On hydrolysis by heating 1.25 g. of this ester in 5 ml. of acetic acid and 10 ml. of 85% sulfuric acid on the steam-bath for 6 hr., there was obtained 3,4,6-trimethylphthalic anhydride, m.p. 123–124°, on crystallization from Skellysolve B. The formation of anhydride locates the original carboxyl group *ortho* to the chlorine.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3. Found: C, 69.4; H, 5.3.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF FLORIDA, GAINESVILLE, FLA.]

The Stereochemistry and Reaction Path of Borohydride Reductions of 4-*t*-Butylcyclohexanone in Diglyme[1]

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The stereochemistry of the reduction of 4-*t*-butylcyclohexanone with a variety of borohydrides has been examined. All reductions were effected in the same solvent (diglyme) and at the same temperature (20°). In an attempt to gain some information regarding the stereochemistry of the first step of the borohydride reductions, the reactions were studied in the presence of triethylamine, a reagent which stops the reductions after the first hydride has been used. That the reductions in the presence of the amine actually gave some indication of the stereochemistry of the first step in a normal borohydride reduction was demonstrated by examining the stereochemistry of the reduction of the ketone with diborane in the presence of the sodium salt of 4-*t*-butylcyclohexanol. The fact that the first step in the reduction led to less of the *axial* (*cis*) alcohol than the average of all four steps is interpreted as indicating that at least one of the last three steps in the reduction must involve alkoxy borohydride. It was also found that, in diglyme, the lithium cation affects the stereochemistry of the reduction.

Although the stereochemistry of the reduction of alicyclic and polycyclic ketones with various borohydrides has been rather thoroughly investigated,[2-6] interpretation of the results has invariably been confused by the fact that the stereochemistry of the first step which is generally agreed to involve the borohydride ion[7-10] could not be isolated from the last three steps. In fact, although Brown and his co-workers[9,10] have specifically stated that the last three steps in borohydride reductions involve the alkoxy borohydrides, the fact that it has been previously found[11,12] that diborane effects

$$R_2CO + BH_4^- \longrightarrow H_3BOCHR_2^-$$

$$R_2CO + H_3BOCHR_2^- \longrightarrow H_2B(OCHR_2)_2^-$$

$$R_2CO + H_2B(OCHR_2)_2^- \longrightarrow HB(OCHR_2)_3^-$$

$$R_2CO + HB(OCHR_2)_3^- \longrightarrow B(OCHR_2)_4^-$$

very rapid reduction of a ketone suggested to us the possibility that one, two or all three of the last three steps of the borohydride reduction could conceivably involve borine (or diborane) and its alkoxy derivatives.

$$R_2CO + BH_4^- \longrightarrow R_2CHO^- + BH_3$$

$$R_2CO + BH_3 \longrightarrow R_2CHOBH_2$$

$$R_2CO + R_2CHOBH_2 \longrightarrow (R_2CHO)_2BH$$

$$R_2CO + (R_2CHO)_2BH \longrightarrow (R_2CHO)_3B$$

Considering this possibility, the nature of the problem of assigning the steric requirements of the borohydride ion from studies of the stereochemistry of borohydride reductions can best be presented in the way of an example. The reduction of 4-*t*-butylcyclohexanone with sodium borohydride in diglyme (diethylene glycol dimethyl ether) has been found (see Discussion) to give 21% of the thermodynamically less stable (*axial*) alcohol. If the last three steps in the reduction actually involved only the borines, then, in view of the fact that the reduction with the borines has been found to give only 12.6% of the *axial* isomer (see Discussion), the first step of the reduction would require in the range of 40–50% of the *axial* isomer. If, on the other hand, the last three steps involve only the alkoxy borohydrides, then it follows from the observation that alkoxy borohydrides give more of the *axial* alcohol than the total reduction (see Discussion), and that the first step of the reduction should give less than 20% of the *axial* alcohol. Thus, arguments about the steric requirements of the borohydride ion based solely on averages of the stereochemistry of four reduction steps in which the borohydride ion is the participating species in only one of these steps obviously leave something to be desired.

In the course of our reading, an observation by Brown, Mead and Subba Rao[10] suggested a possible method for obviating this problem. Thus, whereas borohydride reductions generally involve a slow first step followed by three rapid reactions.[8-10] Brown and co-workers found that, in the presence of triethylamine, the reduction stopped after the first step. Although we have found that the reason which was given for this phenomenon was incor-

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(1) Based upon a theses submitted by H. E. Wise, Jr., in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) For by far the most comprehensive study and the best available discussion on this subject, see A. H. Beckett, N. J. Harper, A. D. Balton and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).

(3) W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(4) K. D. Hardy and R. J. Wicker, *ibid.*, **80**, 640 (1958).

(5) W. G. Dauben, E. J. Blanz, Jr., J. Jiu and R. A. Micheli, *ibid.*, **78**, 3572 (1956).

(6) J. B. Umland and B. W. Williams, *J. Org. Chem.*, **21**, 1302 (1956).

(7) L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949).

(8) E. R. Garrett and D. A. Lyttle, *ibid.*, **75**, 6051 (1953).

(9) H. C. Brown, O. H. Wheeler and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957).

(10) H. C. Brown, E. J. Mead and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

(11) H. C. Brown, H. I. Schlesinger and A. B. Burg, *ibid.*, **61**, 673 (1939).

(12) (a) H. C. Brown and B. C. Subba Rao, *ibid.*, **82**, 681 (1960); *J. Org. Chem.*, **22**, 1135 (1957); (b) W. M. Jones, *J. Am. Chem. Soc.*, **82**, 2528 (1960).

rect[13] the mere existence of such an effect was sufficient for our purposes. Thus, it was recognized that an examination of the stereochemistry of the reduction of an appropriate ketone with various borohydrides in the presence of triethylamine should afford some indication of the stereochemistry of the hydride transfer from the borohydride ion alone. To report the results of such a study is the purpose of this paper.

Results and Discussion

Since it was desirable to have a model compound which would remain conformationally homogeneous during the course of the reaction, we selected 4-*t*-butylcyclohexanone for our investigation. This was particularly convenient since a method for accurate analysis of the crude reaction mixtures involving g.l.p.c. had already been developed.[12b,14] Furthermore, in order to eliminate any complicating factors which might arise from temperature variations[7,15] (although such effects were unlikely[2]), all reductions were run in a constant temperature bath at 20°. Since it was certainly desirable to have a solvent in which the borohydrides were sufficiently soluble to allow examination of only homogeneous reaction mixtures and, at the same time, a solvent with which the borohydrides would not undergo reaction, we decided to use diglyme[10] throughout this investigation.

A series of reductions was carried out involving the borohydrides of three different cations with 4-*t*-butylcyclohexanone in a ratio of 1:4 (1:8 for $Mg(BH_4)_2$), thus leading to an evaluation of the effect of the cation on reductions involving all four of the borohydride hydrides. As is summarized in Table I (entries 1, 3 and 4), sodium and magnesium borohydrides gave essentially the same results whereas lithium borohydride gave 5% less of the less stable *axial* isomer. Since our analytical method for determining isomer ratios was accurate ±1%, this difference is certainly real. The reduction of the ketone with sodium borohydride in a 1:1 ratio was also examined. The result (Table I, entry 2) was the same as that observed for the 1:4 ratio above; exactly what would be expected if the suggested[7-10] mechanism involving a slow first hydride transfer is also operative in diglyme solution.

A series of reductions was then carried out involving the borohydrides of the same three cations and 4-*t*-butylcyclohexanone in the presence of triethylamine in a 1:1:1 molar ratio (except magnesium borohydride which was run in a 1:2:2 ratio). Following thorough decomposition of the triethylamine borane resulting from this reduction,[16] the reaction mixtures were analyzed by g.l.p.c. and the results listed in Table I (entries 5, 6 and 7) were observed. Thus, it is seen that, in each case, the first step in the reduction apparently leads to less of the unstable *axial* isomer than the average of the four steps.

TABLE I

ISOMERIC COMPOSITION OF MIXTURES OF *cis* AND *trans*-4-*t*-BUTYLCYCLOHEXANOLS FROM THE REDUCTION OF 4-*t*-BUTYLCYCLOHEXANONE

	Reducing agent	Molar ratio of ketone to the reducing agent	Added reagent[a]	*axial* (*cis*)-4-*t*-Butylcyclohexanol, %
1	$NaBH_4$	4:1	None	21.0
2	$NaBH_4$	1:1	None	20.7
3	$Mg(BH_4)_2$	8:1	None	20.4[b]
4	$LiBH_4$	4:1	None	15.3
5	$NaBH_4$	1:1	Triethylamine	16.4
6	$Mg(BH_4)_2$	2:1	Triethylamine	15.2
7	$LiBH_4$	1:1	Triethylamine	12.8
8	$NaBH_4$	1:1	Pyridine	18.6
9	$NaBH_4$	1:1	N,N-Dimethylaniline	21.0
10	Diborane	[c]	None	8[d]
11	Diborane	[e]	None	12.6
12	$Al(BH_4)_3$	12:1	None	20.3
13	$Al(BH_4)_8$	3:1	Triethylamine[f]	32.5

[a] In all reactions run with added amine, the ketone: amine ratio was unity.[f] [b] This value represents an average as explained in the Experimental. [c] In this reduction, an excess of diborane was used. [d] This is an approximate value since the gas chromatography standard curve is not considered reliable in this range. [e] In this reduction, an excess of ketone was used. [f] In this reduction, a molar ratio of ketone to triethylamine of 3:8 was used.

It was recognized, however, that before the above data could be intelligently interpreted, one question certainly deserved rather detailed perusal. This was the question of the role of the triethylamine in the reduction. Thus, in addition to stopping the reduction after transfer of one hydride from the borohydride, the triethylamine was found by Brown, Mead and Subba Rao[10] to accelerate drastically the rate of the reduction. In an attempt to determine whether or not the amine was influencing the stereochemistry of the reduction, we felt that we might gain some information by examining the reductions with sodium borohydride in the presence of a series of amines of varying sizes (Table I, entries 5, 8 and 9). To our initial surprise, it was found that the stereochemistry in the presence of pyridine and N,N-dimethylaniline did not follow the anticipated order. The stereo-

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(13) Brown, Mead and Subba Rao attributed this effect to the idea that triethylamine would not be able to participate in the displacement of a hydride from an alkoxy borohydride as efficiently as it could from a borohydride. Actually, the reduction stops after the first hydride ion is transferred to the carbonyl compound because the triethylamine reacts with the borine moiety to give triethylamine borane which apparently does *not* react with the sodium alkoxide to give the alkoxy borohydride but, instead, remains in solution as the amine borane (Et_3N-BH_3). This was suggested at once to us by the fact that we had previously found that trimethylamine borane is a very poor reducing species[12b] (in the absence of Lewis acids). Examination of the reaction mixtures from the reductions in the presence of triethylamine showed that the amine borane was, indeed, present.

(14) E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957).

(15) H. R. Nace and G. L. O'Connor, *ibid.*, **73**, 5824 (1951).

(16) All of the amine borane must be removed from the reaction mixture before injecting it into the vapor fractometer. If this is not accomplished the column is rendered completely useless for further alcohol analyses. This was an odd phenomenon and one that plagued us for some time. For some unknown reason, once a sample of the amine borane has passed through the column the column apparently absorbs the alcohol since, under normal conditions, no alcohol peaks whatsoever are observed thereafter. In one case, after several passes of alcohol into the system, approximately ten times the normal size sample was injected into the column and a small peak was observed in the alcohol region. However, even after this, a normal sized sample still showed no peaks for alcohol. Oddly enough, the ketone peak still appeared in the normal position and these columns have since been used successfully for a variety of other purposes and have behaved like normal Tide columns.

chemistry did change with each amine, but it was found that the relationship actually existed between the stereochemistry and strength of the base. This is interpreted as resulting from the fact that the weaker the base, the less efficiently it stops the reaction after the first step. Thus, the stereochemistry of the reduction in the presence of pyridine approaches that of the pure sodium borohydride reduction and, with the even weaker base N,N-dimethylaniline, the stereochemistry becomes identical with that of the borohydride in the absence of amine. Furthermore, a mixture of ketone, pyridine borane and sodium methoxide in diglyme were allowed to stand under the reaction conditions and, indeed, reduction did take place.

Finally, other amines (*e.g.*, tri-*i*-propylamine) gave amine boranes which could not, under any set of attempted conditions, be completely hydrolyzed, thus making analyses impossible. Thus, it cannot be unequivocally concluded that triethylamine does not affect the stereochemistry of the reduction. However, in view of the suggested[10] manner in which the amine accelerates the reaction, there can be little doubt but that any effect that the amine might have on the stereochemistry of the reduction would be to increase the amount of the *axial* isomer due to an increase in the importance of steric approach control.[3] Thus, it can be rather safely concluded that the values given in Table I (entries 5, 6 and 7) are maximum values for the amount of *axial* isomer produced in the first step of the reduction.

However, we felt that it might be possible to gain still further evidence for this conclusion by simulating the most probable situation existing in solution following the intermolecular transfer of the first hydride and, in this manner, examine the stereochemistry of the three last steps combined. This, in turn, would allow us to calculate at least the general range of the stereochemistry of the first step. This was accomplished by mixing 4-*t*-butylcyclohexanone with the sodium salt of the alcohol in approximately a ratio of 3:1. Diborane was then passed very slowly into the solution. Hydrolysis of the reaction mixture and analysis of the resulting product showed the mixture to contain 19.4% of the *axial* isomer. From this information, and knowing the composition of the starting alkoxide, it was possible to calculate (the reduction was quantitative; thus no problem was introduced at this point) that the actual reduction gave a mixture of 24% of the *axial* isomer and 76% of *equatorial* material. Assuming that this is an average of the last three steps, the stereochemistry of the first step was calculated as leading to 11% of the *axial* isomer. Although it was recognized that the 11% figure is only approximate due to the error inherent in the analytical technique,[17] the 11% figure is certainly in the right range to support the experimental results presented which indicate that less *axial* isomer is produced in the first reduction step than in the last three.

From this information, it should be possible to conclude whether or not the borines are responsible for the ketone reductions in the last three steps. It has been reported[12b] that the diborane reduction of 4-*t*-butylcyclohexanone with diborane in diglyme at 0° leads to a mixture of alcohol isomers consisting of only 8.5% of the *axial* isomer. However, it was recognized that this figure could not be used in determining whether or not the borines play a role in these reductions since it was demonstrated by Brown, Schlesinger and Burg[11] that in the presence of excess reducing agent diborane reductions of ketones involve use of only two of the BH_3 hydrogens, the reaction stopping at the dialkoxy borine. The above reduction was effected with excess diborane. 4-*t*-Butylcyclohexanone was therefore reduced with diborane under conditions which, at all times, maintained an excess of ketone in solution. Under these conditions, the reduction was found to give 12.6% of the *axial* isomer. From these data, it can be calculated that, if the last three steps employed only the borines, then the first reduction step must give approximately 45% of the *axial* isomer. It is therefore obvious that all of the last three reduction steps do not involve the borines. Furthermore, since the observations of Brown, Schlesinger and Burg[11] make it clear that the dialkoxyborine is the least active reducing agent of the three possibilities whereas Brown and co-workers[9,10,18] have made quite a reasonable argument that the trialkoxy borohydrides should be the most reactive of the alkoxy borohydrides, then there can be little doubt but that the agent which effects the last step in the reductions is the trialkoxy borohydride. It was hoped, at this point, that the last step could be studied directly by alternately synthesizing the tri-4-*t*-butylcyclohexyloxy borohydride and examining the stereochemistry of the reduction of the ketone with this reagent. Unfortunately, all attempts to effect the synthesis of this material failed. Thus, it is still not possible to decide just what species are actually involved in the two intermediate steps of a normal borohydride reduction.

With reference to the effect of the cations, we found it rather interesting that, whereas the sodium and magnesium borohydrides gave identical stereochemical results both in all four steps and in the first step, the lithium borohydride gave somewhat different results (Table I, entries 1–7). This was particularly interesting since the literature contains some difference of opinion regarding the participation of the cation in borohydride reductions. Thus, Hardy and Wicker[4] report a difference in the stereochemistry of the reduction of 2-methylcyclohexanone when sodium borohydride is compared with potassium borohydride. Beckett, *et al.*,[2] on the other hand, made the very reasonable suggestion that this difference may have resulted from a change in solvent rather than a change in cation. To support this suggestion they cite the fact that the reduction of tropinone with sodium borohydride and potassium borohydride in water give the same mixture of stereoisomeric tropines. Furthermore, they report that lithium borohydride in tetrahydrofuran, again, gives the same results as the sodium and potassium borohydrides in water.

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[17] An error of ±1% in the 24.5% figure introduces a possible error of ±7% in the calculated amount of the *axial* isomer in the first step.

[18] H. C. Brown, E. J. Mead and C. J. Shoaf, *J. Am. Chem. Soc.*, **78**, 3616 (1956).

From these observations, Beckett and co-workers conclude that the cation is probably not participating in the reduction. However, our results in which lithium borohydride and sodium borohydride give different results in the *same* solvent lead us to conclude that the lithium ion, at least in diglyme, does participate in the reduction. Furthermore, despite the fact that it is certainly difficult to draw an accurate picture of just what part the lithium ion does play, the fact that this cation has been found to increase the reducing properties of the borohydride in diglyme[10] solvent and the fact that the amount of the *axial* isomer decreases in the presence of the lithium ion are both certainly consistent with a suggestion that lithium is actually assisting in the polarization of the carbon oxygen double bond and, at the same time, increasing the effective size of the oxygen.

Finally, we felt that it would be interesting to examine the stereochemistry of the reduction of 4-*t*-butylcyclohexanone with a Group III cation. For this study, we selected aluminum borohydride which we felt would be particularly interesting in view of the known structure[19] of this material which causes one to conclude that there is a great deal of covalent character in the bonding between the aluminum and the borohydrides, probably involving a total of six aluminum-hydrogen-boron three-center bonds. When the reduction was effected in diglyme solution, surprisingly enough, the reaction gave the same ratio of *cis*:*trans* isomers (Table I, entry 12) as did the sodium and magnesium borohydrides. Furthermore, the reduction was effected in the presence of a large excess of triethylamine. It will be seen that the stereochemistry of the reduction changes markedly to give approximately 33% of the *axial*-alcohol (Table I, entry 13). Although it is tempting to draw conclusions from these observations; the fact that aluminum borohydride is known to react readily with both dimethyl ether and trimethylamine[20] to give complex reaction mixtures prevents us from suggesting any interpretation whatsoever of this data.

Experimental

Materials.—Lithium borohydride, sodium borohydride and a 53% dispersion of sodium hydride in mineral oil were obtained from Metal Hydrides, Inc., and were not further purified. In some of the earlier experiments, less pure sodium borohydride was purified by the method of Brown, Mead and Subba Rao.[10] Diglyme (diethyleneglycol dimethyl ether) was obtained from the Ansul Chemical Co. and purified by the method of Brown, Mead and Subba Rao.[10] The 4-*t*-butylcyclohexanone obtained from the Dow Chemical Co. was purified by recrystallization from pentane to constant m.p. Triethylamine was distilled over acetic anhydride followed by distillation over potassium hydroxide pellets.

For the purpose of calibrating the vapor fractometer, pure *cis*- and *trans*-4-*t*-butylcyclohexanol were prepared by the method of Winstein and Holness.[21]

Sodium Borohydride Solution.—A 100-ml. volumetric flask was baked dry, flushed with dry nitrogen, corked and accurately tared. Sodium borohydride was transferred to this flask in a dry-box (under nitrogen) and the flask accurately re-weighed. Dry diglyme was added to the flask in the dry-box. When the flask had then cooled back down to room temperature, the solution was made up to 100 ml. The solution was then transferred in the dry-box to a bottle fitted with a rubber cap suitable for multiple syringe withdrawals. The solution was then removed from the dry-box and 1-ml. aliquots titrated with standard KIO_3 to determine the actual hydride content. The solution which was used was found by titration to contain 0.827 mmole per ml.

Lithium Borohydride Solution.—A 25-ml. volumetric flask was baked dry, flushed with dry nitrogen, corked and placed in the dry-box. Enough $LiBH_4$ was added to the flask to exceed the solubility limits of the salt in 25 ml. of diglyme (0.4493 g.). Diglyme was added and the mixture swirled to aid in solution. The excess precipitate was allowed to settle and the clear solution transferred to a bottle fitted with a rubber cap suitable for multiple syringe withdrawals. Titration of 1-ml. aliquots with standard KIO_3 showed the solution to contain 0.5602 mmole per ml.

4-*t*-Butylcyclohexanone Solution.—Since the ketone is not hygroscopic, it was weighed accurately outside the dry-box into a 100-ml. volumetric flask which had been baked dry and flushed with dry nitrogen. The flask was then transferred to the dry-box and diglyme was added to about 5-10 ml. less than volumn. After the cool solution (from endothermic solution) had come to room temperature, the solution was made up to 100 ml. The clear solution was then transferred to a syringe bottle with a special rubber stopper. The solution contained 1 mmole per ml.

General Procedure for Borohydride Reductions.—A specially prepared 13-ml. tube, sealed at one end, was baked dry, flushed with dry nitrogen and capped with a rubber stopper suitable for injections. The solutions were injected in appropriate amounts using a hypodermic syringe of 2-ml. capacity which had also been baked dry. The tube was then placed in a constant temperature bath (20°) for 2 or 3 days, during which time it was removed periodically and agitated.

The general workup procedure for a reduction in the absence of amine was to pour the reaction mixture into 100-150 ml. of water, add several drops of HCl and shake thoroughly in a separatory funnel. The alcohol which separated was then extracted with pentane. The pentane layer was then washed twice with dilute HCl and once with water. After drying over anhydrous sodium sulfate the solution was concentrated by distilling off the pentane through a 1-foot column packed with steel sponge.

The general procedure for working up the reaction mixtures containing the amines is: The mixture was poured into a solution of 10 ml. of isopropyl alcohol, 10 ml. of 10% KIO_3 solution and about 20 ml. of water. The purpose of this procedure was to decompose the amine-borane complex which formed during the reaction. After shaking the mixture in a separatory funnel and allowing it to stand for about 15 minutes, pentane was added to extract the alcohol. After separation of the two layers, the pentane layer was washed twice with dilute HCl and once with water. Sometimes iodine formed in the aqueous layer upon the addition of the acid. This was removed by washing with 10% sodium thiosulfate solution followed by water. The pentane solution was dried over sodium sulfate and most of the pentane removed as before. However, in order to avoid ruining the column, before injecting the residue into the vapor fractometer it was checked for B-H stretch (4.2-4.3μ) by infrared. If any B-H was present, the workup procedure was repeated.

In one run with triethylamine, the reaction mixture was worked up in the same way as the reaction mixture from the borohydride reductions in the absence of the amine. Comparison of the infrared spectrum with the spectra of the two alcohols and the spectrum of triethylamine borane prepared from triethylamine and diborane showed quite conclusively that the reaction product contained a large quantity of triethylamine borane.

Magnesium Borohydride Reductions.—Kollonitsch, Fuchs and Gabor[22] have reported the preparation of alkaline earth borohydrides by the reaction of sodium borohydride with the appropriate metal chloride. These reactions were carried out in extremely dry alcoholic solutions, giving about 80% yields of products based on unreacted sodium boro-

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[19] A. R. Emery and R. C. Taylor, *Spectrochim. Acta*, **16**, 1455 (1960); R. A. Ogg, Jr., and J. D. Ray, *Disc. Faraday Soc.*, **19**, 246 (1955); W. C. Price, *J. Chem. Phys.*, **17**, 1044 (1949).

[20] H. I. Schlesinger, R. T. Sanderson and A. B. Burg, *J. Am. Chem. Soc.*, **62**, 3421 (1940).

[21] S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

[22] J. Kollonitsch, O. Fuchs and V. Gabor, *Nature*, **175**, 346 (1955).

hydride. Application of this metathetical process for the production of magnesium borohydride for our study consisted of generating the magnesium borohydride *in situ* by mixing sodium borohydride in diglyme with anhydrous magnesium chloride and then adding the ketone to this mixture. To ascertain whether the magnesium was actually involved in the reduction, a series of four reductions was examined in which the quantity of magnesium chloride was varied from the stoichiometrically calculated amount of magnesium chloride to one-fourth this amount. All of these reductions gave, within experimental error of ±1%, the same isomeric mixture of alcohols. However, there was a marked difference in the extent of reduction. As would be expected, the amount of reduction in a given time was directly dependent on the amount of magnesium chloride present.

Reductions with Diborane.—Diborane was generated external to the reaction flask by adding diglyme saturated with sodium borohydride to boron fluoride etherate.[23] Reductions were run under an atmosphere of nitrogen and diborane which escaped reacting in the reaction mixture was exited through an acetone trap and vented to the hood.

Prior to the diborane generation, solid ketone and, in one reaction, the sodium salt of the alcohol had been weighed and added to the reaction flask while it was being flushed with nitrogen. Enough diglyme was added to bring the end of the addition tube, fitted with a scintered glass plug, just below the surface of the solution. Diborane was then generated by adding the solution of sodium borohydride to the boron fluoride. Following completion of the reaction the reaction mixture was worked up in the same way that was employed for the borohydride reductions in the absence of amine.

Preparations of the Sodium Salt of 4-*t*-Butylcyclohexanol.—Several methods of preparing the alkoxide were attempted before a usable product was obtained. The method which finally produced a material which we felt was suitable for use involved stirring a mixture of 53% sodium hydride–mineral oil dispersion with an excess of the alcohol in diglyme at about 130° until hydrogen evolution had ceased. The resulting slurry was filtered under nitrogen and washed with fresh diglyme. The residue was then transferred in a dry-box to a sublimation apparatus where the remaining diglyme and alcohol were removed by heating overnight under vacuum. Analysis of the product was effected both by hydrolyzing weighed samples followed by titration with standard acid and by hydrolyzing and weighing the recovered alcohol. In analyzing the product, it was assumed that all of the alcohol had been removed from the reaction product by sublimation and that the principal contaminant was sodium hydroxide. By using these assumptions and titrating with standard acid, two samples were calculated to contain 78 and 77% of the 4-*t*-butylcyclohexanol. Calculating the percentage, alkoxide from the recovered alcohol of the two samples gave 68 and 74%, respectively. In view of the fact that the results from the experiments with the alkoxide and diborane could, as a result of the error inherent in the experimental technique, give only crude approximations of the isomeric ratio of products resulting from the first step of the reduction, the above approximate composition was certainly close enough for our purposes. For example, by simple calculations it can be easily shown that a variation of 20% in the amount of alkoxide used to calculate the composition of the first step causes a variation of only 3.5% in the calculated first step. For the results reported in the Discussion section, a value of 70% alkoxide was used.

One very interesting observation that was made in this connection was the fact that, whereas the commercial alcohol from which the alkoxide was synthesized contained 19.3% of the *axial* isomer, the alkoxide, upon hydrolysis, gave a product that contained only 2% of the *axial* isomer. Since separation of the alcohols by the physical manipulations is very unlikely, equilibration of the alkoxides apparently occurred during the reaction. We are planning on examining this further. The observed ratio of isomers was, of course, used in all of the calculations.

Preparation of Aluminum Borohydride.—Aluminum borohydride was prepared by the method of Schlesinger, Brown and Hyde.[24] Reductions with aluminum borohydride were carried out in 13 × 130 mm. tubes, sealed at one end and fitted with a stopcock and a 10/30 standard taper male joint at the other. Before placing any materials in a tube, it was first evacuated and flushed twice with nitrogen. Filled with nitrogen under positive pressure, the tube was removed from the vacuum line with its stopcock closed. Diglyme, ketone (in diglyme), etc., were introduced into the tube by means of a long hypodermic needle which extended down through the stopcock. This minimized the amount of air present in the tube. The tube was then reattached to the vacuum line and cooled in a Dry Ice–acetone-bath. The system was then evacuated and the flask containing the diglyme, etc., closed off from the rest of the system. The flask containing aluminum borohydride was then allowed to warm up until the pressure rose sufficiently to introduce the appropriate amount of aluminum borohydride. The necessary pressure had been pre-determined by standard means. When the proper pressure differential was reached, the aluminum borohydride container was closed off from the rest of the system and cooled in a liquid nitrogen-bath. The reaction tube was then cooled in a liquid nitrogen-bath and the aluminum borohydride allowed to condense in the reaction tube. Condensation was allowed to proceed until the pressure had been reduced to its original reading. The reaction tube stopcock was then closed and the rest of the system thoroughly flushed with nitrogen. The reaction tube was then removed and allowed to come to 20°. It was maintained at this temperature for 2 or 3 days and then worked up in the usual way.

Gas Chromatographic Analyses of the Reduction Products.—For the g.l.p.c. analyses, a Perkin-Elmer model 154-B vapor fractometer was used. This was operated at 140° and 25 p.s.i. internal pressure and utilized an 18-ft. coiled 0.25 in. copper tube packed with 30–60 mesh Tide detergent which had been obtained from F. & M. Scientific Corp.

Before the column was used for analysis, it was "baked" in the heating chamber of the fractometer for about 18 hours at a temperature of 180–190° and a helium pressure of 10 p.s.i. to remove excess liquid phase from the detergent packing. The liquid phase comes off initially in a discontinuous fashion, finally leveling off to a constant flow which continues through the operational life of the column.

The column was standardized by making up samples of the two isomeric alcohols of known composition and plotting the ratio of the *cis*:*trans* peak heights *vs*. the known compositions. Furthermore, it was found that the consistency of the peak height ratios improved markedly when the absolute height of the peaks was reasonably constant. For that reason injections of varying amounts of the sample were made until trial and error indicated the size sample that was necessary to give a *trans* peak height of 12 to 15 cm. By using this precaution, the reproducibility of the analyses was well within a ±1% deviation. Several measurements were taken on each sample and the average value is reported. Samples were injected in pentane solution.

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[23] H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **81**, 6428 (1959).

[24] H. I. Schlesinger, H. C. Brown and E. K. Hyde, *ibid.*, **75**, 209 (1953).