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Stereoselectivity of Lithium Aluminum Hydride and Lithium Alkoxyaluminohydride Reductions of 3,3,5-Trimethylcyclohexanone in Diethyl Ether

Robert J. McMahon, Karl E. Wiegers, and Stanley G. Smith*

School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

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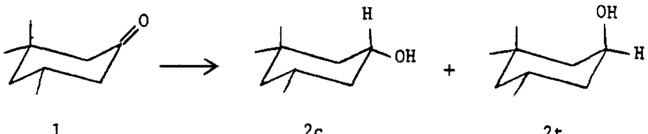
The stereochemistry of lithium aluminum hydride and lithium *tert*-butoxyaluminohydride reductions of 3,3,5-trimethylcyclohexanone in diethyl ether has been studied. An unusual nonmonotonic dependence of the percentage of *trans*-3,3,5-trimethylcyclohexanol formed upon the ratio of [*t*-BuOH]:[$LiAlH_4$] is observed. These unusual results have led to the use of diol addends to $LiAlH_4$ solutions in order to probe the role of disproportionation upon stereoselectivity. Lithium mono-*tert*-butoxyaluminohydride is proposed to have a radically different stereoselectivity from that of either $LiAlH_4$ or $LiAl(O\text{-}t\text{-}Bu)_3H$.

The stereochemistry of reduction of carbonyl compounds by lithium aluminum hydride and its alkoxide derivatives has been a subject of active interest for many years. Theories concerning the stereoselectivity of complex metal hydride reductions of cyclohexanones have been the center of considerable controversy.[1] Enantioselective reductions have been achieved by employing mixtures of $LiAlH_4$ and chiral addends,[2] but rationalization of the observed asymmetric induction has not always been straightforward. Recently, experiments employing kinetic,[3,4,5a] stereochemical,[4,5b] and optical activity[6] probes have provided further insight into the mechanism of reduction of ketones by lithium aluminum hydride and have implicated disproportionation[7] as a major factor in reductions by lithium alkoxyaluminohydrides in ether solvents.

3,3,5-Trimethylcyclohexanone (1) often has been used as a model substrate for investigation of the stereoselectivity of reducing agents, as judged by the relative amounts of *cis*- and *trans*-3,3,5-trimethylcyclohexanols (**2c** and **2t**, respectively) formed. Literature values for the fraction of **2t** formed upon reduction of 1 by $LiAlH_4$ in diethyl ether range from 52% to 68%.[5b,7,8] The preferential formation of the axial alcohol **2t** is in contrast to the predominant axial attack observed in the $LiAlH_4$ reduction of most unhindered cyclohexanones; most explanations of this reversal of stereoselectivity cite the axial 3-methyl substituent as inhibiting axial attack at the carbonyl group.

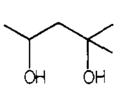


1 2c 2t

We have carried out the $LiAlH_4$ reduction of 1 utilizing the efficient mixing jet in a stopped-flow spectrophotometer to mix the ketone and hydride solutions. (This reaction is too rapid to permit measurement of reaction rates by using existing stopped-flow equipment.) Under these conditions of excess hydride, 71% of **2t** is formed reproducibly, compared to 61% when the reaction is carried out in the normal preparative fashion. The rapid mixing technique used should minimize aberrations in the data caused by local concentrations of ketone and consequent reduction through secondary alkoxyaluminohydrides, so that the 71:29 ratio of equatorial–axial hydride attack is probably a more accurate estimate of the true stereochemistry of reduction of 1 by $LiAlH_4$ in ether than was previously available.[5b,7,8]

The stereochemistry of reduction of 1 by a series of $LiAlH_4$ solutions containing 0–3 equiv of *tert*-butyl alcohol was determined, again by using the stopped-flow apparatus to ensure adequate mixing. As seen in Figure 1, the percentage of **2t** formed exhibits an unusual nonmonotonic dependence upon the [*t*-BuOH]:[$LiAlH_4$] ratio, reaching a minimum of ca. 52% when 2.3 equiv of alcohol is present. These data clearly indicate that a significant fraction of the reduction takes place via one or more of the *tert*-butoxyaluminohydride species, whereas in the slower reductions of substituted benzophenones, $LiAlH_4$ monomer (formed by disproportionation) is the kinetically dominant reducing agent.[3] It is interesting that the stereoselectivities of $LiAlH_4$ and $LiAl(O\text{-}t\text{-}Bu)_3H$ (which is stable to disproportionation in ether[3,7,9]) are nearly identical.[10] Therefore, either mono- or di-*tert*-butoxyaluminohydride reduces 1 with a stereoselectivity very different from that of either $LiAlH_4$ or $LiAl(O\text{-}t\text{-}Bu)_3H$. Alternatively, reduction by an aggregated alkoxyaluminohydride species may account for the change in stereochemistry observed, although a satisfactory interpretation of the previous kinetic data[3] did not require the participation of other than monomeric alkoxide species.

In an effort to model the active reducing agents in solution, 2-methyl-2,4-pentanediol (3) was added to $LiAlH_4$ to simulate the di-*tert*-butoxyaluminohydride species.[12]



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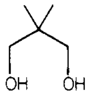

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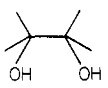

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[1] For a recent review, see D. C. Wigfield, *Tetrahedron*, **35**, 449 (1979).

[2] (a) R. Noyori, I. Tomino, and Y. Tanimoto, *J. Am. Chem. Soc.*, **101**, 3129 (1979); (b) T. H. Johnson and K. C. Klein, *J. Org. Chem.*, **44**, 461 (1979), and references therein.

[3] K. E. Wiegers and S. G. Smith, *J. Am. Chem. Soc.*, **99**, 1480 (1977).

[4] K. E. Wiegers and S. G. Smith, *J. Org. Chem.*, **43**, 1126 (1978).

[5] (a) E. C. Ashby and J. R. Boone, *J. Am. Chem. Soc.*, **98**, 5524 (1976); (b) E. C. Ashby and J. R. Boone, *J. Org. Chem.*, **41**, 2890 (1976).

[6] T. H. Johnson and G. Rangarajan, *J. Org. Chem.*, **44**, 3966 (1979).

[7] H. Haubenstock and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2363 (1962).

[8] E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2441 (1970).

[9] (a) E. C. Ashby, F. R. Dobbs, and H. P. Hopkins, Jr., *J. Am. Chem. Soc.*, **97**, 3158 (1975); (b) H. C. Brown and H. R. Deck, *ibid.*, **87**, 5620 (1965); (c) H. C. Brown and R. F. McFarlin, *ibid.*, **80**, 5372 (1958).

[10] The stereochemistry of reduction by $LiAl(O\text{-}t\text{-}Bu)_3H$ does not depend upon the mixing method used, as expected for this much slower[11] reaction.

[11] J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Lett.*, 6127 (1968).

[12] 2,4-Dimethyl-2,4-pentanediol would be a better model, but a precipitate was observed at a [diol]:[$LiAlH_4$] ratio of 0.4.

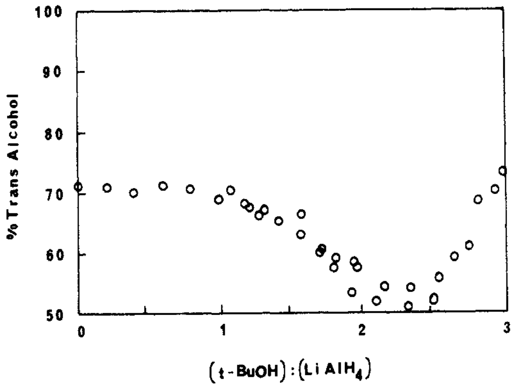


Figure 1. Plot of percent *trans*-3,3,5-trimethylcyclohexanol formed vs. the ratio of *tert*-butyl alcohol to lithium aluminum hydride in diethyl ether at 25.0 °C.

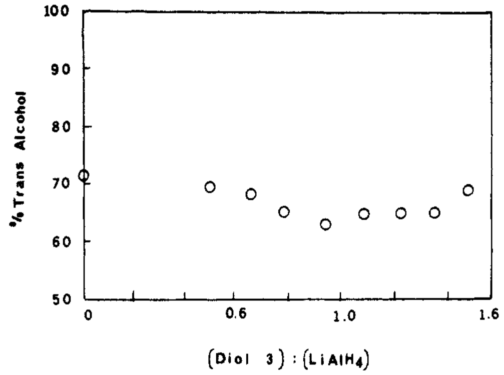
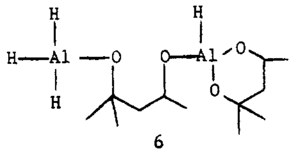


Figure 2. Plot of percent *trans*-3,3,5-trimethylcyclohexanol formed vs. the ratio of [3]:[$LiAlH_4$] in diethyl ether at 25.0 °C.

The results (Figure 2) do not show the dramatic minimum in the percentage of **2t** formed that was seen in the case of reduction by the *tert*-butoxides. To ensure that these results were not an anomaly peculiar to diol **3**, reduction was also carried out in the presence of diols **4** and **5** (Figure 3). The absence of a pronounced minimum in the case of all three diols indicates that $LiAl(O\text{-}t\text{-}Bu)_2H_2$ is probably not responsible for the change in stereoselectivity depicted in Figure 1. The possibility of partial reduction by mixed alkoxyaluminohydride aggregates (e.g., **6**) cannot be ruled out.



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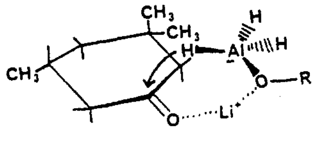
The remaining conclusion is that the mono-*tert*-butoxyaluminohydride is most likely responsible for the observed change in stereoselectivity. The presence of a single oxygen atom in the alkoxide moiety permits formation of a cyclic six-membered transition state as shown in structure I. In the case of di- or tri-*tert*-butoxyaluminohydride,



I

the lithium ion is probably associated between the two or three oxygen atoms of the alkoxide moieties and therefore is not able to direct the reducing agent into the position shown in I. Since the alkoxide group is directed away from the cyclohexanone ring, it does not interact with the axial 3-methyl substituent.

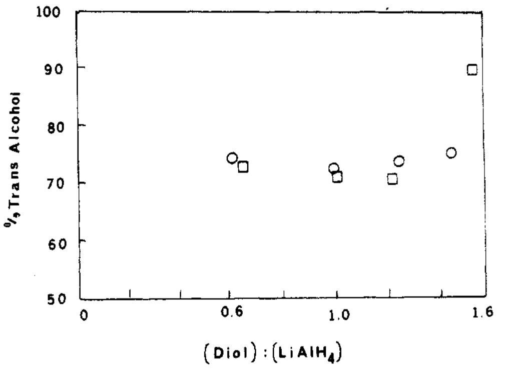


Figure 3. Plot of percent *trans*-3,3,5-trimethylcyclohexanol formed vs. the ratio of [4]:[$LiAlH_4$] (○) and [5]:[$LiAlH_4$] (□) in diethyl ether at 25.0 °C.

Evidence for lithium ion participation in directing stereoselective reductions of heterosubstituted cyclohexanones has been proposed in the past[13,14] and is consistent with the present data. The reduction of **1** by *tert*-butoxyaluminohydrides in tetrahydrofuran (THF) does not show this effect,[4] perhaps as a result of increased solvation of lithium ion by THF compared to ether. The alkoxide oxygen cannot compete as effectively for the lithium ion, thereby decreasing its directing ability.

Although specific rate constants are not known for the reduction of **1** by aluminohydride reagents in diethyl ether, it is believed that reduction by $LiAlH_4$ is much faster than that by the mono-*tert*-butoxide, which is in turn faster than reduction by the di-*tert*-butoxide.[3,4] As long as $LiAlH_4$ is present in solution, reduction will proceed through that species. Only at [*t*-BuOH]:[$LiAlH_4$] ratios near 2 is the concentration of mono-*tert*-butoxide (which is present as a consequence of disproportionation) high enough and the concentration of $LiAlH_4$ low enough to actually observe the effects of reduction by the mono-*tert*-butoxide. Even though the concentration of di-*tert*-butoxide at these ratios is significant, its reactivity is probably low enough so that it does not participate in reduction to a significant extent. The actual distribution of the various alkoxyaluminohydride species present at a given ratio of alcohol to $LiAlH_4$ is not known.

This proposal explains the results obtained when the reaction of **1** with $LiAlH_4$ is carried out under conditions of inadequate mixing. If local concentrations develop, reduction will proceed through the monoalkoxyaluminohydride derived from the ketone, which favors formation of the equatorial alcohol **2c**. As a result, the amount of axial alcohol **2t** will be lower than that obtained under efficient mixing conditions (71% of **2t**).

The data in Figure 3 also indicate that, when ca. 1.5 equiv of diol are present in the hydride solution, reaction with **1** yields 75% of alcohol **2t** in the case of diol **4** but 90% of **2t** with diol **5**. The latter value is among the highest ever reported for reduction of ketone **1** by an alkoxyaluminohydride reagent in diethyl ether. The different stereochemistry observed in the cases of the bis primary alcohol **4** and the bis tertiary alcohol **5** are similar to results obtained with methoxides and *tert*-butoxides in THF[4] and suggest that the extent of disproportionation of primary and tertiary alkoxyaluminohydrides may be

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(13) E. Costes, C. Bernard, and L. Lattes, *Tetrahedron Lett.*, 1185 (1976).

(14) C. Bernard, M. Maurette, and A. Lattes, *Bull. Soc. Chim. Fr.*, 145 (1976).

different in diethyl ether solvent as well as in THF.

Experimental Section

Materials. Lithium aluminum hydride (Ventron) was used without further purification. Solutions of $LiAlH_4$ were analyzed for total hydride concentration by the Felkin iodine titration method.[15] A quantity of sample was injected into 0.4 N iodine in benzene. Water, ethanol, and acetic acid were added, and the solution was back-titrated with standard 0.1 N sodium thiosulfate.

3,3,5-Trimethylcyclohexanone (**1**) was prepared by the catalytic hydrogenation of isophorone as described elsewhere.[4] *tert*-Butyl alcohol (Baker) was dried by passage through a 40-cm column of Linde 4-Å molecular sieves, followed by distillation. 2-Methyl-2,4-pentanediol (**3**, Eastman) was dried over 4-Å molecular sieves. 2,3-Dimethyl-2,3-butanediol (**4**, Aldrich) and 2,2-dimethyl-1,3-propanediol (**5**, Aldrich) were dissolved in anhydrous ether, and the solutions were dried over 4-Å molecular sieves. The sieves were filtered off over a pad of glass wool in a nitrogen-filled glovebag, and solvents were removed on a rotary evaporator. The rotary evaporator was vented with dry nitrogen.

Solutions. Solutions of lithium aluminum hydride were prepared in an all-glass, grease-free Schlenk apparatus. The system was dried under vacuum and purged with argon several times prior to use. All manipulations were carried out under positive argon pressure. Residual oxygen was scavenged from Linde high-purity argon by passage through a 30 cm × 5 cm diameter column of BASF Corp. BTS catalyst. The argon was then passed through a similar column of Linde 4-Å molecular sieves to remove H_2O.

Reagent grade diethyl ether (Mallinckrodt) was distilled from $LiAlH_4$ through a 20-cm Vigreux column onto $LiAlH_4$. The solution was stirred for 30 min, and then after being allowed to settle it was filtered twice through sintered glass and was delivered to silicone rubber-serum-capped bottles. All $LiAlH_4$ solutions were clear and colorless.

Solutions of 3,3,5-trimethylcyclohexanone were prepared by injecting a weighed amount of ketone into vacuum-dried bottles of diethyl ether distilled from $LiAlH_4$. The volume of solvent was calculated from its weight.

Alkoxyaluminohydride solutions were prepared in one of two fashions. In the case of liquid alcohols, a weighed amount of alcohol was injected slowly into a known volume of standardized $LiAlH_4$ solution. Solutions with $[t\text{-BuOH}]:[LiAlH_4]$ ratios greater than ca. 2.5 formed white $LiAlH(O\text{-}t\text{-}Bu)_3$ precipitates. All solutions of 2-methyl-2,4-pentanediol (**3**) were clear and colorless. Solid alcohols **4** and **5** were dissolved in a minimum amount of diethyl ether distilled from sodium benzophenone ketyl. A weighed amount of a solution of known concentration was injected into a known volume of standardized $LiAlH_4$. Both of these solutions formed precipitates at $[\text{diol}]:[LiAlH_4]$ ratios greater than ca. 1.25.

Reduction Products. Equal volumes of ketone and hydride solutions were mixed at 25.0 °C by using an ultraviolet stopped-flow spectrophotometer described previously.[16] Hydride concentrations were 0.027–0.055 M, and the concentration of ketone **1** was ca. 0.005 M. After being allowed to stand approximately 1 min, the effluent from the instrument was quenched in 0.1 M aqueous phosphate buffer (75 mL; pH = 7) at 0 °C. The organic layer was removed. The aqueous layer was acidified with 1 N H_2SO_4 to dissolve the salts, followed by extraction with ether (2 × 25 mL). The ethereal layers were combined, washed with 10% aqueous $NaHCO_3$ (1 × 30 mL), and dried over $MgSO_4$. After filtration, the solvent was removed on a rotary evaporator or by fractional distillation. The residue was analyzed by gas chromatography on a F&M Model 700 gas chromatograph equipped with a thermal conductivity detector. Peak areas were measured by disk integration.

Products of the reduction of **1** using *tert*-butyl alcohol or **3** were separated on a 12 ft × 0.125 in., 15% Carbowax 20M on 60/80 Chromosorb W (DMCS) column, with an oven temperature of 150 °C and a helium flow rate of 20 mL/min. The following compounds are listed in order of increasing retention times: *tert*-butyl alcohol, **1**, **2t**, **2c**, **3**. Compounds **2t** and **2c** were isolated by preparative gas chromatography, and the structural assignments were confirmed by comparing their melting points with those reported in the literature.[17]

Products of the reduction of **1** using **4** or **5** were separated on a 12 ft × 0.125 in., 15% FFAP on 60/80 Chromosorb W (DMCS) column, with an oven temperature of 110 °C and a helium flow rate of 25 mL/min. Mesitylene was used as an internal standard. The retention time of **2c** was 40 min. The following compounds are listed in order of increasing retention times: mesitylene, **1**, **5**, **2t**, **2c**. Compound **4** was very highly retained and occasionally bled off the column, causing base-line interference.

Analyses of product mixtures containing any one of the diols sometimes showed early peaks of significant size in the gas chromatograms, which were presumed, on the basis of absolute yield calculations, to be diol elimination products.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. **1**, 873-94-9; **2c**, 933-48-2; **2t**, 767-54-4; **3**, 107-41-5; **4**, 126-30-7; **5**, 76-09-5; diethyl ether, 60-29-7; $LiAlH_4$, 16853-85-3; *t*-BuOH, 75-65-0; $LiAlH(O\text{-}t\text{-}Bu)_3$, 17476-04-9; $LiAlH_3(O\text{-}t\text{-}Bu)$, 24507-64-0; $LiAlH_2(O\text{-}t\text{-}Bu)_2$, 24315-46-6.

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[15] H. Felkin, *Bull. Soc. Chim. Fr.*, 347 (1951).

[16] S. G. Smith, L. F. Charbonneau, D. P. Novak, and T. L. Brown, *J. Am. Chem. Soc.*, **94**, 7059 (1972).

[17] E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961).

Lithium Aluminum Hydride–Aluminum Hydride Reduction of Sultones

Michael B. Smith and Joseph Wolinsky*

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

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Lithium aluminum hydride–aluminum hydride reduction of secondary and tertiary (C–O) substituted γ-sultones or α-alkyl-β′-hydroxy γ-sultones yields mercapto alcohols and mercapto diols, respectively, in fair to good yield. These products result from S–O cleavage of the sultone ring. Primary sultones and α-dialkyl-β′-hydroxy γ-sultones give predominantly C–O cleavage to form sulfonic acid derivatives. δ-Sultones are much less reactive toward the mixed hydride, and refluxing in dioxane is required for their reduction.

Dithianes,[1] sulfides,[2] sulfoxides[3] and sulfones[4] have found extensive and practical use as activating and masking groups in synthetic organic chemistry.[5] The comparable use of sultones[6] has been severely limited by

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