Kinetics and Mechanism of Lithium Aluminum Hydride and Lithium Alkoxyaluminohydride Reductions of Ketones in Tetrahydrofuran

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The kinetics of reaction of camphor with excess lithium and sodium aluminum hydride were studied by stopped-flow UV spectroscopy in tetrahydrofuran solution at 25.0 °C. The reductions are first order in camphor and first order in $LiAlH_4$. Reduction by $NaAlH_4$ is ca. ten times slower than reduction by $LiAlH_4$, and the pseudo-first-order rate constants are nonlinearly dependent upon $NaAlH_4$ concentration. The kinetics and products of reaction of camphor and the products of reaction of 3,3,5-trimethylcyclohexanone with lithium *tert*-butoxyaluminohydrides and lithium methoxyaluminohydrides are consistent with disproportionation of the alkoxide species, with reduction taking place predominantly through $LiAlH_4$ itself. The rate of reduction of camphor by $LiAlH_4$ is depressed by the addition of either lithium bromide or crown ether **4**. The rate decreases linearly with increasing [crown ether]/[$LiAlH_4$] ratio but is nonzero at a ratio of 1.0. A complex of the crown ether and $LiAlH_4$ was isolated, and the rate of reaction of the complex with camphor was measured.

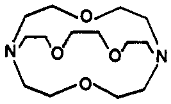
The mechanism and stereochemistry of reduction of ketones by lithium aluminum hydride and its alkoxide derivatives have been the subject of much investigation. Most mechanistic proposals have been based on the relative yields of epimeric alcohols formed upon reduction of model ketones by various hydride reagents.[2-12] In addition, some kinetic studies have been conducted.[13-16]

Mechanistic studies have been limited by a lack of information regarding the composition of complex metal hydrides in solution. Ashby, Dobbs, and Hopkins recently reported the results of association measurements on several complex metal hydrides in diethyl ether and tetrahydrofuran (THF) solutions.[17] Both lithium and sodium aluminum hydride are reported to exist as ion pairs or triple ions in THF,[17a] with the association i values for both hydrides ranging from about 1.0 at 0.04 m to 1.7 at 0.4 m. In contrast, $LiAlH_4$ in ether is more highly associated, with i varying from 1.75 to 2.2 between 0.1 and 0.45 m.[17b] Association curves for some lithium methoxy- and *tert*-butoxyaluminohydrides in THF were also reported.[17b]

Recently we reported on the kinetics of reduction of several alkyl-substituted benzophenones by $LiAlH_4$ and lithium *tert*-butoxyaluminohydrides in ether.[16] With $LiAlH_4$ in ether we found that the principal reducing agent in solution is monomeric lithium aluminum hydride, although the dimer may exhibit a small reactivity with less hindered ketones. The lithium *tert*-butoxyaluminohydride system is characterized by partial disproportionation[3,18] of the alkoxides, and the available data indicate that $LiAlH_4$ is the dominant reducing agent, although lithium mono-*tert*-butoxyaluminohydride may also serve as a hydride donor.

In contrast to these kinetic results obtained in ether, the reduction of 2,4,6-trimethylbenzophenone by $LiAlH_4$ and $NaAlH_4$ in THF was reported to be first order in ketone and first order in hydride,[15] as were the reactions of some substituted benzophenones[14] and cyclohexanones[13] with $LiAl(O\text{-}t\text{-}Bu)_3H$ in THF.

The role of the cation in ketone reductions with aluminohydrides has received much attention. The requirement of electrophilic catalysis, either by a cation or by protic solvent, in reductions with the related borohydrides is well-documented,[19] and House[20] has suggested that the mechanism of reduction of ketones by $LiAlH_4$ involves prior or concurrent association of the lithium ion with the carbonyl oxygen atom. It has been suggested that the reduction of 2,4,6-trimethylbenzophenone in THF involves the solvent-separated $LiAlH_4$ ion pair as the reactive species, with the lithium ion coordinated to the carbonyl oxygen in a six-centered transition state.[15] Pierre and Handel[21] concluded that the lithium ion is an essential catalyst in the aluminohydride reduction of many functional groups, based on the observation of no reaction in the presence of the lithium ion complexing agent [2.1.1]cryptand (**1**). Variations in the stereochemistry of reduction of ketones with the nature or concentration of cation have been interpreted in terms of complexation of the carbonyl oxygen by the cation prior to or synchronous with hydride transfer.[10,21c,d]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The purpose of the present research was to determine the kinetics and mechanism of reduction of ketones by lithium aluminum hydride and the lithium methoxy- and *tert*-butoxyaluminohydrides in THF solution. Camphor (**2**) was selected as a substrate because of its convenient rate level and because of its previous use in studies of stereoselectivity of complex metal hydrides.[4,10b] The quantitative dependence of the rate of reduction upon lithium ion concentration was also investigated. Studies of lithium ion dependence and of reduction by the lithium methoxyaluminohydrides were hindered in diethyl ether by solubility limitations.

Results and Discussion

Reduction of Camphor by $LiAlH_4$. The rate of disappearance of camphor was measured at 290 nm by stopped-flow ultraviolet spectroscopy at 25.0 °C in THF solution at ketone concentrations of 0.003–0.0102 M and $LiAlH_4$ concentrations of 0.0208–0.177 M. In all cases excellent adherence to a first-order rate law was observed throughout a kinetic run. The measured first-order rate constants were independent of initial ketone concentration, indicating the reaction to be first order in camphor.

The dependence of the observed first-order rate constants upon the concentration of $LiAlH_4$ is linear with zero intercept (Figure 1), indicating the reduction of camphor to be first order in $LiAlH_4$ in tetrahydrofuran solvent (eq 1). Unweighted linear least-squares analysis of the kinetic data in Figure 1 yields a second-order rate constant k_1 of 181 ± 5 $M^{-1}\,s^{-1}$ (r = 0.994).

$$-d[\text{camphor}]/dt = k_1[LiAlH_4][\text{camphor}] \qquad (1)$$

These kinetic orders are in agreement with the report[15] that the reduction of 2,4,6-trimethylbenzophenone in THF is first

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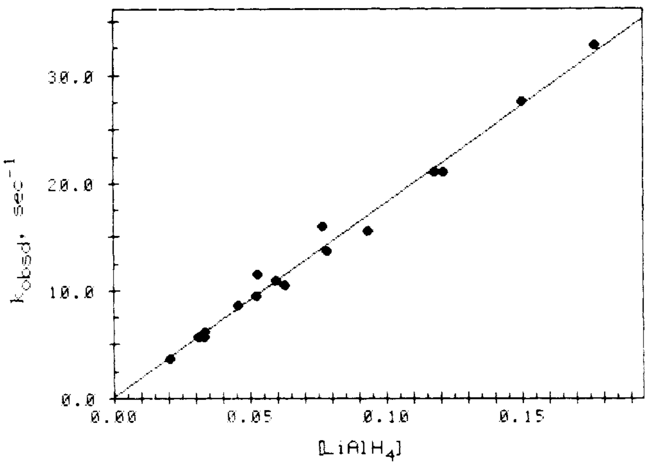


Figure 1. Plot of k_{obsd} vs. [LiAlH$_4$] for reduction of camphor in THF at 25.0 °C.

order in ketone and in LiAlH$_4$. However, these results are in marked contrast to the observed one-half order in LiAlH$_4$ for reduction of 2,4,6-trimethylbenzophenone in diethyl ether.[16] The one-half order dependence was ascribed to reaction taking place primarily through monomeric lithium aluminum hydride in equilibrium with the dimer, which predominates in solution. That reduction of camphor in THF is first order in LiAlH$_4$ is consistent with the known[17] lesser degree of molecular association of LiAlH$_4$ in THF than in ether.

Reduction of Camphor by Lithium Alkoxyaluminohydrides. The kinetics of reaction of camphor with a series of reagents prepared by adding various quantities of dry *tert*-butyl alcohol or methanol to standard stock solutions of LiAlH$_4$ in THF also were measured. The observed pseudo-first-order rate constants decrease markedly as the molar ratio of alcohol to LiAlH$_4$ increases from 0 to 3. The variation in rate constants with the [*t*-BuOH]/[LiAlH$_4$] ratio is seen in Figure 2 and the variation with the [CH$_3$OH]/[LiAlH$_4$] ratio in Figure 3. The measured values of k_{obsd} are divided by k_{obsd} for LiAlH$_4$ alone at the concentration of total aluminum used in order to obtain the relative rate constant, k_{rel}. Each reaction displayed good first-order kinetics within a run.

The dependence of k_{rel} upon the [*t*-BuOH]/[LiAlH$_4$] ratio for reduction of camphor (Figure 2) is very similar in shape to the corresponding curves obtained for reductions of several benzophenones in ether.[16] The effect of *t*-BuOH on k_{rel} thus may be interpreted in terms of disproportionation of the alkoxyaluminohydrides to regenerate LiAlH$_4$, as in the following equations. In the absence of adequate data, all hydride species are assumed to be monomeric in this scheme.

$$2\mathrm{LiAl(O}\text{-}t\text{-}\mathrm{Bu)H_3} \xrightleftharpoons{K_1} \mathrm{LiAlH_4} + \mathrm{LiAl(O}\text{-}t\text{-}\mathrm{Bu)_2H_2}$$

$$2\mathrm{LiAl(O}\text{-}t\text{-}\mathrm{Bu)_2H_2} \xrightleftharpoons{K_2} \mathrm{LiAl(O}\text{-}t\text{-}\mathrm{Bu)H_3} + \mathrm{LiAl(O}\text{-}t\text{-}\mathrm{Bu)_3H}$$

$$k_{calcd} = k_1[\mathrm{LiAlH_4}] + k_2[\mathrm{LiAl(O}\text{-}t\text{-}\mathrm{Bu)H_3}] \quad (2)$$

It was not necessary to consider the third stage of disproportionation, since LiAl(O-*t*-Bu)$_4$ cannot be formed in THF under these conditions.[22]

Computer simulation of the kinetic data using this model was carried out using the interactive graphics of the PLATO IV computer-based education system.[23] The equilibrium concentrations of all hydride species at a given ratio of alcohol to LiAlH$_4$ were calculated to satisfy the specified values of the disproportionation equilibrium constants. A theoretical curve of k_{rel} vs. [*t*-BuOH]/[LiAlH$_4$] was then calculated using the known value of the rate constant for reaction of LiAlH$_4$ with camphor. A very good fit to the data is obtained when a term representing the contribution from the mono-*tert*-butoxyaluminohydride species is included in the rate law (eq 2). The curve shown in Figure 2 was calculated from eq 2 using values of 0.3 for K_1, 0.05 for K_2, 181 for k_1, and 120 for k_2. While there is some uncertainty in the numerical values of these parameters, it is clear that the mechanism of reaction of camphor with the lithium *tert*-butoxyaluminohydrides in THF is very similar to that of analogous reactions in diethyl ether.

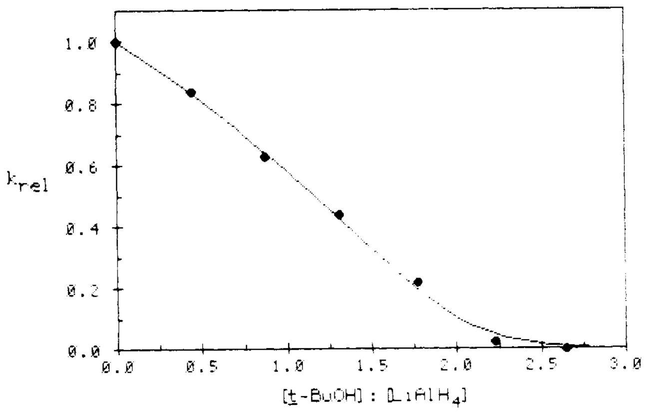


Figure 2. Plot of k_{rel} vs. [*t*-BuOH]/[LiAlH$_4$] for reduction of camphor (0.01 M). Initial LiAlH$_4$ concentration 0.118 M. The line was calculated from eq 2.

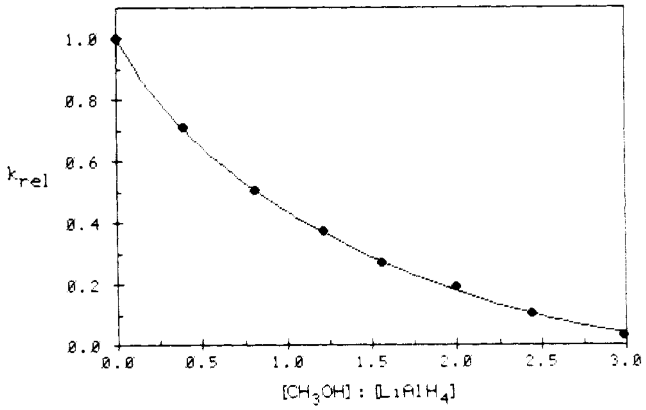


Figure 3. Plot of k_{rel} vs. [CH$_3$OH]/[LiAlH$_4$] for reduction of camphor (7.5×10^{-3} M). Initial LiAlH$_4$ concentration 0.0768 M. The line was calculated from eq 3.

The dependence of k_{rel} upon the [CH$_3$OH]/[LiAlH$_4$] ratio (Figure 3) is markedly different from that seen with the *tert*-butoxyaluminohydrides. Not only are the shapes of the curves different, but the relative reactivity at a molar ratio of 3.0 is much greater in the methoxyaluminohydride system. The work of Brown and Shoaf[24] indicates that all four hydrides on LiAlH$_4$ may react with methanol in THF, and thus a more extensive disproportionation scheme is indicated than used for the *tert*-butoxyaluminohydrides.[17b] All methoxides were regarded as monomeric in the absence of definitive association data.

$$2\mathrm{LiAl(OCH_3)H_3} \xrightleftharpoons{K_1} \mathrm{LiAlH_4} + \mathrm{LiAl(OCH_3)_2H_2}$$

$$2\mathrm{LiAl(OCH_3)_2H_2} \xrightleftharpoons{K_2} \mathrm{LiAl(OCH_3)H_3} + \mathrm{LiAl(OCH_3)_3H}$$

$$2\mathrm{LiAl(OCH_3)_3H} \xrightleftharpoons{K_3} \mathrm{LiAl(OCH_3)_2H_2} + \mathrm{LiAl(OCH_3)_4}$$

$$k_{calcd} = k_1[\mathrm{LiAlH_4}] \quad (3)$$

Table I. Products from Reaction of Lithium *tert*-Butoxyaluminohydrides with Camphor in THF at 25.0 °C[a]

[*t*-BuOH]/[$LiAlH_4$]	% exo alcohol[b]
0.0	92
0.446	92
0.874	90
1.31	91
1.77	90
2.23	91
2.65	91
3.00	96

[a] Total Al concentration = 0.118 M. Camphor = ca. 0.01 M. [b] Average of 3–5 quantitative gas chromatographic analyses. All values have an uncertainty of ca. ±1.5%.

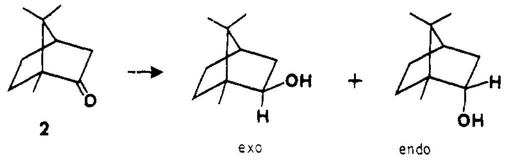
Table II. Products from Reaction of Lithium Methoxyaluminohydrides with Camphor in THF at 25.0 °C[a]

[CH_3OH]/[$LiAlH_4$]	% exo alcohol[b]
0.0	93
0.391	92
0.813	93
1.22	93
1.56	92
2.00	93
2.44	92
3.14	92

[a] Total Al concentration = 0.0768 M. Camphor = ca. 0.0075 M. [b] Average of 3–5 quantitative gas chromatographic analyses. All values have an uncertainty of ca. ±1%.

Computer modeling of the data in Figure 3 according to this scheme leads to an excellent fit using values of $K_1 = K_2 = K_3 = 0.9$, with only $LiAlH_4$ regarded as an active reducing agent ($k_1 = 181$ in eq 3). While the simple assumptions of monomeric hydrides and equality of the equilibrium constants are not necessarily accurate, the data do not require postulation of a more complicated reaction scheme.

The available evidence which indicates that disproportionation takes place in both the lithium methoxyaluminohydride and *tert*-butoxyaluminohydride systems in THF[18,24] suggests that discrete species containing one or two alkoxide ligands are *not* formed when 1 or 2 equiv of alcohol react with $LiAlH_4$. Reported association data[17b] on such alkoxyaluminohydrides probably represent a weighted average degree of association of all species present in solution. Associated species may be involved in the alkoxyaluminohydride reactions but are not required to describe these kinetic data.



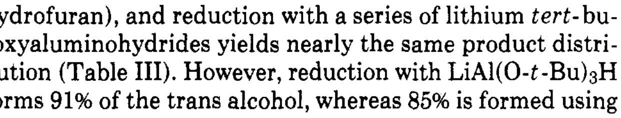
Products of Reaction of Ketones with Lithium Alkoxyaluminohydrides. The products of reduction of camphor (**2**) by the various alkoxyaluminohydrides were determined by gas chromatographic analysis of the quenched effluent from the stopped-flow instrument. Within experimental error, reduction with all of the lithium *tert*-butoxyaluminohydride solutions yielded the same mixture of products as obtained from reduction by $LiAlH_4$ itself, containing an average of 91% of the exo alcohol (Table I). ($LiAlH_4$ reduction of camphor in THF is reported to yield 91–92% of the exo alcohol.[4,10b]) However, reduction by $LiAl(O\text{-}t\text{-}Bu)_3H$ formed 96% of the exo alcohol (lit.[4] 97%). These data suggest that $LiAlH_4$ is responsible for most of the reduction of camphor, regardless of the [*t*-BuOH]/[$LiAlH_4$] ratio, in agreement with the kinetic data. Similarly, reduction of camphor with all of the methoxyaluminohydride solutions gave an essentially constant 92% exo alcohol (Table II), as did reaction with stoichiometric $LiAl(OCH_3)_3H$ (lit.[4] 99%). The kinetic evidence for three stages of disproportionation does indicate that the trimethoxide species should exhibit a selectivity comparable to that of pure $LiAlH_4$, as observed. The discrepancy between the present and the reported values for reduction by $LiAl(OCH_3)_3H$ may be due to the fact that reactions were carried out at different temperatures.

Table III. Products from Reaction of Lithium *tert*-Butoxyaluminohydrides with 3,3,5-Trimethylcyclohexanone in THF at 25.0 °C[a]

[*t*-BuOH]/[$LiAlH_4$]	% trans alcohol[b]
0.0	83
0.413	83
0.773	82
1.17	82
1.58	82
1.97	82
2.57	77
3.00	91

[a] Total Al concentration = 0.0635 M. Ketone = ca. 0.006 M. [b] Average of 3–5 quantitative gas chromatographic analyses. All values have an uncertainty of ca. ±1%.

Camphor may not be a very sensitive probe for changes in stereochemistry of reduction, since it is a highly hindered ketone which exhibits a substantial bias for formation of a single product even upon reaction with $LiAlH_4$. Therefore, the products of reduction of 3,3,5-trimethylcyclohexanone (**3**) by



the lithium methoxy- and *tert*-butoxyaluminohydrides were also determined, using the efficient mixing chamber in the stopped-flow instrument. (The rate of reaction of ketone **3** with $LiAlH_4$ is too rapid to measure with our current stopped-flow equipment.) Reduction by $LiAlH_4$ yields 83% *trans*-3,3,5-trimethylcyclohexanol (lit.[3,10b] 74–89% in tetrahydrofuran), and reduction with a series of lithium *tert*-butoxyaluminohydrides yields nearly the same product distribution (Table III). However, reduction with $LiAl(O\text{-}t\text{-}Bu)_3H$ forms 91% of the trans alcohol, whereas 85% is formed using stoichiometric $LiAl(OCH_3)_3H$. These results further support the concept of disproportionation and predominant reaction through $LiAlH_4$, although $LiAl(O\text{-}t\text{-}Bu)_3H$ itself does exhibit a greater stereoselectivity than do the other *tert*-butoxyaluminohydride solutions, suggesting that it does not undergo disproportionation.

Reduction of Camphor by $NaAlH_4$. The rate of reduction with $NaAlH_4$ was measured at hydride concentrations of 0.0222–0.185 M in THF. As seen in Figure 4, the pseudo-first-order rate constants exhibit a nonlinear dependence upon the $NaAlH_4$ concentration, with an apparent order of 0.73. Ashby and Boone[15] reported that reduction of 2,4,6-trimethylbenzophenone with dilute solutions of $NaAlH_4$ in THF is first order in hydride. Our attempts to examine the carbonyl region of the infrared spectrum of a reacting solution of camphor and sodium aluminum hydride were unsuccessful due to interfering absorbances by solvent and hydride. The

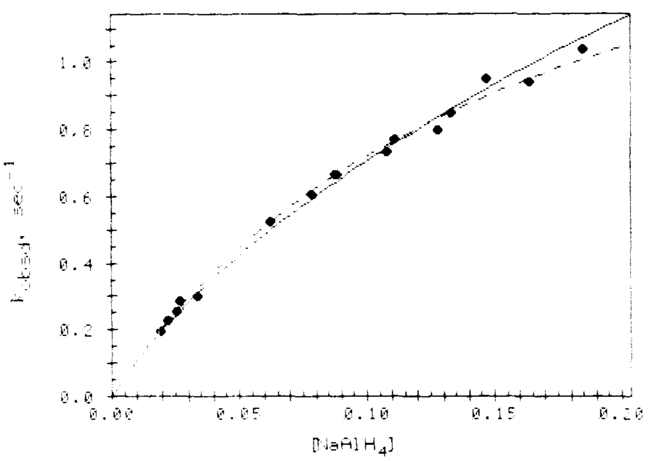


Figure 4. Plot of k_{obsd} vs. [NaAlH$_4$] for reduction of camphor in THF at 25.0 °C. The solid line was calculated from eq 4. The dashed line was calculated assuming the formation of an intermediate.

Table IV. Products from Reaction of Lithium Methoxyaluminohydrides with 3,3,5-Trimethylcyclohexanone in THF at 25.0 °C[a]

[CH$_3$OH]/[LiAlH$_4$]	% trans alcohol[b]
0.0	82
0.427	82
0.868	80
1.24	80
1.70	81
2.03	80
2.52	80
3.03	85

[a] Total Al concentration = 0.0445 M. Ketone = ca. 0.005 M. [b] Average of 3–5 quantitative gas chromatographic analyses. All values have an uncertainty of ca. ±1%.

reduction of camphor by NaAlH$_4$ formed 90% of the exo alcohol.

Several mechanistic possibilities could give rise to curvature in the plot of k_{obsd} vs. [NaAlH$_4$]. The curvature may be due to molecular association of the hydride, with reaction taking place via a monomeric species (as seen in reactions of organolithium reagents[25] and lithium aluminum hydride[16] with ketones in ether); or it could reflect the presence of an intermediate along the reaction pathway (as seen in reactions of Grignard reagents with ketones[26]).

Ashby's data suggest that NaAlH$_4$ is moderately associated in THF solution,[17b] and if monomeric NaAlH$_4$ is the reactive species, then an apparent order in stoichiometric NaAlH$_4$ less than 1.0 would be observed. Thus, the mechanism below may be used to describe the data in Figure 4. A good fit to the data is obtained using values of 6 M^{-1} for K and 12 M^{-1} s^{-1} for k_3; the theoretical plot of k_{obsd} vs. stoichiometric [NaAlH$_4$] is the solid line in Figure 4.

$$2\mathrm{NaAlH_4} \xrightleftharpoons{K} (\mathrm{NaAlH_4})_2$$

$$\mathrm{NaAlH_4} + \text{camphor} \xrightarrow{k_3} \text{products}$$

$$k_{obsd} = k_3[\mathrm{NaAlH_4}] \tag{4}$$

The expected association i values calculated for NaAlH$_4$ using the value of 6 M^{-1} for the monomer–dimer equilibrium constant give qualitative agreement with Ashby's experimental data. However, it is not entirely satisfying to explain the different kinetic behavior of reactions of LiAlH$_4$ and NaAlH$_4$ on the basis of association, as the states of aggregation for both hydrides are reported to be very similar.[17b] Differences in the relative reactivities of monomer and dimer in the two cases could account for the different shapes of the curves in Figures 1 and 4.

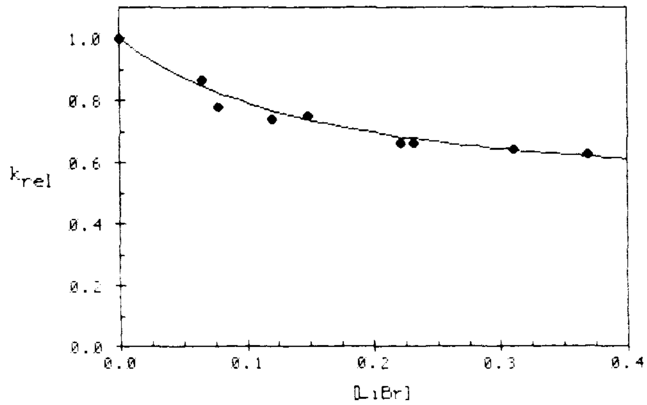


Figure 5. Plot of k_{rel} vs. [LiBr] for the reduction of camphor (4.92 × 10^{-3} M) with 0.053 M LiAlH$_4$ in THF at 25.0 °C.

The data in Figure 4 were also analyzed in terms of formation of an intermediate. The theoretical curve calculated on this basis is the dashed line in Figure 4, and clearly describes the data quite well. However, the results of UV spectral studies of ketones in the presence of LiClO$_4$ and NaClO$_4$ (see Experimental Section) suggest that complexation of the carbonyl group in camphor takes place less readily with a sodium ion than with a lithium ion. The formation of an intermediate of this type between camphor and NaAlH$_4$ is thus regarded as unlikely.

Both the association model and the intermediate model can yield comparable fits to the experimental kinetic data. We conclude that it is not possible to distinguish between these mechanistic possibilities using the available data. It is of interest to note that, below about 0.05 M, the association model, the presence of an intermediate, and a simple second-order reaction all will approach a linear dependence of k_{obsd} upon the NaAlH$_4$ concentration. It is thus likely that the apparent discrepancy between our results on the NaAlH$_4$ reduction of camphor and those of Ashby[15] for the reduction of 2,4,6-trimethylbenzophenone simply reflects the fact that Ashby's experiments were conducted using quite dilute (<0.05 M) solutions of NaAlH$_4$, in which any curvature may be so slight as to go undetected.

Effect of Lithium Ion Concentration on Reduction of Camphor by LiAlH$_4$. The rate of reduction of acetone by sodium or lithium borohydride in isopropyl alcohol is enhanced by the addition of lithium salts.[19b] In contrast, Figure 5 shows that the addition of lithium bromide (0.06–0.37 M) depresses the rate of reaction of camphor with lithium aluminum hydride in THF. The shape of the curve in Figure 5 is suggestive of an equilibrium process and could result from formation of a less reactive LiBr–ketone complex (reducing the concentration of free ketone), or from association of LiBr with LiAlH$_4$ (reducing the concentration of monomeric LiAlH$_4$). In addition, the relatively polar character of the lithium bromide in these solutions may be exerting a medium effect upon the reaction.

The rate of reaction of camphor with LiAlH$_4$ was also measured as a function of the ratio of the crown ether 4 to LiAlH$_4$. This macrocyclic ligand was selected because of its strong complexation behavior toward lithium ion,[27] its ready accessibility from inexpensive starting materials,[28] the solubility of the resulting crown ether–LiAlH$_4$ complex in THF,[29] and the presence of the tetrahydrofuran moiety in the ligand itself. Figure 6 shows that the rate of reaction of camphor with LiAlH$_4$ decreases linearly with increasing [crown ether]/

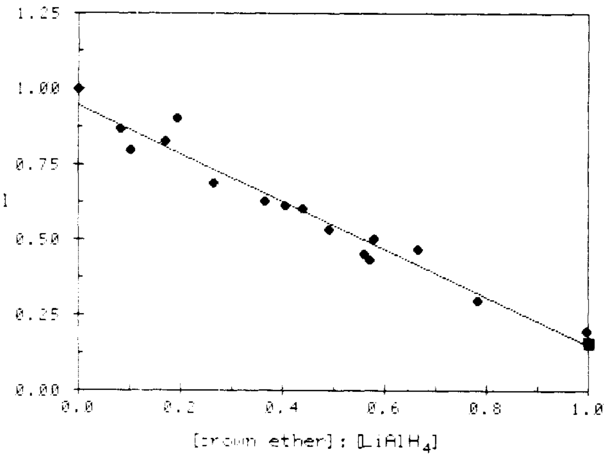
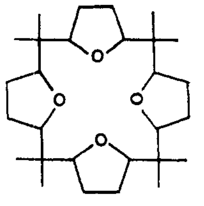


Figure 6. Plot of k_{rel} vs. [crown ether]/[$LiAlH_4$] for reduction of camphor (ca. 4 × 10^{-3} M) with 0.0314 M $LiAlH_4$ in THF at 25.0 °C. The least-squares line through the data is shown. The square point was obtained from a solution of the 1:1 crown ether–$LiAlH_4$ complex.

[$LiAlH_4$] ratio. The least-squares line through the data has a slope of −0.80 ± 0.05 (r = 0.976). However, reaction is still observed when 1 equiv of crown ether has been added. This suggests that either the complexed $LiAlH_4$ is an active reducing agent or the equilibrium constant for complex formation is small and incomplete complexation takes place. The lack of curvature in the data and the estimated value of 10^6 for the equilibrium constant for formation of the 1:1 crown ether–lithium picrate complex[27] argue against only weak complex formation between $LiAlH_4$ and crown ether.



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The 1:1 complex formed between $LiAlH_4$ and the crown ether can be isolated by crystallization from THF. This complex is moderately soluble in THF and reduces camphor with a second-order rate constant of 30 M^{-1} s^{-1}, assuming that the reaction is first order in complex. This rate constant corresponds to a relative rate constant of 0.17 compared to $LiAlH_4$ alone, in excellent agreement with the data shown in Figure 6. The products from this reaction contained 95% of the exo alcohol.

Thus, it appears that reaction may take place either through free $LiAlH_4$ or through the complexed hydride, which probably resembles the solvent-separated ion pair of $LiAlH_4$ in THF. Both the kinetic results and reported association data[17] suggest that the free AlH_4^- ion is not an active reducing agent. By comparison, addition of 2 equiv of a polyamine chelating ligand to $LiAlH_4$ in THF reduced its reactivity toward 2,4,6-trimethylbenzophenone by about a factor of 2,[15] whereas reduction of ketones in ethereal solvents has been variously reported to be partially[30] or completely[21] inhibited in the presence of the [2.1.1]cryptand **1**.[29] It has also been observed that, besides $LiAlH_4$ and $NaAlH_4$, both $KAlH_4$ and even NR_4AlH_4 (tri-*n*-octyl-*n*-propylammonium aluminum hydride) can reduce ketone **3** in THF, albeit with differing stereochemistry.[10b] It is thus likely that, while the cation is probably involved in the transition state for aluminohydride reductions of ketones, the lithium ion does not seem to be an indispensible catalyst[21] required for reduction to take place.

Experimental Section

General. Ultraviolet spectra were recorded with a Perkin-Elmer Model 202 spectrophotometer using matched 1-cm quartz cells. Nuclear magnetic resonance spectra were obtained on Varian T-60 and EM-390 spectrometers. Analytical data were obtained by Mr. J. Nemeth and associates at the University of Illinois. Capillary melting points were taken on a Büchi melting point apparatus and are uncorrected. All kinetic measurements were performed under pseudo-first-order conditions of excess hydride on a stopped-flow ultraviolet spectrophotometer which has been described previously.[25] Data collection and analysis were as described previously.[16] Absorbance changes of 0.1 were typically monitored at 290 nm.

Materials. D-Camphor and lithium tri-*tert*-butoxyaluminohydride were obtained from the Aldrich Chemical Co. and were used as received. 3,3,5-Trimethylcyclohexanone (**3**) was prepared by catalytic hydrogenation of 3,5,5-trimethylcyclohex-2-enone. $LiClO_4$ and $NaClO_4$ (G. Frederick Smith Chemical Co.) and LiBr (Mallinckrodt N. F.) were dried to constant weight over P_2O_5 at 0.1 Torr and 110 °C. $LiAlH_4$ (Ventron) and $NaAlH_4$ (Ventron) were recrystallized from ether–benzene or THF–benzene as previously described.[16] *tert*-Butyl alcohol was dried by passage through a 40-cm column packed with activated 4 Å molecular sieves, followed by distillation under N_2. Methanol was dried by passage through molecular sieves, followed by distillation from magnesium methoxide under N_2. Solutions of $NaAlH_4$ and $LiAlH_4$ were prepared under argon using Mallinckrodt reagent THF distilled from $LiAlH_4$ in an all glass apparatus. Solutions of $LiAlH_4$ and $NaAlH_4$ were analyzed by Felkin's iodine titration method.[31] Alkoxyaluminohydride solutions were prepared as described previously[16] and were clear, colorless, and stable.

Product Analyses. The effluent from the stopped-flow instrument was quenched on ether-drenched crushed ice, which was then acidified with dilute H_2SO_4 to dissolve the salts formed. The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with 10% aqueous $NaHCO_3$ and with water, dried over $MgSO_4$, and filtered, and the solvents were removed by careful fractional distillation. The pot residue was subjected to repetitive quantitative gas chromatographic analysis on an F & M Model 700 chromatograph equipped with a thermal conductivity detector.

Borneol and isoborneol were separated on a 12 ft × 0.125 in. Carbowax 20M on 60/80 Chromosorb W (DMCS) column, using a column temperature of 135 °C and an He flow rate of 25 mL/min. *cis*- and *trans*-3,3,5-trimethylcyclohexanol were separated on the same column, at 125 °C and 25 mL/min of He. Peak areas were measured by disk integration and were corrected for thermal conductivity responses. Identification of the reduction products from camphor was achieved by comparison with authentic samples (Aldrich). The order of elution was camphor, exo alcohol, endo alcohol. The reduction products from 3,3,5-trimethylcyclohexanone were separated by preparative gas chromatography on a 12 ft × 0.25 in. 10% Carbowax 20M on 60/80 Chromosorb W (DMCS) column at 125 °C. The first eluted alcohol had a melting point of 58.5–59.5 °C and was determined to be *trans*-3,3,5-trimethylcyclohexanol (lit.[32] 58.5 °C). The second compound had a melting point of 36.0–36.5 °C and was identified as the cis alcohol (lit.[32] 36–38 °C). No unreacted ketone nor extraneous peaks were ever observed.

Reductions carried out in flasks in the usual preparative fashion had internal standards added. Mesitylene was used as standard for reductions of ketone **3**, and ketone **3** was used in reductions of camphor. Yields measured in this way were normally 100 ± 10%. The reductions of ketones **2** and **3** by $LiAl(O\text{-}t\text{-}Bu)_3H$ and $LiAl(OCH_3)_3H$ were conducted in flasks.

2,2,7,7,12,12,17,17-Octamethyl-21,22,23,24-tetraoxaperhydroquaterene (4).[28] Anhydrous $LiClO_4$ (2.12 g, 0.2 mol) was placed in a 300-mL flask fitted with a mechanical stirrer and reflux condenser. Absolute ethanol (60 mL) was added, and the mixture was stirred until homogeneous. Concentrated HCl (32 mL) and 46.4 g (0.8 mol) of acetone were added, then 27.2 g (0.4 mol) of furan was added in one portion. After stirring at room temperature 1.5 h, 20 mL of H_2O was added. The mixture was extracted with 3 × 80 mL of benzene, and the organic layer was washed with water. Benzene was removed under vacuum, ethanol was added, and the white solid was washed with several portions of cold ethanol. The product was recrystallized from ethanol to yield 12.6 g (29%) of the unsaturated macrocycle, mp 232–235 °C (lit.[28] 238–240 °C). This product was hydrogenated over 1 g of 5% Pd/C in absolute ethanol at 105 °C and 1600 psi of H_2 for 4.5

h. The reaction mixture was filtered, and the filtrate was concentrated to dryness under reduced pressure. The filter cake was dissolved in hot chloroform and filtered, and the chloroform was removed under vacuum to yield another portion of product. The combined products were recrystallized from $CHCl_3$–EtOH to yield the crown ether **4** in 57% yield as a mixture of isomers (by NMR), mp 206–209 °C (lit.[28] 208–211 °C). Anal. C, H.

Complex of LiAlH$_4$ and Crown Ether 4. LiAlH$_4$ (34 mL, 0.0627 M) in THF was added to 1.24 g (2.77 mmol) of crown ether. The crown ether dissolved completely with shaking, and a precipitate gradually appeared upon standing. The solution was filtered in an argon-filled dry box, and the filtrate was concentrated by distillation to afford a second crop of crystals. The combined dried products had a weight of about 0.5 g. The white crystals melted with hydrogen evolution at ca. 235 °C. The NMR spectrum (CD_2Cl_2) resembled the spectrum of the crown ether but had substantial shifts in some peak positions. Elemental analysis: C, 68.56; H, 10.65; Al, 4.90 (which is close to that expected for a 1:1 complex between LiAlH$_4$ and the crown ether: Calcd for $C_{28}H_{52}O_4LiAl$: C, 69.09; H, 10.80; Al, 5.53. The incorporation of one molecule of THF into the LiAlH$_4$–crown ether crystals provides an elemental composition which is in very close agreement with that found (Calcd for $C_{32}H_{60}O_5LiAl$: C, 68.77; H, 10.84; Al, 4.83).

UV Spectra of Ketones in the Presence of LiClO$_4$ and NaClO$_4$. The UV spectrum of benzophenone (6.91×10^{-5} M) in diethyl ether was measured in the presence of anhydrous LiClO$_4$ (0–2.03 M), with an equivalent concentration of LiClO$_4$ in the reference beam. The $\pi\pi^*$ band gradually shifted from λ_{max} at 247.5 nm (ϵ 18 820) to λ_{max} at 258 nm ($\epsilon_{apparent}$ 14 070), with an isosbestic point at 253.5 nm, indicating the formation of a complex between LiClO$_4$ and the carbonyl group. An equilibrium constant of ca. 2 was estimated for complex formation.

The UV spectrum of camphor (0.0416 M) was measured in THF in the presence of LiClO$_4$ (0–1.51 M). In contrast to the red shift observed with benzophenone and LiClO$_4$ in ether, λ_{max} of the $n\pi^*$ band of camphor shifted from 290 nm (ϵ 26.6) to 286.5 nm ($\epsilon_{apparent}$ 31.3), a blue shift. An isosbestic point was observed at 297 nm.

The UV spectrum of camphor in THF in the presence of anhydrous NaClO$_4$ (0–1.3 M) showed no change in curve shape of λ_{max}.

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Registry No.—**4**, 50451-63-3; **4** (LiAlH$_4$ complex), 64475-64-5; **4** (LiAlH$_4$/THF complex), 64475-63-4; acetone, 67-64-1; furan, 110-00-9; LiAlH$_4$, 16853-85-3; benzophenone, 119-61-9; camphor, 464-49-3; NaAlH$_4$, 13770-96-2; LiBr, 7550-35-8; 3,3,5-trimethylcyclohexanone, 873-94-9; THF, 109-99-9.

References and Notes

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