transferred to the autoclave. The autoclave was sealed, deoxygenated with a purge of N_2, and heated to 80 °C under 240 atm of carbon monoxide. After rocking the reactor at temperature for 3–6 h, the apparatus was allowed to cool, and the clear reddish-brown, liquid product recovered. Typical analyses data are as follows: 1-heptene conversion 95%, yield of methyl C_8 acid ester 88 mol %, selectivity to linear methyl octanoate 88 mol %, material balance, 97%.

The methyl C_8 acid esters may be recovered from the crude product liquid by fractional distillation in vacuo. Anal. Calcd for $C_7H_{15}COOCH_3$: C, 68.3; H, 11.4. Found: C, 68.4; H, 11.6.

Kinetic Measurements. Degassed solvent (70 ml) and methanol (15 ml) containing a weighed quantity of palladium complex (0.5–1.0 mmol) and tin(II) chloride dihydrate (2.5–20 mmol) were introduced into the glass-lined autoclave, and flushed with N_2. The clear, red solution was heated to temperature under a small pressure of carbon monoxide (5–10 atm), a mixture of olefin (50–200 mmol) and solvent (5 ml) injected from a side ampule, and the pressure adjusted with CO. The rate of carbonylation was monitored by withdrawing liquid samples (0.5 ml) at regular time periods. The samples were rapidly cooled and analyzed by GLC for olefin and methyl ester content with the aid of standard calibration curves.

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Supplementary Material Available. Table VI describing 1-heptene carbonylation in tritiated methyl isobutyl ketone (1 page). Ordering information is given on any current masthead page.

Registry No.—$[(C_6H_5)_3P]_2PdCl_2$, 13965-03-2; $[(p\text{-}CH_3C_6H_4)_3P]_2PdCl_2$, 31173-63-4; $[(p\text{-}CH_3OC_6H_4)_3P]_2PdCl_2$, 56781-20-5; $[(p\text{-}ClC_6H_4)_3P]_2PdCl_2$, 57457-62-2; $[(o\text{-}CH_3OC_6H_4)_3P]_2PdCl_2$, 57512-77-3; $[C_6H_5(CH_3)_2P]_2PdCl_2$, 15616-85-0; $[(C_6H_5O)_3P]_2PdCl_2$, 29891-44-9; $[(C_6H_5)_3As]_2PdCl_2$, 14126-26-2; $[(C_6H_5)_3P]_2PdI_2$, 23523-32-2; $SnCl_2$, 7772-99-8; $GeCl_2$, 10060-11-4; SnI_2, 10294-70-9; $PbCl_2$, 7758-95-4; $SnCl(Ph)_3$, 639-58-7; propylene, 115-07-1; 1-pentene, 109-67-1; 1-heptene, 592-76-7; 1-undecene, 821-95-4; 1-eicosene, 3452-07-1; 4-methyl-1-pentene, 691-37-2; 3-methyl-1-pentene, 760-20-3; 2-methyl-1-pentene, 763-29-1; cyclooctene, 931-88-4; *trans*-2-heptene, 14686-13-6; *cis*-2-heptene, 6443-92-1; *cis*-3-heptene, 7642-10-6; *trans*-5-decene, 14686-14-7; methanol, 67-56-1; 1-hexanol, 111-27-3; 2-propanol, 67-63-0; 2-chloroethanol, 107-07-3; phenol, 108-95-2; ethanethiol, 75-08-1.

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Stereochemistry of Reduction of Ketones by Simple and Complex Metal Hydrides of the Main Group Elements

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The stereochemistry of reduction of selected ketones by a variety of simple and complex main group metal hydrides, both old and new, has been investigated under identical conditions of solvent, concentration, stoichiometry, temperature, and reaction time for comparison purposes. The stereochemical results of these studies are discussed in terms of steric approach control, torsional strain, compression effect, change in conformation of the ketone, and orbital distortion theory. The stereochemistry of reduction of complex aluminohydrides is shown to be dependent on the nature of the cation. Comparison of $LiAlH_4$ and $LiBH_4$ as reducing agents toward ketones shows $LiBH_4$ to be less sensitive to steric interactions. Reduction of 2-methylcyclohexanone with $ClMgAlH_4$ and $Mg(AlH_4)_2$ gave results best explained by assuming complexation of the carbonyl oxygen by magnesium followed by a change in the conformation of the ketone (methyl group equatorial to axial). Results obtained from reduction studies of substituted cyclopentanones and *cis*-2-methyl-4-*tert*-butylcyclohexanone do not suggest the presence of a compression effect in metal hydride reductions. A study of the reduction of ketones by $LiAl(OR)_3H$ compounds shows the stereochemistry to be independent of concentration. The stereochemistry of reduction of ketones by $LiAlH_4$ and $LiAlD_4$ is similar.

In recent years the area of stereoselective reduction of ketones by AlH_3, $LiAlH_4$, and their alkoxy derivatives has been investigated by several workers.[1,2]

Stereochemical results were first explained by Dauben, who suggested the concepts of "product development and steric approach control".[3] While "steric approach control" appears

to be an unquestionably valid concept, the concept of product development control has been questioned. In this connection Cherest and Felkin have introduced the concept of torsional strain[4-7] as an alternative to "product development control." Other alternatives to the concept of "product development control" have been suggested;[8,9] however, the concept of torsional strain seems to be the concept best accepted at the present time.[10,11] However, recently orbital symmetry arguments[12] and unequal distortion of electron density[13] about the carbonyl group have been advanced as possible factors in stereochemical control of metal hydride reduction of ketones. Thus factors, other than "steric approach control", that determine the stereochemistry of metal hydride reduction of ketones remain an area of great interest and controversy.

The importance of the cation in ketone reductions has been investigated for complex metal borohydrides. The borohydride ion was found to require a protic solvent or the presence of lithium or magnesium ions in order to be effective in the reduction of esters[14] and ketones.[15] The lithium ion may catalyze the reduction by polarizing the B–H bond or the C=O bond. On the other hand, $NaAlH_4$[16] and its alkoxy derivatives[17] as well as NR_4AlH_4 compounds[18] are known to reduce ketones; therefore, the lithium ion is not necessary for the reduction of ketones by complex aluminohydrides. It has been suggested[1] that reduction of ketones by $LiAlH_4$ may involve a prior or synchronous association of the carbonyl oxygen atom with the lithium cation which assists the hydrogen transfer.

If complexation of the carbonyl group is rate determining, then reaction rates should reflect the rate of complexation of the ketone by the hydride. However, because of the large difference in the rate of reduction of a series of cyclohexanones with $LiAl(OBu\text{-}t)_3H$,[11] it was concluded that complexation of the ketone by the hydride was not rate determining as the rate of complexation should be about equal for the series. It was pointed out, however, that the importance of complexation of the carbonyl group by the hydride on the stereochemistry of such reductions is not known.

Reduction of 3,3,5-trimethylcyclohexanone by $LiAlH_4$ in diethyl ether and tetrahydrofuran (THF) gives different results, namely, 55 and 75% equatorial attack, respectively.[19] Therefore, solvation of the $LiAlH_4$ appears to be important in determining the stereochemistry of reduction of ketones. Recently we have determined that $LiAlH_4$ has a much higher molar conductance in THF than in diethyl ether.[20] This observation suggests that $LiAlH_4$ in THF is more selective than in diethyl ether because $LiAlH_4$ is a solvent separated ion pair in THF while it is best described as a contact ion pair in diethyl ether. It has also been suggested[21] that the greater stereoselectivity of $LiAl(OCH_3)_3H$ compared to $LiAl(OBu\text{-}t)_3H$ could be ascribed to the higher degree of association of $LiAl(OCH_3)_3H$ and hence its greater steric requirement.

Unfortunately, the value of the literature for comparing one hydride reduction to another is often diminished significantly because of the wide variation in experimental conditions used. The purpose of this work was to evaluate complex aluminohydrides as stereoselective reducing agents toward model ketones under identical conditions with the hope that emerging patterns might appear. Reactant concentration, temperature, cation, solvent, stoichiometry, and order of addition of reactant were held constant for each study. For example, it was thought that if the nature of the cation was important it would be reflected in the stereochemical results provided that all the data was collected at the same temperature, solvent, concentration, etc. Other studies carried out involve an evaluation of a large number of simple and complex metal hydrides (other than aluminohydrides) as stereoselective reducing agents and the effect of concentration and hence association on stereoselectivity.

Results and Discussion

A variety of complex metal hydrides were allowed to reduce several ketones which had the possibility of giving, on hydrolysis, isomeric alcohols. The ketones employed reflect different degrees of steric hindrance at the carbonyl group and ranged from relatively flexible cyclic ketones, e.g., 2-methylcyclohexanone, to rigid bicyclic ketones, e.g., norcamphor. The homogeneous reductions were carried out at 0 °C for 2 h in THF using two ratios of hydride to ketone (H^-/ketone = 6 and H^-/ketone = 1). The heterogeneous reductions were carried out at room temperature in the presence of excess hydride. The ketones used in this study are 4-*tert*-butylcyclohexanone (I), 2-methylcyclohexanone (II), 3,3,5-trimethylcyclohexanone (III), norcamphor (IV), and camphor (V). The results of the reductions of the above ketones with $LiAlH_4$, $NaAlH_4$, NR_4AlH_4 (NR_4 = tri-*n*-octyl-*n*-propylammonium ion), $Mg(AlH_4)_2$, and $ClMgAlH_4$ are given in Table I. The reactions were carried out under identical conditions except in those cases where the hydride had limited solubility [$Mg(AlH_4)_2$ and $ClMgAlH_4$].

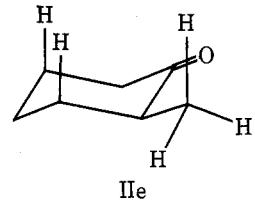
Reduction of 4-*tert*-Butylcyclohexanone (I). All the hydrides in Table I behave similarly toward I, although a trend may be suggested involving $LiAlH_4$, $NaAlH_4$, and NR_4AlH_4. The 10% equatorial attack observed for $LiAlH_4$ represents a 1.0:9.0 ratio of products while the 15% equatorial attack for NR_4AlH_4 represents a 1.0:5.7 ratio of products. In spite of the limitations of GLC analysis to determine absolute yield data, the results were entirely reproducible.

In the case of I, steric hindrance and torsional strain favor different directions of attack. Torsional strain appears to be the dominant factor (Table I) in that predominant axial attack is observed. Why $LiAlH_4$ and $ClMgAlH_4$ might experience torsional strain more than other hydrides is not readily apparent, but it is clear that the difference is not great. It is also clear from Table I that the hydride:ketone ratio is of little importance with all the hydrides studied.

4-*tert*-Butylcyclohexanone should be a good model for the chair form of cyclohexanone. The *tert*-butyl group is locked in an equatorial position and is removed from the reaction center. Its inductive, steric, and field effects on the reaction center should be minimal. Therefore, the data in Table I for ketone I should represent accurately the ratio of axial:equatorial attack on the chair conformation of cyclohexanone.

Reduction of 2-Methylcyclohexanone (II). The hydrides in Table I are less similar in their selectivity toward II compared to I. Magnesium aluminum hydride and $ClMgAlH_4$ give 12–24% more apparent equatorial attack than $LiAlH_4$ toward II, whereas little difference (0–3%) was observed in the reaction of I. The other hydrides ($NaAlH_4$ and NR_4AlH_4) are similar to $LiAlH_4$ and give about 25% apparent equatorial attack.

All of the hydrides studied should give more equatorial attack on II than I, if the reactive conformation is considered to be IIe. It has been suggested[22] that the hydrogen atoms of



IIe

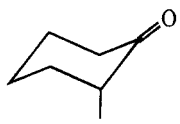
the methyl group introduce a third, 1,3-diaxial interaction with respect to the incoming nucleophile. This effect will, of course, retard axial attack. Reaction of II through the flexible forms (the various boat and twist-boat conformations) has also been suggested[23] to explain the increase in equatorial attack on II over I. This increase in apparent equatorial attack has

Table I. Reductions of Some Representative Ketones with a Series of Complex Aluminohydrides ($MAlH_4$) in THF

Ketone[a]	Hydride[a]	H^-/ketone = 6		H^-/ketone = 1	
		% equatorial or exo Attack	Yield[b]	% equatorial or exo Attack	Yield[b]
4-*tert*-Butylcyclohexanone (I)	$LiAlH_4$	10	103	8	94 (2)
	$NaAlH_4$	13	104	12	98
	NR_4AlH_4	15	99	14	80 (12)
	$Mg(AlH_4)_2$[c]	13	99 (2)	14	75 (14)
	$ClMgAlH_4$[d]	10	86 (2)	10	85 (18)
2-Methylcyclohexanone (II)	$LiAlH_4$	24	96	25	96
	$NaAlH_4$	29	91	28	96
	NR_4AlH_4	26	84	27	77 (11)
	$Mg(AlH_4)_2$[c]	48	90	49	81 (10)
	$Mg(AlH_4)_2$[e]	48	96		
	$ClMgAlH_4$[d]	36	94	43	83 (14)
3,3,5-Trimethylcyclohexanone (III)	$LiAlH_4$	80	108	75	96 (6)
	$NaAlH_4$	59	100	65	102 (2)
	NR_4AlH_4	55	106 (2)	55	80 (25)
	$Mg(AlH_4)_2$[c]	61	102	56	86 (9)
	$ClMgAlH_4$[d]	71	100	61	81 (18)
Norcamphor (IV)	$LiAlH_4$	91	98	90	97 (6)
	$NaAlH_4$	83	100	82	89 (11)
	NR_4AlH_4	74	106 (2)	76	73 (20)
	$Mg(AlH_4)_2$[c]	87	102	86	94 (9)
	$ClMgAlH_4$[d]	92	98	88	83 (16)
Camphor (V)	$LiAlH_4$	9	99	10	68 (26)
	$NaAlH_4$	12	98	12	79 (25)
	NR_4AlH_4	12	82 (26)	13	46 (57)
	$Mg(AlH_4)_2$[c]	26	101	25	84 (16)
	$Mg(AlH_4)_2$[e]	25	100		
	$ClMgAlH_4$[d]	19	96	22	69 (39)

[a] The initial concentration of hydride and ketone was 0.50 M. Ketone was added to hydride when $H^-/K = 6$. Hydride was added to ketone when $H^-/K = 1$. The reaction was carried out at 0 °C and quenched after 2 h. [b] Absolute yield measured with an internal standard. The percent recovered ketone is given in parentheses. [c] 0.25 M ketone was added directly to the solid $Mg(AlH_4)_2$ in the ratios H^-/ketone = 8 and 1. The $Mg(AlH_4)_2$ contained NaCl. $Mg(AlH_4)_2$ has a small solubility in THF since it can be extracted from NaCl with THF. [d] The initial concentrations of $ClMgAlH_4$ and ketone were 0.19 and 0.25 M, respectively. [e] Same as *c* except $Mg(AlH_4)_2$ with no NaCl present.

also been attributed[3,24] to reaction of the chair conformation with the methyl group axial (IIa). Axial attack on this con-



IIa

formation would give the cis alcohol accounting for the increase in apparent equatorial attack on II over I. 2-Methylcyclohexanone is reported[25] to exist in such a conformation (IIa) to the extent of approximately 5% at ambient temperature. On the other hand, it has been reported[2] that $LiAlH_4$ gives 91% axial attack on *cis*-2-methyl-4-*tert*-butylcyclohexanone. This result shows that the introduction of an equatorial 2-methyl group on I has not increased steric hindrance to axial attack since 4-*tert*-butylcyclohexanone gives 90% axial attack with $LiAlH_4$. The implication then is that decreased axial attack on 2-methylcyclohexanone is not due to the pseudoaxial hydrogen of the 2-methyl group, but probably due to reaction via conformer IIa. Increased axial attack on conformer IIa can be explained by steric repulsion of the substituents in the 2(CH_3), 6(H) axial positions thus forcing the conformation more in the direction of a half-chair. As we shall see a little later in this paper, the above data could not be reproduced; as a matter of fact, the data obtained from the present studies indicate that indeed the pseudoaxial hydrogen of the 2-methyl group does provide steric hindrance to axial attack since reaction of $LiAlH_4$ with *cis*-2-methyl-4-*tert*-butylcyclohexanone gave twice as much equatorial attack as the reaction with 4-*tert*-butylcyclohexanone.

Magnesium aluminum hydride and $ClMgAlH_4$ give considerably more equatorial attack on II than $LiAlH_4$ while their results with I were similar to $LiAlH_4$. An explanation based on steric hindrance was considered first. If $ClMgAlH_4$ and $Mg(AlH_4)_2$ have a larger steric requirement than $LiAlH_4$, then these compounds would possibly attack conformation IIe less from the axial side due to an increase steric hindrance introduced by the quasi-axial hydrogen of the methyl group. Such an explanation based on steric hindrance should also be consistent with observed stereochemical results for reduction of other ketones by $LiAlH_4$, $ClMgAlH_4$, and $Mg(AlH_4)_2$ and not conveniently invoked to explain the results with II. Magnesium aluminum hydride and $ClMgAlH_4$ give more axial attack on 3,3,5-trimethylcyclohexanone (III) and more exo attack on camphor (V); thus, they have an apparent smaller steric requirement than $LiAlH_4$ in these two cases.

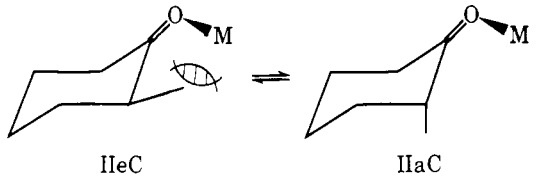
It was next considered that possibly more of conformation IIa is involved in the reaction when II is reduced by $ClMgAlH_4$ and $Mg(AlH_4)_2$ than $LiAlH_4$. Such an explanation may be made by assuming that the cation, M^+, of $MAlH_4$ associates with the carbonyl oxygen during the reduction step. If the cation complexes the carbonyl oxygen prior to or concurrent with reduction, then the $MgCl^+$ or $MgAlH_4^+$ being larger than Li^+ would interact more with the methyl group of IIe and force more of the reaction to proceed through the chair conformation IIa. Such a conformation produces less interaction be-

tween the cation as it complexes the carbonyl oxygen atom and the methyl group.

Reduction of *cis*-2-methyl-4-*tert*-butylcyclohexanone (VI) by $LiAlH_4$, $ClMgAlH_4$, and $Mg(AlH_4)$ was carried out[26] to investigate the possibility that cation complexation of the carbonyl oxygen satisfactorily explains the reduction data obtained for II. In the case of VI the methyl group is locked in an equatorial position and since a change in conformation cannot easily occur, the stereochemical outcome should be nearly the same with all three hydrides as in the case of I.

Table II shows the extent of apparent equatorial attack on I, II, and VI. The order of apparent equatorial attack on II (IIe) is $LiAlH_4 < ClMgAlH_4 < Mg(AlH_4)_2$. The hydrides show less variation in the amount of equatorial attack on I and VI than II. Each hydride gives about twice the amount of equatorial attack on VI as I. Since the results of this study show the steric requirement of each hydride to be nearly the same toward VI, the conclusion is that more of conformation IIa is involved in the reduction of II by $Mg(AlH_4)_2$ and $ClMgAlH_4$ than by $LiAlH_4$. Although the hydrides give more equatorial attack on VI than I, the important consideration is that the amount of equatorial attack is about the same for each hydride. It is clear from this work that the amount of equatorial attack on VI is too small to explain the amount of apparent equatorial attack on II as taking place only through conformation IIe.

It has been shown that lithium and magnesium salts or protic solvents catalyze[14,15] borohydride reduction of ketones and esters. These results suggest a mechanism for ketone reduction by $LiAlH_4$ involving prior or concurrent association of the carbonyl oxygen with Li^+ as the hydride is transferred. If complexation of the carbonyl group occurs during reduction, then the concentration of IIaC (and its transition state corresponding to axial attack) should increase relative to IIa since the energy difference between IIaC and IIeC is less than be-



(1)

IIeC IIaC

tween IIa and IIe. Therefore, it is not surprising that more reaction proceeds through IIaC with bulkier complexing agents such as $-MgCl^+$ and $-MgAlH_4^+$ than with a smaller complexing agent such as Li^+. We have previously shown that a ketone will associate with the lithium cation in tetrahydrofuran solution.[20]

Each hydride in Table II gives twice the amount of equatorial attack on VI as compared to I. Reduction of I, II, and VI by $LiAlH_4$ gives 10, 24, and 19% equatorial attack, respectively. If both conformations IIa (5%) and IIe (95%) have the same rate of reaction, then 19% equatorial attack on IIe by $LiAlH_4$ (since VI gives 19% equatorial attack) plus a large amount of axial attack on IIa (present in 5%) produce approximately 24% apparent equatorial attack on II which is what is experimentally observed. Thus the results indicating that the C-2 methyl group does hinder axial attack can be explained by assuming that the C-2 methyl (1) blocks the axial approach of the aluminohydride ion from a direction perpendicular to the plane of the carbonyl group; (2) blocks the hydride from moving into an axial position after complexation of the oxygen atom; and/or (3) causes steric strain involving the cation as it complexes the oxygen atom thus causing part of the reduction to occur via the flexible form.

Chloromagnesium aluminum hydride exhibits a change in selectivity when the ratio of hydride to II is varied but $Mg(AlH_4)_2$ does not show such a change. Results with II involving the other hydrides in Table I show that selectivity is insensitive to ratio of reactants. Since $Mg(AlH_4)_2$ is only slightly soluble in THF, its reactions reported in Table I are probably only occurring in solution at one ratio (H^-/ketone ≤ 1, i.e., excess ketone) even though the measured ratios are different. Since $ClMgAlH_4$ is soluble in THF, the results do indeed reflect reaction at two different ratios (H^-/ketone = 1 and 6). A change in stereochemistry for $ClMgAlH_4$ with ratio of reactants occurs not only for II but also for III, IV, and V (Table I). The effect of ratio of reactants on stereochemistry is negligible for $LiAlH_4$ and ketones I–V except maybe for III (Tables I and VI). Eliel has interpreted[19,27] such results as indicating that $LiAlH_4$ is the reducing agent at all ratios because the following disproportionation reactions are very rapid.

$$4/n\,LiAl(OR)_nH_{(4-n)} \rightarrow (4-n)/n\,LiAlH_4 + LiAl(OR)_4 \quad (2)$$

$$n = 1, 2, \text{ or } 3$$

If any alkoxy intermediates were reacting one would expect the steric requirement of the intermediate to be greater than $LiAlH_4$ and hence attack on the ketone from the least hindered side should increase. However, when III, IV, and V (H^-/ketone = 1) are allowed to react with $ClMgAlH_4$ the results show increased attack from the more hindered side of the ketone than when excess hydride is used and thus resemble more the results obtained using $Mg(AlH_4)_2$. Although no explanations appear particularly convincing it is possible that the intermediates formed on reduction of $ClMgAlH_4$ with ketones ($ClMgAlH_nOR_{4-n}$) disproportionate to $Mg(AlH_4)_2$ and thus the results resemble those obtained with $Mg(AlH_4)_2$.

Table II. Percent Cis Alcohol from the Reaction of Complex Metal Hydrides with Cyclohexanones in THF

Hydride[a]	I 4-*tert*-Butylcyclohexanone	II 2-Methylcyclohexanone	VI *cis*-2-Methyl 4-*tert*-butylcyclohexanone
$LiAlH_4$[b]	10	24	19[c]
$LiAlH_4$	8	25	
$ClMgAlH_4$[b]	10	36	21[c]
$ClMgAlH_4$	10	43	21[c]
$Mg(AlH_4)_2$[b]	13	48	27,[c] 26[d]
$Mg(AlH_4)_2$	14	49	

[a] See footnotes *a*, *c*, and *d* of Table I. [b] Excess hydride [c] Ratio measured by GLC analysis [d] Ratio measured by NMR analysis.

Reduction of 3,3,5-Trimethylcyclohexanone (III). Ketone III introduces a methyl group in the C-3 axial position which severely hinders axial attack on this cyclohexanone. The largest difference in selectivity of the hydrides studied occurs with this ketone (Table I). Equatorial attack predominates for all hydrides and ratios of reactants (55–80%). Steric hindrance is experienced more by $LiAlH_4$ than the other hydrides and results in the largest amount of equatorial attack (8). The order of selectivity is $LiAlH_4 > ClMgAlH_4 > Mg(AlH_4)_2 \approx NaAlH_4 > NR_4AlH_4$.

Reduction of Norcamphor (IV). Reductions of IV show a similar trend in selectivities of the hydrides as III: $LiAlH_4 \approx ClMgAlH_4 > MgAlH_4 > NaAlH_4 > NR_4AlH_4$. Steric hindrance and torsional strain favor opposite sides of attack in I, II, III, and V but not necessarily in IV where both effects might favor exo attack. It is important to note that when a hydride attacks endo, torsional strain occurs between the C_1–C_6 bond and the newly forming C_1–H bond. Although reductions of I and II are governed largely by torsional strain

and III and V by steric hindrance, it is not so easy to decide the predominant factor that governs the reduction of IV. It is likely that both torsional strain and steric hindrance are important in the reduction of IV. Lithium aluminum hydride shows a similar degree of selectivity for IV and V (91% of the less stable isomer). If steric hindrance was the only important factor controlling the selectivity of a hydride toward IV as probably it is in V, then the other hydrides should show the same degree of selectivity for IV as they do V, just as $LiAlH_4$ does; however, this is not the case; thus factors other than steric hindrance must be important. Since I gives similar results with each hydride and torsional strain is believed to be the governing factor in the stereochemistry of reduction, it may be expected that each hydride would give about the same results with IV if torsional strain was the only important factor controlling stereochemistry, but neither is this the case. The large amount of exo attack on IV by all the hydrides can probably be best attributed to the fact that it is favored by both steric hindrance and torsional strain. The 18% spread in the selectivity of the hydrides may be attributed to how each hydride experiences the steric hindrance; thus they follow a trend similar to III.

Reduction of Camphor (V). The hydrides $LiAlH_4$, $NaAlH_4$, and NR_4AlH_4 are similar in their selectivity toward V; they give 87–91% endo attack. The syn C-7 methyl group severely blocks exo attack and the results are as expected. The hydrides $ClMgAlH_4$ and $Mg(AlH_4)_2$ give less endo attack (81 and 74%, respectively) than the other hydrides. This is unexpected since they appeared to experience steric hindrance more than $NaAlH_4$ and NR_4AlH_4 with III and IV. If torsional strain is used to explain why $ClMgAlH_4$ and $Mg(AlH_4)_2$ give more exo attack on V than the other hydrides, then it is difficult to explain why they give more equatorial attack on III than $NaAlH_4$ and NR_4AlH_4. Perhaps forces other than steric hindrance and torsional strain influence the stereochemical outcome of reductions of ketones.

General Considerations Concerning Aluminohydrides as Reducing Agents. The stereoselectivity of hydride reduction of ketones can be seen from Table I to have some dependence upon the cation present. If the hydrides containing magnesium are not considered, the smaller the cation (greater charge density) the more the hydride will attack from a particular side of I, III, and IV. Results with ketones II and V are too similar to allow any conclusions. It does appear that $LiAlH_4$ is the most selective hydride in attacking either side of the carbonyl group whether the stereochemistry is controlled by steric hindrance or torsional strain. This means that $LiAlH_4$ experiences torsional strain or steric hindrance more than the other hydrides, depending on the nature of the ketone.

The difference in selectivities may be due to two possible factors: (1) the cation participates directly in the step in which the stereochemistry is determined, or (2) the cation alters the reducing species in solution. Probably the most apparent mechanism by which the lithium ion may participate directly in the reaction would be for it to complex the ketone during reduction. Brown has shown that the lithium ion catalyzed the reduction of ketones by the borohydride ion in aprotic solvents because $LiBH_4$ reduces acetone in aprotic solvents and $NaBH_4$ does not.[14] The lithium ion may enter into catalysis by either polarizing the carbonyl bond or the B–H bond.[14] If complexation of the carbonyl oxygen by the cation were to occur, the resulting influence on the stereochemistry is not readily apparent for all ketones even though its possible importance in the reduction of II was discussed. Since $NaAlH_4$ and NR_4AlH_4 will reduce ketones, it is apparently not necessary for the reaction of the aluminohydride ion to require the presence of the lithium cation. Since the reduction of V by NR_4AlH_4 is slower than by $LiAlH_4$ (Table I), the lithium ion must catalyze the reaction in some manner. Since the lithium cation will associate with ketones in tetrahydrofuran,[20] it is not only possible but probable that the lithium cation polarizes the carbonyl group increasing the rate of reaction.

It should not be overlooked that solvation of the cation may alter the reducing species. Reduction of III by $LiAlH_4$ in diethyl ether gives only 55% equatorial attack compared to 75% in THF[15] as solvent. This difference may be attributed to solvation of the cation. Since solvation of $MAlH_4$ varies with M, the stereochemistry should also depend on M due to a change in the ion pair structure and steric requirement of the hydride. In addition, the presence of a solvated cation in the transition state may require more order in the transition state for hydride transfer, thus a greater selectivity.

The magnesium cation is about the same size[28] as the lithium cation but carried a +2 charge instead of +1. In light of the above discussion $Mg(AlH_4)_2$ and $ClMgAlH_4$ may be expected to be more selective than $LiAlH_4$ toward III, IV, and V because the magnesium cation would have a larger charge density than the lithium cation. This is not observed. It probably is unfair to try to make such a comparison between $Mg(AlH_4)_2$ and $ClMgAlH_4$, and $LiAlH_4$ because the nature of the species in solution could be quite different.

Table III. Reductions of Some Representative Ketones with $LiBH_4$ in THF

	H^-/ketone = 6		H^-/ketone = 1	
Ketone[a]	% equatorial or exo attack	% yield[b]	% equatorial or exo attack	% yield[b]
I	7	97	8	92
II	29	92	36	95 (2)
III	53	95	60	96
IV	82	103	90	88
V	31	100[c,d]	26	94 (6)[c,e]

[a] See footnote *a* Table I. [b] Absolute yield measured with an internal standard. [c] Relative yield. [d] 98% reaction in 9 days determined by uv spectroscopy. Reaction was quenched after 10 days. [e] 91% reaction in 31 days as determined by uv spectroscopy. Reaction was quenched after 31 days.

Reductions with $LiBH_4$. Ketones I–V were reduced with $LiBH_4$ under identical conditions as with $LiAlH_4$. The results are tabulated in Table III. Reductions with $LiBH_4$ were slower than with $LiAlH_4$. Reactions with III, IV, and V were followed spectrophotometrically to assure completion of reaction before quenching since considerable reduction was found to occur upon quenching.

Lithium borohydride gives results similar to $LiAlH_4$ for I and II where torsional strain is believed to be the controlling factor in determining the direction of attack. When the reduction is controlled by steric hindrance (III, IV, and V) $LiBH_4$ gives more attack than $LiAlH_4$ from the more hindered side. This is consistent with the fact that the borohydride ion is smaller[29] than the aluminohydride ion or that $LiBH_4$ is less solvated[20] than $LiAlH_4$ in THF; thus it has a smaller steric requirement. When the ratio of H^-/ketone = 1, $LiBH_4$ gives more attack from the least hindered side of the ketone in all cases than when $LiBH_4$ is used in excess. This is consistent with more of the reduction occurring via alkoxy intermediates at low hydride:ketone ratios.[30]

Reduction of Cyclopentanones. In order to compare the reduction of cyclopentanones to alkylation results using CH_3MgBr and $Al(CH_3)_3$,[31] 2-methylcyclopentanone (VII), 3-methylcyclopentanone (VIII), and *cis*-3,4-dimethylcyclopentanone (IX) were reduced with $LiAlH_4$ (Table IV).

The preferred conformation of cyclopentanone (half-chair model) has a C_2 axis of symmetry[32] which allows equal attack

Table IV. Reduction of Methyl Substituted Cyclopentanones with $LiAlH_4$, $Mg(AlH_4)_2$, and $ClMgAlH_4$ in THF

		H^-/ketone = 6		H^-/ketone = 1	
Ketone[a]	Hydride[a]	% cis attack	Yield[b]	% cis attack	Yield[b]
2-Methylcyclopentanone (VII)	$LiAlH_4$	84[c,d]	100	84[c,d]	100
	$ClMgAlH_4$	65[c]	100	58[c]	91
	$Mg(AlH_4)_2$	45[c]	99		
3-Methylcyclopentanone (VIII)	$LiAlH_4$	27[d]	100	29[d]	92
	$ClMgAlH_4$	25[d]			
	$Mg(AlH_4)_2$	20[d]			
cis-3,4-Dimethylcyclopentanone (IX)	$LiAlH_4$	10[d]	100	10[d]	90
	$ClMgAlH_4$	10[d]			
	$Mg(AlH_4)_2$	10[d]			

[a] See footnotes *a*, *c*, and *d* of Table I. [b] Relative yields based on GLC analysis. [c] Ratio of products measured by GLC analysis. [d] Ratio of products measured by NMR in Me_2SO-d_6.

from either side; however, substituents distort the symmetry causing one side to be attacked more easily than the other. Since VII is attacked 84% cis (with respect to the methyl group) by $LiAlH_4$, any steric hindrance from the C-2 methyl group seems to be minor. The methyl group is probably in a quasi-equatorial position and offers less steric hindrance than torsional strain by the quasi-axial hydrogen at C-2 on the other side of the ring.[2] Common methylating reagents [$Al(CH_3)_3$, CH_3MgBr] are slightly hindered by the methyl group and give about 40% cis attack.[31]

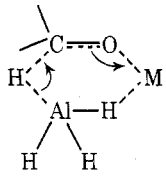
The ketone VIII is attacked 71–73% trans by $LiAlH_4$. This may at first glance be ascribed to steric hindrance of the C-3 methyl group blocking cis attack since the introduction of an axial C-3 methyl group on a cyclohexanone ring results in a large decrease in axial attack, from 90% to 20% (ketones I and III). This observation in the cyclohexanone case is clearly ascribed to steric hindrance. However, since the cyclohexanone chair conformation does not allow equal attack on both sides while the half-chair conformation of cyclopentanone does, it is important to note that the C-3 methyl group of VIII only changes the preferred direction of attack from 50% to 72%. This is less than for the C-2 methyl group of VII (50 to 84%) whose stereochemistry of reduction is not controlled by steric hindrance, but probably by torsional strain. Several methylating reagents, which usually have larger steric requirements than hydrides, give[31] only 60% trans attack on VIII. It is also reported that VIII and 3-*tert*-butylcyclopentanone are attacked the same amount trans (60%) by $LiAlH_4$[33] in diethyl ether. These results indicate that torsional strain or factors other than steric hindrance control the stereochemistry of reduction and alkylation of VIII. The C-3 methyl group is probably in a quasi-equatorial position and offers little steric hindrance to cis attack.

On the other hand, the vicinal methyl groups of IX probably twist in a manner to avoid eclipsing each other. One takes a quasi-axial position and the other a quasi-equatorial position. The quasi-axial methyl group now can hinder cis attack on the carbonyl group; thus $LiAlH_4$ attacks IX 90% from the trans side. Methylating reagents also give[31] about 90% trans attack.

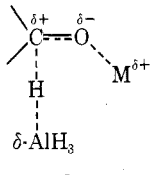
The large amount of apparent equatorial attack on II by $ClMgAlH_4$ and $Mg(AlH_4)_2$ was explained by the magnesium ion complexing the carbonyl oxygen and sterically interacting with the equatorial C-2 methyl group and forcing it into an axial position. This steric interaction is somewhat similar to the "compression effect" used[31] to explain alkylation of cyclohexanones in benzene with $Al(CH_3)_3$. The "compression effect" involves compression of the complexed carbonyl group against unequal substituents above or below the plane of the carbonyl group. The "compression effect" favors attack from the side of the carbonyl group which will relieve the compression strain. The "compression effect", however, exactly as described for alkylation, does not seem to be operating in the cases considered here. If it was, the amount of axial attack on VI by $LiAlH_4$, $ClMgAlH_4$, and $Mg(AlH_4)_2$ should be greater than on I, whereas the opposite is observed.

To investigate the "compression effect" further, VII was reduced using $ClMgAlH_4$ and $Mg(AlH_4)_2$. It has been previously pointed out[31] that VII is a good model to test for the "compression effect". Results of the reduction of VII by $ClMgAlH_4$ and $Mg(AlH_4)_2$ (Table IV) are opposite to that expected for the "compression effect", that is, more trans attack is observed than in the case of $LiAlH_4$. Thus, it is concluded that the "compression effect" is minor or inoperative in the reduction of ketones VI and VII by complex metal hydrides.

It appears that if $ClMg^+$ or AlH_4Mg^+ complex the carbonyl group of VII it pushes the methyl group from its quasi-equatorial position to a more axial position which increases steric hindrance to cis attack. It is also possible that the methyl group prevents the aluminohydride ion, via a six-center transition state, from swinging around to attack cis as the magnesium ion complexes the carbonyl oxygen.



Reduction of VIII and IX by $ClMgAlH_4$ and $Mg(AlH_4)_2$ gives results which are very similar to those with $LiAlH_4$. Chloromagnesium aluminum hydride and $Mg(AlH_4)_2$ also give results with I, III, and IV which are similar to those with $LiAlH_4$ and $NaAlH_4$. However, they give different results with II, V, and VII, where each ketone has a C-2 methyl group. A mechanism consistent with these results involves association of the carbonyl oxygen with the cation. Steric interaction between the substituent at C-2 and the complexing cation could alter the stereochemistry depending on the size of the complexing agent and how strongly it complexes the oxygen atom.



Reduction of Ketones by Insoluble Hydrides. The crystal lattice network of an insoluble hydride should present

Table V. Reduction of 4-*tert*-Butylcyclohexanone, 3,3,5-Trimethylcyclohexanone, and Camphor with Some Insoluble Complex Metal Hydrides

Hydride[a]	Solvent	H^-/ketone	Concn of ketone, M	% equatorial or endo attack	% yield[b]	Time, h
			4-*tert*-Butylcyclohexanone (I)			
MgH_2	THF	2.0	0.077	64	14 (76)	24
MgH_2	THF	0.91	0.13	65	6 (78)	24
$NaZnH_3$	THF	2.7	0.13	28	13 (50)	87
Li_2ZnH_4	THF	4.1	0.13	36	97 (trace)	87
$NaMgH_3$	THF	4.0	0.13	10	36 (39)	87
NR_4MgH_3	THF	1.4	0.13	trace	4 (72)	87
Na_3AlH_6	Benzene	10.7	0.13	30	28 (58)	87
Na_3AlH_6	THF	11.0	0.13	24	49 (42)	87
Na_3AlH_6	THF	12.3	0.13	15	25[c]	3
Na_3AlH_6	THF	12.3	0.13	16	28[c]	15
Na_3AlH_6	THF	12.3	0.13	22	39[c]	43
Na_3AlH_6	THF	12.3	0.13	25	55[c]	87
			3,3,5-Trimethylcyclohexanone (III)			
MgH_2	THF	2.0	0.046	45	23 (79)	24
MgH_2	THF	1.5[d]	0.062	20	12 (94)	24
Na_3AlH_6	THF	6.2	0.13	75	82 (17)	85
Na_3AlH_6	Benzene	6.3	0.19	65	68 (5)	85
Na_3AlH_6	THF	5.0[e]	0.42	68	25 (61)	85
Na_3AlH_6	Benzene	4.8[f]	0.33	61	37 (45)	85
			Camphor (V)			
MgH_2	THF	2.0	0.046	79	24 (74)	28
Na_3AlH_6	THF	6.7	0.13	90	64 (46)	85
Na_4AlH_6	Benzene	6.1	0.13	75	19 (85)	85

[a] Reaction mixture stirred continuously at room temperature. [b] Absolute yield measured with an internal standard. Percent recovered ketone is given in parentheses. [c] Relative yield. [d] 1.28 mmol of ketone and 1.76 mmol of alcohol (75% axial) were added to 2.28 mmol of MgH_2. [e] 3.90 mmol of ketone and 5.38 mmol of alcohol (70% axial) were added to 7.70 mmol of Na_3AlH_6. [f] 3.90 mmol of ketone and 3.16 mmol of alcohol (70% axial) were added to 5.64 mmol of Na_3AlH_6.

a large steric requirement to a ketone, and thus should provide a high degree of selectivity. Several insoluble hydrides were investigated in order to test this concept. The results are tabulated in Table V.

The most reactive hydride based on percentage of recovered I is Li_2ZnH_4 and the least reactive is NR_4MgH_3. The amount of equatorial attack on I varied from 10 to 65%. Although MgH_2 and Na_3AlH_6 give more equatorial attack on I than $LiAlH_4$, they give less equatorial and endo attack on III and V, respectively, than $LiAlH_4$. Equilibration during reduction was shown to be important for MgH_2, but not the other hydrides used in this study. The reaction of III and a mixture of 3,3,5-trimethylcyclohexanols (75% trans) with MgH_2 gave a mixture of alcohols which was 20% trans with only 12% reduction of the ketone. Equilibration is probably occurring via a Meerwein–Ponndorf process through $Mg(OR)_2$ as an intermediate. The fact that MgH_2 equilibrates a mixture of 3,3,5-trimethylcyclohexanols is indicative of cation complexation in reduction since association of $Mg(OR)_2$ with ketone in the Meerwein–Ponndorf equilibration is necessary.

The reaction of III and a mixture of its alcohols (70% trans) with Na_3AlH_6 showed little or no equilibration. The recovered ketone, at least for Na_3AlH_6, may not be attributed to enolate formation since reaction samples to which $LiAlH_4$ was added before quenching gave about 1% recovered ketone, indicating that the ketone was unreacted and not enolized. The insoluble hydrides are capable of reducing ketones, but have no advantage in terms of stereochemical selectivity over more common reducing agents.

Selectivity of $LiAl(OR)_3H$ as a Reducing Agent. It was reported that the stereoselectivity of $LiAl(OCH_3)_3H$ toward II in THF depends on the concentration of the hydride in the reaction mixture.[21] The increased steric requirement of $LiAl(OCH_3)_3H$ over $LiAl(OBu\text{-}t)_3H$ was explained by the greater association of $LiAl(OCH_3)_3H$ compared to $LiAl(OBu\text{-}t)_3H$ in THF. It was felt that these results should be checked since the previous results were obtained with only one ketone, II, which may have been a poor choice since the results of the present work show that the stereoselectivity seems to depend on which conformation reacts. The ketones I and II were examined over a 100-fold change in concentration of hydride, using $LiAlH_4$, $LiAl(OCH_3)_3H$, and $LiAl(OBu\text{-}t)_3H$. The results are given in Table VI. These data show that there is no change in selectivity with concentration of hydride although $LiAl(OCH_3)_3H$ associates appreciably with an increase in concentration whereas $LiAl(OBu\text{-}t)_3H$ is monomeric over a wide concentration range. These results suggest that in the reaction of $LiAl(OCH_3)_3H$ with I or II the same species is involved, probably the monomer; therefore the increased association of $LiAl(OCH_3)_3H$ with concentration cannot be the reason for its greater selectivity compared to $LiAl(OBu\text{-}t)_3H$.

These results leave us with no explanation for the difference in the selectivities of $LiAl(OCH_3)_3H$ and $LiAl(OBu\text{-}t)_3H$. Reaction of $LiAl(OBu\text{-}t)_3H$ via $Al(OBu\text{-}t)_2H$ as an intermediate[27,34] does not seem likely since it has been shown that $LiAl(OBu\text{-}t)_3H$ and $Al(OBu\text{-}t)_2H$ exhibit different stereoselectivities toward certain ketones.[21] Reaction of $LiAl(OBu\text{-}t)_3H$ via $LiAlH_4$ from disproportionation does not seem likely either since $LiAlH_4$ will react with certain substrates that $LiAl(OBu\text{-}t)_3H$ will not[35] and also the selectivity of $LiAlH_4$ toward II compared to $LiAl(OBu\text{-}t)_3H$ is quite different. We have found that the equivalent molar conductance[20] of $LiAl(OCH_3)_3H$ (2.32 mhos/cm^2 at 0.1 M) is much greater in THF than that of $LiAl(OBu\text{-}t)_3H$ (0.0124 mhos/cm^2 at 0.1 M) indicating that the former is considerably more solvated. Greater solvation of $LiAl(OCH_3)_3H$ and hence a

Table VI. Reduction of 4-*tert*-Butylcyclohexanone and 2-Methylcyclohexane with $LiAl(OBu\text{-}t)_3H$, $LiAl(OCH_3)_3H$, and $LiAlH_4$ at Varying Concentrations in THF

Ketone[a]	Hydride[a]	Initial concn of hydride, M	% equatorial attack	Yield
4-*tert*-Butylcyclohexanone (I)	$LiAl(OBu\text{-}t)_3H$	0.0051	10	112
		0.055	10	114 (1)
		0.51	11	113
	$LiAl(OCH_3)_3H$	0.0051	41	85 (14)
		0.055	41	119
		0.58	44	97
	$LiAlH_4$	0.0049	8	105 (1)
		0.056	9	103
		0.62	10	112
2-Methylcyclohexanone (II)	$LiAl(OBu\text{-}t)_3H$	0.0051	35	66[b]
		0.055	34	103
		0.51	36	99
	$LiAl(OCH_3)_3H$	0.0032	65 (63)[c]	40[b]
		0.0051	63[d]	76[b]
		0.0053	68 (68[c]	57[b]
		0.0080	66 (67)[c]	37[b]
		0.055	65[d]	97
		0.58	63[d]	109
	$LiAlH_4$	0.0049	19	65
		0.056	21	100
		0.62	24	109

[a] 0.5 M ketone added to hydride at 0 °C in THF. Ratio $H^-/K = 1.5$. The reaction was quenched after 2 h. [b] Reaction mixture was concentrated after quenching with an aspirator. Some of the product was probably lost under reduced pressure which accounts for the low yield. [c] The value in parentheses was obtained with a flame ionization GLC before the solution was concentrated. [d] Second preparation of $LiAl(OCH_3)_3H$.

Table VII. Reaction of 3,3,5-Trimethylcyclohexanone with $LiAlH_4$ and $NaAlH_4$ at Various Concentrations in THF

Hydride[a]	Initial concn of hydride,[a] M	Ratio H^-/ketone	% equatorial attack	Yield[b]
$LiAlH_4$[c]	0.0020	8.0	89.4	106 (3)
	0.012	6.0	82.4	105 (2)
	0.051	5.8	79.4	107
	0.11	5.8	79.9	98
	0.29	6.0	76.8	98
	0.38	6.0	75.6	102
	0.73	5.8	75.0	99
	1.0	5.8	74.6	98
$NaAlH_4$[c]	0.012	6.4	68.2	105 (2)
	0.055	5.9	60.4	108
	0.12	5.9	57.7	103
	0.39	6.2	55.5	104
	1.0	6.7	51.3	100
$LiAlH_4$[d]	0.0097	1.0	76.4	80 (8)
	0.048	1.0	75.7	96 (4)
	0.048	1.0	76.5	92 (4)
	0.12	1.0	73.6	95 (2)
	0.20	1.0	71.9	97
	0.20	1.0	70.7	99
	0.20	1.0	71.0	98
	0.50	1.0	65.5	95

[a] Reaction at 0 °C in THF for 2 h. [b] Absolute yield measured with an internal standard. The percent of recovered ketones is given in parentheses. [c] 1.0 M ketone added to hydride. [d] 1.0 M $LiAlH_4$ added to ketone. The concentration of $LiAlH_4$ reported is based on the resulting volume of reaction mixture.

higher steric requirement could be the reason for greater selectivity compared to $LiAl(OBu\text{-}t)_3H$.

The stereoselectivity of $LiAlH_4$ toward I is essentially independent of concentration. However, results with II indicate that there may be some dependence on concentration. On the other hand, when III was allowed to react with $LiAlH_4$ and $NaAlH_4$ at varying concentrations, selectivity was definitely shown to be a function of concentration (Table VII).

Both $LiAlH_4$ and $NaAlH_4$ are more selective toward III at lower concentrations, although both $LiAlH_4$ and $NaAlH_4$ have been shown to be more associated at higher concentrations.[20] It is clear from these results that the more highly associated species are not the reactive intermediates. In THF $LiAlH_4$ is best represented by solvent separated ion pairs and $NaAlH_4$ by a mixture of solvent separated and contact ion pairs. Thus $LiAlH_4$ being more solvated should have a greater steric requirement and give more equational attack on III than N_2AlH_4 as observed. Since solvation is greater at lower concentrations, both $LiAlH_4$ and N_2AlH_4 should have a higher steric requirement at lower concentrations and give more

Table VIII. Reduction of 4-*tert*-Butylcyclohexanone and 3,3,5-Trimethylcyclohexanone with Lithium Triaryloxy Aluminohydrides in THF

Aryloxy group	% equatorial attack[a]	% yield[b]
4-*tert*-Butylcyclohexanone		
4-Chlorophenoxy[c]	8	101
Phenoxy[d]	7	92
4-*tert*-Butylphenoxy[e]	7	92
3,3,5-Trimethylcyclohexanone		
4-Chlorophenoxy[c]	65	92
Phenoxy[d]	63	92
4-*tert*-Butylphenoxy[e]	61	94

[a] The ratio of H^-/ketone in all cases was 1.5. Ketone (0.50 M) was added to the hydride at 0 °C. Th reaction was quenched after 2 h. The phenol was extracted with NaOH before GLC analysis was carried out. [b] Absolute yield measured with an internal standard. [c] 0.40 M initial concentration. [d] 0.37 M initial concentration. [e] 0.39 M initial concentration.

Table IX. Reduction of 3,3,5-Trimethylcyclohexanone by $LiAlH_4$ and $NaAlH_4$ and Tri-*n*-octyl-*n*-propylammonium Aluminum Hydride

Hydride[a]	Solvent	Concn, M	% equatorial attack
$LiAlH_4$	Ether	0.1	68
$LiAlH_4$	Ether	0.5	55
$LiAlH_4$	THF	0.1	82
$LiAlH_4$	DME	0.1	78
$NaAlH_4$	THF	0.1	64
$NaAlH_4$	DME	0.1	63
$(n\text{-}C_8H_{17})_3(n\text{-}C_3H_7)\text{-}NAlH_4$	Benzene	0.1	47

[a] The ketone in the appropriate solvent was added to the hydride solution (H^-/ketone = 6). The reaction was quenched after 2 h at 0 °C.

equatorial attack. It is interesting that selectivity involving $NaAlH_4$ in THF and $LiAlH_4$ in diethyl ether is comparable. This result is consistent with the above interpretation since solvation of $NaAlH_4$ in THF is similar to that of $LiAlH_4$ in diethyl ether.[20]

Electronic Effects. Because the selectivity of $LiAl(OCH_3)_3H$ toward II showed no dependence on concentration, it was decided that electronic effects should be investigated. A series of para-substituted phenoxy derivatives of $LiAlH_4$ was examined with ketones I and III. When the substituents were *tert*-butyl, hydrogen, and chlorine, the results obtained with I and III showed no change in selectivity (Table VIII). Electronic effects, within a series of similar hydrides, seem to be of little importance. Surprisingly lithium triphenoxyaluminohydrides attack I and III more from the axial side than $LiAlH_4$, thus exhibiting a less apparent steric requirement. This is not inconsistent with the expected lower solvation and monomeric nature of $LiAl(OPh)_3H$ compound compared to $LiAlH_4$.

Solvation Effects. It has been shown[20] that in THF, $LiAlH_4$ is primarily a solvent separated ion pair at 0.1 M while it is predominantly a contact ion pair in diethyl ether at the same concentration. It was also shown[20] that four THF molecules will specifically solvate the lithium cation in diethyl ether solution. It was further suggested[20] that the difference in selectivity of $LiAlH_4$ in diethyl ether and THF may be attributed to the nature of the ion pair present in solution.

Table X. Reduction of 3,3,5-Trimethylcyclohexanone in Diethyl Ether by $LiAlH_4$ at Varying THF:$LiAlH_4$ Ratios

THF/$LiAlH_4$[a]	% THF	% equatorial attack
0	0	68
1	0.82	68
2	1.6	69
3	2.5	69
4	3.3	70
5	4.1	69
6	4.9	69
7	5.7	70
8	6.6	69
10	8.2	71
15	12	75
18	15	76
24	20	76
30	25	79
36	30	79
43	35	81
61	50	81
THF	100	82

[a] The ketone in diethyl ether solvent was added to the hydride in diethyl ether–THF mixed solvent (H^-/ketone = 6). The initial concentration of the ketone and hydride was 0.10 M. Temperature 0 °C. Reaction time was 2 h.

Table IX gives the results of reduction of III with $LiAlH_4$ and $NaAlH_4$ 0.1 M in diethyl ether, THF, and DME. In diethyl ether, $LiAlH_4$ gives 14% less equatorial attack than in THF. The observed 68% equatorial attack in diethyl ether does not agree well with the reported[19] value of 55%. However, reduction at 0.5 M does give 55% equatorial attack and hence the difference is due to a difference in concentration. Sodium aluminum hydride is insoluble in diethyl ether and gives only trace amounts of reaction. If solvation is important it was initially thought that $NaAlH_4$ in DME, a bidentate ligand, may differ from $NaAlH_4$ in THF as $LiAlH_4$ differs in THF from diethyl ether. However, $NaAlH_4$ in THF and DME gives similar results as does $LiAlH_4$ in the same two solvents. The indication is that THF and DME are similar toward $LiAlH_4$ and $NaAlH_4$ in terms of their solvating power and ability to form solvent separated ion pairs. Since $LiAlH_4$ in THF is more selective (82% equatorial attack) in its reaction with III than $NaAlH_4$ in THF (64% equatorial attack) or $LiAlH_4$ in ether (68% equatorial attack), it appears once again that solvent separated ion pairs provide for greater attack from the least hindered side of the molecule. Reduction of III by NR_4AlH_4 in benzene is the least selective solvent system (47% equatorial attack) in Table IX, and reduction of I by NR_4AlH_4 in benzene gives the same results (10% equatorial attack) as in THF. These results are consistent as well with the idea expressed above in that NR_4AlH_4 compounds would not be expected to be highly solvated in either benzene or THF and hence would not be very selective. The fact that reduction of I by NR_4AlH_4 was comparable in benzene to that in THF is further evidence that NR_4^+ is not solvated by THF and that solvation of cations such as Li^+ is very important in determining the selectivity of reduction.

Reduction of III by $LiAlH_4$ in the mixed solvent THF–diethyl ether was carried out at a ratio of THF to $LiAlH_4$ from 1 to 61. If the difference between $LiAlH_4$ in diethyl ether and THF is that one is a contact ion pair and the other is solvent separated, then the selectivity of $LiAlH_4$ should change noticeably at THF:$LiAlH_4$ = 4. We have shown by NMR that the first 4 mol of THF added to a diethyl ether solution of $LiAlH_4$ specifically solvate the lithium cation.[20] The selectivity does not change drastically at any THF:$LiAlH_4$ ratio (Table X).

Table XI. Reduction of 3,3,5-Trimethylcyclohexanone by $LiAlH_4$ in Diethyl Ether, Diethyl Ether–Benzene Mixtures, and THF at Varying Amine:$LiAlH_4$ Ratios

Solvent	Amine/$LiAlH_4$	Solubility of complex	% equatorial attack
Ether	0.5[b]	Sol	68
Ether	1.0[b]	Sol	69
Ether	2.0[b]	Insol	71
Ether	4.0[b]	Insol	72
Ether/benzene 93%	0.5[b]	Insol	64
Ether/benzene 85%	1.0[b]	Sol	68
Ether/benzene 94%	2.0[b]	Sol	70
Ether/benzene 94%	4.0[b]	Sol	71
THF	1.0[c]	Sol	74
THF	2.0[c]	Sol	74

[a] Ketone in diethyl ether added to $LiAlH_4$ in diethyl ether or ketone in benzene added to $LiAlH_4$ in mixed solvent (H^-/ketone = 6). The initial concentration of the ketone and hydride was 0.10 M. Temperature 0 °C. Reaction time was 2 h. [b] Amine is *N,N,N′,N′*-tetramethylethylenediamine. [c] Amine is *N,N,N′,N″,N‴,N⁗*-hexamethyltriethylenetetraamine.

Of course there should be a difference in the solvation of $LiAlH_4$·4THF in THF and $LiAlH_4$·4THF in ether. The fact that the selectivity increases gradually as the THF:$LiAlH_4$ ratio increases indicates that secondary solvation involving more than 4 mol of THF per mole of $LiAlH_4$ is involved in the reactive species and that the optimum degree of ion pair separation is brought about by more than 4 mol of THF per mole of $LiAlH_4$.

Similar experiments were carried out by adding tetramethylethylenediamine (TMED) to $LiAlH_4$ in diethyl ether and diethyl ether–benzene mixtures. Very little change in selectivity with TMED:$LiAlH_4$ ratio (Table XI) was observed. The reduction of III by $LiAlH_4$ in THF in the presence of *N,N,N′,N″,N‴,N⁗*-hexamethyltriethylenetetraamine showed a decrease in selectivity from 82% equatorial attack in THF to 74%.

Table XII shows the results of reducing 3,3,5-trimethylcyclohexanone (III) with a variety of complex aluminum hydrides and solvent systems. Lithium aluminum hydride in THF is the most selective (82% equatorial attack). In cases where the cation is probably less solvated (entries 1–6) than $LiAlH_4$ in THF, the system is less selective. In cases where the cation is solvated by a single solvent molecule (crown ether), the system is also less selective. These results are consistent with the suggestion that complexation of the carbonyl oxygen by the cation takes place followed by transfer of the hydride to the carbonyl carbon. Removal of the cation from participation in the reaction pathway, either because of its inability to associate with the ketone or because it is complexed by another reagent, decreases the selectivity. Lithium aluminum hydride in THF represents the system involving the most ordering of *solvent and ketone* about the cation. This maximum in the amount of order in the system allows $LiAlH_4$ in THF to be the most selective.

Evaluation of Stereoselectivity of Other Hydrides. Data concerning the stereochemistry of reduction of a series of ketones with HBeCl and AlH_3 in diethyl ether and $LiAlH_4$, $LiAlD_4$, and $LiZnMe_2H$·AlH_3 in THF are tabulated in Table XIII. The reactions were run at 0 °C at a concentration of 0.10 M. The AlH_3 used in these studies is soluble in diethyl ether.[36] Results using AlH_3 in ether are similar to those observed for AlH_3 in THF. Although AlH_3 in diethyl ether gives almost twice the amount of equatorial attack on 4-*tert*-butylcyclohexanone as $LiAlH_4$ in THF, it is less selective toward camphor (V).

Table XII. Reduction of 3,3,5-trimethylcyclohexanone by $MAlH_4$ in Various Solvent Systems

Entry	$MAlH_4$	Solvent	% equatorial attack
1	NR_4AlH_4[b]	Benzene	47
2	NR_4AlH_4[b]	THF	55
3	$KAlH_4$	THF	60
4	$NaAlH_4$	THF	64
5	$NaAlH_4$	DME	63
6	$LiAlH_4$	Ether	68
7	$LiAlH_4$	THF	82
8	$LiAlH_4$	DME	78
9	$LiAlH_4$	Ether (+ TMED)	70
10	$LiAlH_4$	THF (+ amine)[a]	74
11	$NaAlH_4$	THF (+ crown ether)[c,e]	61
12	$NaAlH_4$	THF (+ crown ether)[d,e]	51
13	$KAlH_4$	THF (+ crown ether)[c,f]	50
14	$KAlH_4$	THF (+ crown ether)[d,f]	44

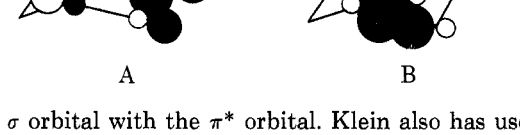
[a] *N,N,N′,N″,N‴,N⁗*-Hexamethyltriethylenetetraamine. [b] Tri-*n*-octyl-*n*-propylammonium aluminum hydride. [c] Dicyclohexyl-18-crown-6. [d] Dibenzo-18-crown-6. [e] Crown ether: $NaAlH_4$ = 1.1 [f] Crown ether: $KAlH_4$ = 2.2.

The new hydride $LiZnMe_2H$·AlH_3 gave more equatorial attack on I and III than did $LiAlH_4$. There is no methylation product according to gas chromatographic analysis.

Results using $LiAlH_4$ and $LiAlD_4$ are very similar. Therefore, there is no significant primary isotope effect influencing the stereoselectivity of $LiAlH_4$ reduction of ketones.

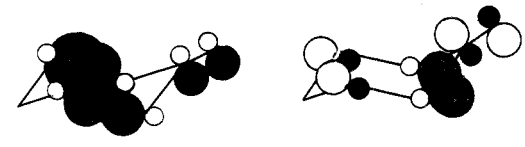
The new hydride HBeCl[37] is quite similar to $LiAlH_4$ in selectivity except for the reduction of 4-*tert*-butylcyclohexanone. It gives 46% equatorial attack which is comparable to $LiAl(OCH_3)_3H$ (44%). What causes HBeCl to have a larger steric requirement than $LiAlH_4$ is not readily apparent. The increased steric strain could be attributed to the fact that HBeCl is a dimer;[37] on the other hand, if this explanation is correct, HBeCl should be more selective than $LiAlH_4$ toward V, which it is not. More detailed mechanistic information is necessary to convincingly explain these results.

Orbital Symmetry Explanation of Stereochemical Results. Since the completion of the experimental work reported herein, Klein and others[13,38,39] have proposed a new theory of stereochemical control based on orbital symmetry arguments. Klein[12,39] has represented the orbital distortions involved in electrophilic attack and nucleophilic attack on cyclohexanone by A and B, respectively. A represents the interaction of the symmetrical β C–C σ^* orbital with the π orbital and B represents the interaction of the symmetrical β



A B

C–C σ orbital with the π^* orbital. Klein also has used the symmetrical σ–π interaction and the symmetrical σ^*–π^* interaction to demonstrate the distortion of the HOMO and LUMO of cyclohexanone. These interactions are represented in C and D. The carbonyl carbon atom's p orbital of the



C D

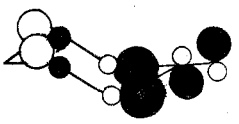
Table XIII. Reduction of Some Representative Ketones with Some Soluble Metal Hydrides

Ketone[a-c]	Hydride[c]	H^-/ketone	Solvent	% equatorial or exo attack
I	HBeCl	2	Ether	46
I	HBeCl	1	Ether	43
III	HBeCl	2	Ether	83
III	HBeCl	1	Ether	85
IV	HBeCl	2	Ether	92
V	HBeCl	2	Ether	14
I	$LiAlH_4$	6	THF	10
I	$LiAlD_4$	6	THF	9
III	$LiAlH_4$	6	THF	82
III	$LiAlD_4$	6	THF	85
IV	$LiAlH_4$	6	THF	93
IV	$LiAlD_4$	6	THF	92
V	$LiAlH_4$	6	THF	8
V	$LiAlD_4$	6	THF	8
I	AlH_3	4.5	Ether	19
I	AlH_3	1	Ether	18
III	AlH_3	4.5	Ether	77
III	AlH_3	1	Ether	66
IV	AlH_3	4.5	Ether	96
V	AlH_3	4.5	Ether	18
I	$LiZn(CH_3)_2H{\cdot}AlH_3$	6	THF	17
III	$LiZn(CH_3)_2H{\cdot}AlH_3$	6	THF	93

[a] Ketone in the appropriate solvent was added to the hydride. Temperature 0 °C. Reaction time was 2 h. [b] I = 4-*tert*-butylcyclohexanone, III = 3,3,5-trimethylcyclohexanone, IV = norcamphor, V = camphor. [c] All hydrides and ketones were initially 0.10 M.

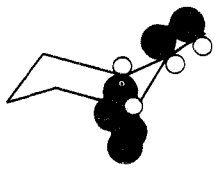
HOMO is distorted to the equatorial side in A and C; therefore an electrophilic reagent is expected to attack the cyclohexanone from the electron-dense equatorial side. Similarly a nucleophile is more likely to attack the axial side because the carbonyl carbon atom's p orbital of the LUMO is distorted to that side as shown in B and D. Klein has pointed out that the axial β C–H bonds could in principle interact with the carbonyl carbon of cyclohexanone, but its effects would be expected to be opposite to the β C–C bonds because the two bond systems are antisymmetric about the C_6–C_1–C_2 plane and hyperconjugation of the π bond with the β C–C bonds is favored because they are more polarizable than the C–H bonds. However, Klein has further pointed out that involvement of the β C–C bonds and the axial β C–H bonds may be different in electrophilic and nucleophilic reactions.

It seems to us that the LUMO arising from the β C–C σ^*–π^* interaction (D) is better represented by E, which would allow

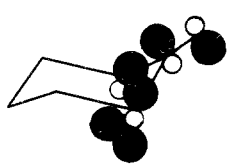


E

more overlap between the σ^* and π^* orbitals. E does not predict axial attack by a nucleophile, which is what is usually observed for hydrides. F and G demonstrate the HOMO and



F

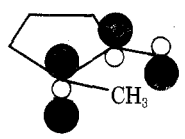


G

LUMO, respectively, for interaction of the π bond with the axial β C–H (σ–π and σ^*–π^* interactions). G, as does B, predicts axial attack by nucleophiles. However, it should be pointed out that F does not predict equatorial attack by a nucleophile.

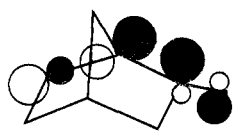
The reductions reported here were evaluated by considering several figures of orbital distortion (similar to B, D, E, and G) for each ketone. It was found that the reductions of the unhindered ketones reported here are consistently in agreement with the orbital distortion arising from axial (or pseudoaxial) β C–H σ^*–π^* interaction (similar to G). The only precedents for selecting one figure over another was their agreement or disagreement with observed results. Selecting figures on other bases, especially for the cyclohexanone ring system, is not straightforward and may be indeterminate.[13b]

H favors cis attack on VII (the methyl group is pseudo-



H

equatorial) as is observed for $LiAlH_4$. J favors exo attack on IV as is observed for all hydrides studied.



LUMO
J

Orbital distortion also allows an alternate explanation for the observed stereochemistry of II and VII with $Mg(AlH_4)_2$ and $ClMgAlH_4$.

Examination of conformations IIa and IIe suggest that IIa should be more able to stabilize an induced positive charge at the carbonyl carbon than IIe[39,40] because hyperconjugation should be greater for the more polarizable axial β C–C bond of IIa than the axial β C–H bond of IIe. Thus, this increased stabilization allows more of the reaction to proceed by IIa in the case of $Mg(AlH_4)_2$ and $ClMgAlH_4$ than $LiAlH_4$ (assuming that Mg^{2+} polarizes the carbonyl C–O bond more than Li^+). In the case of VII (Table IV) the difference in the stereochemical results with $Mg(AlH_4)_2$ and $ClMgAH_4$ as compared

to $LiAlH_4$ may be explained also by a change in conformation, i.e. reaction via the conformation of VII with the methyl group in a pseudoaxial position. The same two explanations applied to II for a change in conformation may be applied to VII. Additionally, an increase in the influence of orbital distortion for $Mg(AlH_4)_2$ and $ClMgAlH_4$ over $LiAlH_4$ (assuming that Mg^{2+} polarizes the carbonyl C–O bond more than Li^+) would be consistent with their greater amounts of axial attack on III and exo attack on V than $LiAlH_4$.

Conclusions

The most prominent theories of stereochemical control for reduction of ketones by metal hydrides are product development control, steric approach control, and torsional strain. The results reported in Table I show that $LiAlH_4$ gives more axial attack on 4-*tert*-butylcyclohexanone (I) and more equatorial attack on 3,3,5-trimethylcyclohexanone (III) than $NaAlH_4$. If these results are explained in terms of product development control and steric approach control, then $NaAlH_4$ in the case of I has an early transition state compared to $LiAlH_4$ whereas in the case of III a later transition state is involved. However, it seems reasonable that $NaAlH_4$ would have a transition state which is consistently earlier or later than that of $LiAlH_4$ with all ketones. If torsional strain and steric approach control are used to explain the above results, there is no necessity to invoke the concept of early and late transition states. For this reason and because of prior work of Eliel[10] and Klein,[11] product development control was not considered a viable concept in explaining the stereochemical results reported in this work.

The stereochemical evaluation of the $MAlH_4$ series as stereoselective reducing agents on selected model ketones show that results are dependent on the nature of M^+. This suggests that the reducing agent is the ion pair $M^+AlH_4^-$ and not just AlH_4^-. Comparison of $LiAlH_4$ to $LiBH_4$, showed $LiBH_4$ to be less selective toward III, IV, and V which may be explained on the basis that the BH_4^- ion is smaller than the AlH_4^- ion.

It was further demonstrated that the different conformations of a conformationally mobile ketone such as 2-methylcyclohexanone (II) are important in determining the stereochemical results of $MAlH_4$ reduction. Because the degree to which different conformations of II participate in the reduction of $MAlH_4$ as M^+ is varied from Li^+ to $ClMg^+$ to AlH_4Mg^+, it was suggested that the cation complexes the carbonyl oxygen, interacting with the C-2 methyl group, and effects a change in the conformation of the ketone during reduction.

The recently reported "compression effect" for controlling the stereochemistry of alkylation of cyclohexanones and cyclopentanones with excess $Al(CH_3)_3$ in benzene does not seem to be operative in the reduction of the ketones using complex metal hydrides.

Contrary to previous reports, the selectivity of $LiAl(OCH_3)_3H$ is independent of concentration. Therefore, its greater selectivity over $LiAl(OBu\text{-}t)_3H$ does not depend on its greater degree of association at higher concentrations compared to $Li(OBu\text{-}t)_3H$ which is monomeric at all concentrations. The only explanation for the greater degree of selectivity of $LiAl(OCH_3)_3H$ compared to $LiAl(OBu\text{-}t)_3H$ is that conductance measurement indicate that $LiAl(OCH_3)_3H$ is more highly solvated and several aspects of the present studies indicate that the more highly solvated hydrides are more selective in attack at the least hindered side of the ketone.

Solvation and concentration studies conducted by reduction of 3,3,5-trimethylcyclohexanone (III) with $LiAlH_4$ showed $LiAlH_4$ to be more selective at lower concentrations in THF, and more selective in THF than diethyl ether. The greater selectivity of $LiAlH_4$ in THF could not be attributed to any specific solvation (e.g., $LiAlH_4 \cdot 4THF$), but rather to a more general solvation of the Li^+ cations in which selectivity was shown to be a formation of both primary and secondary solvation.

Certain stereochemical results were shown to be consistent with distortion of the π^* orbital due to interaction with $\beta\sigma^*$ (or σ) orbitals. The different possible orbital interactions must be studied in more detail in order to determine the most favorable interaction and to see if this interaction agrees with the observed stereochemistry of reduction. We have attempted to explain the stereochemical results reported herein with a consistent type of orbital interaction (σ^*–π^*); however, we realize that a specific type of orbital interaction may vary considerably from ketone to ketone and with the mechanism of reduction (or addition).

Experimental Section

Materials. Fisher reagent grade anhydrous diethyl ether was distilled under nitrogen from $LiAlH_4$ prior to use. Fisher reagent grade tetrahydrofuran (THF), benzene, and 1,2-dimethoxyethane (DME) were distilled under nitrogen from $NaAlH_4$ prior to use. Fisher reagent grade *N,N,N',N'*-tetramethylethylenediamine (TMED) was distilled from and stored over Linde 4A Molecular Sieve. A commerical sample (Ames Laboratory) of *N,N,N',N'',N''',N'''*-hexamethyltriethylenetetraamine was vacuum distilled (67–70 °C, 0.05 mm) from 4A molecular sieve and immediately used. Dibenzo-18-crown-6 and dicyclohexyl-18-crown-6 ethers were obtained from Drs. D. J. Cram and H. O. House, respectively, and were used without further purification. 2-Methylcyclohexanone (Eastman), norcamphor (Aldrich), camphor (Aldrich), 3,3,5-trimethylcyclohexanone (Chemical Samples), and 4-*tert*-butylcyclohexanone (Frinton) were purified by vacuum distillation or sublimation. 2-Methylcyclopentanone, 3-methylcyclopentanone, and *cis*-3,4-dimethylcyclopentanone (Chemical Samples) were used without further purification except for drying with activated Linde 4A Molecular Sieve. *cis*-2-Methyl-4-*tert*-butylcyclohexanone (98% pure by gas chromatographic analysis) was obtained by the method of Allinger.[41] Solutions of ketones were prepared by dissolving a known amount of ketone in a known volume of solvent using syringes and flasks fitted with a three-way stopcock and which had been flash flamed under nitrogen. Lithium aluminum hydride, $NaAlH_4$, $LiAlD_4$, and $LiBH_4$ were obtained from Alfa Inorganics. Solutions were prepared by distilling solvent onto the hydride and stirring the resulting slurry at least 24 h. The slurry was filtered in a drybox through a fritted glass funnel. The clear and colorless solutions of $LiAlH_4$, $LiAlD_4$, and $NaAlH_4$ were standardized by aluminum and gas evolution analysis. The $LiBH_4$, which also was clear and colorless, was standardized by lithium analysis.

Tri-*n*-octyl-*n*-propylammonium aluminum hydride (NR_4AlH_4) was prepared as reported previously.[18] A THF solution was standardized by aluminum analysis (Al:H ratio = 1.00:3.83). The solvent was removed from this solution under vacuum resulting in the isolation of a cream-colored solid. The solid was dissolved in benzene and the benzene removed under vacuum overnight followed by redissolution of the resulting powder in benzene to give a clear yellow solution (H:Al:Br = 3.77:1.00:0.001).

Magnesium aluminum hydride and $ClMgAlH_4$ were prepared by previously reported methods.[42] The $Mg(AlH_4)_2$ prepared was a white solid which exhibited a Mg:Al:H ratio of 0.92:2.00:7.76. A THF solution of $ClMgAlH_4$ exhibited a Cl:Mg:Al:H ratio of 0.97:0.97:1.00:3.92.

Activated magnesium hydride was prepared from NaH and activated $MgBr_2$ as previously described.[43] A measured volume of the MgH_2–NaBr slurry was removed with stirring and standarized by hydrogen analysis (gas evolution). The MgH_2 was not dried in order to avoid loss of activity.

Sodium aluminum hexahydride (Na_3AlH_6) was prepared as previously described[44] by allowing sodium, aluminum, and hydrogen to react at 2000 psi and 160 °C in toluene. Analysis of the resulting solid gave the ratio Na:Al:H = 3.0:1.1:6.2. X-ray powder diffraction analysis showed only lines reported for Na_3AlH_6.

The other hydrides used in this study, Li_2ZnH_4,[45] $LiZn(CH_3)_2H \cdot AlH_3$,[46] $NaMgH_3$,[47] NR_4MgH_3[47] (NR_4 = tri-*n*-octyl-*n*-propylammonium ion), $KAlH_4$,[48] HBeCl,[37] and AlH_3,[36] were also obtained by previously reported methods.

Methanol and *tert*-butyl alcohol were distilled from magnesium and sodium, respectively. Phenol, 4-*tert*-butylphenol, and 4-chlorophenol were dried under vacuum at room temperature and stored over

activated 4A molecular sieve in THF. The trialkoxy and triaryloxy derivatives of $LiAlH_4$ were prepared by slowly adding 3 mol of the alcohol or phenol in THF to 1 mol of $LiAlH_4$ in THF. The lithium trimethoxyaluminohydride was prepared at 0 °C and used within 24 h. The analyses were as follows: lithium trimethoxyaluminohydride, Al:H = 1.00:0.99; lithium tri-*tert*-butoxyaluminohydride, Al:H = 1.00:1.00; lithium triphenoxyaluminohydride, Al:H = 1.00:0.98; lithium tri-4-chlorophenoxyaluminohydride, Al:H = 1.00:0.97; lithium tri-4-*tert*-butylphenoxyaluminohydride, Al:H = 1.00:0.97.

Magnesium analyses were carried out by EDTA titration of an aliquot of the hydrolyzed sample at pH 10 using Eriochrome Black T as an indicator (aluminum if present was masked with triethanolamine). Aluminum analyses were carried out by EDTA–zinc acetate back titration at pH 4 using dithizone as an indicator. Halide analyses were carried out by Volhard titration. Hydride analyses were carried out by measuring the volume of H_2 evolved by an aliquot of the sample on hydrolysis. Lithium and sodium analyses were carried out by flame photometry.

Reduction Procedures. A 50 ml Erlenmeyer flask with a magnetic stirring bar was flash flamed under nitrogen and then fitted with a rubber septum. The homogeneous reactions were run at two ratios, H^-/ketone = 6.0 and H^-/ketone = 1. For the excess hydride reactions 6.0 ml of 0.50 M hydride in THF was added to the flask. The flask was cooled to 0 °C and 4.0 ml of 0.50 M ketone in THF added. In the reactions with excess ketone, 2.0 ml of hydride solution was added to 8.0 ml of ketone at 0 °C. The reactions were quenched after about 2 h with distilled water or a saturated NH_4Cl solution. The internal standard was added and GLC analyses were carried out.

Samples of norcamphor and 3,3,5-trimethylcyclohexanone reacting with $LiBH_4$ were removed periodically and the absorbance of the n $\rightarrow \pi^*$ transition measured. The reactions were complete within 2 h. Reactions of camphor require a longer time before completion.

The heterogeneous reactions required adding the solid hydride to a tared flask in a drybox. With the weight of hydride known, the appropriate volumes of solvents and ketone solutions were added. The MgH_2 was not weighed but a measured volume of the slurry was added to the flask. The reactions were run with excess hydride and constant stirring.

The reactions of 3,3,5-trimethylcyclohexanone (III) with $LiAlH_4$ in diethyl ether and THF mixtures were run at 0 °C for 2 h. To a known amount of a standard solution of $LiAlH_4$ in diethyl ether was added diethyl ether and a THF–diethyl ether mixture so that the resulting solution was 0.10 M in $LiAlH_4$ and the ratio THF:Li was known. The THF:Li ratio varied from 1.0 to 61. To this solution was added the appropriate amount of III (0.10 M in diethyl ether) so that the ratio H^-/ketone = 6.0.

Reactions of III with $LiAlH_4$ in diethyl ether in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMED) were conducted similarly. Benzene was added to certain reactions to help increase the solubility of the complex when the complex was insoluble in diethyl ether. Reaction of III with $LiAlH_4$ in THF in the presence of *N,N,N',N'',N''',N'''*-hexamethyltriethylenetetraamine was also conducted similarly.

The reactions of III with $LiAlH_4$ in diethyl ether, and $NaAlH_4$ and $KAlH_4$ in THF, in the presence of crown ethers were conducted at 0 °C for 2 h. To a known weight of crown ethers was added solvent, then the hydride solution followed by ketone.

A 20-ft 5% Carbowax 20M on Chromosorb G or 15-ft 10% Carbowax 20M on Diatoport S column was used to separate the products of reaction of camphor (V) (150 °C), norcamphor (IV) (125 °C), 3,3,5-trimethylcyclohexanone (III) (125 °C), and 4-*tert*-butylcyclohexanone (I) (150 °C). Products from 2-methylcyclohexanone (II) and 2-methylcyclopentanone (VII) were separated on a 15-ft 5% diglycerol column at 75 °C.

Retention times varied slightly from column to column. For ketones I, II, III, IV, V, and VII the order of elution was always the same: the ketone first; the axial alcohol (I, II, III), exo alcohol (IV, V), and cis alcohol (II, VII) second; and equatorial alcohol (I, II, III), endo alcohol (IV, V), and trans alcohol (II, VII) last. The *cis*-2-methyl-4-*tert*-butylcyclohexanone and its alcohols were separated on a 10-ft 10% Carbowax 6M on Chromosorb G at 180 °C. The order of elution was ketone, axial alcohol, equatorial alcohol.

Relative retention times are given for each ketone, cis or exo alcohol, trans or endo alcohol, and standard, respectively as follows: I, 1.00, 1.11, 1.32, 0.65; II, 1.00, 2.25, 2.95, 1.28; III, 1.00, 1.69, 1.44, 3.06; IV, 1.00, 1.46, 1.56, 0.83; V, 1.00, 1.39, 1.53, 0.62; VI, 1.00, 1.74, 2.33, (−); and VII, 1.00, 2.33, 3.30, (−). The internal standard used to measure yields for ketones I, II, IV, and V was III. Ethyl benzoate was used as the internal standard for III. No internal standard was used with VI and VII. Ratio of alcohols were also determined by NMR for VI and VII (also VIII and IX). The weight percent recovery of product for NMR purposes was 80% or better.

The reactions of the cyclopentanones were carried out as described above. The reaction mixture was quenched and dried with $MgSO_4$. The clear portion of the mixture was removed and put in another flask. The $MgSO_4$ and hydrolysates were washed several times with diethyl ether. The washings were combined and added to the original solutions. The solvent was then removed under reduced pressure and 0.5–1.0 ml of Me_2SO-d_6 added. Me_4Si was the reference.

The ratio of 2-methylcyclopentanols, 3-methylcyclopentanols, and *cis*-3,4-dimethylcyclopentanols was measured by NMR in Me_2SO-d_6. The assignments for the hydroxyl protons have been described by Battioni.[33] The hydroxyl proton NMR signal locations are *cis*-2-methylcyclopentanol, δ 4.10; *trans*-2-methylcyclopentanol, 4.38; *cis*-3-methylcyclopentanol, 4.35; *trans*-3-methylcyclopentanol, 4.26; *cis,cis*-3,4-dimethylcyclopentanol, 4.37; and *trans,trans*-3,4-dimethylcyclopentanol, 4.23.

The ratio of alcohols from reduction of *cis*-2-methyl-4-*tert*-butylcyclohexanone with $Mg(AlH_4)_2$ was also measured by NMR. Results from NMR and GLC analyses were in complete agreement. The hydroxyl proton NMR signals are located at δ 4.32 and 4.00 for the equatorial and axial alcohols, respectively, in Me_2SO-d_6 with Me_4Si as the reference.

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Registry No.—I, 98-53-3; II, 583-60-8; III, 873-94-9; IV, 497-38-1; V, 76-22-2; VI, 3211-27-6; VII, 1120-72-5; VIII, 1757-42-2; IX, 19550-72-2; $LiAlH_4$, 16853-85-3; $NaAlH_4$, 13770-96-2; $Mg(AlH_4)_2$, 30472-12-9; $ClMgAlH_4$, 12522-22-4; MgH_2, 7693-27-8; $NaZnH_3$, 34397-46-1; Li_2ZnH_4, 38829-84-4; $NaMgH_3$, 59034-14-9; Na_3AlH_6, 17069-12-4; $LiAl(OBu\text{-}t)_3H$, 17476-04-9; $LiAl(OCH_3)_3H$, 12076-93-6; $Li(Cl\text{-}p\text{-}C_6H_4O)_3AlH$, 59034-15-0; $Li(PhO)_3AlH$, 59034-16-1; $Li(t\text{-}Bu\text{-}p\text{-}C_6H_4O)AlH$, 59034-17-2; $(n\text{-}C_8H_{17})_3(n\text{-}C_3H_7)NAlH_4$, 26026-60-8; $KAlH_4$, 16903-34-7; HBeCl, 42016-55-7; $LiAlD_4$, 14128-54-2; $LiZn(CH_3)_2H{\cdot}AlH_3$, 59092-43-2.

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Stereochemical Control of Reductions. 5.[1] Effects of Electron Density and Solvent on Group Haptophilicity[2]

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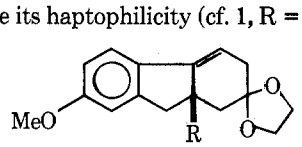
7-Methoxy-10a-hydroxymethyl-1,2,3,9,10,10a-hexahydrophenanthrene (**2**) was synthesized and the stereochemistry of its cis (**8**) and trans (**5**) reduction products established. The directive effect of the CH_2OH group was examined by heterogeneous catalytic hydrogenation of **2** over a Pd/C catalyst, leading to cis–trans mixtures whose proportion of **8** increased (6–61%) as the solvent dielectric constant was lowered (DMF, EtOH, THF, DME, diglyme, Bu_2O, dioxane, hexane). This is interpreted primarily in terms of competition between substrate CH_2OH and solvent for active catalyst sites. Use of a Pt/C catalyst gave a nearly identical solvent order, but with higher proportions of **8** throughout (9–80%). Compound **2** was converted to its Li, Na, and K alkoxides and these, when hydrogenated over Pd/C in diglyme, gave increasing proportions of **8** (60–69%) in the product mixture compared to the protonated group (23%). This is interpreted as reflecting increasing electron density available to bind oxygen to the catalyst surface during reduction. These principles may be useful in improving stereochemical control in catalytic hydrogenation.

Numerous reports[4] of heterogeneous catalytic hydrogenations deal with instances in which the presence of certain functional groups in the substrate molecule has led to product stereochemistry opposite that expected on the basis of steric hindrance.[4b] This evidently can arise from a propensity of the functional group, most frequently hydroxyl, to bind to the catalyst surface during reduction in such a way as to enforce addition of hydrogen from its own side of the molecule, an effect we have termed haptophilicity.[5]

Our previous work[5] on the directing effects of various substrate functional groups during hydrogenation led us to the general conclusion that a group's haptophilicity is probably directly related to, among other things, its ability to donate electrons toward the catalytic surface. This conclusion suggested to us several specific ways in which the haptophilicities of groups might be altered so as to affect predictably the stereochemistry of reductions. For example, conversion of an acidic group to its anion should increase its electron-donating ability and hence its haptophilicity (cf. **1**, R = COOH, COOLi,



1

COONa).[5] Additionally, the effective haptophilicity of many R groups would probably be increased if competition from polar and especially hydroxylic solvents were eliminated, since OH has a high haptophilicity.

Synthesis and Stereochemistry of Materials. We wished to test these ideas experimentally; however, it was clear that for several R groups the system **1** would be insensitive to increases in haptophilicity, leading to higher percentages of cis product, simply because the percentage of cis product was already very high (e.g., R = CH_2OH → 95% cis).[5,6] For this reason we have turned our attention to the closely related system **2**, which was prepared by reduction of the known ester **3**.[7] Compound **2** not only was soluble in a variety of solvents of low polarity but, on catalytic hydrogenation under reaction conditions similar to those used with **1**, gave a product mixture rich in the trans isomer (94% trans, 6% cis), allowing us ample leeway in enhancing the haptophilicity of the CH_2OH group. This relatively high percentage of trans product obtained from **2** supports our previous speculation[5] that the ketal group in **1** may be haptophilically involved in the contrastingly high cis specificity (95%) observed in hydrogenation of **1**, R = CH_2OH.[5,6] Scheme I shows the sequences by which the

Scheme I