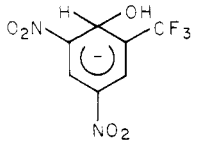
Table V. Kinetic and Equilibrium Parameters for Complexes 3 and 8 in Dimethyl Sulfoxide-Water Mixtures

	8[a]	3[b]
	Water[c]	
10^2k_1, M^{-1} s^{-1}	15.9	1.53
k_{-1}, s^{-1}	80.6	0.368
10^3K, M^{-1}	2.0	31.1
	60% Me_2SO	
k_1, M^{-1} s^{-1}	24.6	0.458
10^2k_{-1}, s^{-1}	46	2.62
K, M^{-1}	53.5	17.5
	70% Me_2SO	
k_1, M^{-1} s^{-1}	126	1.99
10^2k_{-1}, s^{-1}	8.6	0.78
K, M^{-1}	1460	254

[a] F. Millot and F. Terrier, *Bull. Soc. Chim. Fr.*, 9, 1823 (1974) (at 20 °C). [b] This work. [c] Values extrapolated.

as a function of mole fraction of Me_2SO (Figure 2) is a straight line, as seems to be a common finding in Meisenheimer chemistry.[21]

In Table V we compare rate and equilibrium parameters for 3 and 8.



8

We note that in water solution 3 is more stable than 8, $K_1(3)/K_1(8) = 15.6$, and the higher stability of 3 is more the result of slower rate of decomposition than of faster rate of formation. The equilibrium constant for the 1:1 sulfite ion complex of trinitrobenzene is 2.83×10^{-2} M^{-1},[22] whereas that of dimethylpicramide is 3×10^4 [10b] at 25 °C, and again, the backward reactions are responsible for the differences in the equilibrium constants. After the stabilities of complexes with different X substituents[10b] at C-1 were compared, it was suggested that the effect of X on the stability of complexes is mainly due to its effect on solvation of the complex rather than its electronic nature. The much smaller rate constant for the decomposition of 3 with respect to that for 8 may be the result of better solvation of complex 3 by water through hydrogen bonding to the amine group. As Me_2SO replaces water in the solvent, the stabilization of 3 relative to 8 decreases since less water is available to hydrogen bond to the amine group in the complex, and consequently the ratio $k_{-1}(3)/k_{-1}(8)$ decreases.

(20) (a) J. W. Larsen, K. Amin, and J. H. Fendler, *J. Am. Chem. Soc.*, 93, 2910 (1971); (b) J. H. Fendler and J. W. Larsen, *J. Org. Chem.*, 37, 2608 (1972).
(21) F. Terrier, F. Millot, and J. Morelli, *J. Org. Chem.*, 41, 3892 (1976).
(22) C. F. Bernasconi and R. Bergstrom, *J. Am. Chem. Soc.*, 95, 3603 (1973).

Experimental Section

Trifluralin (2) was obtained from a commercial sample of Treflan (Eli Lilly) and purified by recrystallization from ethanol; mp 46-47 °C (lit. mp 46-47 °C).[23]

Me_2SO was dried on 5A-type molecular sieves and vacuum distilled. Solvent mixtures were made up from the desired number of volumes of Me_2SO in 100 volumes of solution. The mole fraction of Me_2SO was determined by weighing the Me_2SO and the final solution.

^1H NMR studies were carried out on a Varian T 60 spectrophotometer at the probe temperature, and the absorption is reported in δ values, relative to Me_4Si.

Absorbance measurements were obtained by using a Beckman 24 spectrophotometer.

Kinetic measurements were made by rapidly injecting about 10 μL of complex 3 prepared in 80% Me_2SO into the thermostated cell of the spectrophotometer and recording the decrease in absorbance at 430 nm. The temperature inside the cell was maintained at 25 ± 0.5 °C. In solutions where the amount of 3 formed was considerable, we measured the attainment of equilibrium for the formation of 3, starting from a solution of 2. Both methods give the same results. Changes in the wavelength of measurements did not change the observed rate.

Acknowledgment. This research was supported in part by the Consejo Nacional de Investigaciones Cientificas y Tecnicas and Secretaria de Estado de Ciencia y Tecnologia, Argentina.

Registry No. 2, 3765-92-2; 3, 72283-22-8; potassium hydroxide, 1310-58-3.

(23) "The Merck Index", Paul G. Stecker, Ed., Merck & Co., New York, 1968, p 1074.

Kinetics and Activation Parameters for the Reduction of Alkylcyclohexanones by Lithium Tri-*tert*-butoxyaluminohydride[1]

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Received July 17, 1979

The kinetics of reduction of 15 cyclohexanones by lithium tri-*tert*-butoxyaluminohydride in tetrahydrofuran solvent are reported. The data confirm that the reaction is well represented by a simple second-order kinetic process. Second-order rate constants determined at various temperatures are recorded and the activation parameters determined. Rate constants vary from 5.0×10^{-3} to 4.4 L mol^{-1} s^{-1}; these rate constants exceed those of reduction by $NaBH_4$ by factors varying from 50 (unhindered cyclohexanones) to 450 (hindered cyclohexanones). The reductions appear to be nearly isoenthalpic, all but three of the values of $\Delta H^{\ddagger}$ being in the range 6.8 ± 0.8 kcal mol^{-1}. Variations in rates between ketones are caused by changes in $\Delta S^{\ddagger}$, and entropy is also more significant than enthalpy in the free-energy barrier to reaction. Mechanistic aspects of the reduction are discussed.

Despite the intensive use of complex metal hydrides as versatile and stereoselective reducing agents in synthetic organic chemistry over the past three decades, the parallel development of rigorous mechanistic information on these

0022-3263/80/1945-0653$01.00/0

Table I. Extinction Coefficients for Cyclohexanones in Tetrahydrofuran

	λ_{max}, nm	ϵ, L mol^{-1} cm^{-1}			
		283 K	292 K	298 K	305 K
1	288	15.0	14.9	15.1	14.8
2	289	15.1	15.0	15.1	15.1
3	288	15.2	15.1	14.7	14.8
4	288	15.9	15.6	15.8	15.8
5	287	16.7	16.5	16.4	16.5
6	287	17.3	17.2	17.2	17.2
7	290	18.9	18.8	18.8	18.8
8	290	17.7	18.0	18.1	17.7
9	286	18.1	18.2	18.6	18.7
10	290	18.2	18.3	20.9	18.3
11	290	19.8	19.8	19.6	19.7
12	290	15.9	16.5	16.6	16.4
13	290	16.1	16.7	16.6	16.6
14	295	16.5	16.9	17.0	16.6
15	295	14.6	14.6	14.6	14.6

reactions has been slow.[2] Of the various systems available for investigation, sodium borohydride reduction of ketones has received the most attention. This is partly because the intriguing variation of stereoselectivity as a function of ketone structure[2,3] is well illustrated by this system and partly because the study of these reductions does not present severe experimental difficulties.

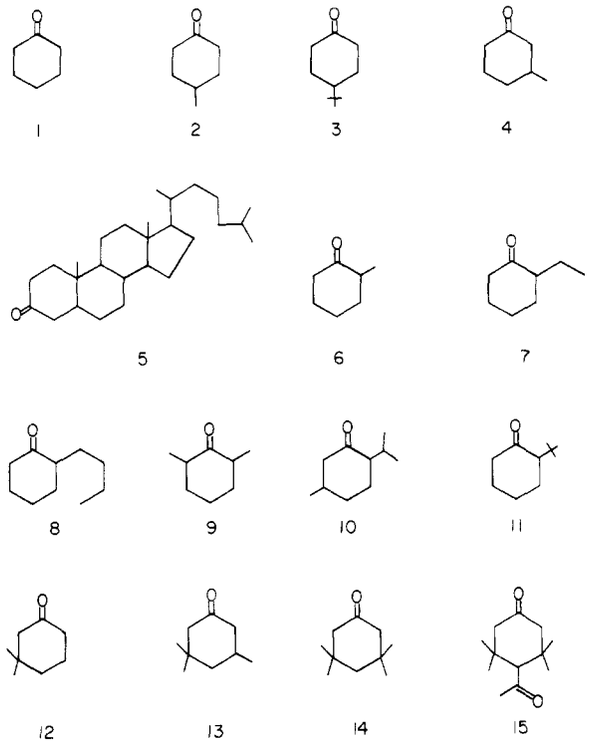
Sooner or later, however, mechanistic investigations on sodium borohydride reductions run into a rather intractable interpretative roadblock. This arises directly from the four hydrides in the molecule, all of which are available for reduction; as a consequence of this one has to recognize (a) that stereochemistry arises from reduction by the combination of all available hydrides, yet the kinetics are determined only by the first transfer, (b) that isotope-effect studies involve the combination of primary and secondary effects, and (c) that disproportionation of intermediate alkoxyborohydride species may play a role in the overall reaction process.[2,4]

All of these difficulties are removed by switching attention to a reductant containing only one available hydride for reduction. For this purpose we have selected lithium tri-*tert*-butoxyaluminohydride[1] (LTBA). This reagent, first reported by Brown and McFarlin in 1958[6] has the following desirable features: (a) like sodium borohydride, the spectrum of stereoselectivities as a function of ketone structure is exhibited;[2] (b) the reagent is prepared by a well-documented and straightforward process;[6] (c) the reagent is stable and, although more reactive than sodium borohydride, is far less violent than lithium aluminum hydride;[6] (d) unlike some other complex metal hydrides, the reagent is monomeric in tetrahydrofuran (THF) solution and is not subject to disproportionation.[7,8]

In this paper we wish to report kinetics and activation parameters of the reduction of a series of alkylcyclohexanones by lithium tri-*tert*-butoxyaluminohydride.

Results and Discussion

Ketones Studied. The following 15 cyclohexanones were employed in this study.



Previous Work. LTBA has been used in three previous kinetic investigations of the reduction of ketones. The most comprehensive and best documented work is that of Ayres, Kirk, and Sawdaye,[9] who measured the rates of reduction of a series of *p,p'*-disubstituted benzophenones in tetrahydrofuran at 0 °C. Using a gas–liquid chromatographic technique, they found an acceptable fit with the expected second-order rate expression, in agreement with the previous work of Klein et al.[10] A tenfold excess of hydride was used and the reaction monitored for the first 30% of the reaction. The slope of the resultant Hammett plot was 2.13, consistent with the reducing species being $^-Al(O\text{-}t\text{-}Bu)_3H$ rather than a neutral aluminum species (ρ for AlH_3 reductions being 0.89).

Klein et al.[10] measured the rates of reduction of five alkylcyclohexanones at 30 °C by using a spectrophotometric method. A large excess of hydride was used, and pseudo-first-order plots of ketone disappearance were constructed. On this basis it was concluded that the reaction was first order in each component. It was determined that the reaction was neither diffusion controlled nor mixing controlled, and thus specific rate constants for axial and equatorial attack could be calculated from the product epimer ratio. However, the method of determination of hydride concentration was not specified, and the spectral readings were taken at 285 nm. In our experience the wavelength of maximum absorption for the more hindered alkylcyclohexanones is 295 nm. Both of these factors may cause error in the rate-constant determination.

(1) This is the name used by the majority of chemists actually using this compound. For anyone wishing to do a search on this compound it may be useful to know that *Chemical Abstracts* currently refers to it as Aluminate (1-), hydrotris(2-methyl-2-propanolato) lithium.

(2) For recent summaries in this and related areas see: E. C. Ashby, J. Laemmle, and H. M. Neumann, *Acc. Chem. Res.*, **7**, 272 (1974); E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, **75**, 521 (1975); D. C. Wigfield, *Tetrahedron*, **35**, 449 (1979); J. R. Boone and E. C. Ashby, *Top. Stereochem.*, in press (and references cited in these articles).

(3) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(4) Evidence that the *mono*alkoxyborohydride species do not disproportionate has been presented.[5]

(5) D. C. Wigfield and F. W. Gowland, *Can. J. Chem.*, **56**, 786 (1978).

(6) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **80**, 5372 (1958).

(7) E. C. Ashby, J. P. Swenain, and F. R. Dobbs, *J. Org. Chem.*, **36**, 196 (1971).

(8) E. C. Ashby, F. R. Dobbs, and H. P. Hopkins, Jr., *J. Am. Chem. Soc.*, **97**, 3158 (1975).

(9) D. C. Ayres, R. Sawdaye, and D. N. Kirk, *J. Chem. Soc. B*, 1133 (1970).

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

Calvet and Levisailles[11] have reported the optical rotatory dispersion kinetics of a series of 3-keto steroids, variously substituted at the 1- and 5-positions. Neither the temperature nor the method of hydride analysis used in this work were specified. On the basis of rate-constant comparisons, these workers concluded that the transition state in the reaction is productlike; in contrast, Klein et al.[10] concluded that product-development control was not operative.

Spectral Absorbance of Ketones. Following the decline of the n–π^* ketone absorption band as a means of following the disappearance of ketone has, in our hands, been a highly satisfactory method for measuring the rates of sodium borohydride reduction of ketones.[12-15] In order to employ the same methodology for LTBA reductions, one is first required to measure the wavelength of maximum absorption of the ketone in the solvent to be used (tetrahydrofuran) and the extinction coefficients as a function of the temperature at which kinetic runs are planned. These data are shown in Table I. It is to be noted that small variations occur in the values of ϵ as a function of temperature and that there is substantial variation in the wavelength of maximum absorption as a function of ketone structure.

Kinetic Method. For the range of ketones studied, the time for completion of reaction varied from 90 s to 30 min. This range could conveniently be covered by using conventional spectrophotometric equipment. All solutions were equilibrated to the temperature required, and the reaction was initiated by injection of the ketone solution directly into the UV cell containing the other components, with simultaneous activation of the chart recorder. The mixing time (1.5 s) is small in comparison with the time for the overall reaction. Details of the method are contained in the Experimental Section.

Kinetic Order. Previous workers have concluded that the reduction of ketones by LTBA is a second-order reaction, first order in both LTBA and ketone. This is an important conclusion because it clearly rules out any mechanisms in which more than one LTBA moiety is involved (e.g., six-membered cyclic transition states). Because of this and our subsequent intention to exploit the kinetics of the reaction to probe other aspects of the mechanism, we felt it desirable to put this point beyond doubt. Previous determinations had used artificially high concentrations of hydride, and no investigation had reported the somewhat more stringent test of using approximately equimolar solutions of ketone and hydride with application of the normal second-order rate-equation plot.

When this test was applied, a series of discrepancies in the results became apparent. These were traced to the standardization of LTBA for which we had employed the usual titrimetric analysis based on reaction with iodine. Investigation of this analytical procedure in comparison with other methods showed that reaction of LTBA with iodine is a totally unsuitable reaction for analytical standardization of LTBA. Two reactions with stoichiometry differing by a factor of 2 can occur, and the competition between the two reactions is concentration dependent. Data based on this method of analysis are, therefore, meaningless. Details of this analytical investigation have been published previously.[16,17]

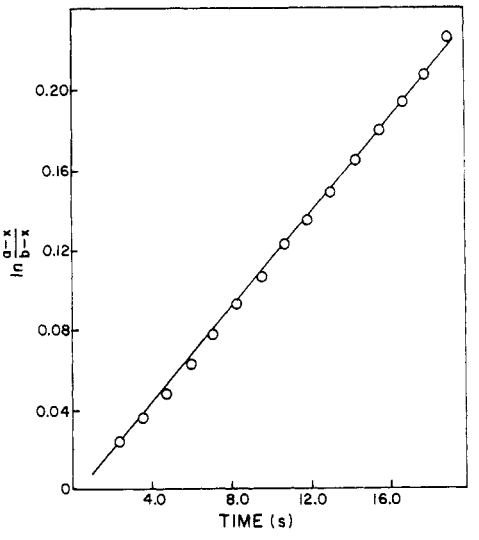


Figure 1. Typical second-order rate plot for the reduction of cyclohexanones by LTBA in tetrahydrofuran at 298 K.

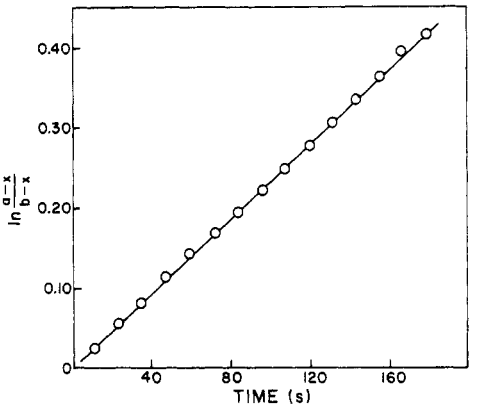


Figure 2. Typical second-order rate plot for the reduction of 3,3,5,5-tetramethylcyclohexanone by LTBA in tetrahydrofuran at 298 K.

Table II. Initial Rates of Reduction of 3,3,5-Trimethylcyclohexanone by LTBA at 298 K as a Function of [LTBA][a]

10^2[LTBA], M	$10^5(dx/dt)$, M s^{-1}	10^2[LTBA], M	$10^5(dx/dt)$, M s^{-1}
0.443	3.21	1.320	7.55
0.660	3.36	1.668	10.78
0.866	4.95	2.140	13.32
1.055	5.64	2.300	16.00
1.072	5.87		

[a] [Ketone] = 2.72×10^{-2} M.

Using the method of standardization of LTBA which employs either spectrophotometric or gas chromatographic assay based on reaction with cyclohexanone,[16,17] we made kinetic runs and constructed the usual second-order plots,

(11) A. Calvet and J. Levisailles, *Tetrahedron Lett.*, 2157 (1972).
(12) D. C. Wigfield and D. J. Phelps, *Can. J. Chem.*, **50**, 388 (1972).
(13) D. C. Wigfield and D. J. Phelps, *J. Chem. Soc., Perkin Trans. 2*, 680 (1972).
(14) D. C. Wigfield and D. J. Phelps, *J. Am. Chem. Soc.*, **96**, 543 (1974).
(15) D. C. Wigfield and D. J. Phelps, *J. Org. Chem.*, **41**, 2396 (1976).
(16) D. C. Wigfield and F. W. Gowland, *Can. J. Chem.*, **55**, 3616 (1977).
(17) In this connection it may be significant that the previously reported rate constants (three ketones)[10] differ from ours by approximately a factor of 2.
(18) The overall stoichiometry of reaction between ketones and LTBA is known to be 1:1.[19] Thus, the assay of freshly prepared LTBA solutions based on the cyclohexanone reaction corresponds closely to the gravimetric assay. The assay also agrees with the titrimetric assay for certain well-defined concentration ratios (LTBA/iodine) where one or the other reaction predominates.[16]
(19) H. C. Brown and H. R. Deck, *J. Am. Chem. Soc.*, **87**, 5620 (1965).

Table III. Second-Order Rate Constants for the Reduction of Cyclohexanones by LTBA in Tetrahydrofuran

	10^2k, L mol^{-1} s^{-1}				
	283 K	292 K	298 K	305 K	298 K[c]
1	191 ± 3	240 ± 18	331 ± 8	488 ± 57	7.65[a]
2	243 ± 1	287 ± 18	439 ± 16	593 ± 32	8.90[b]
3	190 ± 25	235 ± 5	342 ± 18	456 ± 14	8.56[b]
4	147 ± 4	184 ± 3	280 ± 13	337 ± 41	6.05[b]
5		194 ± 7	256 ± 14	312 ± 21	4.56[b]
6	98.5 ± 3	129 ± 3	171 ± 13	242 ± 31	1.49[a]
7	57.6 ± 1.8	74.5 ± 4.7	106 ± 12	136 ± 10	0.712[a]
8	47.1 ± 1.3	65.4 ± 3.5	87.5 ± 10.4	108 ± 7	0.669[a]
9	27.7 ± 1.7	37.1 ± 2.0	45.5 ± 2.0	75.3 ± 6.5	
10	3.68 ± 0.09	6.83 ± 0.2	7.98 ± 1.0	11.8 ± 1.7	0.142[a]
11		0.383 ± 0.014	0.498 ± 0.04	0.712 ± 0.09	
12	7.34 ± 0.3	12.7 ± 0.5	17.5 ± 0.8	20.7 ± 0.9	0.249[b]
13	7.53 ± 0.02	12.7 ± 0.3	17.4 ± 0.8	20.8 ± 1.5	0.218[b]
14	3.94 ± 0.2	6.27 ± 0.1	8.94 ± 0.4	10.6 ± 1.0	0.0192[b]
15		9.66 ± 0.8	12.3 ± 1.6	15.9 ± 1.3	

[a] Reference 14. [b] Reference 15. [c] Corresponding value for $NaBH_4$/*i*-PrOH reduction.

$\ln (a - x)/(b - x)$ vs. t (a and b, initial concentrations of reactants; x, amount reacted at time t). In all cases, with ketone–hydride concentration ratios varying between 0.5 and 2.0, excellent linear correlations were obtained. Figures 1 and 2 illustrate typical kinetic plots for reduction of cyclohexanone (1) and 3,3,5,5-tetramethylcyclohexanone (14), respectively.

The plots of the logarithms of initial rates vs. the logarithms of concentrations of each reagent were also applied to confirm the first-order dependence on each reagent. If the rate expression is written as in eq 1, then, with the

$$dx/dt = k[A]^a[B]^b \quad (1)$$

concentration of one reagent (say B) held constant, a plot of log (dx/dt) vs. log [A] gives a line of slope a. Such data for the reduction of 3,3,5-trimethylcyclohexanone with variation of [LTBA] are shown in Table II and Figure 3, regression analysis of which gives a slope of 1.03 for the order with respect to LTBA. Similar plots to determine the order with respect to ketone also confirm the order of unity; in this case, however, the evidence was already strong from the linearity of the pseudo-first-order plots of Klein et al.[10]

The combination of these data provide strong experimental support for the conclusion of previous workers[9-11] that the reduction of ketones by LTBA is well represented by a second-order process, first order in each component.

Rate of Ketone Reductions. From the integrated second-order rate equation (eq 2), rate constants were obtained from plots of $\ln (a - x)/(b - x)$ vs. t. A summary of these rate constants is shown in Table III.

$$\frac{1}{a - b} \ln \frac{b(a - x)}{a(b - x)} = kt \quad (2)$$

Because the same reaction on the ketone is involved in both cases, it is interesting to compare these second-order rate constants of LTBA reduction in tetrahydrofuran solvent with those previously obtained on sodium borohydride reductions in isopropyl alcohol solvent.[14,15] The factor by which the cyclohexanones are reduced faster by LTBA than by $NaBH_4$ is seen to vary significantly. For ordinary nonhindered cyclohexanones (e.g., 1–4) this factor is approximately 40–50 times faster. Contrary to what one might expect, however, bearing in mind the structures and bulk of the two reductants, the rates of LTBA reductions are in general much *less* sensitive to steric hindrance around the carbonyl group than are $NaBH_4$ reductions. Thus this rate ratio steadily increases as the steric hindrance around the carbonyl group increases, and, for example, 3,3,5,5-tetramethylcyclohexanone (14) is reduced about 450 times faster by LTBA than by $NaBH_4$. This is an interesting point that will be commented on later.

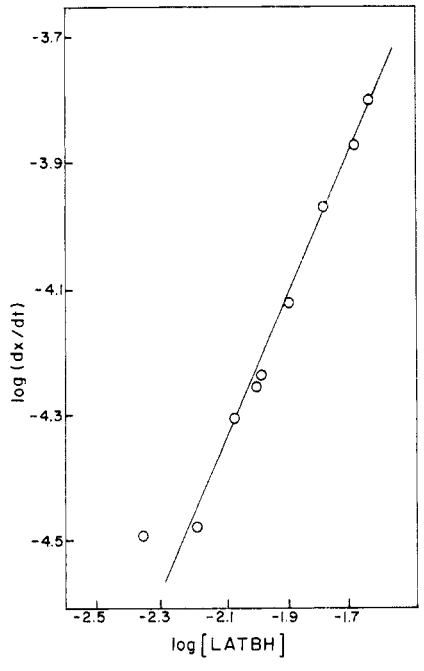


Figure 3. Determination of kinetic order with respect to [LTBA] by a plot of log (initial rate) vs. log [LTBA] for the reduction of 3,3,5-trimethylcyclohexanone.

The pattern of rate changes as a function of ketone structure between the two reductants is, however, very similar. Thus, for example, 4-substitution (2, 3) on the cyclohexanone ring causes a small acceleration in the rate of reduction, whereas 3-substitution (equatorial) (4, 5) causes a small retardation, and axial 3-substitution (12–15) causes a severe retardation. All these effects apply to reduction by both reductants. A difference in sensitivity, however, is noted in the effect of 2-substitution on the cyclohexanone ring. Small substituents (e.g., 6, 7, 8) cause a moderate rate decrease for reduction by both LTBA and $NaBH_4$. For large substituents, however, the effect on LTBA reductants is dramatic. Menthone (10), with an isopropyl group at C-2, is reduced by LTBA even slower than the highly hindered ketone 14. In contrast, the rate ratio for $NaBH_4$ reductions is a factor of about 7 in favor of menthone. 2-*tert*-Butylcyclohexanone (11) is reduced by LTBA at a rate approaching 10^3 times slower than that

Table IV. Stereochemical Product Ratios and Specific Rate Constants for Axial and Equatorial Attack

	ax/eq prod ratio[a]	10^2k, L mol^{-1} s^{-1} (298 K)	
		ax attack[e]	eq attack[e]
1	10:90[b]	298 (6.58)	33 (1.07)
2	15:85	373 (7.65)	66 (1.25)
3	10:90	308 (7.36)	34 (1.20)
4	13:87	244 (5.20)	36 (0.85)
5	9:91	233 (4.29)	23 (0.27)
6	36:64	109 (1.04)	62 (0.45)
7	36:64	68 (0.463)	38 (0.249)
8	34:66	58 (0.435)	30 (0.234)
9	46:54	25	21
10	38:62	4.9 (9.8×10^{-2})	3.0 (4.4×10^{-2})
11	58:42	0.21	0.29
12	89:11[c]	1.9 (0.120)	16 (0.129)
13	89:11	1.9 (0.105)	15 (0.113)
14	95:5[d]	0.45 (9.6×10^{-4})	8.5 (1.82×10^{-2})
15	95:5[d]	0.62	12

[a] ±2%. [b] Product ratio for 3. [c] Product ratio for 15. [d] Cf. ref 22. [e] Values for $NaBH_4$ reduction in parentheses for comparison.[14,15]

of cyclohexanone. This effect of the substituent at C-2 is one which should be considered in reaching mechanistic conclusions.

Stereochemical Product Ratios. Stereochemical product ratios of the reduction of ketones **1–15** are shown in Table IV, together with the specific rate constants for axial and equatorial attack that follow by subdivision of the overall rate constants (Table III) by these ratios. Inspection of these data and comparisons with similar data on the $NaBH_4$ reductions[15] reiterate the point that LTBA reductions are less sensitive to steric bulk around the carbonyl group than are $NaBH_4$ reductions. Comparison of rates of axial attack on cyclohexanone and on 3,3,5,5-tetramethylcyclohexanone, for example, give a rate ratio of 7000 in $NaBH_4$ reductions[15] compared with only 660 in the present LTBA reductions. Comparison of equatorial attack on the same two ketones gives a ratio of 58 for $NaBH_4$ reduction[15] but of less than 4 for LTBA reduction. The fact that *both* axial and equatorial attack exhibit decreased sensitivity toward ketone substituents leads to remarkably similar stereochemical product ratios for reductions by these two reductants, LTBA and $NaBH_4$.

We have previously pointed out that equatorial attack is less sensitive to ketone substituents than is axial attack.[15] Equatorial attack by LTBA, therefore, has the combination of decreased sensitivity, and inspection of the final column of Table IV shows that these rate constants, with the exception of the 2-substituted cyclohexanones **10** and **11**, all lie within a factor of 10 of each other.

Activation Parameters. Various factors, especially solvent volatility, prevent the LTBA reductions from being studied over wide temperature ranges. However, the rates were measured over the limited range available; these rate constants are listed in Table III. Plots of ln kT^{-1} vs. T^{-1} give the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the reductions. These values are given in Table V and the Arrhenius plots in Figure 4.

It is instructive to compare the values of these activation parameters with those previously obtained for sodium borohydride reductions.[15] Taking cyclohexanone reduction as a starting comparison, the LTBA reduction is approximately 50 times faster. This difference is apparently entirely due to differences in entropy of activation. The enthalpy of activation for the $NaBH_4$ reduction (6.4 kcal mol^{-1}) is actually slightly more favorable than that for LTBA reduction (6.7 kcal mol^{-1}). There is, however, over

Table V. Activation Parameters for the Reduction of Cyclohexanones by LTBA in Tetrahydrofuran

	$\Delta G^{\ddagger}$, kcal mol^{-1} (298 K)	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal deg^{-1} mol^{-1}
1	16.7 ± 1.3	6.71 ± 0.39	−33.4 ± 3.1
2	16.5 ± 1.4	6.61 ± 0.46	−33.2 ± 3.2
3	16.7 ± 1.2	6.42 ± 0.35	−34.4 ± 3.0
4	16.8 ± 1.3	6.22 ± 0.36	−35.6 ± 3.0
5	16.8 ± 1.1	5.84 ± 0.28	−36.9 ± 2.7
6	17.0 ± 1.1	6.40 ± 0.26	−35.7 ± 2.7
7	17.4 ± 1.1	6.30 ± 0.26	−37.2 ± 2.7
8	17.4 ± 1.0	6.20 ± 0.24	−37.9 ± 2.6
9	17.8 ± 1.5	6.91 ± 0.46	−36.5 ± 3.4
10	18.9 ± 1.2	8.22 ± 0.31	−35.7 ± 2.9
11	20.5 ± 0.9	7.80 ± 0.16	−42.6 ± 2.4
12	18.5 ± 1.2	7.66 ± 0.34	−36.2 ± 3.0
13	18.5 ± 1.2	7.50 ± 0.31	−36.7 ± 2.9
14	18.9 ± 1.1	7.35 ± 0.27	−38.6 ± 2.8
15	18.6 ± 1.1	6.18 ± 0.16	−41.7 ± 3.1

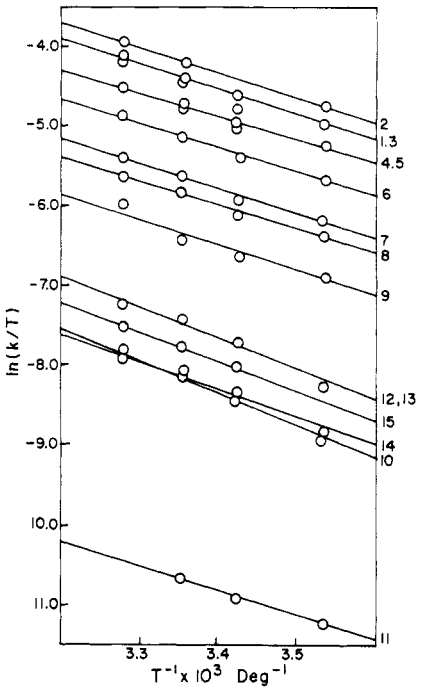


Figure 4. Arrhenius plots for the reduction of cyclohexanones by LTBA in tetrahydrofuran.

an 8 eu difference, giving rise to the faster rate of the LTBA reduction.

In the reductions by $NaBH_4$, we concluded[15] that the reductions had entropy as the major barrier to reduction but that the reactions, in comparing one ketone to another, were enthalpy controlled (i.e., rate changes follow changes in $\Delta H^{\ddagger}$, these changes being slightly opposed by changes in $\Delta S^{\ddagger}$). In the present LTBA reductions, the major component of the barrier is again entropy. The reactions, however, are certainly not enthalpy controlled. The most striking feature of Figure 4 is that the lines are all remarkably parallel. Thus the reductions represent a series of nearly isoenthalpic reactions, changes in rate from one ketone to another being caused by variation in the entropy of activation. A particularly interesting comparison is that of 3,3,5,5-tetramethylcyclohexanone (**14**) with cyclohexanone (**1**) for the two reductants. In the LTBA reaction there is a difference in $\Delta H^{\ddagger}$ between these two reductions of only 0.6 kcal mol^{-1}. In comparison, the $\Delta H^{\ddagger}$ for reduction of **14** by $NaBH_4$ is nearly double that for reduction of **1**.[15] For $NaBH_4$ reduction, the $\Delta S^{\ddagger}$ gets more favorable by about 4 eu in going from **1** to **14**; for LTBA reduction

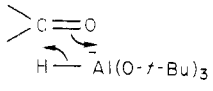
it gets about 5 eu less favorable.

In view of the almost isoenthalpic nature of the LTBA reductions, no useful correlations or deductions may be gained for $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ (isokinetic) plots.

Mechanistic Conclusions. Kinetic data on the LTBA reduction confirm that these reactions appear to be well represented by a second-order process. The most likely interpretation of this is a simple bimolecular reaction, although the kinetic effect of the solvent, if any, has yet to be studied.

There are three clear differences between LTBA and $NaBH_4$ reductions of the same ketones. These are (1) the much more dramatic effect of the axial substituent at C-3 on the rate of the $NaBH_4$ reductions, (2) the pronounced effect on the rate of LTBA reactions of the substituent at C-2, and (3) the enthalpy control of $NaBH_4$ reductions vs. the entropy control of the LTBA reductions. Taking these points in turn, point 1 is to be expected, given the acyclic mechanism proposed for $NaBH_4$ reductions with involvement of hydroxylic solvent,[20] and implies that a different type of mechanism may be involved in LTBA reductions. Point 2 is perhaps to be expected regardless of mechanism simply from the bulk of the LTBA reagent. Point 3 is intriguing but may arise from the increased restriction of rotation about the bonds in the *tert*-butyl groups of LTBA as the environment becomes more hindered.

These data clearly do not yet allow mechanism assignment in this reaction. It is worth noting, however, that the data all appear to be consistent with the simplest possible mechanism—the four-center cycloaddition.



In view of the extra orbitals available to aluminum, it is not entirely obvious that such a process would necessitate a forbidden $[{}_{\sigma}2_s + {}_{\pi}2_s]$ reaction, as would appear to be the case in a four-centered borohydride[21] reaction.

Experimental Section

Reagents. The ketones used were commercially available or were produced by Brown oxidation[22] of commercially available alcohols. Ketone **15** was a gift from Roure-Bertrand et Fils Ltee., France. Ketones were purified by either vacuum distillation or sublimation prior to use and were shown by gas–liquid chromatography (Perkin-Elmer 990 gas chromatograph with a 50 ft × 0.02 in. i.d. SCOT TCEP column) to be >99% pure. Exceptions were ketones **9** and **10** which contained 4 and 6%, respectively, of their epimers.[14] Gas–liquid chromatography was also used as the criterion for ensuring clean reduction of the ketones and identification of products with authentic samples. Lithium tri-*tert*-butoxyaluminohydride was prepared by the method of Brown and Deck.[19]

Spectrophotometry. All spectrophotometric measurements were made on a Beckman Model 25 UV–visible recording spectrophotometer equipped with an electronic temperature control and with a special access lid such that reagents could be injected directly into the cells without opening the lid.

Stereochemical product ratios were determined as described previously.[14,15]

Kinetic Method. The kinetic method employed was based on a spectrophotometric method reported earlier.[13] A solution of centrifuged LTBA in THF was equilibrated at the appropriate temperature for 30 min before use. A 2.0-mL sample of this hydride solution was transferred by pipet into a 3-mL quartz cuvette in the spectrometer. The solution was zeroed at the appropriate wavelength of the ketone to be studied (see Table I). The ketone solution (1.0 mL) in tetrahydrofuran was injected through the spectrophotometer cover; simultaneously with this injection, the chart recorder was activated and the reduction trace obtained. The reproducibility of this injection technique was found to be ±2%. This was determined by injecting the ketone solution into a cuvette containing only solvent. The rate of mixing was sufficient since the ketone reaches its limiting absorbance in less than 1.5 s, but the reaction time varies from 90 s to 30 min for the range of ketones studied. Zero time was taken as the time the ketone was injected and the chart recorder activated. The concentration of the ketone was calculated gravimetrically and checked spectrophotometrically before each kinetic run. The hydride concentration of the LTBA was determined by GLC analysis of reduction mixtures or by a spectral method based upon hydride consumption by excess ketone reported earlier.[16]

Solutions of ketone, hydride, and solvent were thermostated in a GCA/Scientific Precision Circulating 254 bath for at least 30 min before use.

The rate constants were obtained by plotting $\ln (a - x)/(b - x)$ as a function of time, where a is the initial ketone concentration, b is the initial hydride concentration, and x is the concentration of the product alcohol at time t. The slope of this plot is equal to $k(a - b)$. The value of the rate constant is obtained from computer-fitted least-squares analysis of the data. Each kinetic run ordinarily utilized 15–20 data points to obtain the rate constant. The data summarized in Table III arise from a total of approximately 220 kinetic runs. The average number of duplicate runs for each ketone at each temperature was four. Errors quoted are standard deviations. Activation parameters and their associated errors were calculated by least-squares analysis of the Arrhenius plots.

Acknowledgment. We are very grateful to the National Research Council of Canada for continued support of this study.

Registry No. 1, 108-94-1; 2, 589-92-4; 3, 98-53-3; 4, 591-24-2; 5, 566-88-1; 6, 583-60-8; 7, 4423-94-3; 8, 1126-18-7; 9, 2816-57-1; 10, 10458-14-7; 11, 1728-46-7; 12, 2979-19-3; 13, 873-94-9; 14, 14376-79-5; 15, 16556-46-0; cyclohexanol, 108-93-0; *cis*-4-methylcyclohexanol, 7731-28-4; *trans*-4-methylcyclohexanol, 7731-29-5; *cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 937-06-4; *cis*-3-methylcyclohexanol, 5454-79-5; *trans*-3-methylcyclohexanol, 7443-55-2; 5α-cholestan-3α-ol, 516-95-0; 5α-cholestan-3β-ol, 80-97-7; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; *cis*-2-ethylcyclohexanol, 3274-96-2; *trans*-2-ethylcyclohexanol, 4276-43-1; *cis*-2-butylcyclohexanol, 35242-02-5; *trans*-2-butylcyclohexanol, 35242-05-8; 2,6-dimethylcyclohexanol, 5337-72-4; 2-isopropyl-5-methylcyclohexanol, 1490-04-6; *cis*-2-*tert*-butylcyclohexanol, 7214-18-8; *trans*-2-*tert*-butylcyclohexanol, 5448-22-6; 3,3-dimethylcyclohexanol, 767-12-4; *cis*-3,3,5-trimethylcyclohexanol, 933-48-2; *trans*-3,3,5-trimethylcyclohexanol, 767-54-4; 3,3,5,5-tetramethylcyclohexanol, 2650-40-0; *cis*-4-acetyl-3,3,5,5-tetramethylcyclohexanol, 72331-50-1; *trans*-4-acetyl-3,3,5,5-tetramethylcyclohexanol, 72331-51-2.

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