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TITLE OF THESIS.....The Transition State in the Hydride.....
.....Reduction of Ketones.....
.....
UNIVERSITY.....Carleton.....
DEGREE FOR WHICH THESIS WAS PRESENTED.....Ph.D.....
YEAR THIS DEGREE GRANTED.....1973.....

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DATED.....July 26th.....19 73

NL-91 (10-68)

THE TRANSITION STATE IN THE HYDRIDE
REDUCTION OF KETONES

by

David James Phelps, B.A.

A thesis submitted to the faculty of
Graduate Studies in partial fulfilment
of the requirements for the degree of
Doctor of Philosophy

Department of Chemistry

Carleton University

Ottawa, Ontario

July 5, 1973

David James Phelps

1973

The undersigned recommend to the Faculty
of Graduate Studies acceptance of the thesis

"The Transition State in the Hydride
Reduction of Ketones"

submitted by David James Phelps, B.A.,
in partial fulfilment of the requirements for
the degree of Doctor of Philosophy

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ABSTRACT

A spectrophotometric method for determination of the kinetics of reduction of cyclohexanones has been developed and shown to be a satisfactory method. The kinetics of reduction of eight ketones by sodium borohydride and sodium borodeuteride have been measured and the isotope effects obtained. Primary isotope effects for five ketones have been obtained via competition experiments with lithium aluminum tritertiarybutoxyhydride and the corresponding deuteride. The kinetics of the sodium borohydride reduction of nineteen ketones have been measured at a number of temperatures and the activation parameters obtained. Product ratio determinations were carried out at three or more temperatures to allow calculation of specific rate constants and specific activation parameters. Using the activation parameters, overall and specific isokinetic relationships were obtained. A Bronsted-like relationship for the reduction of four unhindered ketones is also reported.

Using the experimental data obtained, the nature of the transition states for the various reductions has been discussed and some conclusions drawn. A redefinition of the terms steric approach control and product development control has also been suggested. Earlier models for the transition state have been discussed in light of the data presented.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge the ideas, enthusiasm and inspiration provided by Dr. D. C. Wigfield throughout this research.

The National Research Council of Canada is thanked for Postgraduate Fellowships, 1971-1973.

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Introduction:

The reduction of cyclic ketones by complex hydrides gives rise to two epimeric alcohols- an axial alcohol via equatorial attack and an equatorial alcohol via axial attack (Figure 1). In general, one alcohol will predominate depending on the environment of the carbonyl group.

Figure 1. Epimeric alcohols from the hydride reduction of 4-*t*-butylcyclohexanone.

Barton (1) summarized some of the earlier literature by pointing out that the thermodynamically more stable equatorial alcohol is formed if the carbonyl is unhindered while the axial epimer results if the carbonyl is hindered. Dauben, Fonken and Noyce (2) postulated the first theory to account for the product ratios in the hydride reduction of cyclohexanones. As a result of studying three ketones and a series of hydride compounds, they proposed that product ratios depended on either of two factors predominating in the reduction; steric approach control or product development control. As defined by Dauben, steric ap-

proach control is a steric postulate involving competitive attacks on the carbonyl from a hindered and a non-hindered side; product development control was referred to as an energy consideration involving the relative stabilities of the possible products. A stability factor was needed because of the premise that unhindered cyclohexanones were symmetrical above and below the plane of the carbonyl and, if only steric effects operated, a 50:50 mixture of epimeric alcohols should be formed. (This premise has since been found incorrect: the angle between the carbonyl and equatorial hydrogens is 4° (3)). Until 1965 it was unanimously agreed that a steric factor and a stability factor were operating in hydride reductions (4-6), depending on the conditions of the reduction (7,8). Brown and Deck (6) wished to modify Dauben's terms to product stability control and steric strain control to call attention to the transition states involved rather than events leading to these transition states, although they were in complete agreement that both factors were operating.

After 1965 most workers took exception to the postulate of Dauben et. al. (2), generally agreeing that product development control was not operating (9-14). One early piece of experimental evidence against product development control was the observa-

tion of more than the equilibrium amount of equatorial alcohol in the lithium aluminum hydride reduction of 4-t-butylcyclohexanone (15).

In the first paper questioning product development control, Richer (9) developed an explanation based solely on steric effects. Since the axial hydrogens in positions 2 and 6 of unhindered cyclohexanones are perpendicular to the plane of the ring while the equatorial hydrogens are very nearly in the plane (3), the stereochemical results of additions on unhindered ketones by groups small enough not to interfere with the 3,5- axial hydrogens will be directed exclusively by the 2,6- axial hydrogens which hinder attack from the equatorial side resulting in the observed preponderance of equatorial alcohol. This can be seen pictorially in Figure 2. If the incoming group is not large enough to interfere with the axial hydrogens in positions 3 and 5, k_{ax} will be favoured over k_{eq} .

Figure 2. Directing effects of the axial hydrogens in unhindered cyclohexanones.

Marshall and Carroll (10) on the basis of molecular models (Figure 3) for the reduction of unhindered cyclohexanones have agreed with Richer (9) that 2,6-axial and 3,5-axial hydrogens control the stereochemistry of the reaction. From their measurements they conclude that axial attack will be favoured at shorter distances from the carbonyl so the hydride must be close to the carbonyl at the transition state to account for the observed product ratios.

Figure 3. The transition state in the reduction of unhindered ketones according to Marshall and Carroll.

Felkin and coworkers (11,12,16), on the basis of a model for torsional strain, have concluded that it is unnecessary to assume a change in transition state from a product-like one (unhindered ketones) to a reactant-like one (hindered ketones). In the transition state for a cyclic ketone it is not possible to minimize both torsional and steric strain. Figure 4 de-

Figure 4. Transition states in additions to cyclohexanones according to Felkin et. al.

picts torsional strain in transition state $A^\ddagger$ leading to axial alcohol and steric strain in transition state $E^\ddagger$ going to equatorial alcohol. In the absence of polar effects, the steric outcome in the reactant-like transition state is determined by the relative magnitudes of strain in $A^\ddagger$ and $E^\ddagger$. For an unhindered ketone, $R_2 = H$, torsional strain will make transition state $E^\ddagger$ favoured while $A^\ddagger$ will be favoured for hindered ketones.

The arguments of Richer (9) and Felkin (11,12,16) appear to be essentially equivalent, Richer terming the effect of the 2,6- axial hydrogens steric, Felkin calling it torsional strain. It is important to realize that all three arguments (9-12,16) necessitate an early transition state.

Eliel and Senda (14) have invoked the Hammond postulate (17) to argue for a reactant-like transition state in which the relative stabilities of the two epimeric alcohols (product development control) should not be important in transition states leading to them. Although not agreeing with Richer's (9) reasoning, Eliel and Senda (14) reach the same conclusion, based on competitive rate studies, that product development control is an unnecessary concept.

To critically examine any of these theories explaining the stereochemical outcome of the hydride reduction of cyclic ketones, it is necessary to have a knowledge of the transition state structure for these reactions. There has been some speculation and some evidence offered on the position along the reaction coordinate and the geometry of the transition state for some hydride transfers.

Position of the transition state on the reaction coordinate.

An early transition state has been pointed to in hydride reductions to explain product ratios (11,12, 16,18), exothermicity (14) or isotope effects (19).

There is also evidence for a late transition state in hydride transfers. Citing a Bronsted general acid catalysis term of 0.9 for the buffer catalyzed hydrolysis of sodium borohydride, Davis et. al. (20)

determined that the hydride was greatly transferred at the transition state. Karabatsos and Althuis (21) argued for a late transition state on the basis of the breakdown of a model for deuteride reduction of aldehydes.

A number of Hammett-type studies on the hydride reductions of ketones have been carried out (22-27). In every case but one (26) the ρ value was positive and greater than 1.4: for the lithium borohydride reduction of substituted benzophenones, $\rho = +2.81$ (24); for the lithium tetrakis-(N-dihydropyridyl)aluminate reductions of substituted benzophenones, $\rho = +1.5$ (24); for the sodium borohydride reduction of substituted fluorenones, $\rho = +2.65$ (22) and $\rho = +3.06$ (27); for the sodium borohydride reduction of substituted acetophenones, $\rho = +3.06$ (25) and $\rho = +2.6$ (23); for the sodium borohydride reduction of 1,5-diarylpenta-1,4-dien-3-ones, $\rho = +0.91$ (26); and for the sodium borohydride reduction of 4-substituted cyclohexanones, $\rho_I = +2.78$ (23). This latter value is particularly interesting when broken up into component parts for formation of cis and trans alcohols; $\rho_{\text{cis}} = +3.78$, $\rho_{\text{trans}} = +1.96$. This indicates a different effect on the two transition states by electronegative substituents at carbon 4. Lamaty *et. al.* (28) have interpreted these rather large positive ρ values to mean that the transition state for hydride reduction is late. Lamaty and coworkers (28-30) cite other evidence

for late transition states. This evidence, however, does not seem compelling and will be discussed in detail further on in this work.

In an interesting study on the reduction of aromatic acid chlorides by sodium borohydride, non-linear Hammett plots were presented as evidence for a change in mechanism depending on substrate (31). However, this result may not be relevant to the reduction of ketones.

Some workers (32-34) advocate a late transition state for hydride reduction solely on the basis of product ratios.

Not much attention has been given to linear free energy relationships (LFER) in the sodium borohydride reduction in spite of the potential for gaining information about the transition state or reaction mechanism. Kwart and coworkers (35) have shown that a LFER exists between the sodium borohydride reduction and the bromination in acetic acid of 4-substituted cyclohexanones. Parry and Warren (27) obtained an isokinetic temperature of 210° K for the NaBH_4 reduction of substituted fluorenones and Cockerill and Rackham (26) have recently obtained an isokinetic temperature of 338° K for the sodium borohydride reduction of unsaturated ketones.

Geometry of the transition state.

To have a complete knowledge of the transition state for a reaction, one needs not only to know the extent of bond making (position along the reaction coordinate) at the transition state but also the spatial distribution of the molecules involved.

The three transition state structures which have been considered for borohydride systems, including hydrolysis, alcoholysis and reduction of carbonyls are 2-centre, 3-centre and 4-centre reactions (Figure 5).

Figure 5. Possible transition state geometries in the reactions of borohydrides.

The 3-centre reaction has been considered for hydrolysis of sodium borohydride (36-38) and alcoholysis of sodium borohydride (39). While all three types of transition state can be envisioned for hydrolysis-type reactions, it is difficult to conceive of a 3-centre transition state for the borohydride reduction of ketones.

The 3-centre complex is favoured by some workers for acid hydrolysis (36,40), while others claim not enough evidence exists to distinguish between 2-centre and 3-centre complexes (37,38). In the hydrolysis of pyridine arylboranes a 2-centre reaction is claimed (41) while a 4-centre transition state is postulated for phenolic hydrolysis of sodium borohydride (39).

In sodium borohydride reductions, however, most workers who consider the geometry of the transition state incline toward a 4-centre reaction path (5,19,42). A number of related hydride transfer reactions have also been considered to be 4-centred (18,36,39,43,44).

The geometry of the transition state is very important in explaining isotope effects. In a non-linear transition state the B-H stretching vibration will not be completely lost and the resultant isotope effect will be small. More O'Ferrall (45,46) has calculated that isotope effects may decrease from 6-8 down to 1-2 if the X-----H-----Y bond angle deviates significantly from 180°. Other workers have also noted that non-linear transition states cause smaller than expected isotope effects (47,48).

Reasons for undertaking the study and general strategy of attack on the problem.

In spite of the well known marked stereoselectivity found in the reduction of cyclohexanones by com-

plex metal hydrides and despite several hypotheses (2,9-12,14), the origin of this stereoselectivity has remained obscure. Since these reductions are kinetically controlled, the key to understanding their course and stereoselectivity lies in a knowledge of the structures of the transition states involved in the various reductions. It was hoped that physical organic studies would reveal the positions of the transition states along the reaction coordinate for the various reductions and determine whether different ketones were reduced via different or essentially identical transition states and that the geometry of the transition state might be elucidated. Because of the confusion surrounding the terms steric approach control and product development control (2) firmer definitions seemed necessary (see Appendix I). With these new definitions and the physical organic data, the question of the origin of the stereoselectivity in these reductions might be more logically and successfully attacked.

Three experimental approaches were conceived; 1) kinetic deuterium isotope effects; 2) enthalpy-entropy (isokinetic) relationships; 3) Bronsted-like relationships. All three methods can detect changes in transition state or mechanism although the first two will not necessarily by themselves place the earliness or the lateness of the transition state. Using the Bronsted relationship, however, it might be possi-

ble to determine the lateness of the transition state and to correlate the Bronsted β with the isokinetic temperatures and kinetic isotope effects. Using the Bronsted relationship and the kinetic isotope effect data and the approach of More O'Ferrall (45,46), it might be possible to determine the geometry of the transition state.

The sum effect of these data would be to picture position and geometry of the various transition states involved in these reductions, this knowledge perhaps leading to the origin of the observed stereoselectivity.

Results and discussion.

Isotope effects.

Literature.

Isotope effects for the hydrolysis of various borohydrides have received much attention. However, prior to the present work, only two papers dealing with isotope effects in the reduction of ketones have appeared. The first (42) concerned the secondary isotope effect for the reduction of α -perdeuterated ketones by sodium borohydride. Not surprisingly, these effects are small and inverse (range in $k_H/k_D = 0.88$ to 1.00). The second paper dealt with isotope effects in the morpholine borane reduction of methylketones (19).

These effects are B-H vs. B-D effects and are typically $k_H/k_D = 1.1$. No work has previously been published¹ on NaBH_4 vs. NaBD_4 isotope effects.

An examination of the results obtained for the kinetic isotope effect in borohydride hydrolysis indicates that inverse or very small isotope effects are the rule. Although several reports claim that isotope effects should be smaller for hydride transfer than for hydrogen atom or proton transfer (49-51), recent evidence (52) indicates that large isotope effects can indeed be obtained in hydride transfers and may be expected to occur.

Assuming that large normal isotope effects can occur in hydride transfers, there are three reasons why a small isotope effect might result. 1) The hydride is substantially transferred before the transition state is reached. 2) The bond to the hydride is only slightly weakened at the transition state. 3) A non-linear transition state is involved. Although some doubt has recently been expressed (53), it is generally considered that the maximum isotope effect will occur when the transition state is symmetrical (54-59). Inverse isotope effects have been considered due to either secondary effects imposed on a small primary effect (20,37,41) or to an inverse primary effect (60).

¹See footnote 41 of reference 37.

Again assuming that large normal isotope effects can occur in hydride transfers, it is noteworthy that all reported isotope effects for hydrolysis of boranes are small (less than 2) or inverse. Small normal isotope effects have been found for the hydrolysis of pyridine diphenylborane (36,43), the reaction of trimethylamine-borane with iodine (61), reduction of methylalkylketones with morpholine borane (19) and the acid hydrolysis of some pyridine monoarylboranes (41). No isotope effect was found for the water hydrolysis of *p*-toluidineborane (62). Inverse effects were found for the methanolysis of lithium borohydride (39), hydrolysis of sodium borohydride (37,63,64) and the acid hydrolysis of some pyridine monoarylboranes (41).

Validity of the spectroscopic method for kinetic measurements.

In order to make measurements of k_H and k_D , it was necessary to select a kinetic method. The kinetics of sodium borohydride reductions have often been studied. They were first done by Garrett and Lytle (65) using a modified titration method (66). Brown and co-workers, using the titration method, showed that the reaction was second order (67-70). The titration method has been used to study rates of reduction of cyclic ketones (67-69), alicyclic ketones (70,71), 4-substi-

tuted cyclohexanones (23) and steroids (65,72,73).

Recently Rickborn and Wuesthoff (74) have followed the kinetics of reduction of cyclohexanones with a potentiometric and a gas chromatographic technique.

The ultraviolet spectroscopic method, following the decrease of the $n-\pi^*$ absorption band in ketones, has been employed for aryl ketone reductions (22,25,27), the sodium borohydride reduction of aryl acid chlorides (31) and α,β -unsaturated ketones (26). Although this method has been used for the reduction of cyclohexanones by lithium aluminum tritertiarybutoxyhydride (75), prior to this study the sodium borohydride reduction of unconjugated ketones had not been followed spectroscopically.

In the course of the current study, it became evident that values of the rate constants obtained by spectral means did not agree well with results obtained by the titrimetric method (23,67,69,72). At first it was thought that this discrepancy was due to experimental error and conditions involved in interlaboratory agreement in kinetics. When it was noticed, however, that for a number of ketones spanning wide ranges of rate constant the ratio $k_{\text{spectral}}/k_{\text{titration}}$ was almost constant (Table 1)¹, it was thought that

¹For convenience, the ketones used in the kinetic studies are shown on a foldout page at the end of this thesis. Numbering used in tables is that of this listing.

some other factor must be operating, as experimental error could not reasonably be expected to be in the same direction and of the same magnitude for ketones with widely divergent rate constant. Rickborn and Wuesthoff (74) had also pointed out that their methods gave higher values than the titration method.

To verify that the spectral method is as accurate and precise as the newer techniques (74) reductions were carried out at 0° to compare spectral results to potentiometric and chromatographic values. Examples of raw data for kinetics and extinction coefficient determinations are given in Appendix II. Table 2 lists the results for all ketones in common in the two studies. Agreement among these three methods is very good, with no method giving consistently higher or lower values than any other.

It was a major point of concern to Rickborn and Wuesthoff (74) that some of Brown's data (67), particularly for those ketones reduced most rapidly, had a significant intercept at zero time, up to 7% of reaction. This implies that a significant portion of the reaction is occurring in a different system; in the case of the titration method, reduction is apparently faster in the aqueous KIO_3 used to quench the sodium borohydride than it is in propan-2-ol. To show that intercepts were zero within experimental error for the spectral method, equation 1 was derived:

Table 1. Comparison of rate constants obtained by the spectral method with those from the periodate titration method at 25° in propan-2-ol.

ketone	$k \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$		
	k_{spectral}	$k_{\text{titration}}$	$k_{\text{spec}}/k_{\text{titr}}$
<u>2</u>	326 $\pm 5^a$	247 ^a (23)	1.32 ^a
<u>3</u>	765 ± 31	565 (68,72)	1.35
<u>3</u>	261 $\pm 5^a$	162 ^a (23)	1.61 ^a
<u>5</u>	456 ± 4	397 (72)	1.15
<u>7</u>	149 ± 3	120 (69)	1.24
<u>67</u>	81.1 ± 3.5	63.0 (67)	1.29
<u>68</u>	16.7 ± 0.4	13.9 (67)	1.20
		average	1.31 ± 0.10

^ameasurement at 0°

Table 2. Comparison of rate constants obtained by the spectral method with those from the potentiometric and chromatographic methods at 0° in propan-2-ol.

ketone	$k \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$				
	k_{spectral}	k_{pot}	k_{chrom}	$\frac{k_{\text{spec}}}{k_{\text{pot}}}$	$\frac{k_{\text{spec}}}{k_{\text{chrom}}}$
<u>1</u> ^a	342 ± 12	294 ± 4	319 ± 4	1.16	1.07
<u>3</u>	261 ± 5	235 ± 9	---	1.11	--
<u>4</u>	187 ± 1	179 ± 3	217 ± 19	1.04	0.86
<u>7</u>	39.0 ± 1.3	42.1 ± 0.6	39.9 ± 0.6	0.93	0.98
<u>17</u> ^a	5.84 ± 0.18	5.32 ± 0.07	---	1.10	--
<u>18</u>	4.76 ± 0.30	4.70 ± 0.09	4.55 ± 0.4	1.01	1.07
<u>20</u>	0.31	0.34 ± 0.03	---	0.91	--
			average	1.04 ± 0.07	1.00 ± 0.08

^aNot included in calculations of intercepts.

$$\% \text{ reaction} = \frac{x}{a} \cdot 100 = 100 \frac{\text{Antilog}_{10} \left[\frac{I(a-4b)}{2.303} \right] - 1}{\left(\frac{a}{4b} \text{Antilog}_{10} \frac{I(a-4b)}{2.303} - 1 \right)} \quad \underline{1}$$

where a = initial ketone concentration, b = initial concentration of borohydride, x = final concentration of alcohol, I = intercept. Equation 1 is derived from the straight line equation 2 by solving for x and rearranging. This analysis of the intercepts was done

$$I = (2.303/a-4b) \log (4b/a) - (a-x/4b-x) \quad \underline{2}$$

only on reductions at 0° for the ketones listed in Table 3, which shows that $I \leq 4 \times 10^{-1}$ ($< 1\%$ reaction) for a representative cross section of ketones spanning rate constant values of almost 10^3 .

Thus the spectral method appears to meet the requirements of reproducibility, accuracy and passage through the origin. This method compares well with potentiometric or chromatographic methods (74) and is very easy and convenient (see experimental).

Reduction of ketones.

As mentioned above, the kinetic deuterium isotope effect is generally conceded to be an experimentally observable measure of the degree of transfer of a hydrogen species at the transition state (54-59). If

¹These values were obtained from a computer programme courtesy of Dr. P. M. Laughton.

Table 3. Kinetic data for the reduction of ketones by sodium borohydride in propan-2-ol at 0°.

ketone	[ketone] $\underline{M} \times 10^2$	$k \times 10^4$ $\underline{M}^{-1} \text{sec}^{-1}$	y intercept (% rx.)	corr. coeff.
<u>3</u> ^a	2.54	264	0	0.999
	3.52	246	3σ (< 1%)	0.999
	3.48	260	4σ (< 1%)	0.999
	2.88	264	0	0.999
	2.87	270	3σ (< 1%)	0.999
average		261 ±5		
<u>4</u>	2.94 ^b	186	0	0.999
	1.86 ^c	188	0	0.999
average		187 ±1		
<u>7</u> ^a	3.69	38.1	0	0.999
	2.51	41.5	0	0.999
	3.42	37.4	3σ (< 1%)	0.999
average		39.0 ±1.3		
<u>18</u> ^a	2.81	4.76	0	0.999
	2.87	5.21	0	0.999
	2.42	4.31	0	0.999
average		4.76 ±0.30		
<u>20</u> ^a	2.48	0.31	0	0.963
	2.57	0.31	0	0.959
average		0.31		

^aNaBH₄ conc. = 0.0103 M^bNaBH₄ conc. = 0.0091 M^cNaBH₄ conc. = 0.0076 M

the Dauben hypothesis (2) were correct, it was anticipated that large steric differences over a series of ketones would cause reduction to occur via different transition states and hence lead to different isotope effects presumably changing in an ordered fashion over the series of ketones studied. The ketones listed in Table 4 were chosen as substrates in the initial study because they offered a large change in product ratio in the sodium borohydride reduction and because they were readily available commercially as either the ketone or the alcohol.

Determination of the product ratios was not straightforward. The major difficulty was in procuring an analytical system which would allow determination of the required ratios without making derivatization necessary. It was desired to analyze the alcohols themselves to insure no changes in ratio occur and to guard against incomplete derivatization. Gas-liquid chromatography (glc) was thought to be the method of choice and did indeed provide the required details. However, initial experiments using a 6 foot, 0.5 inch internal diameter QF-1 packed column in the Hewlett-Packard F and M Scientific 402 High Efficiency Gas Chromatograph did not give baseline separation of most alcoholic pairs and the OV-210 column gave only very faint separation of peaks in the required steroids.

Attention was then given to a nuclear magnetic

resonance (nmr) method of product ratio determination. It is quite well known that the chemical shift (76,77) and the splitting (78) of the methine proton on the hydroxyl-bearing carbon depends on the axial-equatorial nature of the proton. Axial protons appear in the range δ 3.2-3.7 p.p.m. and the equatorial protons in the range 3.6-4.2 p.p.m. Integration of these signals would give the product ratio. Unfortunately, this method was not suitable for the degree of accuracy desired in this study. Using the Varian T-60, it was thought that an error of at least $\pm 5\%$ would accrue on a large, symmetrical peak. In this case, since the total area being integrated was only one proton (out of, for example, 14 protons in monomethylcyclohexanols) and since the peaks are rather broad and, furthermore, since propan-2-ol, the solvent employed in the reductions, gives a signal overlapping with those being examined, the error was thought to be even larger. Another possibility was the use of the shift reagent, europium(III) tris 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,5-octanedione ($\text{Eu}(\text{fod})_3$), to complex with the alcohols. The feasibility of this method has recently been demonstrated (79). If sufficient resolution could be obtained, it would be possible to observe and integrate a methyl doublet since there would be a difference in shift for the two orientations with respect to the hydroxyl oxygen (79). Indeed it was possible

to achieve separation for some mixtures, 3-methylcyclohexanol being the most easily separated. This method, however, was tedious, not always reproducible and required relatively large amounts of pure alcohol and shift reagent. Also, it did not work satisfactorily with a number of the alcohols.

The nmr method, however, was used as a check on the glc product ratio and to make sure of isomer identification. Authentic samples of cis and trans alcohols were available for 2-, 3-, and 4-methylcyclohexanols. For the remaining alcohol mixtures it was necessary to identify the alcohols by other means. For example, two peaks were observed in the commercial sample of 2-t-butylcyclohexanol in the ratio 90:10. Not having an authentic sample of either alcohol, a method of identifying the isomers was required. The nmr gave a value of 86:14 for equatorial:axial proton. This served as good evidence that the sample was predominantly axial alcohol. In cases where the product ratio was quite different from 50:50, the nmr method allowed identification of the predominant alcohol.

The method finally used was a glc one employing the recently purchased Perkin-Elmer 990. The instrumentation, columns and method of obtaining product ratios are described in the experimental section.

The ratio of equatorial:axial alcohol formed in these reductions changes from 94% equatorial to 48%

equatorial (Table 4). The product ratio range is further extended with 3,3,5,5-tetramethylcyclohexanone (20). Although this ketone is symmetrical and no product ratio may be obtained, it is possible to estimate the amount of axial alcohol formed. A simple estimate would be to assume that the effect of two axial methyl groups is just twice that of one methyl group. This is probably a conservative estimate of the amount of axial alcohol formed, because, as Eliel and Senda (14) point out, steric effects are generally more than additive in terms of free energy. Using this approach and the product ratio data of Table 4, the percentage of equatorial alcohol formed in the NaBH_4 reduction of ketone 20 is only 10%. The product ratio difference in attack on 3-methylcyclohexanone (4) and 3,3,5-trimethylcyclohexanone (18) is $86\% - 48\% = 38\%$. The effect of two axial methyl groups is, therefore, 76% and the amount of equatorial alcohol formed in the reduction of ketone 20 is $86\% - 76\% = 10\%$ at 25° . Using the data in Table 1 of Eliel and Senda (14), one calculates only 0.5% equatorial alcohol formed¹. It appears that 90% axial alcohol is a conservative estimate.

¹There appears to be an error in reporting the data of this table (ref. 14) since one would calculate a product ratio of 77% cis alcohol for the NaBH_4 reduction of 3,3,5-trimethylcyclohexanone whereas Eliel actually obtained 64% trans. Furthermore, the authors imply a product ratio of ca. 9% equatorial alcohol for 3,3,5,5-tetramethylcyclohexanone, but one calculates only 0.5% equatorial alcohol from their data.

An independent attempt to estimate the product ratios for 4-acetyl-3,3,5,5-tetramethylcyclohexanone¹ (22), a model for ketone 20, gave conflicting results from the two attempted methods of analysis. Upon exhaustive reduction by sodium borohydride in refluxing propan-2-ol, only one product was observed by glc. However, the nmr spectrum of the pure product in deuteriochloroform showed two 6-proton doublets in the region 0.95-1.25 δ . Since the doublets were not well resolved, only a crude estimate of their ratio could be made. This ratio was ca. 70:30. It was thought that the cause of these doublets was formation of two alcohols, 23 and 24. To rationalize formation of only

Figure 6. Products in the NaBH₄ reduction of ketone 22.

¹Generously supplied by Dr. P. Teisseire.

one peak in the glc, it was considered that, if 23 existed primarily in form 23a and 24 as 24, then the molecules would really be quite similar in terms of shape and polarity because the 4-acetyl group is rather buried by the methyls in either conformation. Nonetheless, it is curious that not even a shoulder could be seen on the glc peak, because no other set of alcohols failed to be separated almost to baseline. If alcohols 23 and 24 did exist, it seemed likely that the mixture was not at equilibrium. Therefore, equilibration over Raney nickel¹ would be expected to alter the product ratio almost exclusively to 24 by analogy with the equilibrium of 25 and 26 which favours 26 95:5 (80).

Figure 7. Epimeric 3,3,5-trimethylcyclohexanols.

¹Experiment performed by Mr. S. Feiner.

The nmr spectrum was indeed altered; apparently the mixture changed from about 70% of what was presumed to be alcohol 23 to about 90-95% of what is presumed to be alcohol 24. The glc retention times of the equilibrated and unequilibrated products were identical upon simultaneous injection.

It was also considered that differences in the nmr could be due to restricted rotation in this molecule. If this were the case and Raney nickel epimerization only changed conformer population, one might anticipate a change upon simply refluxing the alcohols in propan-2-ol. However, refluxing for 36 hrs. caused no change in the nmr spectrum. In view of the uncertainties involved in the nmr spectra and glc, it was difficult to assign a product ratio. The likelihood still exists, however, that considerably more axial alcohol is formed in the reduction of 3,3,5,5-tetramethylcyclohexanone than in that of 3,3,5-trimethylcyclohexanone. In view of the results of Eliel and Senda (14) it appears that the estimate of 90% axial alcohol, although higher than the value apparently allowed by nmr, is not unreasonable and may still be conservative. The product ratio span studied for the $\text{NaBH}_4/\text{NaBD}_4$ reduction therefore ranges from about 95% equatorial alcohol to about 90% axial alcohol.

The kinetics were determined spectrophotometrically by following the disappearance of the $n-\pi^*$ ketone band at the appropriate wavelength (see Table 4

Table 4. Values of the NaBH_4 vs. NaBD_4 deuterium isotope effect in propan-2-ol at 25°.

ketone	$\lambda_{\text{max}}(\text{nm})$	$k_{\text{H}} \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	$k_{\text{D}} \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	$k_{\text{H}}/k_{\text{D}}$	eq:ax alc.
<u>2</u>	285	856 $\pm$ 14	1250 $\pm$ 40	0.68	86 ^b :14 ^a
<u>3</u>	283	765 $\pm$ 31	1290 $\pm$ 41	0.59	---
<u>4</u>	285	605 $\pm$ 12	939 $\pm$ 34	0.64	86 ^a :14 ^b
<u>5</u>	277	456 $\pm$ 4	590 $\pm$ 10	0.77	94:6
<u>7</u>	285	149 $\pm$ 3	198 $\pm$ 7	0.75	70 ^b :30 ^a
<u>17</u>	285	24.9 $\pm$ 1.2	37.1 $\pm$ 1.9	0.68	---
<u>18</u>	287	21.8 $\pm$ 0.4	31.5 $\pm$ 1.6	0.63	48 ^a :52 ^b
<u>20</u>	289	1.92 $\pm$ 0.21	2.72 $\pm$ 0.15	0.71	---

^a_{cis} ^b_{trans}

and experimental section). Treatment of the data by standard second order kinetics, the derivation of which is found in Appendix III, gave satisfactorily reproducible plots with correlation coefficients of about 0.999 (see Tables 5 and 6). Examples of raw data, calculations and plots for kinetics and extinction coefficient determination are given in Appendix II.

Concerning the isotope effects listed in Table 4, a number of points can be made. Firstly, they are all inverse. This was not unexpected since inverse isotope effects have often been found in borohydride hydrolysis (37,39,41). Transfer of the first hydride is rate determining in the sodium borohydride reduction of ketones (Figure 8). This was shown by adherence to second order kinetics (65,67) and by non-kin-

Figure 8. Reaction of ketones with sodium borohydride.

etic means (81). Since the first step is rate determining, the secondary effects of the three deuteriums not being transferred are felt in the rate determining step and are reflected in the observed isotope effect. Halevi (60) has attributed other inverse effects in borohydride chemistry (37) to an inverse primary effect since, in acid hydrolysis, the weaker B-H bond is being replaced by a stronger H-H bond in the transition state. Changes in the other bonds were considered to be of secondary importance.

One piece of experimental evidence against Halevi's argument is the observation by Hawthorne and Lewis (36) that a normal isotope effect of $k_H/k_D = 1.52$ exists in the hydrolysis of diphenylpyridine borane. Since hydrogen is formed in the hydrolysis (equation 3) one would expect by Halevi's reasoning to observe

an inverse isotope effect.

Further interesting data of Davis *et. al.* (20) in the hydolysis of pyridine monoarylboranenes (equation 4) indicates that at least two hydrogens must

be present on boron before an inverse effect is observed.

A last piece of data of Davis and coworkers (20) confirms that breaking a B-H(D) bond with no other deuteriums on boron gives rise to a small normal isotope effect $k_{\text{H}}/k_{\text{D}} = 1.18$ (equations 5 and 6). However, the breaking of a B-H bond when one deuterium is present on boron, a purely secondary effect (equations 5 and 7), gives rise to an inverse isotope effect (value not given). It appears, therefore, by analogy,

that the inverse isotope effect in the $\text{NaBH}_4/\text{NaBD}_4$ reduction of ketones is the result of the inverse secondary effects outweighing a small primary effect.

The most important feature of the isotope effects presented in Table 4 is that there is no trend in the values corresponding to increasing degree of steric hindrance. As mentioned above, if the transition state

were occurring at different points along the reaction coordinate as demanded by the Dauben hypothesis (2), one might expect the isotope effects to vary in the direction of increasing steric hindrance. That this is not observed appears to contradict the Dauben hypothesis.

Additionally, it is clear that the absolute magnitude of the primary isotope effect is small since it is overwhelmed by secondary effects. This was initially taken as being consistent with an early transition state, in agreement with other workers (9-12,16,18). However, a very late transition state would have a small isotope effect as well (48). A non-linear transition state would also be expected to lead to a small isotope effect (45-47) which might be swamped by secondary effects. Finally, since the secondary effects dominate a small primary effect, it is possible that the primary effect is varying sequentially, as predicted, but that secondary effects obscure this trend. This would be possible since the secondary effects would not necessarily be constant for transition states of different geometry.

$\text{LiAl}(\text{O}^t\text{Bu})_3\text{H/D}$ reductions.

Due to the difficulties in interpretation of results found for the $\text{NaBH}_4/\text{NaBD}_4$ isotope effects, it was desirable to study a system which would be unam-

Table 5. Kinetic data for the reduction of ketones by NaBH_4 in propan-2-ol at 25° .

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	corr. coeff.
<u>3</u>	4.44	0.93	72	788	0.999
	4.81	0.93	73	722	0.999
	6.02	0.93	82	731	0.999
	5.27	1.05	69	815	0.999
	5.11	1.05	64	768	0.999
	average 765 ± 31				
<u>2</u>	0.86	0.76	62	865	0.999
	1.57	0.76	54	835	0.999
	0.85	0.77	53	869	0.999
	average 856 ± 14				
<u>4</u>	4.46	1.05	59	620	0.999
	2.37	0.93	66	608	0.999
	4.31	1.05	57	588	0.999
	average 605 ± 12				
<u>5</u>	0.72	1.22	38	453	0.999
	0.72	1.22	40	460	0.999
	average 456 ± 4				
<u>7</u>	4.26	1.71	77	144	0.999
	4.69	1.71	81	154	0.999
	3.94	0.85	64	149	0.999
	5.43	1.71	76	148	0.999
	average 149 ± 3				
<u>17</u>	3.59	0.77	20	23.2	0.999
	2.51	0.77	18	26.0	0.998
	2.22	0.77	18	25.6	0.999
	average 24.9 ± 1.2				
<u>18</u>	4.13	0.66	32	22.2	0.998
	3.44	1.71	48	22.1	0.999
	3.51	1.71	47	21.2	0.999
	average 21.8 ± 0.4				

Table 5. Continued

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $M^{-1} \text{sec}^{-1}$	corr. coeff.
<u>20</u>	2.36	1.71	11	2.33	0.999
	3.45	0.93	12	1.83	0.994
	3.51	0.93	9	1.88	0.977
	4.05	0.93	8	1.63	0.987
	average 1.92 $\pm$ 0.21				

Table 6. Kinetic data for the reduction of ketones by NaBD_4 in propan-2-ol at 25°.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $M^{-1} \text{sec}^{-1}$	corr. coeff.
<u>2</u>	0.98	0.37	50	1320	0.999
	1.05	0.37	47	1241	0.999
	0.80	0.37	36	1197	0.999
	average 1250 $\pm$ 40				
<u>3</u>	4.65	0.87	78	1347	0.999
	4.29	0.87	75	1295	0.999
	4.04	0.87	70	1228	0.999
	average 1290 $\pm$ 41				
<u>4</u>	3.19	1.29	54	936	0.996
	3.19	1.29	48	912	0.999
	1.70	1.29	74	954	0.997
	1.70	1.29	79	1006	0.999
	1.70	1.29	71	889	0.997
	average 939 $\pm$ 34				
<u>5</u>	0.54	0.31	23	610	0.996
	0.65	0.31	25	584	0.999
	0.65	0.31	25	576	0.999
	0.67	0.31	19	588	0.999
	average 590 $\pm$ 10				

Table 6. Continued

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	corr. coeff.
<u>7</u>	2.53	0.45	73	187	0.999
	2.33	0.45	61	193	0.999
	2.29	0.45	68	187	0.999
	5.48	0.92	49	206	0.999
	5.05	0.92	38	201	0.998
	1.95	1.29	48	208	0.997
	4.03	0.88	27	202	0.999
			average	198 ± 7	
<u>17</u>	2.25	0.74	18	36.0	0.999
	2.14	0.74	18	40.3	0.998
	1.54	0.74	16	35.1	0.999
			average	37.1 ± 1.9	
<u>18</u>	3.00	1.29	20	29.1	0.997
	1.99	0.87	21	31.6	0.998
	4.15	0.65	14	33.9	0.999
			average	31.5 ± 1.6	
<u>20</u>	1.36	1.29	5	2.54	0.996
	1.74	0.87	3	2.74	0.969
	2.51	0.87	5	2.87	0.992
			average	2.72 ± 0.15	

biguous. The obvious choice was a situation in which only a primary isotope effect would be encountered so no difficulties would arise due to secondary isotope effects. This meant that a system with only one hydrogen on boron would be required.

A prime consideration for any complex hydride is its availability. Because both the hydride and the deuteride are required and no monodeuterides appear to be commercially available, a good method for synthesizing the deuteride is necessary. Fortunately, most of the monohydrides are synthesizable from NaBH_4 (82) or LiAlH_4 (83,84), and NaBD_4 and LiAlD_4 are commercially available in high isotopic purity.

The first such system considered was $\text{NaBH}(\text{OCH}_3)_3$. This would presumably be a good reducing agent because it is commercially available and serves as a model for the last hydride transfer of NaBH_4 . Unfortunately, this compound was found to be unstable in alcoholic solvents, in agreement with Brown *et. al.* (82) and has a short shelf-life. A commercial sample stored in a closed bottle in a desiccator deteriorated rapidly. Study of this compound was then abandoned.

The next reducing agent which was considered was lithium perhydro-9b-boraphenylhydride (29) available from cis, cis, trans-perhydro-9b-boraphenylene (28)(85,86). Compound 28, centrobor, was successfully made following the literature procedure (85). However, it was very

Figure 9. The synthesis of centrobor hydride.

sensitive to moisture and perhaps air. Centrobor hydride (29) was not isolated due to its sensitivity. It was clear, therefore, that this compound could never be used in a kinetic study in the absence of a dry box which was large enough to contain the spectrophotometer and all chemicals necessary for carrying out the kinetics.

Inability to synthesize centrobor hydride was not considered a great setback, however, due to other difficulties concerning this compound. It is quite likely that reductions with this hydride would have been too fast to measure in any case. Since even the reduction of camphor, which is reduced about 50 times more slowly than 3,3,5,5-tetramethylcyclohexanone by sodium borohydride (69), is 100% complete in less than 1/2 hour (87), it is certain that only the slowest

ketones could be studied using the techniques developed in this work.

A second drawback in the consideration of this hydride is the product ratio distribution. Even unhindered ketones such as 4-methylcyclohexanone give more than 50% axial alcohol upon reduction with centrobor hydride (87). Thus, the product ratio range using this hydride is considerably less than that using NaBH_4 . Of course, knowledge of the factors involved in the formation of axial alcohols would be very interesting.

Having been faced with synthetic difficulties or with problems of stability in the NaBR_3H type compound, it became necessary to pursue the synthesis of an alternate complex hydride. The obvious choice was of the general form $\text{LiAl(OR)}_3\text{H}$. The preparation of these compounds is largely due to H. C. Brown's group and has recently been reviewed (88). Of the readily available alcohols of use in making alkoxyaluminumhydrides, the following four have been most studied and were considered for this study- CH_3OH , $\text{CH}_3\text{CH}_2\text{OH}$, $\text{CH}_3\text{CHOHCH}_3$, $(\text{CH}_3)_3\text{COH}$. The immediate choice was $\text{LiAl(O}^t\text{Bu)}_3\text{H}$ because of its commercial availability and stability.

However, a number of questions needed to be answered before choosing any particular aluminumhydride- how stable is the hydride, is it easily made, does it disproportionate, is it monomeric in solution, is the deuteride readily available and is the product ratio

range suitable for this study? Fortunately, it was not necessary to study the various hydrides in detail to answer these questions since much was known about these compounds. $\text{LiAl}(\text{O}^i\text{Pr})_3\text{H}$ was considered a poor choice because the adducts of LiAlH_4 and propan-2-ol always disproportionate (83,89). The ethoxy adduct was also suspect because significant amounts of di- and tetra-ethoxy derivatives are present upon addition of three equivalents of ethanol to lithium aluminum hydride (83). Lithium aluminumtr*itertiary*butoxyhydride (LATBH) (83,90) and lithium aluminumtrimethoxyhydride (LATMH) (83,84,90) appeared to be good choices as far as stability, disproportionation and ease of synthesis was concerned. It has been shown, however, that LATMH associates considerably in THF solution while LATBH is monomeric at all reasonable concentrations (91). LATBH appeared to be the hydride of choice from its physical properties and from its considerable stability (92,93). The product ratios in THF were also favourable, being very similar to NaBH_4 for unhindered ketones while being more selective (leading to a higher percentage of the less stable alcohol) for hindered ketones (88).

Use of an aluminum hydride introduces a minor complication because it is the B-H vs. B-D primary isotope effect which is desired. However, it is not unlikely that most hydride reductions are governed by the same factors since product ratios and trends in these ratios are rather insensitive to change of the reducing agent.

Having chosen LATBH as the reducing agent most likely to give good results with few complications, an investigation of the kinetics of reduction was in order. A pseudo-first order spectroscopic kinetic study of the reduction of several cyclohexanones has been carried out (75). It was revealed that the rate constants for reduction were very much faster than the NaBH_4 reductions. Even the hindered ketones 18 and 20 are reduced by LATBH faster than cyclohexanone is by NaBH_4 . This pushed the limits of the method and, indeed, made it impossible to apply the spectroscopic method to any ketone reduced more rapidly than ketone 17. In addition, it was difficult to obtain good reproducibility due to the rapid rate of reduction. The values obtained are listed in Table 7.

Since the spectroscopic method held no promise, a stopped-flow study was attempted using a Durrum-Gibson Stopped-Flow Spectrophotometer¹. This method failed to give any results due to experimental and practical difficulties. The obtainable hydride concentration was quite low, about 0.01 M. This in turn limited the ketone concentration which could be used to obtain a large enough absorbance change over the course of the reduction to be readily observed. Additionally, the small path length of the cells in the apparatus

¹Courtesy of Dr. C. H. Langford.

required quite a large concentration of ketone to allow visualization of a signal.

The stopped-flow method was abandoned and a modified stopped-flow method was attempted using the Cary 14 Spectrophotometer. In this method the blank was prepared with 2 ml of standardized hydride solution (94) and 1 ml of THF. Then 2 ml of hydride solution were placed in the sample cell and 1 ml of the ketone solution was injected into the reaction cuvette via syringe through a specially constructed top for the spectrophotometer. Unfortunately, this technique was quite crude, leading to a number of difficulties. The two most troublesome were spillage down the outside of the cuvette and inefficient mixing. This method, therefore, was also abandoned. It may have been possible to perfect this method by designing a more efficient system, but at this time it was decided to obtain the isotope effects via competition experiments, since, unlike the NaBH_4 reductions, actual rate constants and their temperature dependence were not required.

Competition experiments.

If an excess of hydride and deuteride is allowed to compete for a relatively small amount of ketone, the alcohol formed will contain deuterium in proportion to the deuterium isotope effect. If the concentrations of hydride and deuteride are known, one can

Table 7. Kinetic results for the reduction of ketones by synthetic and commercial $\text{LiAl}(\text{O}t\text{Bu})_3\text{H}$.

ketone	# det.	$\frac{[\text{ketone}]}{[\text{hydride}]}$	% red.	$k \times 10^2$ avg. $\text{M}^{-1}\text{sec}^{-1}$	corr. coeff. avg.
<u>20</u> ^a	24	0.30 to 3.28	50	4.22 to 16.6 average 10.2 ± 2.9	0.998
<u>20</u> ^b	15	0.65 to 1.43	42	4.42 to 10.6 average 7.55 ± 1.20	0.999
<u>18</u> ^a	17	0.68 to 2.19	61	9.93 to 22.6 average 15.2 ± 3.6	0.998
<u>18</u> ^b	6	0.43 to 1.11	56	10.7 to 23.5 average 14.9 ± 3.0	0.999
<u>17</u> ^a	5	0.73 to 1.25	43	15.0 to 20.1 average 16.8 ± 1.4	0.999

^acommercial hydride

^bsynthetic hydride

calculate the isotope effect from knowledge of the amount of deuterium incorporation. Mass spectrometry offered a straightforward method for measuring the ratio of deuterated to non-deuterated alcohol¹. It should, in principle, be relatively easy to obtain a quantitative measurement of the amounts of the two alcohols from the parent peaks and to have a check on this ratio using certain peaks arising from well defined splitting patterns. The same splitting pattern, loss of water followed by loss of methyl, is observed for all ketones in this study and is anticipated for any alcohol which can lose a methyl group. There is no loss of the hydrogen at the hydroxyl bearing carbon (95) in cyclohexanol, so there is no difficulty in interpretation for this splitting pattern. Unfortunately, there is a difficulty in using the M-18 peak because the M-18 peak for the deuterated alcohol is at the same mass number as the loss of methyl, M-15, from the ketone. If the ketone is present in even a very small percentage and care is not taken in obtaining the spectrum, a very large amount of the spectrum will actually be due to ketone. This results from the greater volatility of the ketone compared to the alcohol. If the system is not pumped down after the initial pressure increase, there is a danger that

¹Dr. J. L. Holmes of Ottawa University is thanked for discussions concerning mass spectral measurements.

the resultant spectrum will be that of more volatile impurities. Since the spectra of the cyclohexanols contained large apparent M-2 peaks, these peaks were ascribed to ketonic impurity, even though none was seen in the glc of the alcoholic mixtures sent for analysis. That the M-2 peak is not due to any real splitting pattern can be seen by comparison to a published spectrum of 4-t-butylcyclohexanol in which the M-2 peak is almost completely absent (96).

Due to circumstances beyond the control of the author, only a small percentage of the results of the competition experiments is interpretable. On two occasions cyclohexanols were sent for analysis and on one occasion steroids were sent. Both times errors by the analysers resulted in loss of material, poor spectra or both. The results reported in this study are those which could be salvaged from the spectra obtained¹.

The competition experiments were performed by adding the ketone in THF to a solution of known concentrations of LATBH and LATBD. A two-fold excess of each reducing agent was considered to be adequate. The amount and number of ketones studied was limited by the availability of LATBD. The method is described in the experimental section.

The isotope effects were calculated as follows.

¹The Carleton University Chemistry Department does not possess a mass spectrometer suitable for this analysis.

The mass spectrum of the non-deuterated alcohol was taken and the ratio of the M-32:M-33 peaks was measured. This was the experimental measure of the ^{13}C contribution and was used to determine the contribution of the M-33 peak which was actually due to the deuterated alcohol. The following equation was used to calculate the isotope effect:

$$k_{\text{H}}/k_{\text{D}} = M_{\text{D}-33}/M_{\text{D}-32} - (M_{\text{D}-33} \times M_{\text{H}-32}/M_{\text{H}-33}) \times [\text{D}]/[\text{H}] \quad (8)$$

where the subscript D refers to the competition experiments and the subscript H refers to the pure non-deuterated alcohol. The peak sizes were accurately determined using a "travelling microscope" manufactured by J. Swift and Son, London. The isotope effects are reported in Table 8. The errors reported for the cyclohexanols are the average deviations from the average of two different determinations. The steroidal value is the average of five scans of one determination. For the cyclohexanols, the M-33 peaks were used while for the steroids the parent peaks were employed.

It must be emphasized that the results obtained in this study are currently not too firm due to the scarcity of the data and because the conclusions hinge upon the result for 3,3,5,5-tetramethylcyclohexanone. If this value is in error and is actually larger than the value for the unhindered ketones, it would indi-

Table 8. Competition isotope effects for LATBH/LATBD.

ketone	k_H/k_D	eq:ax prod. ratio
<u>2</u>	1.08 $\pm$ 0.04	92:8
<u>9</u>	1.46 $\pm$ 0.15	46:54
<u>11</u>	1.28 $\pm$ 0.01	36:64
<u>21</u>	1.18 $\pm$ 0.02	22:78
<u>20</u>	0.90 $\pm$ 0.02	410: >90 (est)

cate only that the transition state is becoming later, but not necessarily that it is late. Therefore, the results will be interpreted in terms of the observed trend with interjection of the proper cautionary remarks.

There is a very definite trend in the isotope effect with an apparent maximum at approximately a 50:50 mixture of alcohols. The actual values obtained are very intriguing in light of a recent paper by Melander (97) concerning infinitely unsymmetrical transition states. He has concluded that only very reactant-like transition states can be expected to afford isotopic rate ratios very close to unity and that a very product-like transition state would, in principle, be able to give rise to an inverse primary isotope effect. One possible interpretation of the observed trend in the isotope effects is that there exists a change in transition state from a very early one for unhindered ketones to a very late one for hindered ketones. This conclusion, however, which is actually the opposite of the Dauben explanation (2) in which a later transition state would be expected for unhindered ketones, hinges on the data for only one ketone, 20.

Another major conclusion that would seem to follow from these data is that, if the large change in transition state is correct, the transition state must

be non-linear, presumably four centre. This follows because the calculated maximum isotope effect for breaking an Al-H(D) bond is 3.29 and one might expect values of at least 2.2 based on the usual range observed for C-H isotope effects. The observation of a considerably smaller isotope effect and the possibility of a trend from early to late transition state is consistent only with a non-linear transition state.

These two conclusions are clearly vital ones and extreme confidence in the data is necessary to make them. Because of the paucity of data, and in view of some apparently contradictory results in later experiments, these interpretations are questionable and further conclusions will be considered later.

Synthetic ketones.

The studies on the kinetic deuterium isotope effects involved a limited number of ketones. When it became obvious that more ketones were needed for extrathermodynamic studies, and particularly unsymmetrical ketones which give rise to separable epimeric alcohol mixtures, a synthetic course was embarked upon. In view of the main emphasis of this work, it was desired that syntheses be done by known routes through known intermediates to minimize difficulties in perfecting new reactions or characterizing new compounds. It was also desirable to utilize reactions which would lead

to one product or easily separated mixtures. Three types of ketone were required; unhindered, hindered and 2-alkylcyclohexanones.

All of the unhindered ketones employed were commercially available as either the ketone or alcohol (see experimental) with the exception of androstan-3-one (6)¹.

Of the hindered ketones, only 20 was available commercially. 3,3-Dimethylcyclohexanone (17) and 3,3,5-trimethylcyclohexanone (18) were prepared by oxidation of the commercially available alcohols. Androstan-11-one (30)¹ and 4-acetyl-3,3,5,5-tetramethylcyclohexanone (22)² were gifts. The syntheses of other hindered ketones were attempted as described below.

The first synthetic target chosen was cholestan-2-one (21) available by the scheme of Figure 10 (98). This sequence was successful in producing 21³ but the yields decreased dramatically for the last three steps and the purity of the final product suffered. Therefore, the scheme was altered to that of Figure 11⁴. After tedious chromatography and rechromatography, pure 21 was isolated (98,99).

¹This compound was a gift from Dr. J. W. ApSimon.

²This compound was a gift from Dr. P. Teisseire.

³The technical assistance of Mr. F. Gowland and Mr. S. Feiner is acknowledged.

⁴The technical assistance of Mr. F. Gowland, Mr. S. Feiner and Dr. D. C. Wigfield is acknowledged.

Figure 10. Attempted synthesis of cholestan-2-one.

Figure 11. Successful synthesis of cholestan-2-one.

An attractive compound from a stereochemical point of view, lanost-8-en-2-one (44), a 3,3,5,5-tetrasubstituted ketone, was considered available from the published sequences of Figure 12 (100-102). Unfortunately, only the first two steps were realized, yielding lanost-8-en-3-one (16) in good purity¹, and the difficulties of the subsequent steps did not make pursuance worthwhile.

Another attempted synthesis of a 3,3,5,5-tetra-substituted ketone, the pentamethylcyclohexanone 48 is seen in Figure 13. Hydroxymethylene ketone 46 is a known compound (103) and the last two steps of the synthesis have recently been developed by Coates (104). Indeed, compound 47 was arrived at and was shown, by glc and nmr, to exist in a 37:63 mixture of the cis (49) and trans (50) isomers. Unfortunately, the last step of the projected sequence failed. When it became clear, however, that 15 reduced too slowly to allow measurement of kinetics, it was thought that 48 would also suffer this limitation. Hence the sequence was abandoned.

At least one more hindered ketone was required for completion of the study. It was considered that a good general route to the required ketones would be

¹Due to the assistance of Mr. S. Feiner.

Figure 12. Proposed synthesis of lanost-8-en-2-one.

Figure 13. Proposed synthesis of 2,3,3,5,5-penta-methylcyclohexanone.

Figure 14. Geometrical isomers of 2-*n*-butylthiomethy-lene-3,3,5,5-tetramethylcyclohexanone.

available by the 1,4-addition of lithium dialkylcuprates on compound 51. This sequence was attractive because the yields in this reaction are usually very good (105), because the stereochemistry is unambiguous, and because a variety of R groups could be introduced, for example, vinyl, *n*-butyl, *t*-butyl. Also, compound 51 was known and available in high yield in two steps from dimedone (106,107), Figure 16. This sequence even-

Figure 15. General synthesis of 3,3,5-trisubstituted-cyclohexanones.

Figure 16. Synthesis of 5,5-dimethylcyclohex-2-en-1-one.

usually lead to success with compound 52, R = n-Bu. It was, however, very difficult to get pure material, so only one compound was realized by this approach.

The 2-alkylcyclohexanones were more easily obtained since most were commercially available. 2-Methyl-, 2-ethyl- and 2,6-dimethylcyclohexanone were commercial compounds; 2-n-butyl- and 2-t-butylcyclohexanone were synthesized from the alcohols. Menthone (13) was also synthesized from the corresponding alcohol, (-)-menthol (55) but not so straightforwardly. Jones oxidation (108) leads to the equilibrium mixture of menthone (13) and isomenthone (56) because of the highly acidic conditions employed. Even the Moffatt oxidation (109) leads to some isomenthone as well as

Figure 17. Equilibration of menthone and isomenthone.

the difficulty of purifying the product. The method which eventually succeeded in yielding pure (97%) menthone was that of H. C. Brown (110) ($\text{CrO}_3, \text{H}_2\text{SO}_4, \text{Et}_2\text{O}$), a mild, convenient method, certainly the method of choice.

3,3-Dimethyl-6-isopropylcyclohexanone (15) was made via 1,4-addition of lithium dimethylcuprate on commercially available piperitone (57) following the method of Piers and Keziere (111).

Figure 18. Synthesis of 3,3-dimethyl-6-isopropylcyclohexanone.

Activation parameters.

There is no systematic study of the effect of hindrance in cyclohexanones on the activation parameters for sodium borohydride reductions. Indeed, only two cyclohexanones have previously been studied (69). A study of the activation parameters in this reaction was undertaken to establish whether the enthalpy of activation ($\Delta H^\ddagger$) or the entropy of activation ($\Delta S^\ddagger$)

was responsible for the change in reactivity over the series of ketones. This information is necessary for any sensible rationalization of the product ratios. Clearly the rate of reaction is dependent on the degree of hindrance around the carbonyl, which factor also determines the stereochemical product ratio. If entropy changes were accounting for this difference, $\Delta S^\ddagger$ should vary considerably and sequentially for the ketones studied. If, however, enthalpy were responsible, the major changes would be observed in $\Delta H^\ddagger$. Conceivably, both factors could change, in which case the factors involved would not be so clear.

To obtain activation parameters, it was necessary to study the kinetics of reduction at different temperatures. Although there is ample precedent for determinations at only two (69,71) or three temperatures (68, 71), it was felt that at least four temperatures would allow for better precision in activation parameters and more confidence in the results. This is particularly true for $\Delta S^\ddagger$. Small errors, while having only a minor effect on $\Delta H^\ddagger$, the slope, would have a larger influence on the intercept, $\Delta S^\ddagger$.

Unfortunately, the unhindered ketones could generally not be studied at temperatures above 25° due to thermostating difficulties for transfer of solutions to the Gilford spectrophotometer. Also the more slowly reduced ketones were limited to temperatures of 35°

and below because evaporation of solvent began to compete with reduction above this temperature. The lower temperature limit was 0° because of thermostating problems. It is difficult to transfer a solution at 0° to a spectrophotometer at 0° with a warm pipette, causing warming and subsequent cooling which results in kinetic difficulties. This problem was solved for 0° by doing the kinetics in a cold room¹ at about 10°. The use of the cold room had two effects. First it allowed cooling of the pipettes and second it helped control humidity problems. Especially in the summer months, cuvettes in the thermostatted spectrophotometer would precipitate moisture out of the surrounding air, causing condensation on the cuvettes thus vitiating results. Use of the cold room alleviated these difficulties and kinetics could be smoothly carried out.

The results of the kinetics at the various temperatures are summarized in Table 9. Table 10 lists the extinction coefficients and $\lambda_{\max}$. More complete kinetic data are given in Tables 11-16. Using the Eyring equation (9) equation 10 follows, where k_B is

$$k = k_B T/h e^{\Delta S^\ddagger/R} e^{-\Delta H^\ddagger/RT} \quad (9)$$

$$\ln k - \ln k_B T/h = \Delta S^\ddagger/R - (\Delta H^\ddagger/R)(1/T) \quad (10)$$

Boltzmann's constant, h is Planck's constant and T

¹Courtesy of Dr. C. S. Tsai.

Table 9. Summary of rate constants for the sodium borohydride reduction of ketones.

ketone	$k \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$					
	0°	15°	20°	25°	30°	35°
<u>1</u>	342	609	756	890	1049	---
<u>2</u>	326	629	738	856	---	---
<u>3</u>	261	---	620	765	924	---
<u>4</u>	187	426	493	605	---	---
<u>5</u>	136	269	---	456	566	---
<u>6</u>	131	246	338	425	518	---
<u>7</u>	39.0	78.4	---	149	185	224
<u>8</u>	21.6	47.2	---	71.2	84.4	108
<u>9</u>	16.9	40.4	45.4	66.9	---	98.0
<u>10</u>	14.4	---	---	55.7	67.1	74.0
<u>11</u>	7.38	---	23.9 ^a	---	---	51.8
<u>12</u>	8.85	---	27.7 ^a	---	---	51.7
<u>13</u>	3.16	8.55	---	14.2	19.1	---
<u>16</u>	2.40	5.34	6.35	8.59	10.1	12.4
<u>17</u>	5.84	14.4	---	24.9	---	39.6
<u>18</u>	4.76	11.6	---	21.8	---	39.0
<u>19</u>	3.38	---	---	17.6	21.2	28.0
<u>20</u>	0.31	1.06	---	1.92	---	3.76
<u>21</u>	1.26	3.58	4.68	5.98	7.37	9.84
<u>67</u>	---	---	---	81.1	---	---
<u>68</u>	---	---	---	16.7	---	---

^a_{21°}

Table 10. Summary of molar extinction coefficients and $\lambda_{\max}$ at all temperatures in propan-2-ol.

ketone	$\frac{\epsilon}{\lambda_{\max}} \text{ (nm)}$					
	0°	15°	20°	25°	30°	35°
<u>1</u>	16.5	17.3	16.6	16.7	16.3	---
	284	284	284	284	284	
<u>2</u>	18.8	18.8	18.6	19.2	---	---
	285	285	285	285		
<u>3</u>	16.4	16.1	16.5	17.2	17.1	17.6
	283	283	283	283	283	283
<u>4</u>	18.6	18.8	18.5	18.3	18.9	18.6
	285	285	285	285	285	285
<u>5</u>	21.2	20.7	---	20.5	21.2	21.1
	277	277		277	277	277
<u>6</u>	20.8	20.3	20.6	21.1	21.2	---
	285	285	285	285	285	
<u>7</u>	19.1	18.2	---	18.7	18.1	19.1
	286	286		285	286	286
<u>8</u>	20.7	20.4	---	20.8	20.4	20.3
	289	289		289	289	289
<u>9</u>	21.9	21.8	22.0	21.7	---	22.3
	288	288	288	288	288	288
<u>10</u>	24.5	24.4	---	25.2	25.0	25.3
	291	291		291	291	291
<u>13</u>	20.0	20.9	---	21.1	21.0	21.2
	290	290		290	290	290
<u>14</u>	---	---	---	---	---	21.8
						285
<u>15</u>	---	---	---	24.9	---	---
				289		
<u>16</u>	44.1	43.9	43.1	43.2	43.5	42.9
	288	288	288	288	288	288
<u>17</u>	17.3	17.9	---	18.0	---	18.2
	285	285		285		285

Table 10. Continued

ketone	$\frac{\epsilon}{\lambda_{\max}}$ (nm)					
	0°	15°	20°	25°	30°	35°
<u>18</u>	18.9	19.3	---	19.0	---	19.2
	287	287		287		287
<u>19</u>	24.4	25.1	---	24.3	24.1	25.0
	287	287		287	287	287
<u>20</u>	20.3	20.0	---	19.5	---	19.6
	288	288		289		289
<u>21</u>	32.6	31.7	31.8	31.6	32.4	32.5
	286	286	286	286	286	286
<u>67</u>	---	---	---	16.9	---	---
				272		
<u>68</u>	---	---	---	963	---	---
				279		

Table 11. Kinetic data for the reduction of ketones by sodium borohydride in propan-2-ol at 0°.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	corr. coeff.
<u>1</u>	1.87	0.76	39	330	0.999
	2.47	0.76	47	354	0.999
	average 342 ± 12				
<u>2</u>	1.31	0.74	33	321	0.999
	1.31	0.74	37	335	0.999
	1.49	0.74	35	323	0.999
	average 326 ± 5				
<u>3</u>	2.54	1.03	54	264	0.999
	3.52	1.03	49	246	0.999
	3.48	1.03	47	260	0.999
	2.88	1.03	53	264	0.999
	2.87	1.03	48	270	0.999
	average 261 ± 5				
<u>4</u>	1.86	0.76	41	188	0.999
	4.22	0.91	30	186	0.999
	average 187 ± 1				
<u>5</u>	0.38	1.03	44	135	0.998
	0.43	1.03	34	137	0.996
	average 136 ± 1				
<u>6</u>	0.56	0.76	41	134	0.999
	0.57	0.76	45	128	0.999
	average 131 ± 3				
<u>7</u>	3.69	1.03	30	38.1	0.999
	2.51	1.03	35	41.5	0.999
	3.42	1.03	36	37.4	0.999
	average 39.0 ± 1.3				
<u>8</u>	2.18	0.76	12	20.8	0.996
	2.17	0.76	11	22.3	0.992
	average 21.6 ± 0.8				

Table 11. Continued.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $M^{-1}sec^{-1}$	corr. coeff.
<u>9</u>	1.70	0.76	17	16.6	0.999
	1.70	0.76	14	17.1	0.999
	average 16.9 ± 0.2				
<u>10</u>	1.00	0.76	22	15.4	0.999
	1.00	0.76	20	13.4	0.999
	average 14.4 ± 1.0				
<u>11</u>	26.4	4.41	55	7.27	0.998
	23.7	4.41	45	7.48	0.998
	average 7.38 ± 0.10				
<u>12</u>	2.01	4.41	53	9.08	0.998
	2.23	4.41	45	8.62	0.994
	average 8.85 ± 0.23				
<u>13</u>	2.03	0.76	5.2	3.10	0.994
	2.05	0.76	5.4	3.22	0.998
	average 3.16 ± 0.06				
<u>16</u>	0.47	0.76	4.9	2.41	0.969
	0.48	0.76	5.2	2.38	0.984
	average 2.40 ± 0.02				
<u>17</u>	2.95	0.77	8	5.65	0.976
	2.99	0.77	9	6.02	0.965
	average 5.84 ± 0.18				
<u>18</u>	2.81	1.03	15	4.76	0.999
	2.87	1.03	16	5.21	0.999
	2.42	1.03	15	4.31	0.999
	average 4.76 ± 0.30				
<u>19</u>	0.79	0.85	6.0	3.38	0.982
<u>20</u>	2.48	1.03	2.8	0.31	0.963
	2.57	1.03	2.7	0.31	0.959
<u>21</u>	0.32	0.76	4.7	1.24	0.985
	0.32	0.76	4.7	1.29	0.982
	average 1.26 ± 0.02				

Table 12. Kinetic data for the reduction of ketones by sodium borohydride in propan-2-ol at 15°.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $M^{-1}sec^{-1}$	corr. coeff.
<u>1</u>	2.19	0.78	56	615	0.999
	2.26	0.78	47	603	0.999
	average 609 ± 6				
<u>2</u>	1.44	0.76	53	649	0.999
	1.41	0.72	44	620	0.999
	1.41	0.72	49	617	0.999
	average 629 ± 14				
<u>4</u>	2.88	0.95	32	403	0.998
	2.28	0.95	30	449	0.998
	2.28	0.95	29	456	0.999
	2.80	0.95	34	411	0.999
	2.80	0.95	32	410	0.999
	average 426 ± 21				
<u>5</u>	0.58	1.00	29	286	0.999
	0.56	1.00	37	268	0.998
	0.42	1.00	41	252	0.999
	average 269 ± 12				
<u>6</u>	0.56	0.78	55	245	0.999
	0.55	0.78	40	246	0.999
	average 246 ± 0.5				
<u>7</u>	3.25	1.00	32	78.3	0.999
	3.03	1.00	41	77.4	0.999
	2.76	1.00	31	79.4	0.999
	average 78.4 ± 0.7				
<u>8</u>	2.16	0.78	27	47.0	0.998
	2.21	0.78	29	47.5	0.995
	average 47.2 ± 0.2				
<u>9</u>	1.98	0.78	30	39.5	0.998
	2.03	0.78	29	40.9	0.999
	average 40.2 ± 0.7				

Table 12. Continued.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	corr. coeff.
<u>13</u>	1.81	0.78	9	8.58	0.980
	1.79	0.78	8	8.52	0.990
	average 8.55 ± 0.03				
<u>16</u>	0.35	0.78	11	5.21	0.987
	0.37	0.78	9	5.48	0.968
	average 5.34 ± 0.14				
<u>17</u>	1.68	0.77	13	14.5	0.998
	2.03	0.77	12	14.4	0.999
	average 14.4 ± 0.05				
<u>18</u>	1.52	1.00	16	11.2	0.999
	3.00	1.00	18	11.7	0.999
	4.58	1.00	16	11.9	0.996
	average 11.6 ± 0.3				
<u>20</u>	4.69	1.00	4	1.00	0.981
	2.92	1.00	3	1.11	0.986
	2.80	1.00	4	1.07	0.988
	average 1.06 ± 0.04				
<u>21</u>	0.29	0.78	8	3.57	0.979
	0.26	0.78	7	3.60	0.992
	average 3.58 ± 0.02				

Table 13. Kinetic data for the reduction of ketones by sodium borohydride in propan-2-ol at 20°.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $M^{-1}sec^{-1}$	corr. coeff.
<u>1</u>	1.82	0.74	59	763	0.999
	2.52	0.74	49	750	0.999
	average 756 ± 7				
<u>2</u>	1.28	0.77	51	713	0.999
	1.28	0.77	37	737	0.999
	1.40	0.77	52	724	0.999
	1.12	0.76	45	709	0.999
	1.37	0.76	20	763	0.998
	1.24	0.76	42	716	0.999
	1.17	0.76	34	721	0.998
	1.20	0.76	55	767	0.999
	1.34	0.76	55	756	0.999
	1.34	0.76	47	776	0.999
average 738 ± 22					
<u>3</u>	2.39	0.38	50	611	0.999
	2.39	0.38	55	630	0.999
	average 620 ± 10				
<u>4</u>	2.45	0.91	38	488	0.999
	3.34	0.91	43	498	0.999
	average 493 ± 5				
<u>6</u>	1.00	0.74	32	348	0.996
	0.88	0.74	30	327	0.999
	average 338 ± 10				
<u>9</u>	1.24	0.59	31	45.0	0.999
	1.66	0.59	28	45.8	0.999
	average 45.4 ± 0.4				
<u>11</u> ^a	23.8	4.41	37	23.9	0.996
<u>12</u> ^a	2.01	4.41	89	27.7	0.997

^aDetermination at 21°.

Table 13. Continued.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	corr. coeff.
<u>16</u>	0.31	0.74	14	5.90	0.995
	0.36	0.74	15	6.80	0.996
	average 6.35 ± 0.45				
<u>21</u>	0.32	0.74	6	4.32	0.994
	0.31	0.74	9	5.03	0.999
	average 4.68 ± 0.36				

Table 14. Kinetic data for the reduction of ketones by sodium borohydride in propan-2-ol at 25°.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	corr. coeff.
<u>1</u>	2.64	1.88	71	897	0.999
	2.14	1.88	78	882	0.999
	2.51	1.88	77	892	0.999
	average 890 ± 6				
<u>2</u>	0.85	0.77	53	869	0.999
	0.86	0.77	62	865	0.999
	1.57	0.77	54	835	0.999
	average 856 ± 14				
<u>3</u>	4.44	0.93	72	788	0.999
	4.81	0.93	73	722	0.999
	6.02	0.93	82	731	0.999
	5.27	1.05	69	815	0.999
	5.11	1.05	64	768	0.999
	average 765 ± 31				
<u>4</u>	4.46	1.05	59	620	0.999
	2.37	0.93	66	608	0.999
	4.31	1.05	57	588	0.999
	average 605 ± 12				

Table 14. Continued.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	corr. coeff.
<u>5</u>	0.72	1.22	38	453	0.999
	0.72	1.22	40	460	0.999
	average 456 ± 4				
<u>6</u>	0.70	0.94	47	418	0.999
	1.02	0.94	46	431	0.999
	average 425 ± 6				
<u>7</u>	4.26	1.71	77	144	0.999
	4.69	1.71	81	154	0.999
	3.94	0.85	64	149	0.999
	5.43	1.71	76	148	0.999
	average 149 ± 3				
<u>8</u>	4.20	2.07	18	75.2	0.999
	1.41	0.41	25	69.3	0.999
	1.55	0.83	36	69.2	0.999
	average 71.2 ± 2.8				
<u>9</u>	1.31	0.59	44	68.4	0.999
	1.35	0.59	40	65.4	0.999
	average 66.9 ± 1.5				
<u>10</u>	1.12	0.59	39	54.4	0.999
	1.10	0.59	38	57.0	0.999
	average 55.7 ± 1.3				
<u>13</u>	1.64	0.59	13	14.2	0.999
	1.63	0.59	12	14.3	0.999
	average 14.2 ± 0.05				
<u>16</u>	0.42	0.83	10	9.05	0.998
	0.43	0.83	10	8.17	0.999
	0.38	0.59	7	8.24	0.998
	0.36	0.59	10	8.90	0.999
	average 8.59 ± 0.38				

Table 14. Continued.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	corr. coeff.
<u>17</u>	3.59	0.77	20	23.2	0.999
	2.51	0.77	18	26.0	0.998
	2.22	0.77	18	25.6	0.999
	average 24.9 ± 1.2				
<u>18</u>	4.13	0.66	32	22.2	0.998
	3.44	1.71	48	22.1	0.999
	3.51	1.71	47	21.2	0.999
	average 21.8 ± 0.4				
<u>19</u>	1.17	0.85	26	17.5	0.999
	1.18	0.85	25	17.8	0.999
	average 17.6 ± 0.2				
<u>20</u>	2.36	1.71	11	2.33	0.999
	3.45	0.93	12	1.83	0.994
	3.51	0.93	9	1.88	0.977
	4.05	0.93	8	1.63	0.987
	average 1.92 ± 0.21				
<u>21</u>	0.32	0.74	11	6.34	0.998
	0.33	0.74	10	5.61	0.996
	average 5.98 ± 0.37				
<u>67</u>	3.34	1.71	76	82.9	0.999
	3.37	1.71	75	85.9	0.999
	8.32	1.71	69	76.2	0.999
	3.55	0.88	57	83.7	0.999
	3.45	0.88	60	82.3	0.999
	5.25	0.88	67	75.6	0.999
	average 81.1 ± 3.5				
<u>68</u>	0.16	1.71	59	17.3	0.999
	0.16	1.71	64	16.7	0.999
	0.17	1.71	58	16.1	0.999
	average 16.7 ± 0.4				

Table 15. Kinetic data for the reduction of ketones by sodium borohydride in propan-2-ol at 30°.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $M^{-1} sec^{-1}$	corr. coeff.
<u>1</u>	1.31	0.62	68	1106	0.999
	1.70	0.62	67	983	0.999
	1.47	0.62	71	1058	0.999
	average 1049 ± 44				
<u>3</u>	3.18	0.62	78	948	0.999
	1.81	0.62	67	901	0.999
	average 924 ± 24				
<u>5</u>	0.68	0.38	43	582	0.999
	0.59	0.38	22	550	0.999
	average 566 ± 16				
<u>6</u>	0.74	0.62	49	534	0.999
	0.74	0.62	50	501	0.999
	average 518 ± 17				
<u>7</u>	3.59	1.03	13	177	0.997
	3.15	1.03	42	195	0.999
	4.49	1.03	39	184	0.999
	average 185 ± 6				
<u>8</u>	1.73	0.62	36	88.6	0.999
	1.75	0.62	33	80.2	0.999
	average 84.4 ± 4.2				
<u>10</u>	1.26	0.59	43	67.3	0.999
	1.14	0.59	41	70.7	0.999
	1.03	0.59	33	63.7	0.999
	1.35	0.59	45	67.8	0.999
	1.36	0.59	46	66.1	0.999
	average 67.1 ± 1.8				
<u>13</u>	1.39	0.59	14	19.2	0.998
	1.94	0.59	14	19.0	0.996
	average 19.1 ± 0.1				

Table 15. Continued.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $M^{-1} \text{sec}^{-1}$	corr. coeff.
<u>16</u>	0.44	0.62	13	9.8	0.996
	0.42	0.62	11	10.5	0.994
	0.39	0.68	12	10.0	0.998
	average 10.1 ± 0.3				
<u>19</u>	1.02	0.85	19	21.7	0.999
	1.03	0.85	20	20.6	0.999
	average 21.2 ± 0.6				
<u>21</u>	0.29	0.62	17	7.35	0.998
	0.26	0.62	15	7.39	0.996
	average 7.37 ± 0.02				

Table 16. Kinetic data for the reduction of ketones by sodium borohydride in propan-2-ol at 35°.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $M^{-1} \text{sec}^{-1}$	corr. coeff.
<u>7</u>	1.94	1.03	45	235	0.999
	1.94	1.03	84	213	0.999
	average 224 ± 11				
<u>8</u>	1.28	0.62	41	106	0.999
	1.14	0.29	32	109	0.998
	2.19	0.29	58	110	0.999
	average 108 ± 2				
<u>10</u>	1.31	0.29	29	77.6	0.999
	1.04	0.29	29	70.5	0.999
	average 74.0 ± 3.6				
<u>11</u>	22.1	4.41	65	51.8	0.998
<u>12</u>	1.87	4.41	31	51.7	0.999

Table 16. Continued.

ketone	[ketone] $\times 10^2$	[hydride] $\times 10^2$	% red.	$k \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	corr. coeff.
<u>16</u>	0.38	0.62	12	12.9	0.998
	0.50	0.62	11	12.1	0.999
	0.42	0.68	13	12.4	0.999
	0.39	0.29	6	12.1	0.999
	average 12.4 ± 0.3				
<u>17</u>	2.69	0.77	21	41.7	0.998
	3.97	0.77	25	39.1	0.999
	1.27	0.77	15	38.0	0.996
	average 39.6 ± 1.4				
<u>18</u>	2.12	1.21	22	40.5	0.999
	2.44	1.21	20	39.6	0.998
	2.82	1.22	15	36.9	0.999
	average 39.0 ± 1.5				
<u>19</u>	0.78	0.85	26	28.2	0.999
	0.78	0.85	24	27.9	0.999
	average 28.0 ± 0.2				
<u>20</u>	4.02	1.22	6	3.85	0.991
	3.45	1.22	6	3.68	0.996
	average 3.76 ± 0.08				
<u>21</u>	0.25	0.62	12	10.7	0.996
	0.37	0.62	12	8.98	0.998
	average 9.84 ± 0.86				

is the temperature in °K. Equation 10 is that of a straight line. Plotting $\ln k - \ln k_B T/h$ vs. $1/T$, one obtains a line of slope $-\Delta H^\ddagger/R$ and intercept $\Delta S^\ddagger/R$. These plots can be seen in Figure 19. The slopes and intercepts were calculated by least squares analysis on an Olivetti-Underwood Programma 101 Desk Computer¹. The activation parameters are summarized in Table 17. As can be seen, the correlation coefficients are good, in all cases better than 0.99.

Perusal of the data listed in Table 17 makes a few points immediately obvious. 1) $\Delta S^\ddagger$ changes by a smaller amount than $\Delta H^\ddagger$. 2) The entropy change, while not always in the anticipated direction, is opposite to that expected if entropy changes were controlling the reaction. If the reaction were controlled by entropy factors, the more slowly reduced ketones would be expected to have a higher negative entropy, whereas they actually are slightly more favoured, with a less negative entropy of activation. 3) The enthalpy of activation changes regularly in the direction expected and it is this change which controls the observed rate differences. One can conclude that changes in the enthalpy of activation are completely responsible for the increase in activation energy over the series of ketones studied.

¹Programme courtesy of Dr. M. Parris.

Figure 19. Activation parameter plots for the sodium borohydride reduction of ketones.

Table 17. Activation parameters for the sodium borohydride reductions of ketones.

ketone	$\Delta H^\ddagger$ kcal/mole	$\Delta S^\ddagger$ eu	$\Delta G^\ddagger_{298}$ kcal/mole	corr. coeff.
<u>1</u>	5.6 $\pm$ 0.1	-44.7 $\pm$ 0.3	18.9	0.999
<u>2</u>	5.7 $\pm$ 0.2	-44.4 $\pm$ 0.8	18.9	0.997
<u>3</u>	6.4 $\pm$ 0.1	-42.1 $\pm$ 0.1	18.9	0.999
<u>4</u>	7.0 $\pm$ 0.4	-40.4 $\pm$ 1.2	19.0	0.995
<u>5</u>	7.3 $\pm$ 0.4	-40.1 $\pm$ 0.7	19.2	0.998
<u>6</u>	7.1 $\pm$ 0.2	-41.0 $\pm$ 0.8	19.3	0.997
<u>7</u>	7.9 $\pm$ 0.3	-40.6 $\pm$ 1.1	20.0	0.996
<u>8</u>	6.9 $\pm$ 0.1	-45.2 $\pm$ 0.5	20.4	0.999
<u>9</u>	7.7 $\pm$ 0.3	-42.7 $\pm$ 1.1	20.4	0.996
<u>10</u>	7.5 $\pm$ 0.4	-43.8 $\pm$ 1.5	20.6	0.993
<u>11</u>	8.6 $\pm$ 0.1	-41.1 $\pm$ 0.3	20.8	0.999
<u>12</u>	7.8 $\pm$ 0.2	-43.6 $\pm$ 0.5	20.8	0.999
<u>13</u>	9.2 $\pm$ 0.3	-40.6 $\pm$ 0.9	21.3	0.998
<u>16</u>	7.2 $\pm$ 0.2	-48.4 $\pm$ 0.6	21.6	0.998
<u>17</u>	8.5 $\pm$ 0.2	-42.0 $\pm$ 0.8	21.0	0.999
<u>18</u>	9.4 $\pm$ 0.1	-39.3 $\pm$ 0.5	21.1	0.999
<u>19</u>	9.6 $\pm$ 0.2	-39.1 $\pm$ 0.8	21.2	0.999
<u>20</u>	11.1 $\pm$ 0.3	-38.3 $\pm$ 1.1	22.5	0.998
<u>21</u>	9.1 $\pm$ 0.3	-42.7 $\pm$ 1.0	21.8	0.997

Since the reduction of an unsymmetrical ketone will, in principle, give rise to two products, one via equatorial attack and the other via axial attack, one can actually study two different reactions: equatorial attack to yield the axial alcohol and axial attack leading to the equatorial alcohol. Other than the rate constants, product ratio values at the various temperatures should suffice to calculate the specific¹ rate constants and determine the specific activation parameters. For 2-alkylcyclohexanones a further complication must be considered. These compounds are susceptible to epimerization, and it must therefore be determined if prior epimerization affects the product ratio.

In the case of menthone (13) epimerization to isomenthone (56) and reduction of isomenthone could give rise to four alcohols (Figure 20). To determine if epimerization occurs, a 77.5:22.5 mixture of menthone and isomenthone was reduced with sodium borohydride in propan-2-ol for 75 hrs. Glc analysis of the reaction mixture indicated the presence of three compounds- a (24.7%), b (17.1%) and c (58.2%). Simultaneous injection with authentic samples confirmed that b and isomenthone were identical and that c and menthol were identical. Since peak a could be alcohol

¹The word specific is used to denote attack from one side of the carbonyl, either axial or equatorial.

Figure 20. Possible products in the sodium borohydride reduction of menthone.

58, 59 or 60, the reaction mixture was oxidized to the ketone mixture under the non-epimerizing conditions of the Brown oxidation (110). If compound a were alcohol 58, the menthone:isomenthone mixture produced should be $\underline{a} + \underline{b} : \underline{c} = 82.9:17.1$, whereas if a were derived from isomenthone the ratio would be $\underline{c} : \underline{a} + \underline{b} = 58.2:41.8$. The experimentally observed ratio of 84.1:15.9 shows $\underline{a} = \underline{58}$ and nmr analysis of the mixture confirmed these assignments.

Hach et. al. (112) found extensive epimerization in the NaBH_4 reduction of thujone and menthone. They found that 3% water was necessary in the propan-2-ol before epimerization was eliminated. In the current study it has been noted that "wet" solvent gives

rise to non-linear kinetic plots. Davis and Gottbrath (81) also noted this behaviour for the methanolysis of NaBH_4 . Although there is no way to estimate how much water would be present in the propan-2-ol, which was dried and distilled, it does not seem likely that 3 % was present. Nevertheless, no epimerization was noticed in this study.

It appears, therefore, that under the conditions used in this study, isomenthone does not undergo significant reduction and that, although a small amount of epimerization takes place, reduction is considerably faster than epimerization. Therefore, the kinetics can be measured under the same conditions as other ketones and rate constants partitioned in the same way.

Reduction of cis-2,6-dimethylcyclohexanone (11) can give rise to three alcohols as in Figure 21. Glc analysis of the reduction mixtures showed all three alcohols to be formed, although ketone 12 and alcohol 61 were not resolved. After complete reduction with NaBH_4 in propan-2-ol at 21° (70 hrs; no carbonyl in the IR), the areas of the three glc peaks were: a 34.9%, b 53.4%, c 11.6%. Identification of the alcohols was again made by the Brown oxidation (110) and the three possibilities are shown in Table 18. These results clearly show that peak c corresponds to the cis, trans-alcohol 63 and a and b to the two alcohols from

Figure 21. Possible products in the sodium borohydride reduction of 2,6-dimethylcyclohexanone.

Table 18. Identification of alcohols from the sodium borohydride reduction of 2,6-dimethylcyclohexanone.

Origin of alcohols	<u>cis:trans</u> ratio of ketone
<u>c</u> from <u>12</u> ; <u>a,b</u> from <u>11</u>	88.4:11.6
<u>b</u> from <u>12</u> ; <u>a,c</u> from <u>11</u>	46.6:53.4
<u>a</u> from <u>12</u> ; <u>b,c</u> from <u>11</u>	65.1:34.9

Experimentally found 88.5:11.5

cis-2,6-dimethylcyclohexanone (11). It appeared likely that peak a was due to the axial alcohol 61 and peak b to the equatorial alcohol 62 on the basis that in all cases studied the axial alcohol of an axial-equatorial pair has a shorter retention time. This is a general phenomenon for this type of column (113). This conclusion was consistent with nmr analysis of the various reduction mixtures. It was also determined that the alcohol from the trans-ketone 12 existed as 63 rather than 64 from the observation that equatorial proton:axial proton $\approx$ 61 + 63:62.

Glc analysis of product mixtures from the reduction of 2,6-dimethylcyclohexanone consistently showed higher proportions of alcohol 63 than ketone 12 in the starting mixture. Thus it appeared that epimerization of 11 to 12 was occurring followed by reduction of 12 to alcohol 63. This was confirmed by following the reaction progress by glc. This fact coupled with the unavailability of any ketone sample with more than 92% cis isomer rendered the spectrophotometric method of following the reaction kinetics invalid. Therefore, the kinetics were measured by a glc method (see experimental section).

Another question which should be answered before the product ratios can be interpreted in terms of axial or equatorial attack concerns through which conformation the particular cyclohexanone reduces.

The only rigid molecules in this study are the steroids. However, 4-t-butylcyclohexanone and the 3,3,5-tri-substituted ketones are effectively frozen in one conformation because the other chair form would have prohibitive interactions. In the case of 3-methylcyclohexanone (Figure 22), since 4a only accounts for

Figure 22. Conformations of 3-methylcyclohexanone and its reduction products.

about 5 % of the equilibrium mixture and because, by analogy to 3,3-dimethylcyclohexanone, the ratio of rate constants for reduction of 4 to 4a is about 30:1, the percent reaction which might be expected to go through 4a is about $1/20 \times 1/30 = 0.2\%$ and can be essentially ignored.

The major question concerns through which conformation a conformationally mobile 2-alkylcyclohexanone reduces. Since an equatorial group at C-2 may be expected to offer some resistance to attack by borohydride no matter which side it attacks from while an axial group can presumably not interfere with axial attack from the opposite side of the ring, it is not obvious that these ketones reduce through the higher populated ground state with the substituent equatorial. This question will be discussed in detail later when more experimental evidence has been revealed.

Unfortunately, there is some difficulty involved in simply dividing the rate constants by the product ratios to obtain specific rate constants. The sodium borohydride reduction of ketones utilizes all four of the hydrides on boron and transfer of the first hydride is rate determining (65,67,81). Succeeding transfers are considerably faster and are therefore non-kinetic parameters. Thus the validity of the above approach is open to question because 3/4 of the product is produced by intermediates not involved in the

rate expression. Brown and Muzzio (69) were the first to point out these difficulties. However, they could do nothing about determining product ratios of the first step, so they carried on with the method of simply dividing the rate constants by the product ratios. One approximation made by Brown and Muzzio (69) which seems less valid than others was simply dividing the rate constant for reduction of cyclohexanone by two. Brown assigned a theoretical product ratio for cyclohexanone of 50:50, even though aware of Richer's (9) work, stating that this was a "small factor which it appears safe to ignore for the present (69)." By analogy with 4-methyl- or 4-t-butylcyclohexanone one would expect an 85:15 (eq:ax) ratio for cyclohexanone. This is then a 35% error, which was ignored. Summarizing the Brown and Muzzio (69) argument, most of the reductions they studied proceed predominantly (85%) in one direction. The maximum error in the product ratio would then occur if the first step involved formation of 40% of the predominant isomer followed by 100% of that isomer in each succeeding step. This was thought highly improbable. Another observation in favour of this approximation is that reduction of ketone 18 by NaBH_4 and sodium trimethoxyborohydride is not widely different; 56% trans to 65% trans (89).

Two recent papers dealing with sodium borohydride reductions have made important contributions to the

question of product ratio dependence on the various possible reducing agents (74,114). It is known that reduction of ketones by sodium triisopropoxyborohydride is considerably faster than reduction by sodium borohydride (74,115). This corresponds to transfer of the last hydride. It is also known, as a result of adherence to second order kinetics, that the middle two hydride transfers are much faster than the first transfer. Surprisingly, however, Rickborn and Wuesthoff (74) found, in a glc study of this reduction, that the ratio of the two epimeric alcohols changed during the course of the reduction. This implies that one of the hydride transfers other than the first one is relatively slow, slow enough to allow buildup of a species capable of reduction. The fact that deviation from second order kinetics is less than 4% (74) indicates that the next slowest step must still be considerably faster than the first. Wuesthoff (114), in a computer study of the sodium borohydride reduction, has calculated that the second slowest step must have a rate constant about eight times faster than the first transfer and that the next slowest step is transfer of the last hydride. This implies that the reducing species in the last step must be a cyclohexylborate ester or a disproportionation product (74) because reductions done with sodium triisopropoxyborohydride have rate constants more than 25 times that of sodium

borohydride (74). Unfortunately, attempts to synthesize tricyclohexyloxyborohydrides by the general method for synthesizing trialkoxyborohydrides (115) have failed (74,116).

By determining product ratios at various times over the course of a reduction and fitting these points to a curve computed by least squares analysis, the values at 0% and 100% reduction could be found (74). Some of these data are summarized in Table 19.

Table 19. Product ratios early and late in the sodium borohydride reduction, taken from reference 74.

ketone	% alcohol product			% change
	0% reaction	100% reaction		
<u>1</u>	11.2 $\pm$ 0.4	23.9 $\pm$ 0.3	<u>cis</u>	113
<u>4</u>	12.6 $\pm$ 1.2	23.8 $\pm$ 0.1	<u>trans</u>	97
<u>7</u>	25.1 $\pm$ 2.5	39.9 $\pm$ 1.0	<u>cis</u>	59
<u>18</u>	58.1 $\pm$ 1.8	61.7 $\pm$ 0.9	<u>trans</u>	6

Interestingly, ketones which are slowly reduced, for example 18, exhibit little change over the course of the reduction. The trend in all cases is toward increase of the less stable alcohol which is anticipated if a bulkier reducing species is formed over the course of the reaction. The fact that hindered ketones do not exhibit much change in product ratio as the reaction proceeds probably means that steric considerations are already very important without

regard for formation of a bulkier reducing agent. However, the product ratio in the reduction of 18 by sodium triisopropoxyborohydride does change quite dramatically over the course of reduction from 75% trans alcohol at 50% reduction to 86% at 100% reduction (74).

Rickborn and Wuesthoff (74) also question some earlier data (33) on observations of temperature dependence on the reduction process. It is maintained (74) that "the unknown temperature dependence of the reaction of any intermediate alkoxyborohydride species would make interpretation of temperature effects tenuous." Since it was of crucial importance to the current study to have at least an approximation of temperature effects on succeeding hydride transfers, the literature was searched in some detail. Most of the reductions by the species of interest, $\text{LiAl(OR)}_3\text{H}$ and $\text{NaB(OR)}_3\text{H}$, have been carried out at room temperature and much of the early product ratio values must be considered questionable due to lack of good analytical methods for their determination. Nevertheless, the literature results are overwhelmingly in agreement with the direction of the temperature effects for the various reductions.

From this study (see Table 21) the effect of an increase in temperature is to lead to an increase in the less stable alcohol as reported earlier (33). The literature shows this is also true for reductions with

the species: $\text{NaBH}(\text{OCH}_3)_3/\text{H}_2\text{O}$ (4), $\text{NaBH}_4/\text{H}_2\text{O}$ (4), $\text{NaBH}(\text{OCH}_3)_3/\text{CH}_3\text{OH}$ (5), $\text{NaBH}_4/^i\text{PrOH}$ (5), $\text{NaBH}_4/\text{diglyme}$ (5), $\text{NaBH}_4/\text{C}_5\text{H}_5\text{N}$ (5), $\text{LiAlH}_4/\text{diglyme}$, THF and $\text{C}_5\text{H}_5\text{N}$ (5), $\text{NaBH}(\text{O}^i\text{Pr})_3/^i\text{PrOH}$, diglyme (14,117), $\text{LiAl}(\text{OCH}_3)_3/\text{THF}$ (14,89), $\text{LiAl}(\text{O}^t\text{Bu})_3/\text{THF}$ (9,14). In all known literature examples the trend is in the direction observed in this study.

To have independent experimental evidence on the above trends, a brief study of the type carried out by Rickborn and Wuesthoff (74) was done for 2-methylcyclohexanone, the results of which are listed in Table 20.

Table 20. Effect of borohydride:ketone ratio on the stereochemistry of the reduction of 2-methylcyclohexanone as a function of temperature.

$^{\circ}\text{C}$	$[\text{NaBH}_4]/[\text{ketone}]$	% <u>cis</u> alcohol at 100% rx
0 ^a	0.25	39.9
	2.63	30.8
21	0.30	33.6
	1.00	29.5
	2.49	31.0
	2.50	29.8
	0.30	36.2
82	1.00	34.3
	2.49	33.1
	2.50	33.8
	0.30	36.2

^aValues at 0° taken from reference 74.

Because the glc conditions employed in this study do not afford baseline separation of the alcohols and the ketone, it was necessary to measure the product ratio when no ketone was present, that is, at 100% reaction. There appears to be some discrepancy between the data of Rickborn and Wuesthoff (74) and the data of this study. In particular, the temperature dependence appears out of line and the absolute difference in going from a hydride:ketone ratio of about one to about ten is considerably more than for the current study. Attributing these differences to experimental error and carrying on to the purpose of this investigation, it can be seen that a 61° rise in temperature leads to an increase in the amount of the less stable cis alcohol for all concentration ratios. Since the change in this ratio is presumably an indication that the amount of reduction by intermediate species, $\text{NaBH}_n(\text{OR})_{4-n}$, is changing, it would appear that these species have a similar temperature dependence as that observed for NaBH_4 and $\text{NaBH}(\text{OR})_3$. They can not have an appreciable dependence in the opposite direction or the present trend would not be observed. It would thus appear that any approximation made for partitioning rate constants at one temperature would hold for any reasonable temperature.

The important question is that of gaining an estimate of the maximum error to be expected in the use

of NaBH_4 product ratios as models for the transfer of the first hydride. From the data of Rickborn and Wuesthoff (74) the maximum error was 113%, found for the reduction of ketone 1 (Table 19). For most ketones this value is considerably less and is almost negligible for the more slowly reduced ketones. An error of this type in the product ratio leads to incorrect apportioning of the overall rate constant into the two specific rate constants for transfer of the first hydride, leading to incorrect specific activation parameters. The activation entropy, however, has an experimental error of up to 1.5 eu (Table 17) which coincidentally also corresponds to an error of 113% in the rate constant. Thus, although errors in product ratio could cause the specific rate constants to be seriously in error, the additional error in the activation energy, even in the worst cases, is tolerable. In this work specific rate constants are used only as a means of obtaining specific activation parameters.

A very important piece of experimental evidence concerning the stereochemistry of the transfer of the first hydride from sodium borohydride, which was commented upon neither by Brown (69) nor Rickborn (74), is the observation by Jones and Wise (116) that reduction in the presence of triethylamine is halted after transfer of the first hydride. It therefore becomes possible to use this system as a model for transfer of the first hydride, and it is interesting to

observe that the product ratio for the reduction of ketone 2 with NaBH_4 in the presence of triethylamine is 16.4% cis alcohol (116) compared to 14.3% cis alcohol in the absence of triethylamine found in this study, Table 21. Since these values are so close, it would appear that transfer of the first hydride is not stereochemically widely different from the observed value for all four steps, although the possible perturbation of the system by triethylamine must be recognized.

In a recent paper (118) on the sodium borohydride reduction of bicyclo(3,2,1)octanones, the ratio of stereoisomeric alcohols remained constant during reduction from 10% to 100% reaction. The rate constant for one of these compounds is very similar to that of 7 and the product ratios are similar to the unhindered ketones. Perhaps changes of the sort observed by Rickborn and Wuesthoff (74) are not general for bicyclooctanones.

Another piece of experimental evidence in favour of this type of apportionment of rate constants from the current work involves the correlation coefficients of the extrathermodynamic plots (Tables 27 and 28). The values of the correlation coefficient for the specific modes of attack are comparable to or higher than those for the overall reaction indicating that the specific values are nearer to the true picture

and supporting this approach. These values will be discussed in greater detail later.

Although the approach of using product ratios obtained from reduction by all four hydrides is certainly open to question, the above discussion suggests that at least for activation parameter determination tolerable errors are introduced, and it was felt worthwhile to pursue the approach in view of the potential conclusions it might lead to.

Recently two groups of French workers have used the approach of studying specific modes of reduction in the reduction of 2-alkylketones by LiAlH_4 (119) and the reduction of 3-ketosteroids by LATBH (120). Cense (119) argued for a late transition state for axial attack by LiAlH_4 based on product ratio results as a function of temperature. Calvet and Levisalles (120) on the basis of product ratios and kinetics of reduction have concluded that the transition state for equatorial attack by LATBH is not necessarily close to reactants.

With a good analytical method available to study the product ratios, one difficulty still presented itself. In contrast to the apparently large product ratio difference observed when using different ketone:hydride ratios, there is not as large a change in product ratio as temperature changes. Interestingly, Rickborn and Wuesthoff (74) observed the largest con-

centration dependences for the less hindered, more rapidly reduced ketones. Generally the more slowly reduced ketones show a larger temperature dependence. Over the range of temperature employed in the kinetic studies the product ratios for all reductions are practically constant. For this reason reductions were carried out at 0°, room temperature and reflux (82°) to obtain the widest convenient temperature range. Since it was expected that a plot of log (product ratio) vs. 1/T would give a straight line (see derivation), interpolation would give more accurate ratios at intermediate temperatures.

$$k_{eq} = Ae^{-\Delta G_{eq}^{\ddagger}/RT} \quad (11)$$

$$k_{ax} = Ae^{-\Delta G_{ax}^{\ddagger}/RT} \quad (12)$$

$$2.303 \log k_{eq} = 2.303 \log A - \Delta G_{eq}^{\ddagger}/RT \quad (13)$$

$$- 2.303 \log k_{ax} = 2.303 \log A - \Delta G_{ax}^{\ddagger}/RT \quad (14)$$

$$2.303 \log (k_{eq}/k_{ax}) = 0 - \Delta\Delta G^{\ddagger}/RT \quad (15)$$

Table 21 gives values of the product ratio at the specified temperature. In addition, a more detailed study was done on 3,3,5-trimethylcyclohexanone, the results of which are summarized in Table 22. Table 23 gives product ratios and specific rate constants for the ketones employed in this study.

Table 21. % Equatorial alcohol as a function of temperature for reduction by sodium borohydride in propan-2-ol.

ketone	0°	r.t.	82°	corr. coeff.
<u>1</u> ^a	89.6	84.8 ^c	81.0	0.952
<u>2</u> ^a	87.8	85.7 ^d	84.2	0.954
<u>4</u> ^b	88.7	85.2 ^f	81.4	0.981
<u>5</u>	96.4	94.2 ^c	92.2	0.904
<u>6</u>	92.7	90.8 ^g	90.1	0.988
<u>7</u> ^a	73.8	70.6 ^e	65.0	0.985
<u>8</u> ^a	68.5	64.6 ^c	61.6	0.968
<u>9</u> ^a	66.0	64.4 ^c	63.0	0.976
<u>11</u>	62.4	62.0 ^c	60.4	0.993
<u>13</u>	66.8	68.7 ^c	71.8	0.987
<u>14</u> ^a	---	50.4 ^c	43.0	---
<u>15</u> ^a	---	---	40.0	---
<u>16</u>	---	---	~100	---
<u>18</u> ^b	42.0	50.4 ^f	56.4	0.992
<u>19</u> ^b	40.0	45.0 ^f	54.9	0.986
<u>21</u>	43	45 ^c	51	0.998

^atrans alcohol ^bcis alcohol ^c_{21°} ^d_{24°} ^e_{15°}
^f_{35°} ^g_{30°}

Table 22. % Equatorial alcohol in the reduction of 3,3,5-trimethylcyclohexanone by sodium borohydride as a function of temperature.

°C	0°	15°	35°	51°	82°
% eq	42.0	46.6	50.4	52.2	56.9
	41.9	46.0	50.4		55.9
avg.	42.0	46.3	50.4	52.2	56.4

Table 23. Graphical equatorial:axial product ratios and specific rate constants as a function of temperature.

ketone	°C	eq:ax	$k_{ax} \times 10^4$ $M^{-1}sec^{-1}$	$k_{eq} \times 10^4$ $M^{-1}sec^{-1}$
<u>1</u>	0	89:11	304	38
	15	87:13	530	79
	20	87:13	658	98
	25	86:14	765	125
	30	86:14	902	147
<u>2</u>	0	87:13	284	42
	15	87:13	547	82
	20	86:14	635	103
	25	86:14	736	120
<u>3</u>	0	88:12	230	31
	20	86:14	533	87
	25	86:14	658	107
	30	86:14	795	129
<u>4</u>	0	88:12	165	22
	15	87:13	371	55
	20	87:13	429	64
	25	86:14	520	85
<u>5</u>	0	96:4	131	5
	15	95:5	256	13
	25	94:6	429	27
	30	94:6	532	34
<u>6</u>	0	93:7	122	9
	15	92:8	226	20
	20	92:8	311	27
	25	91:9	387	38
	30	91:9	471	47
<u>7</u>	0	73:27	28.5	10.5
	15	71:29	55.7	22.7
	25	70:30	104	45
	30	70:30	130	55
	35	69:31	155	69

Table 23. Continued.

ketone	°C	eq:ax	$k_{ax} \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$	$k_{eq} \times 10^4$ $\text{M}^{-1}\text{sec}^{-1}$
<u>8</u>	0	68:32	14.7	6.9
	15	66:34	31.2	16.0
	25	65:35	46.3	24.9
	30	65:35	54.9	29.5
	35	65:35	70.2	37.8
<u>9</u>	0	66:34	11.2	5.7
	15	65:35	26.3	14.1
	20	65:35	29.5	15.9
	25	65:35	43.5	23.4
	35	64:36	62.7	35.3
<u>10</u>	0	94:6	13.6	0.7
	25	92:8	51.2	4.5
	30	91:9	61.1	6.0
	35	90:10	66.6	7.4
<u>11</u>	0	62:38	4.58	2.80
	21	62:38	14.5	9.1
	35	62:38	32.1	19.7
<u>13</u>	0	67:33	2.12	1.04
	15	68:32	5.81	2.74
	25	69:31	9.8	4.4
	30	70:30	13.4	5.7
<u>17</u>	0	43:57	2.51	3.33
	15	46:54	6.6	7.8
	25	48:52	12.0	12.9
	35	50:50	19.8	19.8
<u>18</u>	0	43:57	2.05	2.71
	15	46:54	5.34	6.26
	25	48:52	10.5	11.3
	35	50:50	19.5	19.5

Table 23. Continued.

ketone	°C	eq:ax	$k_{ax} \times 10^4$ $\underline{M}^{-1} \text{sec}^{-1}$	$k_{eq} \times 10^4$ $\underline{M}^{-1} \text{sec}^{-1}$
<u>19</u>	0	39:61	1.32	2.06
	25	45:55	7.9	9.7
	30	45:55	9.5	11.7
	35	46:54	12.9	15.1
<u>21</u>	0	43:57	0.54	0.72
	15	45:55	1.61	1.97
	20	45:55	2.11	2.57
	25	46:54	2.75	3.23
	30	46:54	3.39	3.98
	35	47:53	4.62	5.22

Since 4-t-butylcyclohexanone is often used as a model for cyclohexanone and since the product ratios for 1, 2 and 4 are very similar indicating little effect on product ratio by remote alkyl groups (see references 23 and 121 for examples of effects by electronegative groups), specific rate constants were estimated for cyclohexanone using the average product ratio for ketones 1 and 2. By the same reasoning, product ratios could be estimated for 3,3-dimethylcyclohexanone using the product ratios of 18 and 19. Not enough of 2,2-dimethyl-4-t-butylcyclohexanone¹ was available for product ratio determinations. Fortunately, there were literature values at two temperatures (9,14) which allowed an estimation of the product ratios and calculation of the specific rate constants.

The correlation coefficients in Table 21 are indicative of a linear relationship (122) since all but cholestan-3-one (5) are greater than 0.95. In no case does the actual value obtained for a given temperature deviate from the computer determined value by more than 2%.

The experimental product ratios obtained require little comment. The unhindered cyclohexanones show the same ratio, predominantly equatorial alcohol. As expected, a small change toward increasing amount of axial alcohol is observed in the 2-alkylcyclohexanones.

¹This compound was a gift from Dr. J. C. Richer.

The only major disparity occurs in the menthone case. Here the product ratio tends toward increasing amount of the more stable menthol with increasing temperature. No ready explanation for this fact has presented itself. The 3,3-disubstituted ketones have very similar product ratios.

The specific activation parameters can be calculated from the specific rate constants of Table 23 and are to be found in Tables 24 and 25. A few points are evident from these data. 1) $\Delta S^\ddagger_{ax} \approx \Delta S^\ddagger_{eq} \approx \text{constant}$. 2) $\Delta H^\ddagger_{ax}$ increases with the degree of hindrance. 3) $\Delta H^\ddagger_{eq}$ increases with the degree of hindrance. 4) $\Delta H^\ddagger_{ax}$ increases more rapidly than $\Delta H^\ddagger_{eq}$. Point 1) clearly shows that the entropy of activation has little effect on the specific reactions in terms of controlling observed rate differences. Additionally, the trend in the specific entropies of activation, as for the overall entropy of activation, is in the opposite direction to the enthalpy change.

Since $\Delta H^\ddagger_{ax}$ and $\Delta H^\ddagger_{eq}$ both increase with increasing steric hindrance, it is clear that both modes of attack are becoming more difficult. The observed increase in equatorial attack comes not as a result of increasing ease of equatorial approach, since this direction of attack is becoming more difficult, but because of a more rapid increase in the difficulty of axial attack. More discussion of these parameters,

Table 24. Specific activation parameters for axial attack.

ketone	$\Delta H^\ddagger$ kcal/mole	$\Delta S^\ddagger$ (eu)	$\Delta G^\ddagger$ kcal/mole	corr. coeff.
<u>1</u>	5.4 $\pm$ 0.1	-45.5 $\pm$ 0.3	19.0	0.999
<u>2</u>	5.6 $\pm$ 0.3	-44.9 $\pm$ 0.9	19.0	0.996
<u>3</u>	6.2 $\pm$ 0.1	-43.0 $\pm$ 0.2	19.0	0.999
<u>4</u>	6.8 $\pm$ 0.4	-41.5 $\pm$ 1.3	19.2	0.994
<u>5</u>	7.2 $\pm$ 0.2	-40.6 $\pm$ 0.7	19.3	0.998
<u>6</u>	7.0 $\pm$ 0.3	-41.6 $\pm$ 0.9	19.4	0.997
<u>7</u>	7.8 $\pm$ 0.3	-41.4 $\pm$ 1.0	20.1	0.997
<u>8</u>	6.8 $\pm$ 0.1	-46.3 $\pm$ 0.5	20.6	0.999
<u>9</u>	7.8 $\pm$ 0.3	-43.4 $\pm$ 1.1	20.7	0.996
<u>10</u>	7.3 $\pm$ 0.4	-44.7 $\pm$ 1.4	20.6	0.994
<u>11</u>	8.6 $\pm$ 0.1	-42.1 $\pm$ 0.3	21.1	0.999
<u>13</u>	9.5 $\pm$ 0.3	-40.5 $\pm$ 0.9	21.6	0.999
<u>17</u>	9.4 $\pm$ 0.1	-40.3 $\pm$ 0.2	21.4	0.999
<u>18</u>	10.3 $\pm$ 0.3	-37.7 $\pm$ 0.9	21.5	0.999
<u>19</u>	10.5 $\pm$ 0.2	-37.8 $\pm$ 0.7	21.8	0.999
<u>21</u>	9.6 $\pm$ 0.3	-42.5 $\pm$ 1.0	22.3	0.997

Table 25. Specific activation parameters for equatorial attack.

ketone	$\Delta H^\ddagger$ kcal/mole	$\Delta S^\ddagger$ (eu)	$\Delta G^\ddagger$ kcal/mole	corr. coeff.
<u>1</u>	6.9 $\pm$ 0.1	-44.0 $\pm$ 0.2	20.0	0.999
<u>2</u>	6.3 $\pm$ 0.2	-46.3 $\pm$ 0.6	20.1	0.999
<u>3</u>	7.4 $\pm$ 0.1	-42.8 $\pm$ 0.5	20.2	0.999
<u>4</u>	8.0 $\pm$ 0.4	-41.0 $\pm$ 1.3	20.2	0.995
<u>5</u>	10.1 $\pm$ 0.2	-36.4 $\pm$ 0.6	20.9	0.999
<u>6</u>	8.6 $\pm$ 0.2	-40.8 $\pm$ 0.8	20.8	0.998
<u>7</u>	8.7 $\pm$ 0.3	-40.2 $\pm$ 0.9	20.7	0.998
<u>8</u>	7.5 $\pm$ 0.2	-45.2 $\pm$ 0.6	21.0	0.999
<u>9</u>	8.2 $\pm$ 0.3	-43.2 $\pm$ 1.1	21.1	0.996
<u>10</u>	10.0 $\pm$ 0.4	-40.3 $\pm$ 1.3	22.0	0.997
<u>11</u>	8.6 $\pm$ 0.1	-43.0 $\pm$ 0.2	21.4	0.999
<u>13</u>	8.7 $\pm$ 0.3	-44.6 $\pm$ 0.9	22.0	0.998
<u>17</u>	8.1 $\pm$ 0.1	-44.7 $\pm$ 0.2	21.4	0.999
<u>18</u>	8.9 $\pm$ 0.2	-42.1 $\pm$ 0.8	21.4	0.999
<u>19</u>	9.1 $\pm$ 0.1	-41.9 $\pm$ 0.4	21.6	0.999
<u>21</u>	8.9 $\pm$ 0.3	-44.8 $\pm$ 0.9	22.2	0.998

particularly in relation to the predictions of earlier theories (2,9-12) will occur later.

Having obtained the specific activation parameters, it becomes possible to tackle the question of the conformation through which 2-alkylcyclohexanones are reduced. The ketones 10 and 11 can be regarded as conformationally pure owing to the highly unlikely situation of the *t*-butyl group assuming an axial configuration and the two methyl groups of 11 becoming 1,3-diaxial to each other. Thus the specific enthalpies of activation can be assigned and compared to those of cyclohexanone as shown in Figure 23.

Figure 23. Enthalpies of activation to attack by sodium borohydride.

From equatorial attack on ketone 11, the effect of two equatorial methyl groups is $8.6 - 7.4 = 1.2$ kcal/mole. If the methyl interactions are additive, this implies an equatorial methyl group impedes attack by 0.6 kcal/mole.

From equatorial attack on ketone 10, the effect

of one equatorial and one axial methyl group is $10.0 - 7.4 = 2.6$ kcals/mole. Since the equatorial group impedes attack by 0.6 kcals/mole, an axial methyl group impedes attack by $2.6 - 0.6 = 2.0$ kcals/mole.

Likewise for axial attack on ketone 11, the effect of two equatorial methyl groups is $8.6 - 6.2 = 2.4$ kcals/mole. Thus an equatorial methyl group impedes attack by 1.2 kcals/mole. From axial attack on ketone 10, the effect of an axial methyl group is $7.3 - 6.2 - 1.2 \approx 0$ kcals/mole. Thus an axial methyl group does not appear to significantly impede axial attack, which is a reasonable conclusion.

Thus it appears that the effect of a 2-substituent depends markedly on whether the substituent is axial or equatorial. In the presence of an equatorial substituent there is an effect slowing equatorial attack by 0.6 kcals/mole but axial attack by 1.2 kcals/mole for an overall effect of -0.6 kcals/mole opposing the natural cyclohexanone preference and thus reducing it from 1.2 to 0.6 kcals/mole. In the presence of an axial substituent, however, there is a strong effect (2.0 kcals/mole) reinforcing the natural attack preference by virtue of the interaction hindering equatorial attack but leaving unchanged the energy requirement for axial attack.

Using the activation enthalpies from the confor-

mationally unambiguous systems 10 and 11, coupled with the knowledge that epimerization does not play a large role in the reduction, it becomes possible to discuss conformationally mobile systems and the question of whether a cis alcohol arises from equatorial attack on a 2-equatorial conformation or axial attack on a 2-axial conformation, or both, and the corresponding question for formation of a trans alcohol. The values of the activation enthalpies for these four possible reactions are shown in Table 26 together with the experimentally obtained values for the reduction of the three conformationally mobile ketones 7, 8 and 9.

Table 26. Enthalpies of activation for different modes of attack on conformationally mobile 2-alkylcyclohexanones.

ketone	formation of <u>cis</u> alcohol		formation of <u>trans</u> alcohol	
<u>7</u>	8.7		7.8	
<u>8</u>	7.5		6.8	
<u>9</u>	8.2		7.8	
mean	8.1		7.5	
	eq. attack on eq. conf.	ax attack on ax conf.	ax attack on eq conf.	eq attack on ax conf.
calc'd	8.0	6.2	7.4	9.4

The value for axial attack on the axial conformation has been calculated to be 6.2 kcals/mole based on the interactions in the model compounds. Unfor-

tunately, this value does not take into account the energy required in going from 7a to 7b, which has been shown to be about 1.8 kcals/mole (123). Thus

Figure 24. Ring flip in 2-methylcyclohexanone.

the calculated value for axial attack on the axial conformation becomes $6.2 + 1.8 = 8.0$ kcals/mole which is the same as that for equatorial attack on the equatorial conformation and very close to the value observed for formation of the cis alcohol.

Hence, the following conclusions can be made concerning the conformation through which conformationally mobile 2-alkylcyclohexanones are reduced.

- 1) Formation of the trans alcohol occurs highly preferentially, if not exclusively via axial attack on the conformation with the alkyl group equatorial. This follows because the experimentally observed enthalpies for formation of the trans alcohol are in close agreement with those predicted for axial attack on the equatorial conformation but are almost 4 kcals/mole different from equatorial attack on the axial conformation.
- 2) Enthalpy factors involved in

formation of the cis alcohol are such as to preclude prediction of the conformation through which this alcohol is being formed and indeed it may arise through both conformations.

Enthalpy-entropy relationship.

Linear free energy relationships (LFER) have been discussed at great length and in great detail (122,124,125). Equation 16 is the enthalpy-entropy or isokinetic relationship. Equation 18 can be simply derived using equations 16 and 17. From equation 18

$$\delta \Delta H^\ddagger = \beta \delta \Delta S^\ddagger \quad (16)$$

$$\delta \Delta G^\ddagger = \delta \Delta H^\ddagger - T \delta \Delta S^\ddagger \quad (17)$$

$$\delta \Delta G^\ddagger = (\beta - T) \delta \Delta S^\ddagger \quad (18)$$

it is seen that, at $\beta = T$, $\delta \Delta G^\ddagger = 0$ and all differences in rate constant vanish. β , the isokinetic temperature, is thus defined as the temperature at which the rate of the reaction in question becomes independent of temperature.

There is a complication and a major assumption involved in writing equations 16 and 18, namely that $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are independent of temperature. In principle, as seen from equations 19 and 20, ΔH and ΔS , for rate and equilibrium processes, are functions

$$(\partial \Delta H / \partial T) = \Delta C_p \quad (19)$$

$$(\partial \Delta S / \partial T) = \Delta C_p / T \quad (20)$$

of temperature. There is a series of approximations which can be used in this regard (equations 21-23).

$$\text{First approximation: } \Delta C_p = 0 \quad (21)$$

$$\text{Second approximation: } d\Delta C_p / dT = 0 \quad (22)$$

$$\text{Third approximation: } d^2 \Delta C_p / dT^2 = 0 \quad (23)$$

The temperature dependence of ΔH and ΔS is usually no greater than the error in measurement except for data of very high accuracy or covering a very wide temperature range (122). It is, therefore, customary to use the first approximation. This is convenient because ΔC_p is not known for many reactions, so second and succeeding approximations would usually require determination of ΔC_p .

Equation 16 may be rewritten as equation 24

$$\Delta H^\ddagger = \Delta H_0^\ddagger + \beta \Delta S^\ddagger \quad (24)$$

where $\Delta H_0^\ddagger$ is the intercept and usually has no physical meaning (124). The isokinetic relationship "can be expected to apply to a series of reactions in which ... structural change does not change the mechanism of the reaction or the nature of the transition state. The existence of the relationship is evidence favoring a constant mechanism for the related series

of reactions" (124). Consequently, a linear relationship is evidence of the same transition state or mechanism.

A number of cautions concerning interpretation and actual linearity of the relationship have been considered (122). Some of the more common and easily dealt with will be briefly discussed. Uncertainty of interpretation of the isokinetic plot is particularly great when β is near the experimental temperature or when β is extremely far from working temperatures (123). Values obtained in this study (362-520°; Tables 27 and 28) are quite a bit above working temperatures (about 300°K) but are in the range of those considered reasonable (400-500°K, 123). Therefore, complications due strictly to temperature considerations should be minimized in the present case.

A straight line relationship will be obtained even in the presence of two or more interaction mechanisms if their β values are equal. The general types of interactions considered are medium and substituent effects, with quantitatively important substituent effects being resonance, polarization or steric changes. In this study there is no change in medium, so there is no effect from this source. In addition, since the substituent changes are saturated alkyl groups, resonance and polarization effects should be minimal. Hence, if more than one interaction

is occurring, it would have to be more than one kind of steric effect. This might appear unlikely at first glance. However, if hydride attack from one side has a different steric effect than from the other side, two different steric effects could arise. It is unlikely, however, that these two effects would have the same β .

Deviations in isokinetic relationships are presumably due to perturbation by one or more additional interaction mechanisms of lesser importance (122). One might, therefore, expect more scatter in the isokinetic plot for overall reduction compared to isokinetic plots for individual modes of attack. This is borne out by the data obtained, particularly the correlation coefficients of Tables 27 and 28.

Turning to the data at hand, it is clear from Figures 25-27 that 1) all of the ketones do not fit on the same correlation line; 2) the unhindered ketones and the hindered ketones do fit on separate correlation lines; 3) isokinetic temperatures are higher for hindered ketones than for nonhindered ketones; 4) there is less scatter for the specific isokinetic plots; 5) some ketones do not fit the correlation line.

Points 1) and 2) are of great importance and allow some crucial conclusions. By the very nature of the isokinetic relationship, the failure of all

Figure 25. Overall enthalpy-entropy relationship.

Figure 26. Specific enthalpy-entropy relationship-axial attack.

Figure 27. Specific enthalpy-entropy relationship-equatorial attack.

Table 27. Overall Enthalpy-entropy relationship.

ketones	β	corr. coeff.
unhindered	362 $\pm$ 24	0.987
all others except <u>7, 16, 20, 21</u>	440 $\pm$ 29	0.981

Table 28. Specific enthalpy-entropy relationships.

ketones	attack	β	corr. coeff.
unhindered	axial	376 $\pm$ 20	0.992
unhindered	equatorial	397 $\pm$ 24	0.989
hindered except <u>7, 16, 21</u>	axial	440 $\pm$ 17	0.994
hindered except <u>7, 13, 16, 21</u>	equatorial	466 $\pm$ 43	0.972

ketones to fall on the line indicates a change in mechanism or transition state for the ketones not on the correlation lines. On the other hand, the observed correlation for unhindered ketones and the different correlation for the hindered ketones indicates no change in mechanism or transition state among the various kinds of ketones. As mentioned in point 4 above, the scatter observed for the overall relationship is expected to be more than for the specific relationships. The difference is, however, not too great. Point 5 is not really surprising; however, it may be quite significant. In a study comprising a

large number of ketones, it is reasonable to expect some deviation. Interestingly, the deviations do appear to be rather regular. In particular, only four ketones, lanost-8-en-3-one (16), cholestan-2-one (21), 3,3,5,5-tetramethylcyclohexanone (20) and 2-methylcyclohexanone (7), fall off the correlation line for the hindered ketones, while none of the unhindered ketones deviate markedly from their correlation line. Ketone 20 is surely very different from the other ketones used in this study. Attention has been drawn to the conformation of this molecule, in particular pointing out the strain involved in the 3,5-diaxial methyls and the change in the angles $C_6-C_1-C_2$ and $C_3-C_4-C_5$ (126). Aside from these differences, this ketone is reduced much more slowly than any other ketone in this study and is very much more hindered than even the 3,3-dimethylcyclohexanones. Consequently, it is not surprising that this ketone behaves quite differently from the other ketones.

Of the other deviant ketones, two are steroids. It would be hoped that the same mechanism would hold for tetracyclic ketones as for monocyclic ones, and the deviations may be experimental error. It is quite interesting in this connection that the other two steroids utilized in this study, while behaving well, are both slightly off the line- to the upper right. It may not be mere coincidence that all four steroidal ketones deviate from their correlation lines in

the same direction. There may be some other perturbation which could cause this behaviour. A possibility could be some type of hydrophobic bonding in these cases which, at the concentrations employed, could cause association of the steroids and exclusion of some of the solvent molecules leading to possible large changes in the entropy of activation. Another explanation depends on the fact that steroids are more rigid than the cyclohexanones and are not flexible enough to accomodate lessening of interactions. These interactions, therefore, will be more serious in the steroids and may cause the observed deviations.

The case of 2-methylcyclohexanone deserves some comment. This ketone falls between the two correlation lines in all three cases, approximately equidistantly in the overall isokinetic relationship and the relationship for axial attack but almost on the line for equatorial attack. It is felt that this ketone could represent the limiting case between hindered and unhindered ketones and hence does not follow either relationship but rather falls in between. One way to test this hypothesis would be by the synthesis of 2-methyl-3- and 4-alkylcyclohexanones. In the absence of other complications, one would expect these ketones to form a correlation line with 2-methylcyclohexanone, if this is the limiting case. However, this is a large undertaking and has not been done in this work.

Points 2) and 3) above are the really interesting ones and make this study worthwhile. They do not, however, make things clear in themselves. There seems to be the indication that the transition state is changing over the series of ketones, but in two discrete steps- one for unhindered and one for hindered ketones. There is also a consistent change toward a higher isokinetic temperature in going from axial to equatorial attack. What does this mean, however? Does a larger β correlate with a later transition state or an earlier one? Are the values in fact significantly different to allow a significantly different transition state? Both are important questions. The second will be dealt with first.

According to Leffler and Grunwald (122) pairs of parallel isokinetic lines are not uncommon and might, for example, result from the effect of steric hindrance on the conformational composition of the reagents or transition state. A certain critical amount of hindrance could cause a new conformation to be favoured, yet the discrete change in conformation need not affect the continuous mechanism. Considering the errors involved in the various specific isokinetic plots, the two pairs might be considered parallel. The overall lines are quite different in slope. There is convincing evidence that axial attack on the 2-alkylcyclohexanones occurs through the confor-

mation with the alkyl group equatorial. It also appears certain that the unhindered ketones reduce predominantly through the same conformation. There is therefore no large change in conformation, no ring flip. There is the possibility, however, that formation of cis-2-alkylcyclohexanols occurs through both conformations. There could be small changes in the hindered ketones because of increasing steric hindrance. However, the best values for the isokinetic plots have a 50° spread, which indicates that they are not too close to being parallel.

Does a large β correlate with a later transition state or an earlier transition state? This is a crucial question, the answer to which would go a long way toward pinning down the transition state structures in the reactions involved, and it will be dealt with in more detail later.

Bronsted-type relationship.

A Bronsted plot is essentially a plot of $\Delta G^\ddagger$ vs. ΔG_0 (127), and the normal interpretation of the slope, which is generally between 0 and +1, is the degree of resemblance of the transition state to products (122). The larger the slope the more the transition state is thought to resemble products. Generally, ΔG is used in preference to ΔH for these plots.

The reason for this seems to simplify to the fact that equilibrium data (ΔG) are more readily available than activation data ($\Delta H^\ddagger$) (127). However, particularly for acid-base reactions, there is compelling evidence that use of ΔG will give a more meaningful relationship. This stems from the fact that acid-base reactions are highly solvent dependent and to interpret the results on a molecular level one would prefer using the least solvent dependent parameter. Bell has shown that this is probably ΔG (127) and that for the acidity of carboxylic acids, ΔH is erratic (127). This has recently been reiterated by Calder and Barton (128) who have pointed out that the acidity of a large number of carboxylic acids is entropy controlled.

There is some question, however, whether ΔG or ΔH should be used in rate correlations. Taft (129) found no firm conclusion as to which should be favoured. More recently a number of workers have commented on this situation (130-132) and it appears that relationships of the type

$$d\Delta H^\ddagger = \alpha d\Delta H_o \quad (25)$$

are valid provided certain restrictions are put on entropy changes in a given series (130). Arnett and coworkers (132) even stated that one might expect to find linear enthalpy relationships under many (but

not all) of the same circumstances where LFER exist.

In the case of the current study, the reaction is dependent on steric factors and both rates and product ratios are enthalpy controlled so entropy changes are less important. Furthermore, only activation parameters are available. This fact makes it impossible to use ΔG vs. $\Delta G^\ddagger$ plots.

The importance of the use of the Bronsted relationship has been mentioned earlier. This would appear to be the only method of determining if the transition state is early or late and permit more meaningful interpretation of the isotope effect and isokinetic data.

To use a relationship of the type in equation 25 it was necessary to obtain ΔH_0 values since $\Delta H^\ddagger$ values were already available (Table 17). This work was carried out at Sherbrooke University by Professor J. E. Desnoyers. Unfortunately, although the reductions are very exothermic, they are also relatively slow. For this reason, only the most rapidly reduced ketones could be studied. This is unfortunate because it does not allow extension to the hindered ketones. The available data are listed in Table 29 and plotted in Figure 28. Two points are immediately obvious. 1) The enthalpies of reaction do not follow a well-behaved trend. 2) Regardless of point 1), the slope is very close to zero. The actual calculated slope

Table 29. Enthalpies of activation and reaction for unhindered cyclohexanones.

ketone	$\Delta H^\ddagger$ kcal/mole	ΔH_0 kcal/mole
<u>1</u>	5.6	-59.6
<u>2</u>	5.7	-64.8
<u>3</u>	6.4	-53.0
<u>4</u>	7.0	-66.7

is -0.02 ± 0.05 and, although the correlation coefficient is very small, even considering the large error the value must be very close to zero. This is interpreted as being good evidence of a very early transition state for the reduction of unhindered ketones.

Interpretation of isotope effects and isokinetic plots in light of the Bronsted slope.

With the knowledge from the Bronsted slope that the transition state in the reduction of unhindered ketones occurs extremely early, a major ambiguity in the interpretation of the isotope effects disappears. The trend of the isotope effects is to larger values with increasing steric hindrance; and, regardless of whether this eventually decreases again, this must correspond to a later transition state for more hindered ketones. The alternative interpretation of the transition state being late for hindered

Figure 28. Bronsted-like relationship for unhindered cyclohexanones.

ketones and gradually becoming earlier with increasing steric hindrance is rendered untenable by the Bronsted slope for unhindered ketones.

This conclusion would also appear to yield an answer to the question previously raised concerning whether a higher isokinetic temperature corresponded to an earlier or later transition state. The hindered ketones have a higher value of β , and thus, in this reaction, higher β appears to correlate with a later transition state.

Despite these two major conclusions being possible, the question of how much later is the transition state for hindered ketones remains unanswered, the present data permitting not even a gross estimate to be made.

Consistency of experimental data with hypotheses.

The Dauben postulate (2) implies a change in transition state from early to late over a spectrum of ketones such as the one employed in this study. If this postulate is valid, therefore, one should observe changes in enthalpy of activation for the two modes of attack and at least two distinct isokinetic relationships (or no correlation if a number of different transition states are involved). Both of these points have been confirmed in this study. However,

one must still determine the position of the transition state on the reaction coordinate to validate this hypothesis, which predicts an early transition state (steric approach control) for hindered ketones and a late transition state (product development control) for unhindered ketones. Clearly, the experimental results do not back up this aspect of the Dauben explanation, but rather they seem to show the opposite. The Bronsted relationship indicates a very early transition state for unhindered ketones and the isokinetic relationships and LATBH/LATBD isotope effects point to a later transition state with increasing hindrance. Thus, Dauben *et. al.* (2) seem to have been correct when predicting a change in transition state but incorrect in the direction of the change.

Richer's explanation (9) can also be discussed in terms of the activation and isokinetic data. In this case the hindered ketones are not discussed because Richer spoke only of 3,5-axial hydrogens *vs.* 2,6-axial hydrogens in the steric control of the reduction. According to Richer one might expect all of the unhindered and 2-alkylcyclohexanones to have very similar activation parameters because all have the same basic interactions with the various axial hydrogens. At least, if the Richer explanation holds, one would expect them all to lie on the same correlation line in the isokinetic relationships. The fact

that the activation parameters change very considerably from 4-methylcyclohexanone through menthone and that the 2-alkylcyclohexanones do not adhere to the same correlation line as the unhindered ketones indicates that other factors than just those discussed by Richer must be operating.

The explanation of Felkin et. al. (11,12) is quite similar to that of Richer, accounting torsional strain responsible for the main interaction for unhindered ketones in a reactant-like transition state. It appears that the torsional strain (refer to Figure 4) should be expected to be rather constant for all of the ketones considered since they all (except 10 and 12) have 2,6-diaxial hydrogens. The fact that $\Delta H_{eq}^\ddagger$ changes quite dramatically and that two different correlation lines are present seems to indicate that the Felkin model also suffers from oversimplification. More factors than simple torsional strain vs. steric strain seem required.

Marshall and Carroll (10) also dealt only with unhindered ketones and a reactant-like transition state, but the results of this study might fit their hypothesis. Since it is the distance of approach of the hydride which is important for this hypothesis, it may be that this distance is being increased for 2-alkylcyclohexanones until it is similar to that for hindered ketones, and hence these two types of compounds follow the same enthalpy-entropy correl-

ation. However, this implies that either the 2-alkylcyclohexanones do not fit the theory of Marshall and Carroll or that the transition state for hindered ketones is an early one, since this theory holds only for an early transition state.

Eliel and Senda (14), on the basis of competitive rates, explained the complex hydride reductions of cyclohexanones in terms of approach control, that is steric strain involving the incoming nucleophile in the transition state, finding that only a minor role at most was played by product development control, which they defined as differences in strain between the oxygen or complexed oxygen in the transition state and ground state. From the present work it appears that there is some of what Eliel (and Dauben) would call product development control, namely the increase in $\Delta H^\ddagger_{eq}$ (Figure 29) operating for hindered ketones and therefore a later transition state. The fact that $\Delta H^\ddagger_{eq}$ increases might be interpreted to mean that the transition state is becoming later over the series studied, due to interactions of the type in Figure 29.

Lamaty and coworkers (28-30) have argued for a late transition state for sodium borohydride reductions, mostly on the basis of a study of adamantanone. By comparing the rates of attack by borohydride and the sulfite anion on adamantanone and 4-*t*-butylcyclohexanone (2), they found that $k_{\text{adamantanone}} \approx 2 k_{\text{ax}}$ for

Figure 29. Major steric interactions in a late transition state for the reduction of hindered ketones.

sulfite attack and $k_{\text{adamantanone}} \approx 2k_{\text{eq}}$ for borohydride attack. They interpreted this in terms of a reactant-like transition state for sulfite addition and a product-like transition state for borohydride reduction. There is, however, an alternate explanation of these data. Attack from either side of the carbonyl group in adamantanone, as pointed out by Lamaty, is equivalent, being equatorial to one ring and axial to another. Attack at this centre on either side, therefore, is equivalent to attack at the least favoured side of 2, regardless of whether this happens to be axial or equatorial. Since there are two equivalent sides to attack, one would predict that $k_{\text{adamantanone}} \approx 2k_u$, where k_u is the rate constant for attack at the least favoured side of 2 by the appropriate nucleophile. This is the observed result and thus it appears that the evidence of Lamaty *et. al.* does not constitute unambiguous evidence for a late transition state in the borohydride reduction

of ketones.

It appears, therefore, that the activation and isokinetic data of this study do not fit any of the published theories, although they all have elements of agreement. The simplest interpretation of the gathered data is to reverse the Dauben explanation and cite an early transition state for unhindered and a later transition state for hindered and 2-alkylcyclohexanones. The lateness of this transition state can not really be stated, since more evidence of the LATBH/LATBD isotopes is required. It seems quite clear, however, that there is a change in transition state toward a later one with increasing hindrance in the ketone.

Conclusions and further discussion.

1) The transition state for the sodium borohydride reduction, at least of unhindered ketones, is basically early. This is shown directly by the Bronsted value of -0.02. Furthermore, the $\text{NaBH}_4/\text{NaBD}_4$ and LATBH/LATBD isotope effects are consistent with an early transition state, although they do not offer proof of one. There is no direct evidence on this question from the isokinetic relationships.

2) The transition states for reduction of un-

hindered ketones and for 2-alkyl- and hindered ketones are different. This is shown unequivocally by the isokinetic data. The LATBH/LATBD isotope effects could be indicative of this. There is no relevant data on this question from the Bronsted relationship.

3) The transition state ranges from very early to not so early. It seems clear from the LATBH/LATBD isotope effects that the transition state is becoming somewhat later with increasing hindrance. It is clear from the isokinetic data that two different transition states are involved for the two sets of ketones. This indicates that one is later than the other and that the hindered ketones have the later transition state. The range of the transition state over the reaction coordinate remains uncertain. From the LATBH/LATBD isotope effect of 3,3,5,5-tetramethylcyclohexanone (20) and the data of Melander (97), it might be concluded that very hindered ketones have very late transition states. This conclusion is tenuous since it is based on only one ketone.

4) The transition states are all at an extremum or are 4-centre or both. This follows from the magnitudes of the isotope effects which are considerably smaller than the predicted maximum.

5) A later transition state corresponds to a higher isokinetic temperature.

6) The order of the lateness of the transition

states as judged from the isokinetic temperatures is hindered, equatorial attack > hindered, axial attack > unhindered, equatorial attack > unhindered, axial attack.

7) No real conclusion can be made on the geometry of the transition state. If the tenuous conclusion of a very late transition state for highly hindered ketones is correct, the transition state must be 4-centre.

Experimental.

General: Melting points were taken on a Fischer-Johns melting point apparatus and are uncorrected. The infra red spectra were measured on a Perkin-Elmer 237B Grating Infrared Spectrophotometer and ultraviolet spectra were recorded on a Perkin-Elmer 202 Ultraviolet-Visible Spectrophotometer. The nuclear magnetic resonance spectra were obtained on a Varian T60 NMR Spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal standard. A Hewlett-Packard F and M Scientific 402 High Efficiency Gas Chromatograph was used for initial glc studies and for checking reaction mixtures prior to workup. A Perkin-Elmer 990 Gas Chromatograph equipped with an Infotronics CRS-208 integrator was used for product ratio determinations. Slopes of the various linear relationships were obtained via a least-squares programme on an Olivetti-Underwood Programma 101 Desk Computer¹ or a Xerox Sigma 7 computer². Mass spectra were done on a Varian anaspect EM600 Mass Spectrometer. The mass spectra for the competition isotope effects were done on the steroid at Ottawa University and on the cyclo-

¹Courtesy of Dr. M. Parris.

²Courtesy of Dr. P. M. Laughton and Mr. J. Bayne.

hexanols at Trent University. Elemental analyses were performed by the Spang Microanalytical Laboratories, Ann Arbor, Michigan.

Reagents: Sodium borohydride (Fisher Scientific or British Drug House) sodium borodeuteride (Merck, Sharpe and Dohme) and lithium aluminum tritertiary-butoxyhydride (Aldrich Chemical Co.) were used without further purification, care being taken to keep them dry. Propan-2-ol (Fisher, spectral grade) was passed through a neutral alumina column, dried over anhydrous calcium sulfate and distilled prior to use. Standard sodium borohydride solutions were made up as follows. About 0.3 g of NaBH_4 was added to 100 ml of propan-2-ol. This was stirred overnight, filtered and standardized: (66) to 25.0 ml of standard 0.1 N KIO_3 (133) was added 2.0 ml of the NaBH_4 solution. This was swirled and allowed to stand 5 minutes to allow complete reaction; 5 ml of 0.1 N HCl was added and the deep red solution titrated with previously standardized 0.1 N $\text{Na}_2\text{S}_2\text{O}_3$ (133). The stock NaBH_4 solution was diluted (10 ml to 15 ml) with propan-2-ol and the resultant solution used in kinetic studies. Cyclohexanone, 3-methylcyclohexanone, 2-methylcyclohexanone, 2-ethylcyclohexanone, 2,6-dimethylcyclohexanone and 3,3,5,5-tetramethylcyclohexanone were commercial compounds which were distilled and shown to be greater than 99% pure by glc before use. Cholestan-

3-one was used without purification. Androstan-3-one and androstan-11-one were gifts from Dr. J. W. ApSimon. 2,2-Dimethyl-4-t-butylcyclohexanone was a gift from Dr. J. C. Richer and 4-acetyl-3,3,5,5-tetramethylcyclohexanone was provided by Dr. P. Teisseire.

Kinetic method, spectrophotometric: For kinetic determinations above 15°, a Haake constant temperature pump was used to maintain the temperature required ($\pm 0.05^\circ$) for a Gilford 240 Spectrophotometer employed to measure the ultraviolet kinetics. At 15° or below, a RTE-3 cooling circulator, Neslab Instruments, Inc., was used to maintain the correct temperature and the spectrophotometer and circulator were both placed in a cold room at 10°. The wavelength was the appropriate absorption maximum for each ketone (Table 10). The reference cell contained 2.0 ml of propan-2-ol and 1.0 ml of standardized NaBH_4 solution in a 1.0 cm pathlength cuvette. The sample cell was prepared by adding the ketone in propan-2-ol solution (2 ml) to 1.0 ml of standardized NaBH_4 solution. The cuvette was quickly inverted three times to insure mixing and placed in the machine for the first reading. Zero time was taken as the half-time of addition. The first reading was generally taken at 35-60 seconds. For the more slowly reduced ketones this first reading was used to calculate the concentration of ketone at time zero while for ketones reduced more rapidly than 2-

methylcyclohexanone, the molarity of the prepared ketone solution was used as the initial concentration. The molar extinction coefficient was used to calculate ketone concentration from absorbances at appropriate time intervals. The data were treated by plotting $\log_{10} 4b(a-x)/a(4b-x)$ against t where a is the initial ketone concentration, b , the initial borohydride concentration and x , concentration of alcohol at time t . The slope, equal to $k(a-4b)/2.303$ where k is the second order rate constant, was computed by least squares analysis. Examples of experimental data can be found in Appendix II while the derivation of the rate expression is found in Appendix III.

Kinetic method, gas chromatographic: 2,6-Dimethylcyclohexanone (150 mg) was weighed into a 5 ml volumetric flask. Standardized hydride solution was added to the mark by pasteur pipette, half addition being taken as zero time. The flask was inverted thirteen times to ensure mixing. Aliquots of the reaction mixture were added to acid for quenching: 6 drops of reaction mixture to two drops of 0.1 N HCl. 0.2 μ l of the quenched aliquot was then injected into the gas chromatograph. This proved a convenient amount to make the largest peak cause full-scale pen deflection and to be able to see the smallest peaks.

Standardization of LATBH: The method of Felkin (94) was used. A typical procedure follows. Iodine (1.7307 g) was weighed into a 50 ml volumetric flask and spectral grade benzene was added to the mark. The solution was 0.1364 M, by calculation. Five ml of I_2 solution was pipetted into an iodine flask to which was added 3 drops of glacial acetic acid. Then this was titrated with standardized aq. $Na_2S_2O_3$ (133). The titration value was 0.1355 M. Generally, the agreement between the two methods was within 2%. LATBH (1.18 g) was weighed into a 250 ml round bottom flask to which about 200 ml of dry (2 hrs reflux over and distillation from $LiAlH_4$) THF was added. This was stirred three hours at room temperature. Five ml of standardized I_2 solution was pipetted into a clean, dry iodine flask. Then 5 ml of LATBH solution was added, the mixture swirled and allowed to stand a few minutes to ensure complete reaction. Then 3 drops of glacial acetic acid were added and titration with aq. $Na_2S_2O_3$ was carried out to the colourless endpoint. The following stoichiometry has been reported for the standardization of $LiAlH_4$:

Therefore, 2 moles of I_2 are required per mole of $LiAlH_4$. Analogously for LATBH,

Only 1/2 mole of iodine is required per mole of LATBH. This is expected since only 1/4 the number of active hydride is present on LATBH compared to LiAlH_4 .

Competition kinetic isotope effects: The ketone (10-30 mg) is weighed into a one dram vial and dissolved in 1. ml of THF. The calculated amounts (two-fold excess) of standardized LATBH and LATBD were added to an erlenmeyer flask (50 or 125 ml, depending on the volumes required) and the flask was swirled well. The ketone was then added by pasteur pipette, mixed well and allowed to stand at r. t. until reaction was complete (17-24 hrs). Then 1 N HCl (1 ml) was added and the THF removed via rotary evaporator, the bath temperature about 25-35°. The residue was worked up by ether-water extraction, dried, the solvent removed and sealed in glass vials for mass spectral analysis.

Product ratio determinations: The following procedure is typical. To a solution of sodium borohydride (0.47 g; 12.4 mmol) in propan-2-ol (50 ml) was added the ketone solution (12.4 mmol) in propan-2-ol (10 ml). The mixture was stirred overnight at the appropriate temperature. Concentrated hydrochloric acid (5 ml) was added to destroy excess borohydride and hydrolyze the borate esters, propan-2-ol was removed via rotary evaporation, and the alcohol products extracted into

ether (2 x 10 ml). The combined ether extracts were dried (Na_2SO_4) and injected into glc. For analysis of cyclohexanols a 50 ft., 0.02 inch internal diameter support-coated open tubular TCEP column was used. Carrier gas flow was 3.6 to 4.1 ml/min, calibrated depending on column oven temperature; injector port 240° , manifold 240° . For analysis of steroids a 12 ft., 0.5 inch internal diameter, 2.5 % XE-60 on 100-120 mesh Gas Chrom Q column was used. Injector port temperature was 265° , manifold 260° . Further data on column oven temperature and retention times of the alcohols are given in Table 30.

4-t-Butylcyclohexanone (2) was obtained from a commercial mixture of the cis and trans alcohols via Jones oxidation (108) in 90% yield: b. p. $80-83^\circ/0.25$ mm. (lit. (134) $84-85^\circ/7$ mm.); m. p. $45-7^\circ$ (lit. (134) $49-50^\circ$).

2-n-Butylcyclohexanone (9) was made from an impure commercial mixture of the alcohols via Brown oxidation (110) in 89% yield (92% pure by glc). Column chromatography (silica gel; pet ether then benzene) afforded pure material; b. p. $105-6^\circ/15$ mm (lit. (135) $93.5-4^\circ/11$ mm); n_D^{20} 1.4528 (lit. (135) 1.4548).

Menthone (13) was made by Brown oxidation (110) of menthol in 69% yield; b. p. $101^\circ/12$ mm (lit. (110) $66-7^\circ/4$ mm); n_D^{20} 1.4497 (lit. (110) 1.4500).

Table 30. Glc data for the separation of alcohols.

ketone	col. oven °C	retention time (min)	
		axial alc.	equatorial alc.
<u>1</u> ^a	114	8.8	10.2
<u>2</u> ^a	130	15.6	20.8
<u>4</u> ^a	118	7.8	9.0
<u>5</u> ^b	249	13.3	14.4
<u>6</u> ^b	210	8.3	9.0
<u>7</u> ^a	84	19.8	21.9
<u>8</u> ^a	114	10.8	12.7
<u>9</u> ^a	120	19.4	21.9
<u>11</u> ^a	108	7.6	8.8
<u>12</u> ^a	108		11.8
<u>13</u> ^a	116	13.8	18.1
<u>14</u> ^a	118	13.2	15.7
<u>15</u> ^a	125	11.6	16.2
<u>16</u> ^b	250	----	21.6
<u>18</u> ^a	118	8.1	10.6
<u>19</u> ^b	115	11.5	14.4
<u>21</u> ^b	253	12.4	14.0

^aTCEP^bXE-60

2-t-Butylcyclohexanone (14) was synthesized from commercial verdol by the Brown oxidation (110) in 87 % yield; b. p. 136-8°/20 mm (lit (136) 80-2°/13 mm); n_D^{20} 1.4565 (lit (136) 1.4561).

3,3-Dimethyl-6-isopropylcyclohexanone (15): To a stirred suspension of copper(I) iodide (20.1 g; 0.106 mole) in anhydrous ether (450 ml) under nitrogen and in an ice bath was added a 1.75 M solution of methyl lithium (88 ml; 0.154 mole) in ether. The suspension was stirred at 0° until a tan colour appeared (5 min.). Piperitone (5.04 g; 0.033 mole) in anhydrous ether (125 ml) was added dropwise over 25 min. The reaction mixture was allowed to stir at 0° for two hours and then poured with stirring into 1 N HCl (1 litre). The mixture was filtered by suction to remove the inorganic precipitate and the aqueous filtrate extracted with ether (10 x 100 ml). The combined extracts were dried (brine; Na_2SO_4) and ether removed by rotary evaporation to give a yellow liquid (5.22 g; 94%). Glc analysis showed the absence of starting ketone but the presence of a major impurity (37%). Column chromatography (silica gel, pet ether) gave 3.0 g of material (90% pure) which was rechromatographed (silica gel, pet ether; pet ether:benzene (1:1)) to afford ketone in a purity of greater than 99%; δ 0.90 (6H,d, J=6Hz), 0.90 (3H,s), 1.02 (3H,s), 1.17 (1H,m), 1.60 (2H,m),

1.80 (2H,m), 2.02 (2H,s); $\nu_{\max}$ 1710 cm^{-1} (carbonyl);
 M/e 168, 153, 126, 111, 98, 83. Anal. Calc. for
 $\text{C}_{11}\text{H}_{20}\text{O}$: C, 78.55; H, 11.86. Found: C, 78.51; H, 11.98.
 Simultaneous injection with a sample kindly supplied
 by Professor G. Stork showed identity of the retention
 times of the two samples.

Lanost-8-en-3-one (16): To a solution of lanost-8-en-3- β -ol (1.04 g; 2.3 mmol) in benzene (50 ml) were added a solution of dicyclohexylcarbodiimide (1.50 g; 7.3 mmol) in dimethyl sulfoxide (10 ml) and pyridinium trifluoroacetate (225 mg; 1.1 mmol). The reaction mixture was maintained at 35° for 50 hrs. Ether (75 ml) was added, followed by solid oxalic acid (1.0 g; 11.1 mmol), and the mixture was stirred overnight, filtered, washed with water (3 x 20 ml), dried (Na_2SO_4) and evaporated. The oxalic acid removes the dicyclohexylcarbodiimide most effectively when in methanol solution. However, if methanol is added first, difficulty is experienced removing dimethyl sulfoxide. Thus the first work-up removes all dimethyl sulfoxide and most dicyclohexylcarbodiimide; the second work-up removes the remaining dicyclohexylcarbodiimide. The residue was taken up in methanol (500 ml) and again stirred with oxalic acid (1 g) overnight. The mixture was evaporated, dissolved in ether (75 ml), washed with water (3 x 10 ml), dried (Na_2SO_4) and evaporated to yield 16 (0.94 g; 94%). Glc analysis of the product

indicated the only impurity to be starting alcohol (4%). Final purification was achieved by chromatography on alumina (Woelm neutral, Activity III), the product being eluted with 10% ether in benzene, and recrystallization from ether-ethanol, giving plates with m. p. 118-9°, $\nu_{\max}(\text{CHCl}_3)$ 1700 cm^{-1} , $\lambda_{\max}$ 295 nm (ϵ , 24) (lit (137) m. p. 119.5-120.5°).

3,3-Dimethylcyclohexanone (17) was obtained from the corresponding alcohol in 50% yield by dichromate oxidation; b. p. 76.0-77°/30mm (lit (138) 62-3°/11 mm).

3,3,5-Trimethylcyclohexanone (18) was synthesized by dichromate oxidation of 3,3,5-trimethylcyclohexanol following the method of Eliel and Haubenstock (139) in 93% yield; b. p. 100-110°/10 mm (lit (139) 73-4°/14 mm); n_D^{20} 1.4522 (lit (139) 1.4461).

5-n-Butyl-3,3-dimethylcyclohexanone (19): To freshly recrystallized tetrakis [iodo-(tri-n-butylphosphine) copper(I)] (12.77 g; 32.5 mmol) prepared by the method of Kauffman and Teter (140) in anhydrous ether (150 ml) under a dry nitrogen atmosphere and in an acetone-ice bath was added n-butyllithium in n-hexane (Ventron, Inc., 2.4 M; 27 ml; 64.8 mmol). After ten minutes of stirring, one half equivalent of 5,5-dimethylcyclohex-2-en-1-one (2.04 g; 16.1 mmol) was added dropwise over 25 minutes. The reaction mixture was stirred two hours at 0° and allowed to warm slowly

to room temperature and stand overnight. The reaction mixture was poured into 200 ml of saturated aq. NH_4Cl , stirred 0.5 hr. and filtered by suction to remove the gelatinous precipitate. After ether extraction (3 x 50 ml), drying of the ether (brine; Na_2SO_4) and removal of ether via rotary evaporation, 10.8 g (405%) of a new crude compound was formed. Glc analysis indicated 99% of a new compound. The IR showed a sharp peak at 1710 cm^{-1} . The material was clearly impure, but the impurity did not appear on glc, and the UV was considerably more intense than expected. Following a suggestion by Hooz and Layton (141), a crude column was done (silica gel, pet ether then benzene), and the carbonyl containing fractions were distilled. Because the material was still impure by UV, the tosylhydrazone derivative was made by the method of Nagata and coworkers (142). The tosylhydrazone was rinsed with absolute ethanol to remove impurities and the ketone regenerated (142), since the tosylhydrazone did not recrystallize. A column (100 g silica gel) was done on the remaining material (3 g) eluting with 1 l. of pet ether, 1 l. of pet ether:benzene (9:1), 1 l. of pet ether:benzene (8:2), 1 l. of pet ether:benzene (7:3), 2.5 l. of pet ether:benzene (1:1) and 3 l. of pet ether:benzene (1:3). 99.3 % pure material, 317 mg, was found in the 75% benzene fractions; λ_{max} 285 nm, ϵ , 25.0; ν_{max} 1750 cm^{-1} .

Calc. for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.04; H, 12.24.

Cholestan-2-one (21): Freshly distilled $BF_3 \cdot Et_2O$ (5 g; 35.2 mmoles) was added to a solution of cholest-2-ene (1 g) in dry ether (40 ml). A solution of $LiAlH_4$ (0.6 g; 15.8 mmol) in Et_2O (30 ml) was added dropwise during 1 hr. under nitrogen with stirring at 0° . The ice bath was removed and the mixture stirred for 1 hr. Water was carefully added and the ether layer extracted with 5 % $NaHCO_3$ solution and dried (brine; Na_2SO_4). The unpurified alcohols (3.85 g) were dissolved in 300 ml of acetone and stirred magnetically. Jones reagent (108) was added dropwise until a persistent orange colour remained. This was stirred overnight, worked up in the usual manner (108) and yielded 3.56 g (92%) of ketone. The ketonic mixture was doubly chromatographed (Fisher Activity I Neutral Alumina, pet ether; pet ether:benzene (1:1)) and recrystallized from pet ether. It was finally purified by preparative layer chromatography (silica gel, benzene) to yield pure material¹: m. p. $128-9^\circ$ (lit (98) $126-7^\circ$).

Centrobor (28): To stirring, hot (140°) isopropylcyclohexane (25 ml) were added dropwise over a three

¹The synthesis was performed by Mr. Fred Gowland and the purification by Dr. D. C. Wigfield.

hour period trans,trans,trans-cyclodeca-1,5,9-triene (10.13 g; 0.062 mole) and triethylamine borane (7.17 g; 0.062 mole) in isopropylcyclohexane (40 ml). The reaction mixture was stirred for two hours. The solvent and triethylamine were distilled off in vacuo. The clear liquid (b. p. 82°/0.25 mm; 5.8 g; 53%) showed no olefinic protons in nmr and had an identical IR to that published (85).

Centrobor hydride (29): To centrobor (0.43 g; 2.4 mmol) in dry THF (60 ml) was added a slight excess of LiH. The reaction was refluxed under nitrogen for five hours and allowed to cool to room temperature before being filtered in a nitrogen atmosphere. Tests for active hydride were negative.

Cholestan-3 β -ol, tosylate (32): To cholestan-3 β -ol (16.0 g; 0.041 mole) in dry pyridine (90 ml; freshly distilled from BaO) was added freshly recrystallized tosyl chloride (16 g; 0.084 mole). The mixture stood at room temperature for 18 hrs. and was then poured with stirring into ice water (500 ml). After the ice had melted, the precipitate was collected by suction filtration and dried to give the desired product (22.8 g; 100 %); m. p. 136-7° (lit (143) 135-6°).

Cholest-2-en (33): To cholestan-3 β -ol, tosylate (7.0 g; 12.8 mmol) in dry benzene (40 ml) was added alumina (Fisher Scientific Activity I, 60 g) and the

mixture allowed to stand for one day. The alumina was then poured onto a column of alumina (150 g) and eluted with pet ether:benzene (90:10) until no more solid came off. This gave a white solid in 71 % yield (3.4 g); m. p. 68-70° (lit (98) 72-3°).

2-Hydroxymethylene-3,3,5,5-tetramethylcyclohexanone

(46): To a magnetically stirred suspension of sodium methoxide (4.07 g; 0.075 mole) in distilled benzene (75 ml) under nitrogen and in an ice bath were added 3,3,5,5-tetramethylcyclohexanone (10.02 g; 0.065 mole) and ethyl formate (8.7 ml; 0.130 mole). This was allowed to warm to room temperature and stirred for 65 hrs. The reaction mixture was poured into ice-water (500 ml), the benzene layer was washed with 4 % NaOH (5 x 25 ml) and the combined aqueous layers washed once with ether (50 ml). The aqueous layer was acidified with 1 N HCl and extracted with ether (5 x 50 ml). The ether was dried (brine, Na₂SO₄) and removed by rotary evaporation to yield the desired product (7.0 g; 58 %); b. p. 134-6°/4.5 mm (lit (103) 104-9°/11 mm).

2-n-Butylthiomethylene-3,3,5,5-tetramethylcyclohex-

anone (47): A solution of the hydroxymethylene ketone (46) (4.32 g; 0.024 mole), n-butylmercaptan (2.80 g; 0.031 mole) and p-toluenesulfonic acid (35 mg) in distilled benzene (100 ml) was refluxed under nitro-

gen employing Dean-Stark conditions until no starting material was indicated by tlc (36 hrs.). The benzene and *n*-butylmercaptan were removed in vacuo, temperature of the distillate not exceeding 25°. Column chromatography (silica gel, 25 g; benzene:pet ether (1:1)) gave the pure product in 32 % yield (1.9 g); δ 1.1 (9H,s), 1.4 (6H,s), 1.5 (2H,m), 1.7 (4H,m), 2.3 (2H,m), 2.8 (2H,m), 7.0 (0.7H,s), 7.8 (0.3H,s).
 Calc. for $C_{15}H_{26}OS$: C, 70.81; H, 10.30; S, 12.60.
 Found: C, 70.80; H, 10.15; S, 12.61.

3-i-Butoxy-5,5-dimethylcyclohex-2-en-1-one (54): Dimedone (21 g; 0.15 mole), distilled benzene (120 ml), isobutyl alcohol (30 ml) and *p*-toluenesulfonic acid (0.5 g) were refluxed under Dean-Stark conditions for 20 hrs. After cooling to room temperature, the reaction mixture was poured into ice-cold saturated aq. $NaHCO_3$ (200 ml). The benzene layer was shaken with the bicarbonate solution, dried over Na_2SO_4 and removed by rotary evaporation to yield 54 plus isobutyl alcohol, which was used in the next step without purification.

5,5-Dimethylcyclohex-2-en-1-one (51): To a suspension of $LiAlH_4$ (2.5 g) in dry ether (300 ml) was added dropwise the impure material from the above reaction. After 20 hrs. 1 *N* HCl (50 ml) was added dropwise and the mixture allowed to stir. The ether layer was

extracted with water (3 x 30 ml), dried over Na_2SO_4 and removed to yield 51 contaminated with isobutyl alcohol. Distillation yielded 9.5 g, a 32 % yield based on dimedone; b. p. $78^\circ/16$ mm (lit (107) $76^\circ/16$ mm).

Lithium aluminum tritertiarybutoxydeuteride: Lithium aluminum deuteride (1.0 g; 0.024 mole) was carefully ground with a mortar and pestle and placed in a 3-necked one litre flask through which dry nitrogen was passed. Ether (refluxed over LiAlH_4 for 3.5 hrs., 800 ml) was then distilled into the flask and the suspension stirred vigorously for 20 hrs. Freshly distilled t-butyl alcohol (5.3 g; 0.072 mole) was added dropwise to the filtered (suction filtration through a sintered glass funnel) solution. Hydrogen gas was evolved and some precipitate was formed. The ether was removed and the white LATBD was oven dried to yield 7.2 g.

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APPENDIX I

The terms product development control and steric approach control.

In 1956 Dauben, Fonken and Noyce (1) articulated the first theory to account for observed differences in product ratio for variously substituted cyclohexanones. Their theory depended upon competition between two different factors; steric approach control and product development control. Steric approach control, as defined by Dauben, is "a steric postulate involving competitive attacks from a favored (unhindered) or an unfavored (hindered) side" while that of product development control is "an energy consideration involving the relative stability of the possible products" (1). Differences in product ratio were judged to arise from dominance of one "control" over the other. A more meaningful and precise definition of these terms was desired because the concepts themselves are quite useful but have often been either misunderstood or misused.

It is important to remember that the sodium borohydride reduction of ketones is a kinetically controlled process. Therefore, the ratio of equatorial to axial alcohol depends only on the relative free energies of the transition states leading to the two diastereomeric products. In a reaction where the product ratio

is being controlled by ease of approach of the attacking reagent (steric approach control), the transition state must necessarily be at an early stage of bond formation. For reactions in which the factors controlling the relative energies of the transition states are similar to those controlling the relative energies of the products (product development control), the structure of the transition state must be similar to the products and a late transition state is involved. Therefore, it would seem that the terms steric approach control and product development control may be redefined in terms of the degree of bonding in the transition state.

Brown and Deck (2) pointed out that the Dauben explanation (1) gives the impression that steric approach control refers to kinetic control while product development control refers to thermodynamic control of the reduction. They, therefore, modified the terms to product stability control and steric strain control to call attention to the transition states involved. Eliel and Senda (3) maintained that product stability control (or product development control) "is, itself, caused by a form of steric strain (involving OH of (sic) a complex thereof) in the transition state..." They redefined both factors in steric terms, taking steric approach control (steric strain control) to refer to the steric strain involving the

incoming nucleophile in the transition state while product development (or stability) control was taken as the difference in strain of the oxygen between the transition state and the ground state.

Using the transition state type of definition, which is more general than Eliel's individual steric interactions, the Dauben explanation of product ratios simplifies to the hypothesis (a) that a late transition state is involved in reduction of unhindered ketones and thus the lower energy equatorial alcohol is produced because the transition state leading to equatorial alcohol is of lower energy than that leading to axial alcohol; (b) that an early transition state is involved in reduction of hindered ketones because transition state energy is being controlled by ease of approach of the hydride species which attacks more easily from the equatorial side, resulting in axial alcohol.

The following definitions, believed to be of more general utility, are suggested. The terms approach control and product development control refer in a relative sense to the position of the transition state along the reaction coordinate, approach control inferring a reactant-like or early transition state and product development control a product-like or late transition state. Steric approach control then becomes a special case of approach control in which

the factors involved are steric.

Professor Dauben has indicated that he is in agreement with the idea of differing degrees of bonding in the transition state, and that these extensions do not constitute a misrepresentation of the original ideas¹.

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¹W. G. Dauben. Personal conversation with D. C. Wigfield, Vancouver, August 1972.

APPENDIX II

Raw data for the determination of extinction coefficients and kinetics.

There are essentially three types of ketones used in this study; cyclohexanones, steroids and acetophenone. The cyclohexanones and steroids have similar extinction coefficients (Table 10), but acetophenone is quite different due to conjugation of the carbonyl with the benzene ring. The extinction coefficient data shows these different types. The primary difference in these ketones is the actual amount of ketone used in a kinetic determination. The amount of steroidal ketones used is governed by solubility which results in low concentrations and low optical density readings. The amount of acetophenone used is governed by the high extinction coefficient and hence a low concentration is required to keep the optical density to a reasonable level. Kinetically there is a large difference between the hindered and unhindered ketones which is reflected in the small changes in optical density and the necessity for taking readings over a longer time interval for the hindered ketones.

Table 31. Beer's law data for representative ketones in propan-2-ol at various temperatures.

ketone	°C	$\lambda_{\max}$	conc. M	absor- bance	ϵ	corr. coeff.
<u>5</u>	0	277	0.0000	0.000	21.2 $\pm$ 0.1	0.9999
			0.00285	0.060		
			0.00528	0.111		
			0.00641	0.137		
			0.00652	0.137		
<u>68</u>	25	279	0.0000	0.000	963 $\pm$ 16	0.9996
			0.000532	0.526		
			0.000703	0.671		
<u>18</u>	25	287	0.0000	0.000	19.0 $\pm$ 0.2	0.9998
			0.0237	0.443		
			0.0271	0.503		
			0.0284	0.538		
			0.0336	0.635		
<u>3</u>	25	283	0.0000	0.000	17.2 $\pm$ 0.1	0.9997
			0.0304	0.524		
			0.0310	0.528		
			0.0312	0.533		
			0.0378	0.634		
			0.0397	0.670		
			0.0403	0.697		
			0.0530	0.903		
			0.0600	1.036

Figure 30. Beer's law plot for cholestan-3-one in propan-2-ol at 0°.

Figure 31. Beer's law plot for acetophenone in propan-2-ol at 25°.

Figure 32 . Beer's law plot for 3,3,5-trimethylcyclohexanone in propan-2-ol at 25°.

Figure 33. Beer's law plot for cyclohexanone in propan-2-ol at 25°.

Table 32. Raw data for the reduction of cholestan-3-one by sodium borohydride in propan-2-ol at 15°.

$$4b = 4.00 \times 10^{-2} \text{ M} \quad 4b/a = 9.524 \quad 2.303/a-4b = -64.3$$

sec	abs.	$a-x \cdot 10^3$	$x \cdot 10^3$	$4b-x \cdot 10^3$	$\frac{a-x}{4b-x}$	$\frac{4b}{a} \frac{a-x}{4b-x}$	$-\log \frac{4b}{a} \frac{a-x}{4b-x}$
45	0.087	4.20	----	-----	-----	-----	-----
60	0.086	4.15	0.05	39.95	0.104	0.990	0.0044
120	0.081	3.91	0.29	39.71	0.098	0.933	0.0301
180	0.076	3.67	0.53	39.47	0.093	0.886	0.0526
300	0.067	3.24	0.96	39.04	0.083	0.790	0.1024
360	0.063	3.04	1.16	38.84	0.078	0.743	0.1290
540	0.053	2.56	1.64	38.36	0.067	0.638	0.1952
600	0.051	2.46	1.74	38.26	0.064	0.610	0.2147

Figure 34 . Typical kinetic plot of the reduction of cholestan-3-one by NaBH_4 in propan-2-ol at 15° .

Table 33. Raw data for the reduction of acetophenone by sodium borohydride in propan-2-ol at 25°.

$$a = 1.72 \times 10^{-3} \text{M} \quad 4b = 6.84 \times 10^{-2} \text{M} \quad 4b/a = 39.77$$

$$2.303/a-4b = -34.5$$

sec	abs.	$a-x$ 10^3	$x \times 10^3$	$4b-x$ 10^3	$\frac{a-x}{4b-x}$	$\frac{4b}{a} \frac{a-x}{4b-x}$	$-\log \frac{4b}{a} \frac{a-x}{4b-x}$
45	1.660	1.72	----	-----	-----	----	-----
60	1.657	1.72	0.00	68.40	0.0251	0.998	0.0009
120	1.647	1.71	0.01	68.39	0.0250	0.994	0.0026
420	1.595	1.66	0.06	68.34	0.0243	0.966	0.0150
480	1.585	1.65	0.07	68.33	0.0241	0.958	0.0186
1020	1.494	1.55	0.17	68.23	0.0227	0.903	0.0443
1080	1.484	1.54	0.18	68.22	0.0226	0.899	0.0462
1620	1.399	1.45	0.27	68.13	0.0213	0.847	0.0721
1680	1.390	1.44	0.28	68.12	0.0211	0.839	0.0762
2280	1.302	1.35	0.37	68.03	0.0198	0.787	0.1040
3000	1.203	1.25	0.47	67.93	0.0184	0.732	0.1355
3840	1.095	1.14	0.58	67.82	0.0168	0.668	0.1752
4740	0.990	1.03	0.69	67.71	0.0152	0.605	0.2182
5520	0.911	0.95	0.77	67.63	0.0140	0.557	0.2541
5700	0.893	0.93	0.79	67.61	0.0138	0.549	0.2604
6480	0.822	0.85	0.87	67.53	0.0126	0.501	0.3002
6780	0.795	0.83	0.89	67.51	0.0123	0.489	0.3107
7980	0.698	0.72	1.00	67.40	0.0107	0.426	0.3706

Figure 35. Typical kinetic plot of the reduction of acetophenone by NaBH_4 in propan-2-ol at 25° .

Table 34. Raw data for the reduction of 3,3,5,5-tetramethylcyclohexanone by sodium borohydride in propan-2-ol at 35°.

$$4b = 4.88 \times 10^{-2} \underline{M} \quad a = 3.45 \times 10^{-2} \underline{M} \quad 4b/a = 1.414$$

$$2.303/a-4b = -161.0$$

sec	abs.	$\frac{a-x}{10^2}$	$x \cdot 10^2$	$\frac{4b-x}{10^2}$	$\frac{a-x}{4b-x}$	$\frac{4b}{a} \frac{a-x}{4b-x}$	$-\log \frac{4b}{a} \frac{a-x}{4b-x}$
45	0.677	3.45	----	----	-----	-----	-----
120	0.676	3.45	0.00	4.88	0.707	1.000	0.0000
300	0.674	3.44	0.01	4.87	0.706	0.998	0.0009
600	0.671	3.42	0.03	4.85	0.705	0.997	0.0013
900	0.667	3.40	0.05	4.83	0.704	0.995	0.0022
1200	0.664	3.39	0.06	4.82	0.703	0.994	0.0026
1500	0.660	3.37	0.08	4.80	0.702	0.993	0.0031
1800	0.656	3.35	0.10	4.78	0.701	0.991	0.0039
2100	0.652	3.33	0.12	4.76	0.700	0.990	0.0044
2400	0.649	3.31	0.14	4.74	0.698	0.987	0.0057
2700	0.646	3.30	0.15	4.73	0.698	0.987	0.0057
3000	0.642	3.28	0.17	4.71	0.696	0.984	0.0070
3300	0.639	3.26	0.19	4.69	0.695	0.983	0.0074
3600	0.636	3.24	0.21	4.67	0.694	0.981	0.0083

Figure 36. Typical kinetic plot of the reduction of 3,3,5,5-tetramethylcyclohexanone by NaBH_4 in propan-2-ol at 35°.

Table 35. Raw data for the reduction of cyclohexanone by sodium borohydride in propan-2-ol at 25°.

$$4b = 4.20 \times 10^{-2} \underline{M} \quad a = \frac{37.6}{5} \frac{\text{mg}}{\text{ml}} \times \frac{2}{3} \times \frac{1}{98.1} = 5.11 \times 10^{-2} \underline{M}$$

$$4b/a = 0.822 \quad 2.303/a-4b = 253.1$$

sec	abs.	$\frac{a-x}{10^2}$	$x \times 10^2$	$\frac{4b-x}{10^2}$	$\frac{a-x}{4b-x}$	$\frac{4b}{a} \frac{a-x}{4b-x}$	$+\log \frac{4b}{a} \frac{a-x}{4b-x}$
40	0.759	4.45	0.66	3.54	1.257	1.033	0.0141
50	0.737	4.31	0.80	3.40	1.268	1.042	0.0179
60	0.719	4.20	0.91	3.29	1.277	1.050	0.0212
90	0.669	3.91	1.20	3.00	1.303	1.071	0.0298
105	0.647	3.78	1.33	2.87	1.317	1.083	0.0346
120	0.627	3.67	1.44	2.76	1.330	1.093	0.0386
150	0.590	3.45	1.66	2.54	1.358	1.116	0.0477
180	0.557	3.26	1.85	2.35	1.387	1.140	0.0569
195	0.543	3.18	1.93	2.27	1.401	1.152	0.0615
210	0.529	3.09	2.02	2.18	1.417	1.165	0.0663
240	0.504	2.95	2.16	2.04	1.446	1.189	0.0752
270	0.482	2.82	2.29	1.91	1.476	1.213	0.0839
300	0.460	2.69	2.42	1.78	1.511	1.242	0.0941
330	0.444	2.60	2.51	1.69	1.538	1.264	0.1017
360	0.427	2.50	2.61	1.59	1.572	1.292	0.1113
390	0.411	2.40	2.71	1.49	1.611	1.324	0.1219

Figure 37. Typical kinetic plot of the reduction of cyclohexanone by NaBH_4 in propan-2-ol at 25° .

APPENDIX III

Derivation of the rate constant for the sodium borohydride reduction of ketones.

The derivation of the kinetic expression used is straightforward and gives a result similar to that of other workers (1-6). Expression (1) is not exactly equal to earlier expressions (1-5) being a factor of four larger. This is because in the spectral method one measures loss of ketone (or formation of alcohol) which is four times that of hydride loss measured by titration methods (1,3-5). It is not exactly clear why Smith and Bayer (2) used the other expression since they too used a spectral method measuring loss of ketone. However, since all other workers have reported their values using the rate expression derived for loss of hydride, the values of this study have been reported in this manner to facilitate comparison of rate constants. Only Sun and delRosario (6), of those who measured loss of ketone, have actually reported this quantity rather than loss of hydride.

NaBH ₄ + ketone		alcohol	
b	a	0	initial
$b - \frac{x}{4}$	a-x	x	time t

$$dx/dt = k(a-x)(b-\frac{x}{4})$$

$$dx/(a-x)(b-\frac{x}{4}) = kdt$$

$$4 \, dx/(a-x)(4b-x) = k \, dt \quad \frac{4}{(a-x)(4b-x)} = \frac{P}{a-x} + \frac{Q}{4b-x}$$

$$\begin{aligned} 4 &= P(4b-x) + Q(a-x) \\ &= P4b - Px + Qa - Qx \\ &= P4b + Qa - x(P + Q) \\ -P - Q &= 0 \\ P &= -Q \end{aligned}$$

$$-4Qb + Qa = 4$$

$$Q(a-4b) = 4$$

$$Q = 4/a-4b$$

$$P = -4/a-4b$$

$$\text{thus } 4/(a-x)(4b-x) =$$

$$-4/(a-4b)(a-x) + 4/(4b-x)(a-4b)$$

therefore,

$$\int_0^x \frac{-4 \, dx}{(a-4b)(a-x)} + \int_0^x \frac{4 \, dx}{(a-4b)(4b-x)} = \int_0^t k \, dt$$

$$-4/a-4b \ln(a-x) \Big|_0^x + 4/a-4b \ln(4b-x) \Big|_0^x = kt$$

$$-4/a-4b \ln \frac{a-x}{a} + 4/a-4b \ln \frac{4b-x}{4b} = kt$$

$$4/a-4b \ln \frac{4b}{a} \frac{(a-x)}{(4b-x)} = kt$$

$$4/a-4b (2.303) \log_{10} \frac{4b(a-x)}{a(4b-x)} = kt \quad (1)$$

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