[c]	Total yield of alcohol (%)
0.25 : 0 : 1	0	3.0	8	100
1 : 0 : 1	0	3.0	7	100
0.25 : 0.1 : 1	0	1.0	37	100
0.25 : 0.25 : 1	65	0.25	40	100
0.25 : 0.25 : 1	25	0.25	40	100
0.25 : 0.25 : 1	0	0.25	42	100
0.25 : 1 : 1	0	1.0	41	100
0.25 : 2 : 1	0	1.0	40	100
1 : 1 : 1	0	1.0	41	100

[a] The concentration of the ketone was 0.25 M; [b] Molar ratio of $LiBH_4$, $B(s\text{-}Bu)_3$, and 4-*t*-butylcyclohexanone; [c] Glpc analysis and normalized percentage.

These observations suggested a possibility of the *in situ* formation of lithium tri-*s*-butylborohydride[12] from tri-*s*-butylborane and lithium trialkoxyborohydride, since trialkoxyborohydride should be formed during the reduction, presumably with a constant amount relative to the amount of the ketone, and 4-*t*-butylcyclohexanone is known to be reduced with lithium tri-*s*-butylborohydride to give 93 % of the *cis*-alcohol. It is believed that the demonstration of the *in situ* formation of lithium tri-*s*-butylborohydride from tri-*s*-butylborane and lithium trialkoxyborohydride might well explain the effect of trialkylborane in the ketone reduction with $LiBH_4$.

Evidence for in situ Formation of Lithium Tri-s-butylborohydride from Tri-s-butylborane and Lithium Trialkoxyborohydride. Dialkoxyborane can react with ketones only in a very sluggish rate, however the addition of small amount of $LiBH_4$ or $Li(RO)_4B$ shows the tremendous rate enhancement of reaction. Therefore, it is believed that dialkoxyborane reacts with $Li(RO)_4B$ to form lithium trialkoxyborohydride, or then to form $LiBH_4$ *via* disproportionation, both can reduce ketones rapidly.[13] Accordingly, in order to find out some evidence for the intermolecular hydride transfer from trialkoxyborohydride to trialkylborane, 4-*t*-butylcyclohexanone was reduced with one equivalent of di-*s*-butoxyborane in the presence of varying equivalents of tri-*s*-butylborane and tetra-*s*-butoxyborohydride under the standard condition (0°, THF). The results are summarized in Table 3, together with the reactions of norcamphor and camphor.

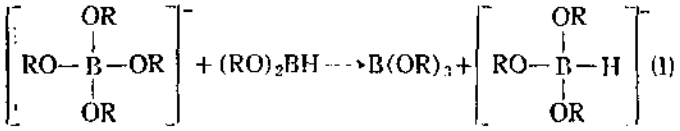
As shown in Table 3, in the absence of tri-*s*-butylborane, 4-*t*-butylcyclohexanone was reduced to give 11.4% of the *cis*-alcohol, but the ratio of the *cis*-alcohol increased as the equivalents of tri-*s*-butylborane and the base increased. Thus, the ratio of *cis*-alcohol was 47 % with 5 mole % of the trialkylborane and the base, 79 % with 25 mole %, 84 % with 50 mole %, and 88 % with 100 mole %. And for the reduction of bicyclic ketones, in the case of norcamphor, 99.5 up % of *endo*-norborneol from norcamphor and 98% of isoborneol from camphor were produced with 50 mole % of the trialkylborane and the base. These results strongly support the *in*

TABLE 3: Stereochemistry on the Ketone Reduction with Di-*s*-butoxyborane-tri-*s*-butylborane-lithium Tetra-*s*-butoxyborohydride system in Tetrahydrofuran at 0°[a]

Hydride system (ketone: R_3B: Base: $(RO)_2BH$)[b]	4-*t*-Butylcyclo-hexanone			Norcamphor			Camphor		
	cis-Alcohol (%)[d]	Yields of alcohols (%)	Time (h)	*endo*-Alcohol (%)[d]	Yields of alcohols (%)	Time (h)	*exo*-Alcohol (%)[d]	Yields of alcohols (%)	Time (h)
1 : 0 : 0.05 : 1[c]	11.4	100	1.0						
1 : 0.05 : 0.05 : 1	47	100	1.0						
1 : 0.25 : 0.25 : 1	79	100	1.0	99	50	1.0			
1 : 0.5 : 0.5 : 1	84	100	1.0	99.5	70	1.0	98	30	1.0
1 : 1 : 1 : 1	88	100	1.0						
Li(s-Bu)$_3$BH[e]	93	100	3.0	99.6	100	0.5	99.6	100	1.0

[a] All reactions were carried out 0.25 *M* in the compound; [b] Molar ratio of ketone, B(*s*-BuO)$_3$, Li(*s*-Bu)$_3$B, and (*s*-BuO)$_2$BH, and the order of addition to the reaction mixture was same as in the order listed; [c] Ketone was added to the mixture of $(RO)_2BH$ and base only in this case; [d] Glpc analysis and normalized percentage; [e] Data from, H. C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, **98**, 3383 (1976).

situ formation of lithium tri-*s*-butylborohydride, as following schemes (eq 1-2), similarly as reported previously by Brown and Hubbard on potossium trialkylborohydride.[12]



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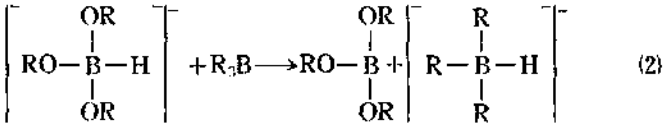

(2)

R = *s*-butyl

Apparently, with the smaller equivalents of the trialkylborane and the base, considerable portion of reduction underwent with the trialkoxyborohydride and/or $LiBH_4$ through disproportionation. The 79 % yield of the *cis*-alcohol with 25 mole % of the trialkylborane and the base suggests the step of the hydride transfer from the trialkoxyborohydride to the trialkyborane (eq 2) be a very rapid one, compared to the relatively slower attack on the ketone from the trialkoxyborohydride.

Conclusion

The stereochemistry of ketone reduction with lithium borohydride was greatly influenced by the presence of trialkylborane. The *in situ* formation of lithium trialkylborohydride from trialkylborane and trialkoxyborohydride was demonstrated as a possible mechanism for the catalytic effect of trialkylborane.

Experimental

4-*t*-Butylcyclohexanone (95+ %, Aldrich) was used without further purification, but norcamphor and camphor were purified by sublimation. THF was dried with excess lithium aluminum hydride and distilled therefrom under the dry nitrogen. Commercial 1 *M* solutions in THF (Aldrich) of triethylborane and tri-*s*-butylborane were used. The solution of $LiBH_4$ in THF was prepared as reported in the previous paper.[10]

Product Analysis. The reaction mixtures were hydrolyzed with water, oxidized with the alkaline hydrogen peroxide, saturated the aqueous layer with anhydrous potassium carbonate, and the organic layer was separated, dried over anhydrous magnesium sulfate and analyzed on a Varian Model 3700 gas chromatograph using a 15 ft × 0.125 in. column packed with 7 % Carbowax 20 M on Chromosob G.

Reaction of 4-t-butylcyclohexanone with Lithium Borohydride in the Presence of Trialkylborane. The reaction of 4-*t*-butylcyclohexanone with one-fourth molar equivalents of lithium borohydride and tri-*s*-butylborane is described as a representative. A pre-dried 100ml hot flask, equipped with a needle inlet and a magnetic stirring bar, was flamed out with Bunsen burner and cooled to 0° in an ice-water bath under a slow stream of dry nitrogen. Into the flask, were added 1 m*l* of 1.05 *M* lithium borohydride solution (1.05 mmoles, 4.2 mmoles in hydride), 1.05 m*l* of 1 *M* THF solution of the trialkylborane, and 12 m*l* of THF. To this mixture, 4 m*l* of pre-cooled 1 *M* THF solution of the ketone (4 mmoles, 0.617 g) was added dropwise with stirring. After reaction for 3.0 h at 0°, the reaction mixture was oxidized with hydrogen peroxide after hydrolysis, worked up, and subjected to glpc analysis to give 42 % of *cis*-alcohol in a total 100 % yield of alcohols.

Reaction of Ketones with the Di-s-butoxyborane-Tri-s-butylborane-Lithium Tetra-s-butoxyborohydride System in THF *at* 0°. The following procedure for the reaction of 4-*t*-butylcyclohexanone with equimolar amounts of tri-*s*-butylborane, lithium tetra-*s*-butoxyborohydride and di-*s*-butoxyborane is illustrative. A 100 m*l* flask was charged with 4 m*l* of pre-cooled 1 *M* THF solution of the ketone, 4.2 m*l* of 1 *M* THF solution of the trialkylborane, and 4.2 m*l* of 1 *M* mixture of the base, successively. To this mixture at 0°, there was added 6 *ml* of preprepared 0.7 *M* THF solution of di-*s*-butoxyborane (prepared from the reaction of two equivalents of 2-butanone and one equivalent of borane THF for 3 hrs at 0°) with a hypodermic syringe drop by drop over a period of 30 min. After the reaction for 1 h at 0°, the reaction mixture was worked up as described above and analyzed by glpc to give 88 % of the *cis*-alcohol. The procedure for the reaction of norcamphor and camphor with a half molar equivalents of tri-alkylborane and the base was same as described above, and the results are summarized in Table 3.

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NMR Chemical Shift for 4d^n Systems (I). Evaluation of the Required Hyperfine Integrals

Sangwoon Ahn† and Hyuck Choon Suh,

Department of Chemistry, Jeonbug National University, Jeonju 520, Korea (Received August 11, 1982)

Kee Hag Lee

Department of Chemistry, Won Kwang University, Iree, Korea

The hyperfine integrals for 4d orbitals have been evaluated adopting a general method which is applicable to a general vector, R, pointing arbitrary direction in space. The operator and the spherical harmonic part of 4d orbitals are expressed in terms of R and r_N and the exponential part, $r^2\exp(-2\beta r)$, of 4d orbitals is also translated as a function of R and r_N and then intergration is performed. The radial integrals for 4d orbitals are tabulated in analytical forms. The hyperfine integrals for 4d orbitals are also represented in analytical forms, using the specific formulas of radial series which we found.

1. Introduction

Since our interest is centered on the NMR shift arising from the electron orbital angular momentum, and the electron spin dipolar–nuclear spin angular momentum interactions for 4d^n systems in the octahedral crystal field, it is necessary to evaluate the hyperfine integrals of the hamiltonian representing the pseudo contact part of hyperfine integrals.[1]

$$H=H_1+H_2 \tag{1}$$

where

$$H_1=\frac{2\mu_0}{4\pi}g_N\mu_B\mu_N\{\boldsymbol{I}_N\cdot\boldsymbol{I}/r_N^3\} \tag{2a}$$

$$H_2=\frac{\mu_0}{4\pi}g_S g_N\mu_B\mu_N\left\{\frac{3(\boldsymbol{r}_N\cdot\boldsymbol{S})\boldsymbol{r}_N\cdot\boldsymbol{I}}{r_N^5}-\frac{\boldsymbol{S}\cdot\boldsymbol{I}}{r_N^3}\right\} \tag{2b}$$

Here the first part represents the Fermi contact term and the second part, H_2, the pseudo contact term. r_N is the radius vector of the electron about the nucleus with nuclear spin angular momentum, I, as shown in Figure 1.

In order to evaluate the hyperfine integrals involving 4d orbitals, we adopt the general method which has been developed by Golding and Stubbs.[2] This method is applicable to a general vector, R, pointing in any direction in space, which

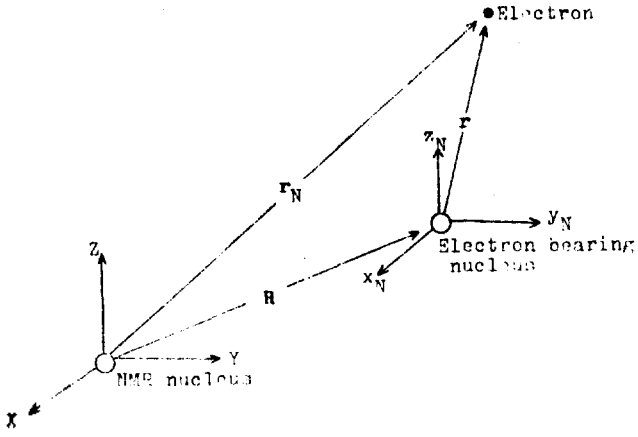

Figure 1. The coordinate system.