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LA THÈSE A ÉTÉ
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STUDIES ON THE HYDRIDE REDUCTION,
OF CYCLOHEXANONES

by

Frederick Ward Gowland, B.Sc.

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

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October, 1977

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The undersigned recommend to the Faculty of Graduate Studies
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ABSTRACT

The participation of hydroxylic solvent in the sodium borohydride reduction of ketones is clarified by determining the order with respect to 2-propanol in diglyme to be $3/2$; solvent isotope effects using 2-propanol- $O-D$ were also used as a probe for the role of solvent in the rate-determining step. The possibility of a disproportionation mechanism operating for the steps involving alkoxyborohydrides following the rate-determining hydride transfer is discussed. Evidence for its dismissal and support for the sequential transfer of hydride from the intermediate alkoxyborohydrides is presented. The degree of solvent exchange in the alkoxyborohydride intermediates and products is explored and found to have little significance in these reductions. The geometry of the transition state is concluded to be acyclic in nature and the position of the transition state to be the later half of the reaction coordinate. The borohydride reduction of ketones in diglyme is shown to occur only under photochemical stimulation, it is possible that this represents the thermally forbidden four-centre mechanism.

Kinetic isotope effects were calculated by the vibrational analysis method as a function of transition state geometry and extent of hydride transfer for the lithium aluminium tri-tert-butoxyhydride reduction of ketones. The experimental kinetic isotope effects using LATBH/LATBD are reported and comparison made with the theoretical isotope effect curves. The transition state for these reductions is concluded to be at half-hydride transfer but no conclusions regarding the geometry of the transition state

are made. The temperature dependence of the reduction rates of LATBH are reported and the reaction is shown to be dominated by entropy considerations.

Product development control or product stability control is shown to be an important consideration in LATBH reductions and more so for NaBH_4 reductions of ketones. Support for this conclusion is drawn from rates of equatorial attack, ρ values, kinetic isotope effects, and the entropies of activation. These data allow for the ordering of reducing agents as a function of position along the reaction coordinate.

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ABBREVIATIONS

‡ - Cross of Lorraine, used to denote transition state properties

GLC - Gas-Liquid-Chromatography

LAH - Lithium Aluminium Hydride

LATBD - Lithium Aluminium Tri-tert-butoxydeuteride

LATBH - Lithium Aluminium Tri-tert-butoxyhydride

LATMH - Lithium Aluminium Trimethoxyhydride

LCAO-SCF - Self-Consistent-Field Calculations based on Linear
Combination of Atomic Orbitals

kH/kD - Kinetic isotope effect

KIE - Kinetic isotope effect

THF - Tetrahydrofuran

ZN - Extent of bond cleavage ~~or~~ formation in the transition state

INTRODUCTION

Ketone Reductions by Complex Metal Hydrides

For over thirty years sodium borohydride (1,2), lithium aluminium hydride (3), and their derivatives have been used to revolutionize the methods for functional group transformation in organic chemistry (4). A very wide range of these derivatives exist which have reducing properties milder than LiAlH_4 and more active than NaBH_4 and are capable of very selective reductions under controlled conditions (4). Although outstanding contributions have been made in the control of stereoselectivity in the reduction of ketones (5,6,7), relatively small strides have been made in the area of reaction mechanisms, which may be the key to understanding the range of stereoselectivities displayed by these metal hydride species.

Sodium borohydride was prepared in 1943 by Schlesinger and Brown (2) in their quest for volatile uranium complexes to aid in the Allied war effort. It was ten years before their studies were reported in the chemical literature. However, in 1949 S. W. Chaikin and W. G. Brown (8) reported that all four hydrides of the sodium borohydride are available for the reduction of aldehydes and ketones. It must be remembered that this reducing capability was an important advance for synthetic organic chemistry, since it offered a mild, high yield alternative to those procedures currently being used.

The names of the reagents used in this thesis are not necessarily correct inorganic nomenclature but are those in common use among organic chemists.

The stereoselectivity of hydride reductions was nicely discussed by Barton (10), concluding that the stereoselectivity was markedly dependent on cyclohexanone structure. Axial attack of hydride to give the equatorial alcohol was observed to predominate when the cyclohexanone was unhindered and equatorial attack to give rise to the axial epimer was the result when the ketone was quite hindered. These ideas based on the, at that time, new concept of conformational analysis (9) were extensively exploited by synthetic organic chemists. However, other factors were recognized to affect the stereoisomer ratio and the Barton concepts could only be used as a rule of thumb. These concepts are illustrated by several examples in FIGURE 1.

FIGURE 1

Control of Stereoselectivity - NaBH_4

Although the qualitative aspects of the stereoselectivity changes had been expounded the quantitative arguments used by mechanistic chemists resulted in a rapid complication of the original ideas defined by Barton.

The first kinetic study was reported by Garrett and Lyttle (13) on the NaBH_4 reduction of 3α -hydroxy- 11α -acetopregnan-20-one. Their data was consistent with a 4:1 stoichiometry of ketone to NaBH_4 and a simple, second-order rate process. This somewhat surprising result, surprising that four successive reductions with conceivably comparable rates of reduction do not give rise to complicated kinetics, places several constraints on the myriad of mechanistic possibilities available to the reduction system.

Two possibilities were suggested by Garrett and Lyttle. The first mechanism proposed was the sequential transfer of hydride to the ketone with the first transfer being rate determining and the next three transfers being fast in comparison. This is illustrated in SCHEME 1.

SCHEME 1

Sequential Mechanism

The second mechanistic consideration was hydrolysis of the intermediates to give H_3BOH , $\text{H}_2\text{B}(\text{OH})_2$ as reducing agents. Little supporting evidence has appeared for this mechanism and this is generally referred to as the sequential mechanism.

Brown, Mead and Subba Rao (14) indicated that the protic solvent was intimately involved in the hydride transfer process and proposed a mechanism involving the simultaneous formation of a boron-oxygen bond with the solvent.

FIGURE 2
Linear Mechanism

They also felt that the sequential mechanism was consistent with their data although they could not rule out an association mechanism between the ketone and borohydride (15).

Jones and Wise (16) in a set of very novel experiments, suggested on the basis of $\text{NEt}_3 \cdot \text{BH}_3$ being the trapped product of reductions done in diglyme, that borane, BH_3 , or its alkoxy derivatives could be the reducing species after the first hydride transfer. However, it was later shown that the BH_3 was probably being generated during workup since no reduction of ketones by NaBH_4 occurs in diglyme (17,26).

SCHEME 2

Borane Mechanism

In 1962 Vail and Wheeler (18) reported a comprehensive study on the reduction of 3-cholestanone as a function of solvent, temperature and reducing agents. They concluded that a cyclic four-centre transition state was most consistent with their data. This transition state was enthusiastically embraced by many of the workers in the field (19,20,41,47,56). This transition state was considered to be consistent with the small inverse isotope effect using NaBD_4 (20,48) and the value of the entropy of activation (15). However, it assigned no role to the crucial protic solvent and little attention was focused on the "allowedness" of the process by application of the Woodward-Hoffmann rules by these workers (19,20,41,47,56).

FIGURE 3

Four-centre Mechanism

House (23), in 1972, proposed a six-centre type of mechanism involving solvent or the metal cation, based not on new experimental evidence but on a review of the existing evidence; examples of these transition states are illustrated in FIGURE 4.

FIGURE 4
House Transition States

Brown and coworkers (17) and recently, Pierre and Handel (54) have shown that Na^+ plays a negligible role in the mechanism of reduction by NaBH_4 and thus the cyclic transition state incorporating solvent joined the linear and four-centre transition states as likely candidates for the geometry of the transition state.

From 1965 to the present, work on the mechanism of reduction was displaced by experiments designed to decide the "lateness" or "earliness" of the reduction process, a concept introduced by Dauben, Fonken and Noyce (24) to account for the product ratios observed in cyclohexanone reductions. Brown and Deck (25), nearly ten years later, modified Dauben's terms of product development control and steric approach control to concepts which dwelt on the actual transition states and not on the reaction coordinate. These

terms which are certainly a more rigorous definition of the processes defined by Dauben were called product stability control and steric strain control. However, it is important to point out that both Dauben and Brown (25,55) felt that both processes were operating because after 1965 most workers concluded (19,27-32) that product development control or product stability control was not important in these reductions. The Richer (27), Felkin (29,30,33), Marshall (28) and Eliel (19) arguments require an early transition state where product development control plays no role.

In contrast to these workers, the consideration of Hammett (21,22,34-40) plots and product ratios (42-46) has led other workers to propose a late or product-like transition state for these reductions. The Hammett results of some selected data are tabulated in TABLE 1.

TABLE 1
Rho Values for Hydride Reductions

<u>Reducing Agent</u>	<u>Substrate</u>	<u>ρ</u>	<u>Reference</u>
LiBH ₄	benzophenones	+2.81	39
NaBH ₄	fluorenones	+2.65	34
NaBH ₄	acetophenones	+3.06	36
		+2.6	35
NaBH ₄	4-substituted cyclohexanones	+2.78	35
LATBH	benzophenones	+2.13	38
LiAlH ₄	acetophenones	+1.95	40
NaO ⁱ Pr	acetophenones	+1.62	21

These results are consistent with the stabilization of charge which is developing on the carbonyl moiety. These relatively large values of ρ were taken to imply that a great deal of charge is transferred from the hydride donor to the carbonyl group in the transition state. This transfer of charge is consistent with considerable rehybridization at the carbonyl and is indicative of a later transition state for these reductions than proposed by the previously discussed workers.

In a comprehensive study of alkyl substituent effects, Rickborn and Wuesthoff (49) noted that the product ratio of most cyclohexanone systems was different at the beginning and end of the reaction and was consistent only with the build up of an intermediate - an alkoxyborohydride. They also noted that NaBH_4 was more sensitive to steric hindrance than were earlier studies using LATBH (50).

By the extensive use of activation parameter data, Wigfield and Phelps (51) showed the reduction by NaBH_4 was dominated by entropy considerations, but controlled by changes in enthalpy from ketone to ketone, and their isokinetic data (52) was consistent with different transition states for axial and equatorial attack as well as for hindered and unhindered ketones. They also reported inverse LATBH/LATBD (53) kinetic isotope effects on highly hindered ketones from mass spectral data which were considered to be consistent with a late or non-linear transition state.

The field of hydride reduction of ketones is thus clouded by several factors;

- (1) The geometry of the transition state is unknown.
- (2) The events after the rate-determining step have never been established.

- (3) The position of the transition has not been clearly defined, is it dependent on ketone or on reducing agent or both?
- (4) The role of product development control is in doubt.

The resolution of these points for the NaBH_4 and the LATBH reduction of ketones would lead to a considerable understanding of the myriad of experimental detail that has been presented over the last thirty years. These problems are approached in this thesis by the following experiments;

- (1) determination of solvent participation in the NaBH_4 reduction of ketones in solvent;
- (2) proof for the sequential or a disproportionation mechanism for the NaBH_4 intermediates;
- (3) determination of the theoretical and experimental kinetic isotope effects for the LATBH reduction of ketones, and thus determination of the geometry and position on the reaction coordinate;
- (4) extrapolating from LATBH, the determination of the position on the reaction coordinate for NaBH_4 ;
- (5) the role of product development control for these two reducing species by kinetic methods.

Since NaBH_4 and LATBH are representatives of the two largest classes of reducing agents, borohydrides and aluminohydrides, they provide models for understanding the origin of stereoselection in these reductions.

RESULTS AND DISCUSSION

NaBH₄ Mechanism Studies

Products of Reduction and Alkoxy Exchange on Boron

One of the most crucial pieces of information in elucidating any reaction mechanism is the structure of the products of the reaction. This information has never been clearly elucidated for the sodium borohydride reduction of ketones. The hydrolysis products of a NaBH₄ reduction of a cyclohexanone system are the epimeric alcohols; it is unknown whether these are also the pre-hydrolysis products or whether they exist in solution as the alkoxyborohydrides.

This fundamental question of the identity of the pre-hydrolysis products is intimately involved in the geometry of the transition state since it obviously determines what products are formed. Three mechanistic possibilities have been proposed for the geometry of the transition state. The linear, acyclic transition state (A) was proposed by Brown and coworkers (15,17), this mechanism has several subtle variations involving solvent and has, unfortunately, been almost totally ignored since its proposal (47).

The four-centre transition state (B), which incidentally would appear to be a symmetry forbidden process (57), was proposed by Vail and Wheeler (18), and exploited by other workers in the field in the quest for the origin of stereoselection (19,20,22,58,59). A novel six-centre mechanism (C) was recently proposed by House (60). These three geometric models are illustrated on the next page.

NaBH₄ Transition States

(A)

(B)

(C)

An important distinction between these mechanisms is available when the immediate products of complete reduction are available (61). all will give a tetraalkoxyborohydride. However, it is the origin of the alkoxy groups which is the point of utmost importance. The alkoxy

groups from (C) and probably (A) are clearly solvent derived whereas the popular (19,20,22,58,59) four-centre transition state has alkoxy groups derivable from the parent ketone. This is illustrated in SCHEME 3.

SCHEME 3

Products of NaBH₄ Reductions

However, this extraordinarily simple mechanistic distinction would be obscured if alkoxy group exchange did occur in the tetraalkoxyborohydrides. This exchange of alkoxy groups has been suggested to possibly occur (49,63) and some experimental work has been done in this area (62). Clearly, without hard experimental evidence on this point, little regarding the mechanism of reduction could be garnered. Thus an investigation of exchange reactions using primary, secondary and tertiary alcohol was examined. The types of exchange reactions investigated are shown in SCHEME 4.

SCHEME 4

Exchange Reactions

R = Me, Et, Prⁱ

R' = cyclohex, sec-but, t-amyl

NaB(OMe)_4 and NaB(OEt)_4 were prepared as previously described by Brown *et al.* (15,64), simply by the reaction of the alcohol with NaBH_4 . $\text{NaB(OPr}^i)_4$ was prepared by reduction of acetone in 2-propanol or by extensive 2-propanol exchange with NaB(OMe)_4 under refluxing conditions. In order to demonstrate a lack of exchange by these experiments it is clearly essential to study the reaction from both sides of SCHEME 4 or from the side which results in removal of the less volatile alcohol, so as to ensure that the tetraalkoxyborohydride product is not simply an artefact of the relative boiling points of the two alcohols.

Exchange reactions were performed by stirring the dissolved tetraalkoxyborohydride in the appropriate alcoholic solvent for 24 hours at room temperature, these conditions are comparable to reduction conditions employed in most kinetic studies on these systems (11). Studying the various possible exchanges using this method confirmed the report of Cunningham and Pretka (62), that primary alkoxy groups were displaced by other alkoxy groups, but showed that little or no exchange of secondary alkoxy groups by secondary alcohols occurred. See TABLE 2.

TABLE 2
Exchange Results at 298°K

<u>R</u>	<u>R'</u>	<u>% Exchange</u>
Me	Et	ca. 100
Me	Pr ⁿ	ca. 100
Me	Pr ⁱ	100
Et	Pr ⁱ	6
Pr ⁱ	cyclohex	1
Et	Bu ^{sec}	0
Pr ⁿ	amyl ^t	0

This lack of secondary exchange, under these mild conditions, clearly makes the mechanistic distinction based on product analyses of the ketone reduction system tenable. Investigation of the tetraalkoxyborohydride products from ketone reduction showed that the alkoxy groups attached to boron were consistently that of the alcohol solvent and not the alcohol from the parent ketone. This finding is illustrated in SCHEME 5.

SCHEME 5

Products of Ketone Reductions with NaBH_4

These results are clearly incompatible with the four-centre mechanism of reduction (B) but are consistent with either (A) or (C) or a subtle variation of either. Experiments probing this vital role of 2-propanol are discussed shortly and are consistent with the above experiments.

An NMR Examination of NaB(OR)_4 Species

Several workers (49,63,65) have alluded to the facile exchange of alkoxy groups on NaB(OR)_4 species. It was the recent work of Pasto et al. (65) in which they could not observe any absorptions in their

^{11}B spectra that would correspond to the alkoxyborate products of reduction, that prompted the study of this question more closely. They rationalized this behaviour as facile alkoxy exchange with solvent and thus a leveling effect in the NMR experiment.

Three tetraalkoxyborohydrides ($\text{R} = \text{Me, Et, iPr}$) were made by standard procedures and the C-13 NMR spectra were recorded in their parent alcohols. In order to properly interpret any results it is important that model compounds be examined to answer two main questions:

- (a) the chemical shift due to boron,
- (b) distortion or broadening due to $^{11}\text{B}-\text{O}-^{13}\text{C}$ coupling.

TABLE 3 is a collection of alcohols, ethers and trialkoxyborate species and their ^{13}C shifts (relative to TMS = 0.0).

TABLE 3

Comparison of ^{13}C Chemical Shifts for Alcohols, Ethers and
Trialkylborates

<u>Alcohol</u>	<u>Ether</u>	<u>Trialkylborate</u>
$\text{CH}_3\text{CH}_2\text{OH}$ (66)	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$ (67)	$\text{CH}_3\text{CH}_2\text{OB}(\text{OCH}_2\text{CH}_3)_2$ (a)
17.9 57.3	17.1 67.1	18.4 60.1
$\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$ (66)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$ (67)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{OB}(\text{OCH}_2\text{CH}_2\text{CH}_3)_2$ (66)
10.3 26.1 63.9	11.1 24.0 73.2	10.3 24.9 64.9
$(\text{CH}_3)_3\text{COH}$ (66)	$(\text{CH}_3)_3\text{COC}(\text{CH}_3)_3$	$(\text{CH}_3)_3\text{COB}(\text{OC}(\text{CH}_3)_3)_2$ (66)
31.6 68.7		30.2 72.0

(a) neat.

From this table it is seen that substitution of boron and two ligands leaves the chemical shift very close to the parent alcohol and about 10ppm upfield from the ether analogue. This is likely due to γ shifts on these carbons from the two other oxygen ligands. This is encouraging as the γ effect goes in the expected direction. No $^{11}\text{B-O-}^{13}\text{C}$ coupling was observed for these species, this was also confirmed in a recent study on sugar-borates by Mazurek and coworkers (68).

Thus, in the spectra of the tetraalkoxyborohydrides, no observable $^{11}\text{B-O-}^{13}\text{C}$ couplings would be expected, and normal carbon-like γ effects likely to be useful in the chemical shift assignments.

To explore this γ effect in highly substituted species more fully, a series of methyl ethers were examined; these are presented in TABLE 4.

TABLE 4
 ^{13}C Shifts of Methyl Ether Model Compounds

<u>Model</u>	<u>^{13}C Shift of OMe^{a} (67)</u>
MeOH	49.0
MeOMe	59.7
MeOEt	57.6
MeOPr ⁱ	54.9
MeOBu ^t	48.6

a from TMS = 0.0

It is seen that in this etheral series γ effects have quite a pronounced effect on the ^{13}C chemical shift. FIGURE 5 shows the

comparison of geometry between tert-butyl methyl ether and tetramethoxy borate. Since they are quite geometrically similar their γ effects (to a first approximation) should be quite similar.

FIGURE 5

In these two compounds the underlined methyl groups would have very similar chemical shifts, δ effects may play a minor role, at best, in this approximation and are neglected. It is expected, then, that tetramethoxyborate would have a chemical shift between 47-50 ppm. The ^{13}C NMR spectrum of $\text{NaB}(\text{OMe})_4$ in MeOH gave two peaks, MeOH at 49.4 and another smaller peak at 48.1 ppm. This peak was assigned to the $\text{NaB}(\text{OMe})_4$ species on the basis of the above arguments.

Similar reasoning for the tetraethoxyborate complex was employed. The data are tabulated in TABLE 5.

TABLE 5

Model Compounds for Tetraethoxyborate C^{13} Shifts

<u>Compound</u>	<u>C_1</u>	<u>C_2</u>
CH_3CH_2OH	57.3	17.9 (17)
$CH_3CH_2OCH_2CH_3$	67.1	17.1 (17)
$(CH_3CH_2O)CHMe$	60.6	15.5 (13)
$(CH_3CH_2O)_3CH$	59.5	15.0 (13)

Since no exact model compound for $NaB(OEt)_4$ exists, it is necessary to extrapolate from triethylorthoformate. If the same gamma effect that was observed in the $NaB(OMe)_4$ is used, then it is predicted that the carbon resonance for $NaB(OEt)_4$ will be at 53-55 ppm., several ppm. upfield from the solvent peak.

Three peaks were observed in the spectrum, two at 57.5 and 18.1, which are attributable to the ethanol carbons, and another peak at 55.6, which may be assigned to the C_1 carbon of the tetraalkoxyborate. The C_2 carbon is almost chemical shift equivalent with the C_2 of the ethanol solvent, only a slight broadening or shoulder was observed in the lower portion of this signal, consistent with the presence of another peak. These two spectra are consistent with an observable compound, this means that exchange is not occurring or is at least slow on the NMR time scale. In the investigation of $NaB(O^iPr)_4$, several attempts to obtain a spectrum failed because of the very limited solubility in propanol. However in one spectrum, a peak not attributable to solvent did appear about 0.8 ppm above the parent alcohol. This very small peak could be due to the $NaB(O^iPr)_4$ species and its chemical shift is consistent with the previous examples. This observation must be treated with caution.

^{13}C Spectra of NaB(OR)_4 Species

- a NaB(OMe)_4
- b MeOH
- c $\text{NaB(OCH}_2\text{CH}_2\text{)}_4$
- d EtOH
- e $\text{NaB(OCH}_2\text{CH}_2\text{)}_4$, EtOH

In view of the ready NMR observation of NaB(OMe)_4 , NaB(OEt)_4 , and the possible observation of $\text{NaB(OPr}^i)_4$, it is interesting to comment on Pasto's observation (65) of the ^{11}B spectra of his compounds.

NaBH_4 is a molecule having tetrahedral symmetry, thus this symmetrical arrangement of protons causes the electric field gradient at the nucleus to become zero and the relaxation processes are dominated by the efficient dipole-dipole process ($^{11}\text{B-H}$). It is interesting to speculate on the properties of a $\text{B(OPr}^i)_4$ species. If the electric field gradient did become zero then relaxation is less efficient because the quadrupolar mechanism may no longer operate. This causes the T_1 to become longer; it is encouraging to note that this has occurred for boron species in less symmetric environments (69,71). Since the quadrupole relaxation mechanism does not contribute to T_1 when the electric field gradient is zero, the T_1 is then dependent on the $^{11}\text{B-H}$ dipole-dipole relaxation mechanism. This efficient mechanism does not have a distance dependence, however the nuclear overhauser effect does and should result in a very small peak enhancement relative to that expected for BH_4 .

However, even if the electric field gradient is non-zero the line width of the $\text{NaB(OPr}^i)_4$ species, in the ^{11}B spectrum, is likely to be quite broad and may not be detectable at low concentrations. Thus it is clear that, unless careful control of instrumental conditions is maintained, the peak due to $\text{NaB(OPr}^i)_4$ may be unobservable.

One other problem exists for the Pasto-Lepeska experiments, under the conditions employed they should have observed an almost immediate precipitation of the $\text{NaB(OPr}^i)_4$ product, thus removing it from the NMR experiment. The use of very high concentrations of NaBH_4 , such

as those employed by Pasto, has led to immediate precipitation during kinetic experiments in this laboratory.

Thus it is possible that the non-observation of other peaks in the ^{11}B spectrum is due to two factors;

- (1) the variety of relaxation processes available to the ^{11}B nucleus,
- (2) precipitation of product.

To ensure that the ^{13}C results were not coincidental artefacts, the proton spectra were investigated for the three species. For the tetramethoxy borate compound a peak was observed upfield of MeOH, consistent with the upfield shift of orthocarbonates (98) from MeOH. Smaller peaks were observed for the $\text{NaB}(\text{OEt})_4$ compound and $\text{NaB}(\text{O}^i\text{Pr})_4$ species, thus providing a confirmation of the ^{13}C results.

Photochemical Borohydride Reductions

The previously presented evidence, which concludes that the four-centre mechanism is not operating in 2-propanol for the NaBH_4 reduction of ketones, is consistent with the present understanding of orbital symmetry (57). This symmetry-forbidden $[\pi 2\text{S} + \pi 2\text{S}]$ cycloaddition apparently does not occur under these thermal conditions. The fact that hydroxylic solvent plays a major role in these reductions is obvious, not only from the previously described experiments, but from the fact that the reduction of ketones does not proceed at a measurable rate in non-hydroxylic solvents such as diglyme (17,26). Obviously, in diglyme the cyclic and acyclic mechanisms involving solvent would not be possible and the orbital symmetry restriction

is an obvious factor that would prevent the four-centre mechanism from prevailing. However, the orbital symmetry rules are reversed for photochemical reactions (57) and it seemed a real possibility that this reduction would occur under appropriate irradiation.

Photochemical catalysis of this reduction was examined (61) by irradiating, at 254 nm, a solution of the ketone and NaBH_4 in diglyme. In diglyme, under photochemical stimulation, the reduction of ketones by sodium borohydride was dramatically accelerated. The question as to whether this was indeed the allowed four-centre process was not in fact rigorously established in this work; it was merely demonstrated that a facile reaction occurred. As indicated in TABLE 6, reduction was generally complete within 20-90 minutes, under conditions where no reaction was detectable in the absence of irradiation.

TABLE 6

Ketone	Photochemical Reduction Data		
	^a % Reduction	Axial/Equatorial Ratios	^c Time of Irradiation
100		20
100	14:86	20
100	12:88	20
100	22:78	20
94 ^b	26:74	90
^d		25
100	56:44	30
100		30

^a GLC percentage, ^b 6% unknown compounds, ^c minutes, ^d mixture too complex for analysis

There are several mechanisms for these photoreductions which seem possible. these are

- (a) the photochemically allowed four-centre process;
- (b) free radical reduction similar to that proposed for the tri-*n*-butyl tin hydride reduction of ketones (72);

and

- (c) photoreduction by the solvent (73).

One factor mitigating against the solvent photoreduction process was the observation that attempted photoreduction of cyclohexanone, in the absence of sodium borohydride, led to less than 1% reduction.

Although insufficient work was performed to distinguish rigorously between the concerted and free-radical mechanisms, it has been observed that free-radical (21) reductions have differing stereochemistries of reduction from concerted reactions (23).

Comparisons of stereoselectivities are shown in TABLE 7.

TABLE 7

Comparison of Reduction Stereoselectivities^a

Ketone	^b NaBH ₄ /Pr ⁱ OH	NaBH ₄ /hν diglyme	hν/Pr ⁱ OH	Sn(Bu ⁿ) ₃ H/benzene
30:70	26:74		24:76
16:84	14:86	21:78	17:83
14:86	12:88	18:82	13:87
15:85	22:78	26:74	14:86
55:45	56:44	32:68	46:54

a axial:equatorial, b references 20,51

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The free-radical processes tend to give more of the thermodynamically stable isomer, probably because the abstraction of hydrogen by the radical intermediate as shown in FIGURE 6 is less sensitive to substituents than the concerted process of NaBH_4 in propanol, which is more sterically demanding.

FIGURE 6

Ketyl Intermediate

Comparisons of the differences in stereoselectivities of the various reductions show that they are not greatly different, but that the photochemical reduction by NaBH_4 tends to follow more closely the thermal NaBH_4 stereoselectivity patterns than the free radical processes. However, because of the differences in solvents between the studies this mechanistic point cannot be regarded rigorously established.

The photochemical reduction of ketones by sodium borohydride does not offer any synthetic advances, it might have been useful if a reversal in stereochemistry had occurred or if a large preponderance of the equatorial isomer had been produced, to complement the selectivity of L-Selectride. However, if the process was the allowed four-centre mechanism, then an obvious synthetic application was open. While esters are not normally reduced by NaBH_4 (74), they might be reduced under these photochemical conditions. If the four-centre transition state

was operative then the reduction would stop at a masked aldehyde species, in a non-hydroxylic solvent like diglyme, which on hydrolysis would yield the aldehyde as the product. This is illustrated in SCHEME 6.

SCHEME 6

Photoreduction of Esters

Studies of the reduction on several esters were attempted (methyl benzoate, lanosteryl acetate, cyclohexanecarboxylic acid methyl ester and ethyl acetate). No aldehyde was isolated in these reductions but small amounts of alcohol were observed. Since the wavelength of irradiation is quite distant from the ester $n-\pi^*$ bond (254 nm versus 203 nm), sensitization by benzene and pyridine was attempted, to no avail. Prolonged irradiation led to alcohol production and no aldehyde formation. This observation is not consistent with the four-centre process, unless the hemi-acetal borate species is breaking up under these conditions. What it may be consistent with, is the free-

radical process similar to $\text{Sn}(\text{Bu}^n)_3\text{H}$ reductions, where the hemi-acetal is produced directly, which then decomposes to the aldehyde and is quickly reduced to the alcohol. This is illustrated in SCHEME 7.

SCHEME 7

Possible Free-radical Mechanism for Ester Reduction

Further mechanistic work on these photoreductions was not considered worthwhile since the reactions are of no obvious synthetic utility.

Kinetic Role of Hydroxylic Solvent

The alkoxy exchange evidence shows that the four-centre transition state (B) is of little significance in the sodium borohydride reduction of ketones in 2-propanol. It does not distinguish, however, between the Brown acyclic mechanism (14,17) and the House cyclic mechanism (60). In order to make such a distinction and ensure that the four-centre

process is not operative, a study of the kinetic role of hydroxylic solvent was undertaken. Although it has been known since 1961 (17) that a hydroxylic solvent is a necessary entity in these reductions, no such study has appeared in the literature. Since no measurable degree of reduction of cyclohexanone by sodium borohydride occurs in pure, dry diglyme (17,26) the pseudo-second order rate constants of reduction as a function of 2-propanol concentration were studied (75), as well, a solvent study using 2-propanol-0-D was initiated.

Considerable difficulty was initially encountered in the solvent order determination kinetics. It was found that unless freshly distilled diglyme (from LiAlH_4) was used, catalysis by a species other than 2-propanol was observed. The plots of absorbance versus time indicated that an initial fast reaction was proceeding simultaneously with a slower reaction. The simplest and most logical explanation for this phenomenon is catalysis by water which corresponds to the fast portion of the reaction and the slow portion of the curve corresponds to the reaction being catalyzed by 2-propanol. Consistent with this is the report by Brown (17,57), that acetone is reduced six times faster in water than in 2-propanol.

The kinetic solvent results are shown graphically as a plot of $\log k_2$ as a function of $\log [2\text{-propanol}]$ in FIGURE 7, the slope of this plot gives the kinetic order of solvent in this system. The kinetic data are presented in the appendix. The results are both satisfying and surprising, satisfying because they continue to erode any support for the four-centre mechanism and surprising because the order with respect to 2-propanol is neither first order nor second order but three-halves. Thus the overall process for sodium borohydride reduction of cyclohexanone in 2-propanol is:

FIGURE 7

Hydroxylic Solvent Order

$$\text{Rate} = k_2[\text{ketone}][\text{borohydride}][\text{Pr}^i\text{OH}]^{3/2}$$

with an overall kinetic order of 7/2 and a rate constant of

$$k = 9.7 \times 10^{-4} \text{ M}^{-5/2} \text{ s}^{-1} \text{ at } 25^\circ \text{C.}$$

This solvent order is clearly inconsistent with the cyclic mechanism which incorporates only one molecule of solvent and consequently also places severe restraints on other possible linear mechanisms. However, a simple interpretation of this value for solvent order is available, and in combination with other, recent data, leads to a new and simple explanation for the stereoselectivity of cyclohexanone reductions.

The half-order is suggestive of solvent pre-dissociation,

where S could represent the solvent, diglyme or one of several species that could be present in the complex reaction mixture, arising from reduction with, or alcoholysis of, sodium borohydride (76). One of the mechanisms of reduction involving this pre-dissociation step is the acyclic "push-pull" mechanism illustrated below.

"Push-pull" Transition State

This mechanism involves one mole of 2-propanol and an isopropoxide

species. If this is the rate-determining reduction step, then the rate expression is that given below.

$$\text{Rate} = k[\text{ketone}][\text{BH}_4^-][\text{Pr}^i\text{OH}][\text{Pr}^i\text{O}^-]$$

If the isopropoxide is derived from the previous equilibrium and if

$$[\text{Pr}^i\text{O}^-] = [\text{SH}]$$

it follows that

$$[\text{Pr}^i\text{O}^-] = K^{1/2}[\text{Pr}^i\text{OH}]$$

where $[\text{S}]$ is disregarded as being constant. Substitution of this quantity into the rate expression results in the experimentally observed kinetic expression.

$$\text{Rate} = kK^{1/2}[\text{ketone}][\text{BH}_4^-][\text{Pr}^i\text{OH}]^{3/2}$$

Although a number of objections may be raised against this simple treatment, some of which will be dealt with shortly, the mechanism is consistent with the recently demonstrated observations that the free alcohol is the ~~product~~ and the alkoxy group attached to boron is solvent derived. It is of considerable interest, that the proposed mechanism is similar to that proposed by H. C. Brown and coworkers (14), as well as their conclusion, that one requirement for this reaction is the ability of the solvent to ionize (17).

One other explanation for the order of 1.5 in solvent could arise from the fortuitous mixing of first and second order processes as illustrated below.

$$\text{Rate} = k'[\text{ketone}][\text{BH}_4^-][\text{Pr}^i\text{OH}] + k''[\text{ketone}][\text{BH}_4^-][\text{Pr}^i\text{OH}]^2$$

The benzidine rearrangement, for example, shows an apparent order of 1.6 for this reason (77). As a test of these equations, plots of $k/[\text{propanol}]$ as a function of $[\text{propanol}]^{1/2}$ and $k/[\text{propanol}]$ as a function of $[\text{propanol}]$ were constructed (FIGURES 8 and 9). The second plot (FIGURE 9) shows more marked curvature than FIGURE 8. This result is inconsistent with the mixture of processes and is in more accord with the proposed mechanism.

The three-halves order may be due to a dielectric effect which is masking the true order by increasing or decreasing the ion association equilibrium for NaBH_4 and hence is responsible for the increase in rate. The dielectric constant for 2-propanol has been reported to be 19.92 (78), whereas no reported dielectric constant for diglyme is available in the literature. However, the molecular polarizability, (α), and the permanent dipole moment (μ), were reported by Lowry and Richardson (79) as $\alpha = 1.379 \times 10^{-23} \text{ cm}^3$ and $\mu = 1.97 \text{ D}$. Using the density published by Riddich et al. (80) for diglyme at 25.0°C as $\rho = 0.9440$ and the equation given by Isaacs (81),

$$\frac{4\pi N}{3} \left[\alpha + \frac{\mu^2}{3kt} \right] = \frac{\epsilon - 1}{\epsilon + 2}$$

where,

$$T = ^\circ\text{K} \quad N = \text{number of molecules/unit volume}$$

FIGURE 8

 $k / [\text{Pr}^i\text{OH}]$ versus $[\text{Pr}^i\text{OH}]^{1/2}$

FIGURE 9

 $k/[\text{Pr}^i\text{OH}]$ versus $[\text{Pr}^i\text{OH}]$

the dielectric constant can be calculated to be 13.29. This value is much higher than the usual dielectric constants for ethers which usually range between 4 and 7 (32). The fact that the dielectric constants for diglyme and 2-propanol are not too dissimilar means that in a mixed solvent, where the dielectric constant is between 13 and 20, the ion-pairing will be much more similar than would normally be the case for an ether mixed with an alcohol. This may not contribute significantly to the order determination plots.

Not only do problems exist for differences in ion pairing in this media but the problem of specific solvation is certainly ignored in this work. A comprehensive critique of the problem has recently appeared (82), in which they discuss reasons why solvolysis reactions do not appear second order in mixed solvent systems. In the borohydride kinetics in diglyme with 2-propanol added, the ketone or borohydride may be preferentially solvated by either 2-propanol or diglyme. This would certainly obscure any results that are based on the assumption that the solution is a random mixture of solvents. This would mean that the 3/2 result is not interpretive.

The concept of nucleophilic attack aiding in hydride reduction is certainly not a new concept (83-86), and in fact, the feature of nucleophilic attack on apparently negatively charged sites, is not without precedent (87). However LCAO-SCF calculations have shown (88) that the boron of BH_4^- is, in fact, slightly electron deficient with all of the negative charge spread on the hydrogens. These findings should remove any electrostatic objections to this mechanism and, in fact, only add to its probability.

It is noteworthy that, in the presently proposed mechanism, no role is assigned to the sodium cation. Although studies have shown

that in some related reductions, the cation plays an important role (17,54,89), there is no evidence for a role for Na^+ in NaBH_4 reductions in 2-propanol. Evidence to the contrary does exist however, Brown *et al.* (17) have shown that there is only a negligible rate increase upon the addition of NaI , while the opposite is true for the results of Li^+ addition. Pierre and Handel (54) have recently demonstrated the ineffectiveness of crown ethers in preventing NaBH_4 reductions in methanol. Thus, there remains little doubt that the sodium counterion plays, at best, a minor part in the mechanism of reduction.

The stereochemical implications of the acyclic transition state are startling in view of two recent pieces of related evidence. In 1974, Lehn and coworkers (90) reported their *ab initio* calculations on the reaction of hydride ion and formaldehyde; conceptually the simplest reducing system. They concluded that the hydride ion approaches the carbonyl group, not at 90° but from behind the carbonyl at an angle between 126° and 110° . The second, unrelated piece of evidence, concerns the rules for quantitative prediction of stereoselectivity in cyclohexanone reductions based on enthalpy substituent effects (91). These enthalpy substituent impedance effects are shown in SCHEME 8

SCHEME 8

Enthalpy Impedance Effects (Kcal/mole) of
Methyl Groups to Attack by BH_4^-

FIGURE 10

Attack at the Lehn angle

What is curious about these increments is the strangely large (1.2 kcal/mole) hindrance to equatorial attack offered by a methyl substituent in the four-axial position, an increment that is certainly difficult to rationalize with current mechanistic thinking on these reductions.

In order to account for this effect, it is necessary to coordinate the concept of a long, acyclic transition state approaching the carbonyl at, or near, the Lehn angle. The steric and stereochemical implications of this proposal are immediately obvious upon inspection of FIGURE 10, which illustrates the effect of a four-methyl group on equatorial attack at the extreme of the Lehn angle range. In axial attack, the species approaching at 126° must pass between the axial hydrogens at C-3 and C-5, and no other serious interactions are met. In equatorial attack, there is a similar interaction at C-2 and C-6 as the species passes between these two axial hydrogens. What is not evident from FIGURE 10 is that groups at C-4 lie in the same vertical plane as does the carbonyl moiety. Molecular models indicate that a group attacking the carbonyl at 126° approaches as closely to the axial group at C-4 as it does to the other axial groups, which are known to have a marked effect on stereoselectivity. Thus, given this mechanism, it is predicted that equatorial attack is normally less favoured than axial attack and that a methyl group at the C-4 axial position should cause a significant further barrier to equatorial attack. The two most puzzling stereochemical observations in this field are thus easily rationalized using an acyclic transition state model.

To provide further support for this mechanism, catalysis by sodium isopropoxide and the effect of deuterated solvent were explored. If sodium isopropoxide catalyzed the rate of reduction, then this

would offer substantial evidence for the linear mechanism proposed.

Considerable difficulties, however, were encountered with these experiments. Because of solubility problems, the catalysis in 2-propanol could not be done using the spectrophotometric method of rate measurement. This method was useless because of precipitation occurring after sixty seconds of reaction. Gas-liquid chromatography of reaction mixtures were measured after two minutes, and although, the reactions containing isopropoxide had proceeded slightly further towards completion, the increase (5-10%) was considered to be too slight to be of any interpretable significance.

It is clear that further experimentation is required along these lines. Sodium borohydride solutions are themselves very basic (63) and clearly proper measurements of basicity in the absence and presence of isopropoxide in these solutions are required, before any definite conclusions concerning catalysis, or non-catalysis, by isopropoxide can be reached. What is clear, however, is that the addition of sodium isopropoxide does affect the course of reduction, because of the precipitation of $\text{NaB}(\text{Pr}^i\text{O})_4$ from the solution.

Thus, although the acyclic mechanism is apparently the simplest rationalization of the 3/2 order, and also provides a new stereoselectivity rationalization, the mechanism situation, in 2-propanol, must, at the present time, still be regarded as open.

Solvent Isotope Effects

Since the experiment searching for base catalysis ended quite inconclusively, the solvent isotope effects using Pr^1OD were explored. The use of deuterated solvent would appear to offer an immediate distinction between some of the possible reaction mechanisms. The four-centre transition state would have little or no solvent isotope effect, the Brown acyclic mechanism would have a secondary isotope effect, while the House cyclic mechanism would have a primary effect, but subject to a geometric constraint. The effects of geometry on an isotope effect are known and are explored more extensively in the section on LATBH calculations. Solvent isotope effects have been used extensively in the pursuit of reaction mechanisms. Several solvent isotope effects have been reported in studies involving analogues of sodium borohydride. Kreevoy and Hutchins (92) reported a solvent isotope effect ($k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$) of 9 ± 2 for the hydrolysis of NaBH_4 , which proceeds through the novel H_2BH_3^+ intermediate by rate limiting proton transfer. Borch, Bernstein, and Durst (93) report that the NaBH_3CN reduction of cyclohexanone has a solvent isotope effect, $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$, of 0.43, while White and Kelly (94) determined the reduction of acetone by morpholine borane to have a solvent isotope effect of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.36$. Both of the results argue strongly in favour of ketone protonation, in a fast preequilibrium step, such as that written below.

No results using Pr^iOD appear in the literature, and in fact relatively little work has been done on non-aqueous solvent isotope effects (95). However, the interpretation of the isotope effects is not complicated by exchange with NaBH_4 , or with any other species present in the reaction mixture.

The kinetics of reduction in Pr^iOD were hampered by several factors:

- (1) the expense of Pr^iOD precluded an extensive study in this solvent,
- (2) purification of Pr^iOD is difficult because of the exchangeable hydrogen.

As well unexpected problems were encountered with the solubility of NaBH_4 and $\text{NaB}(\text{OPr}^i)_4$ in Pr^iOD , and this limited the work that was done. Two ketones were investigated, cyclohexanone and 3,3,5-trimethylcyclohexanone. The data are summarized in TABLE 8 and the data are presented, in more detail, in the appendix.

TABLE 8

Solvent Isotope Effects

<u>Ketone</u>	<u>$k(\text{Pr}^i\text{OH})^a$</u>	<u>$k(\text{Pr}^i\text{OD})^a$</u>	<u>$k(\text{Pr}^i\text{OH})/k(\text{Pr}^i\text{OD})$</u>
765	351	2.2
22.8	15.3	1.5

$a \text{ } 1 \text{ mol}^{-1} \text{ s}^{-1} \times 10^4$

These data are surprising in light of the previous work in $\text{H}_2\text{O}/\text{D}_2\text{O}$; these solvent isotope effects are both normal, in contrast to the inverse effects. However, these values are not large and are consistent with the House mechanism and the $3/2$ order mechanism suggested. The House mechanism proposes an angle of about $129-109^\circ$ for the B-H-C segment of the transition state and the observed values are consistent with this value, since the kinetic isotope effect is dependent on geometry (96). These primary isotope effects are not consistent with the mechanism proposed by Durst and coworkers (93), or by White and Kelly (94), where a preequilibrium step gives rise to an inverse effect. However, if another proton transfer occurs in the rate-determining step which will be a primary effect (97), then the inverse effect will be overcome and a small primary effect is observed. These values of 2.2 and 1.5 for the solvent isotope effect are thus consistent not only with the proposed mechanism, but also with the House cyclic mechanism.

Sequential Mechanism

Garrett and Lyttle (13) first pointed out that the kinetics of reduction of a pregnanone derivative by NaBH_4 in MeOH, were consistent with a second-order process of a 4:1 ketone to borohydride stoichiometry. It is quite surprising that such a simple kinetic expression can be written for this process, but these workers pointed out that it is consistent with the first hydride transfer being the rate-determining step and reduction by the remaining three hydrides occurring much faster. In a computer study, that was aimed at studying the change in product ratio as the extent of reduction proceeded, Wuesthoff (99)

concluded that the rates of hydride transfer increased in the following order:

$$k_1 < k_2 < k_3 \sim k_4$$

This would allow for the buildup of a trialkoxyborohydride which would be consistent with the observation of product ratio changes throughout the reaction (49). This general kind of mechanism has three major schemes associated with it. These are illustrated as SCHEMES 9, 10 and 11 below.

SCHEME 9

Sequential Mechanism - Non-hydrolysis

In order to avoid the unappetizing prospect of having tri- or tetrasteroidal boron complexes as intermediates in such a mechanism, Garrett and Lytle suggested hydrolysis of the intermediate alkoxyborohydride (and presumably alcoholysis in 2-propanol) after reduction. However, the alkoxyborohydrides initially formed would still be those from the ketone. This is shown in SCHEME 10.

SCHEME 10

Sequential Mechanism - Alcoholysis

This scheme would give the proper final product of reduction, a tetraalkoxyborohydride with alkoxy groups derived from the solvent. However, it has been demonstrated that a step similar to that occurring after k_4 in SCHEME 10 does not occur readily under the conditions of a normal reduction. This would mean that the isolated product would have 3 alkoxy groups from the solvent and one from the parent ketone. This is nicely illustrated in the example below.

The observed result, the isolation of $\text{NaB}(\text{OPr}^i)_4$, is, however, consistent with concomitant solvent assistance, as illustrated in SCHEME 11, to yield a tetraalkoxyborohydride derived strictly from the solvent.

SCHEME 11

Solvent Assisted Sequential Mechanism

This mechanism was first suggested by H. C. Brown et al. (15,17), and the proposed mechanism is very similar and was discussed, in more detail, in an earlier section.

However, another mechanism very distinct from these sequential mechanisms may be envisaged. Disproportionation of the intermediate alkoxyboranes to form NaBH_4 as the major reducing agent is quite possible. Disproportionation may be considered to give rise to only NaBH_4 , or NaBH_4 and an alkoxyborohydride, as reducing agents. These complete and incomplete disproportionation schemes are illustrated in SCHEMES 12, 13, 14 and 15.

SCHEME 12

Complete Disproportionation of NaBH_4

In the complete disproportionation scheme, NaBH_4 is the only reducing agent. In order that this scheme be consistent with the observed kinetic characteristics and stoichiometry, then, the reduction step, k_1 must be much slower than any subsequent disproportionations. Only the trialkoxyborohydrides are considered to be stable, among the alkoxyborohydrides, and the very fast reduction of ketones by $\text{NaB}(\text{OPr}^i)_3\text{H}$ in 2-propanol (49,100) is not consistent with this complete disproportionation scheme. As well, the observed dependence of product ratio with extent of reaction is consistent with the presence of intermediates.

No evidence has alluded to the stability of the mono- and dialkoxyborohydrides; any experiments which have attempted to yield mono- or dialkoxyborohydrides (2,49) have resulted only in

disproportionation. This would suggest a mechanism where disproportionation is halted after the formation of the trialkoxyborohydride, which then reduces another molecule of ketone.

SCHEME 13

Incomplete Disproportionation of NaBH_4

The possibility exists however, that the di- and trialkoxyborohydrides reduce ketones faster than they disproportionate. This leaves the monoalkoxyborohydride as the only species capable of disproportionation, thus giving rise to three reducing agents, BH_4^- , $\text{H}_2\text{B}(\text{OPr}^i)_2$ and $\text{HB}(\text{OPr}^i)_3$. This scheme is outlined in SCHEME 14.

SCHEME 14

Partial Disproportionation of NaBH₄

The final disproportionation possibility is that the mono- and trialkoxyborohydrides are stable with respect to disproportionation, but the dialkoxy species are not. While no evidence exists for their stability, their rate of reduction may be much slower than any disproportionation reactions and, thus, should be dealt with. This possibility is illustrated in SCHEME 15.

Interestingly, this reaction does not disproportionate to BH_4^- at any time. The sequential mechanism requires four different reducing species giving rise to four different degrees of stereoselectivity. The disproportionation schemes require one, two, or three reducing agents. The modest change in stereochemical product ratio (49) in these

SCHEME 15

Partial Disproportionation of NaBH_4

reductions is most consistent with the incomplete disproportionation mechanism, possible with the sequential mechanism and unlikely with the complete disproportionation scheme.

Thus we are left in a serious dilemma - do borohydride reductions occur by the sequential mechanism or by a disproportionation mechanism?

Fortunately, a rather simple experiment served to distinguish between the majority of the mechanisms. In the disproportionation mechanisms the alkoxyborohydrides disproportionate to give BH_4^- , except for the specific case outlined in SCHEME 15. Thus, if NaBD_4 were present, then interception of the intermediate alkoxyborohydrides by $\bar{\text{BH}}_3(\text{OR})$, $\bar{\text{BD}}_3(\text{OR})$ et cetera would give rise to mixed borohydrides $\bar{\text{BH}}_n\text{D}_{4-n}$. When less than a stoichiometric amount of ketone is used, then, the borohydride that is isolated from the reaction mixture would be substantially isotopically mixed if the disproportionation were operating, and if the sequential mechanism were the dominant process,

then a discrete mixture of borohydride and borodeuteride would be isolated. Proton magnetic resonance spectra (101) of authentic isotopically mixed borohydrides were obtained by hydrolysis of NaBH_4 in refluxing D_2O (92). The spectral differences between this mixed species and the product isolated from the reduction mixture is shown in FIGURE 11. Table 9 is a summary of the reaction schemes and TABLE 10 lists the results of the scrambling experiments.

TABLE 9

Summary of Reaction Schemes

<u>Scheme</u>	<u>BH_4^- Regenerated</u>
11	No
12	Yes
13	Yes
14	Yes
15	No

TABLE 10

Results of Attempted Scrambling Experiments

<u>Ketone</u>	<u>$\text{BH}_4^-/\text{BD}_4^-$</u>	<u>Hydride/Ketone</u>	<u>NMR Results</u>
0.429	2.01	No Exchange
	0.529	2.00	No Exchange
	1.59	1.98	No Exchange
0.550	2.02	No Exchange
	0.916	1.97	No Exchange

FIGURE 11

In contrast to the case of borohydride hydrolysis, under no circumstances is there any evidence of the formation of isotopically mixed borohydrides in ketone reductions. Cyclohexanone, however, is one of the least likely ketones to cause isotopic scrambling of NaBH_4 because of its rapid rate of reduction. Since solvent alkoxy groups become attached to boron in the reduction, the rate of disproportionation of intermediates is, presumably, essentially independent of the ketone being reduced. In contrast, the rate of ketone reduction varies widely; 3,3,5,5-tetramethylcyclohexanone is reduced slower than cyclohexanone by a factor of almost 400 (11,49,51) and thus the possibility of disproportionation playing a role is greatly enhanced. However, the results of TABLE 10 show that, even in this case, there is no evidence of the formation of isotopically mixed borohydrides. These spectral results are consistent only with two reaction pathways; the sequential mechanism and the dialkoxyborohydride disproportionation mechanism.

To differentiate between these two possibilities, information on the third and fourth hydride transfer is required. Rickborn and Wuesthoff (49) reported several interesting results on the reduction of trimethylcyclohexanone by $\text{NaB(OPr}^i)_3\text{H}$ in 2-propanol. Previous work had shown that this compound did not disproportionate in THF solution, however, the results of Rickborn *et al.* are most easily explained by a disproportionation mechanism for this species in 2-propanol. They found that;

- (a) there was an extremely fast reaction consuming one-half of the reactants followed by a slower reaction which consumed the remainder of the ketone,
- (b) the product ratio varied from 75% axial, at the end of the first reaction, to 87% axial, at the end of the slower reaction

for 3,3,5-trimethylcyclohexanone.

These results are consistent with two reducing agents, each having a different stereochemical outcome proceeding at different rates. Rickborn *et al.* (49) suggest that disproportionation of the trialkoxyborohydride accounts for these points.

However, departing from their arguments leads to a simpler conclusion. Both the borohydride species are capable of reducing ketones in the following manner.

Since two reducing agents are required to explain the kinetic and stereochemical results, then, the rate of interconversion of the two species must be slow in comparison to reduction of a ketone. This means that,

$$k_2 \gg k_3 \gg k_1, k_{-1}$$

This interesting result means that the rate of reduction by the trialkoxyborohydride greatly exceeds the rate of disproportionation - otherwise only one reducing agent would be present, giving rise to only one kinetic line and a constant degree of stereoselectivity.

Thus, under normal reduction conditions where $\text{HB}(\text{OPr}^i)_3$ is produced, it is obvious that it will reduce faster than disproportionate and the only reason disproportionation is observed in 2-propanol is because the other process may not compete. There, however, remains the remote possibility that Rickborn made $\text{BH}_2(\text{OPr}^i)_2$ and $\text{B}(\text{OPr}^i)_4$, and that they do not disproportionate in any fashion or $\text{BH}(\text{OPr}^i)_3$ disproportionates completely in 2-propanol. If this were the case, then, the sequential mechanism would be established for this species.

If k_2 is greater than k_3 , then, the kinetic and stereochemical results would be rationalized, as well, the fact that each reducing species act for only 50% of the reaction would no longer be coincidental, but demanded by the kinetics. This would be a pure sequential mechanism proceeding from the dialkoxy species. Since it has been shown that the mechanism is sequential up to the dialkoxy species, then the whole sequence would be the sequential mechanism.

Conclusions

The results of the work on NaBH_4 are briefly summarized in this section and further commented on, at the end of the thesis.

- (1) The alkoxy groups of the boron containing product are solvent derived.
- (2) The products, $\text{NaB}(\text{OPr}^i)_4$, do not exchange with the solvent under mild reduction conditions.
- (3) The photochemical induced reaction of NaBH_4 with ketones in

diglyme is a facile process and may represent the photochemically allowed four-centre process.

- (4) The kinetic order of 2-propanol, in diglyme, is three-halves.
- (5) An acyclic mechanism most easily accounts for these data.
- (6) No sodium or isopropoxide catalysis was observed, although this may not necessarily exclude the acyclic mechanism.
- (7) A primary solvent isotope effect using Pr^iOD is consistent with the six-centre or the acyclic mechanism.
- (8) No isotope exchange occurs between NaBH_4 and NaBD_4 during reduction - thus eliminating the possibility of most disproportionation reactions occurring to any significant extent.
- (9) The first and second hydrides of a NaBH_4 reduction are transferred in a sequential manner.

Thus, the known detail of the sodium borohydride reduction mechanism has been expanded and can be summarized briefly as below.

" NaBH_4 reduces ketones with the breakage of a B-H bond being rate determining simultaneously with rupture of an H-O bond of the solvent. The first step after the rate determining step is sequential. The following hydride transfers may be sequential or due to disproportionation steps. The alkoxy ligands of the boron containing product are solvent derived."

Mechanism of LATBH Reduction

General

The mechanism of reduction by NaBH_4 is a very complex one, for several reasons;

- (1) four hydrides are present, thus obscuring the kinetic isotope effect interpretation,
- (2) the hydride transfers after the rate-determining step are difficult to probe,
- (3) hydroxylic solvent plays a dominant role in these reductions.

These problems could be alleviated by using a monohydride reagent, such as $\text{LiB}(\text{Et})_3\text{H}$, for which the kinetic isotope effect would be interpretable. There are no other hydrides to be transferred in subsequent steps nor is there a possibility of solvent participation in this reaction. However, this reaction is much too fast to be followed by conventional kinetics; stop-flow methods using aromatic ketones would be ideal for this species. Competition isotope effects would also be a useful probe for the mechanism. Little is known, however, about the status of these species in solution and attention was turned to a more well studied reducing species, lithium aluminium tri-tert-butoxyhydride (LATBH).

LATBH has several key advantages that make its choice, as the reducing species to be studied, important.

- (1) LATBH is easy to prepare and is not markedly sensitive to air nor moisture.
- (2) Only one hydride is available for transfer, providing a useful handle for isotope experiments.

- (3) The association of LATBH in solution has been studied.
- (4) The stereochemistry of reduction by this species has been well documented.
- (5) Several kinetic studies have already appeared using this reagent.

The mechanism of reduction by LATBH involves two important concepts, the geometry of the transition state and the position on the reaction coordinate. These two concepts are probed by the use of kinetic isotope effects which are complemented by a theoretical study of the effect of geometry and extent of hydride transfer on the kinetic isotope effect.

Kinetic Isotope Effect Calculations

General

The calculation of kinetic isotope effects for the reduction of ketones by LATBH/LATBD, was done to aid in the interpretation of the experimentally observed kinetic isotope effects. These calculations were accomplished using computer programmes, based on the F-G matrix method (105), developed by Schachtschneider and Snyder (106) and modified by Wolfsberg and Stern (107), and more recently developed by Saunders (108). The required input for these programmes consists of masses, molecular geometries and force constants for LATBH, LATBD and a ketone model. The KIE are calculated as defined by transition state theory without a tunnelling correction. The Bell (109) tunnelling correction is then applied to the KIE to account for the possibility of tunnelling in this reaction.

Method Verification

It was necessary to modify the programme received from Saunders (108,171) in order that the programme run on the Carleton Xerox-Sigma-9 system. (Rochester has an IBM-360 computing system). To ensure that the calculated results were not an artefact due to these minor changes, data available from Saunders (171) was run. An attempt to reproduce the isotope effects calculated by Saunders' input was also accomplished, by setting up the appropriate models and defining force constants and other parameters in an analagous manner. The model that was chosen for this study was the β -elimination of ethyl chloride by hydroxide ion. The results are reported in TABLE 11.

TABLE 11

Comparison of KIE Calculated for the β -Elimination of Ethyl Chloride by Hydroxide

<u>KIE</u> <u>ZN^a</u>	<u>Saunders Data</u> <u>on IBM 360</u>	<u>Saunders Data</u> <u>on Xerox Sigma 9</u>	<u>Reproduction of Saunders</u> <u>Model on Sigma 9</u>
0.1	3.19	3.21	3.13
0.5	5.81	5.73	5.67
0.9	2.04	2.05	2.04

^a ZN is the extent of C-H bond breakage in the transition state.

It is clear that satisfactory reproduction of the isotope effects was accomplished, and that the computer programmes would give information consistent with that interpreted by Saunders and coworkers (108).

Armed with these encouraging results attention was then turned to the LATBH/LATBD system.

LATBH/LATBD System

Calculation of Ground State Parameters

A simplified model of LATBH was used for the ground state calculations, in this model the tert-butyl group is considered to have a point mass of 57 amu at the central carbon. This cut-off procedure has been justified by the work of Stern and Wolfsberg (107), who found that atoms two bonds away from the site of isotopic substitution did not affect the calculated isotope effects. This procedure allows for much less computer time being used since the isotope effect is dependent (usually) only on force constant changes at the site of isotopic substitution, and calculations on portions of a molecule remote from the reacting centre are redundant, since they tend to cancel in the final calculations.

FIGURE 12

LATBH Model for Ground State Calculations.

Since no x-ray or diffraction data were available for LATBH, an x-ray study was considered. Upon consultation, with the x-ray spectroscopist (110) at Carleton, it was learned that, unless a near perfect crystal was available, the critical Al-H bond length and O-Al-H angle could not be accurately determined. LATBH has been reported to sublime at 280° (111), it was hoped that sublimation might lead to a crystal suitable for analysis, however, under the conditions employed in this work only amorphous LATBH was obtained. Frustrated in these attempts a CNINDO calculation (112) was performed on aluminium trimethoxy hydride to try to determine the Al-H bond distance. As this was a very expensive programme to run, the geometry was assumed for most of the molecule and the Al-H bond distance was varied. However, under the conditions defined, this approach was abandoned because the total energy never converged at a reasonable value of $r(\text{Al-H})$. See TABLE 12 and FIGURE 13.

TABLE 12
CNINDO Calculations on LATMH

<u>Bond Length</u> <u>(Al-H) Å</u>	<u>Total Energy (au)</u>	<u>Electronic Distribution of H</u>
1.55	-86.3340217	1.2489
1.61	-86.3427676	1.2545
1.65	-86.3465300	1.2584
1.70	-86.3491674	1.2633
1.75	-86.3497577	1.2683

FIGURE 13

CNINDO CALCULATIONS FOR THE
Al-H BONDLENGTH IN LATMH

Santry and Segal (113), in their pioneering work on the CNDO application to second-row atoms, found that d orbitals have a significant effect on the properties of the molecule. It is their feeling that most of the second-row elements are not properly parameterized and will lead to quite anomalous results. This is certainly the indication in this preliminary study, although variation of other bond-lengths might have lead to a better Al-H value, it was felt that reliable data would likely not be obtained from this approach.

To obtain reasonable values of bond lengths and bond angles it was necessary to consider compounds of similar structure, whose molecular parameters are well known and then extrapolate or interpolate to obtain reasonable values for LATBH.

The choice of appropriate bond lengths for LATBH were deemed the most important parameter. The Al-H bond length varies considerably depending on the choice of the model. The data are collated in TABLE 13 and consist of molecular orbital calculations, ionic radii calculations and x-ray data.

TABLE 13

Al-H Bond LengthAl-H Bond Length ($\overset{\circ}{\text{A}}$)

2.05	ionic radii calculation (114)
1.65	AlH_4^- M.O. calculation (115)
1.57	AlH_4^- M.O. calculation (116)
1.547	LiAlH_4 x-ray data (117)
1.55	LiAlH_4 x-ray data (118)
1.72	AlH_3 x-ray data (119)

The ionic radii calculations are the most inconsistent of these values and are neglected because they are subject to the largest error; since LATBH more closely resembles LiAlH_4 than AlH_3 the value of $1.55 \text{ \AA}$ for the ground state bond length was used. This value of $1.55 \text{ \AA}$ seems to be quite reasonable since hybridization provides for the major changes in bond lengths (120), at least for the first row elements and its extension to second row elements appears likely.

A variety of Al-O bond lengths are reported in the literature, this is because most species containing Al-O bonds tend to be polymers or dimers and the oxygen may coordinate several centres simultaneously. Literature values for this bond length are gathered in TABLE 14 and consist of x-ray data and ionic radii calculations.

TABLE 14.

Al-O Bond Length

<u>Al-O Bond Length ($\text{\AA}$)</u>	<u>Source</u>
1.91, 1.89, 1.86, 1.97	Al_2O_3 (121)
1.93	ionic radii (122)
1.68, 1.81	$\text{Al}_2\text{O}(\text{2-methyl-8-quinolinol})_4$ (123)
1.76	$\text{Al}_2\text{O}_7\text{H}_6^{-2}$ (124)
1.98, 1.89	$\text{Ba}_2\text{Al}_2(\text{OH})_{10}$ (125)
1.85-1.98	AlO_4 species (126)
1.77-1.80 $\pm$ 6	AlO_4 species (127)
1.83	crystal radii calculation (114)
1.90	$\text{Al}(\text{AcAc})_3$ (128)

Faced with this incredible array of numbers the Al-O bond length was set at $1.85 \text{ \AA}$. This value is consistent with the ionic radii (128) calculations and falls almost half-way between the values cited for four coordinated aluminium (126,127). While this may not seem to be a very satisfactory approximation, Wolfsberg and Stern have pointed out that the calculated isotope effects are insensitive to the choice of geometry, within fairly broad limits (107).

The other molecular parameters for the ground state were easily settled, the C-O bond length used was $1.38 \text{ \AA}$ (129), the standard bond length for this species while the O-Al-H angle was set at 108° and the Al-O-C angle at 109° . This model is only a slightly distorted tetrahedron about the Al centre; it is known from x-ray studies that AlH_4^- is tetrahedral (117) and it follows that LATBH will also be nearly tetrahedral. Some distortion by the three tert-butoxy groups might be expected but the Al-O bond length is larger than the common organic bonds and this interaction is probably less than in the all carbon case. The value of the Al-O-C angle is also somewhat uncertain since for HOH the angle is 104.5° and for dimethyl ether it is 111.6° (130), - being unsure of the effects of the aluminium the angle of 109° represents a good compromise. The standard angle about oxygen in molecular orbital calculations is 109.47° (131) and thus reinforces the choice for this angle.

After reasonable geometries for the ground state were arrived at, the estimation of good force constants for the isotopic vibrations were then considered. The stretching and bending frequencies for LATBH had been reported by Ashby (132) (under unstated conditions), while the other bending, stretching and torsional frequencies could only be estimated from the literature and approximate force constants applied.

TABLE 15 is a compilation of the literature frequencies for LATBH and analogous compounds. This lengthy table is then summarized, in TABLE 16, for a clearer representation of the data.

TABLE 15

Literature Data for Ground State Frequencies

<u>Compound</u>	<u>Vibration</u>	<u>Frequency (cm⁻¹)</u>	
LATBH	$\nu(\text{Al-H})$	1760	(132)
	$\delta(\text{Al-H})$	788, 772	
LiAlH_4	$\nu(\text{Al-H})$	1757	(133)
	$\nu(\text{Al-H})$	1657	
	$\delta(\text{Al-H})$	772	
	$\delta(\text{Al-H})$	760	
LiAlD_4	$\nu(\text{Al-H})$	1250	(133)
	$\nu(\text{Al-H})$	1220	
	$\delta(\text{Al-H})$	549	
	$\delta(\text{Al-H})$	560	
$\text{Al}(\text{OH})_4^-$	$\nu(\text{Al-O})$	615, 720	(134)
	$\delta(\text{Al-O})$	300, 370	
Bridged (Al-O-Al)	$\nu(\text{Al-O})$	750-800	(135)
CaAl_2O_4	$\nu(\text{Al-O})$	700-900	(136)
$\text{Al}(\text{AcAc})_2$	$\nu(\text{Al-O})$	697, 676, 464	(137)
AlO_4	$\nu(\text{Al-O})$	870, 770, 728	(126)
$\text{Al}(\text{O}^i\text{Pr})_3$	$\nu(\text{Al-O})$	695	(138)

TABLE 16

Synopsis of Literature Data

<u>Vibration</u>	<u>Frequency (cm⁻¹)</u>
$\nu(\text{Al-H})$	1760
$\nu(\text{Al-O})$	600-700
$\nu(\text{C-O})$	900-1100
$\delta(\text{O-Al-H})$	788-772
$\delta(\text{O-Al-O})$	370-300
$\delta(\text{C-O-Al})$	—
$\tau(\text{H-Al-O-C})$	—

The estimation of the ground state force constants was done on a trial and error basis. The calculated frequencies are presented with their force constants in TABLE 17.

TABLE 17

Ground State Frequencies and Force Constants

<u>Vibration</u>	<u>Calculated Frequency (cm⁻¹)</u>	<u>Force Constant (Mdyn/Å)</u>
$\nu(\text{Al-H})$	1759.6, 1268.1	1.78
$\nu(\text{Al-O})$	678.3, 548.2	3.80
$\nu(\text{C-O})$	930.0, 914.8	5.36
$\delta(\text{O-Al-H})$	845.5, 774.2	0.30
$\delta(\text{O-Al-O})$	354.8, 353.1	0.32
$\delta(\text{C-O-Al})$	205.9, 204.7	0.32
$\tau(\text{H-Al-O-C})$	192.0, 144.36	0.02

These calculated frequencies may be compared with the expected values from the literature in TABLE 16. The agreement between TABLE 16 and TABLE 17 is quite good, except for the O-Al-H bend which is apparently mixing in with the Al-O stretching motion to give rise to the two isotopically sensitive bands. This mixing of vibrational modes causes the stretching (Al-O) and bending (O-Al-H) to lose their separate identities; this is the expected result (139) when the symmetry is lowered so much and the two vibrations are of similar energy.

Since frequencies for $\delta(\text{C-O-Al})$ and $\tau(\text{H-Al-O-C})$ were not available in the literature, their force constants were set at 0.32 and 0.02 mdyn/Å respectively. The bending force constant, $\delta(\text{C-O-Al})$, was set at 0.32 because it was a value that was about one tenth of the Al-O stretching constant and it is apparent that bending force constants are usually of this order of magnitude (140). An error in the assignment of this bending frequency would not be expected to affect the calculated KIE in any manner because of the isotopic insensitivity of the mode (205.7 cm^{-1} , 204.7 cm^{-1}). Very few torsional frequencies are reported in the literature, the value obtained in the EtCl model of Saunders for this H-C-C-S torsion was 201 cm^{-1} and 173 cm^{-1} using 0.02 mdyn/Å, because of the lack of other data the torsion was for H-Al-O-C was also set at 0.02 mdyn/Å and gave a reasonably close value of 192 and 144 cm^{-1} . In common with the practice of Saunders (108), these force constants were kept low to minimize their effect on the isotope effect.

Transition State Parameters

The models used in the transition state analyses are simplified

by the use of the cut-off procedure (107) invoked earlier for the ground state analysis. In all the transition state models the cyclohexanone moiety has been simplified to an acetone-like fragment with the α carbons having masses of thirty-nine a.m.u. each. Eight transition state models were investigated; these models probed the angle of hydride transfer, the degree of hybridization, and the "concertedness" of the reaction.

In these transition state models, the LATBH was altered to reflect the weakening of the Al-H bond in the AlH_3 (119) dimer. The hydride to carbon acceptor distance was 1.21 Å in the transition state; the bond distance of a regular C-H bond is 1.08 Å (7). These two distances were kept fixed throughout all the transition states studied. The carbonyl bond length changes from 1.22 Å in cyclohexanone (141) to 1.38 Å in cyclohexanol (129) and for the transition state it was set at 1.30 Å for all calculations.

The rest of the geometry of the cyclohexanone portion of the transition state was that defined by Allinger (141), while the geometry of the LATBH moiety is that of the ground state. FIGURE 14 gives the transition state geometry for the first transition state considered.

Transition State Model 1; 180° - 90°

This transition state was chosen because it represents the concept of linear hydrogen transfer (Al-H-C angle = 180°), perpendicular to the plane defined by the carbon-oxygen skeleton of the cyclohexanone portion of the transition state (H-C-O angle = 90°). This is referred to as the 180° - 90° model and is illustrated in FIGURE 14.

FIGURE 14

Transition State Geometry Parameters; 180° - 90°

$$\begin{aligned} r(\text{Al-H}) &= 1.80 \text{ \AA} \\ r(\text{H-C}) &= 1.21 \text{ \AA} \\ r(\text{C=O}) &= 1.30 \text{ \AA} \\ r(\text{C-C}) &= 1.54 \text{ \AA} \end{aligned}$$

Nineteen internal coordinates were used to generate the G-matrix for this transition state. These are listed in TABLE 18 with the overall changes in the force constants and their variation as the extent of hydride transfer is considered. The variation of the force constants was similar to that used by Saunders and Katz in their calculations (108).

The imaginary reaction coordinate frequency, ($\nu_i^\ddagger$), for each transition state, was introduced by using appropriate off-diagonal elements to allow the F determinant, which contains the reacting stretching bonds, to become zero. Using the parameters and method of Saunders (108), three off-diagonal elements are defined.

TABLE 18

Internal Coordinates for Transition State 1; 180° - 90°

<u>Internal Coordinate</u>	<u>Force Constant^a</u> (GS → Product)	<u>Force Constant</u> <u>Variation^{a,b}</u>
$\nu(\text{C}=\text{O})$	10.8 → 5.36	$(10.8-5.36)(1-\text{ZN}) + 5.36$
$\nu(\text{C}-\text{H}^-)$	0 → 4.8	4.8 ZN
$\nu(\text{H}-\text{Al})$	1.77 → 0	$1.77(1-\text{ZN})$
$\nu(\text{Al}-\text{O})$	3.5	
$\nu(\text{O}-\text{C})$	5.36	
$\nu(\text{C}-\text{C})$	4.8	
$\nu(\text{C}-\text{Hax})$	4.8	
$\delta(\text{tBu}-\text{O}-\text{Al})$	0.32	
$\delta(\text{H}^+-\text{C}=\text{O})$	0 → 0.717	0.717 ZN
$\delta(\text{H}^+-\text{C}-\text{C})$	0 → 0.606	0.606 ZN
$\delta(\text{C}-\text{C}-\text{Hax})$	0.606	
$\delta(\text{C}-\text{C}-\text{C})$	0.63	
$\delta(\text{Al}-\text{H}-\text{C})^c$	0 → 0.30	$0.30(\text{ZN})(1-\text{ZN})$
$\delta(\text{O}-\text{Al}-\text{H})$	0.30 → 0	$0.30(1-\text{ZN})$
$\tau(\text{tBu}-\text{O}-\text{Al}-\text{H}^-)$	0.02 → 0	$0.20(\text{ZN})(1-\text{ZN})$
$\tau(\text{O}-\text{Al}-\text{C}=\text{O})$	0 → 0.03	$0.03(\text{ZN})(1-\text{ZN})$
$\tau(\text{O}-\text{Al}-\text{C}-\text{C})$	0 → 0.03	$0.03(\text{ZN})(1-\text{ZN})$
$\tau(\text{H}-\text{C}-\text{C}-\text{H}^-)$	0 → 0.02	$0.02(\text{ZN})(1-\text{ZN})$

a all force constants are in mdyn/Å

b ZN is the extent of Al-H bond rupture

c linear bending pair

$$F_{12} = A(F_{11}F_{22})^{1/2}$$

$$F_{23} = B(F_{22}F_{33})^{1/2}$$

$$F_{34} = C(F_{33}F_{44})^{1/2}$$

Expansion after substitution into the determinant yields equation

$$1 - C^2 - B^2 - A^2 + A^2C^2 = D$$

From this equation Saunders has shown that permissible values of A, B, and C parameters may be calculated, consistent with a given value of D (108). These parameters are regarded as measures of the extent of coupling of the stretching motions in the transition state, and thus the idea of concertedness enters the problem. It is interesting to note, that Saunders (108) considers, that only positive values of A, B and C have any physical connotation, for only then are the reacting atoms forced to move in the proper directions to form products in the reaction coordinate motion.

A tunnelling correction is normally not required when the barrier to reaction is zero, however, as the barrier to reaction increases the tunnelling also increases. Since, there is an experimental barrier to reaction of ~18 kcal/mole a non-flat barrier was chosen which requires a tunnelling correction, as well, the use of bending modes, in the isotopic description of the transition state, has also been cited as requiring a tunnelling correction factor (142). This last consideration seems somewhat more empirical than the first, which has quite solid theoretical and experimental (109) evidence. The tunnelling correction is dealt with in a later section.

The curvature of the reaction barrier is dependent on the value of B previously defined (108). A barrier to reaction exists if the curvature of the potential energy surface is negative and this curvature is related to the interaction force constant, F_{23} (143). If $F_{23} > (F_{22}F_{33})^{1/2}$ or if $B > 1.0$ then the curvature of the potential energy surface is negative and the barrier to reaction exists. The value of F_{23} determines the degree of proton tunneling (109,143) since it determines the magnitude of the imaginary reaction coordinate frequency (143).

Other interaction force constants were introduced to allow for Al-O stretching coupling with the Al-H motion and the analogous coupling of C-H with the C=O stretching. The inclusion of these force constants gives an idea of the concerted motion in the models studied. It would seem certain that some degree of concomitant motion exists in these reactions because the products are much lower in energy and a totally non-concerted mechanism would have a very large energy requirement. The question remains as to whether the correct degree of concertedness has been chosen. This question must await the development of good potential energy surfaces for these reactions.

TABLE 19 reproduces the machine calculations for the 180° - 90° transition state; ZN is the extent of Al-H bond rupture, kH/kD is the calculated isotope effect (without the tunneling correction), RZPE is the zero-point-energy ratio, RBEXC is the ratio of thermally excited vibrations, RATIF is the ratio of imaginary frequencies and $\nu_{LH}^\ddagger$ is the imaginary frequency for the hydrogen isotope. FIGURE 15 is a plot of isotope effect as a function of extent of Al-H bond rupture (ZN).

FIGURE 15
180°-90° LINEAR TRANSITION STATE
 k_H/k_D AS A FUNCTION OF ZN

TABLE 19
Calculated KIE Parameters for 180°-90° Model

<u>ZN</u>	<u>k_H/k_D</u>	<u>RZPE</u>	<u>RBEXC</u>	<u>RATIF</u>	<u>$\nu_{LH}^{\ddagger a}$</u>
0.125	1.90	1.71	1.09	1.23	-405
0.250	1.84	1.56	1.16	1.35	-612
0.375	1.55	1.30	1.18	1.33	-585
0.500	1.16	0.946	1.18	1.23	-432
0.625	0.830	0.790	1.17	1.13	-274
0.750	0.585	0.496	1.16	1.06	-159
0.875	0.417	0.359	1.15	1.03	-85

a cm^{-1}

Several important points are immediately obvious when the plot of k_H/k_D versus ZN is viewed (FIGURE 15).

1. The largest calculated isotope effect is between 0.2 and 0.3 of the Al-H bond breakage and has a value of nearly 2.
2. The isotope effect becomes unity at two places on the potential energy surface, at an infinitely early transition state and between 0.5 and 0.6 Al-H bond breakage.
3. For the last half of the reaction coordinate the isotope effect becomes increasingly inverse.

The asymmetry of the calculated curve provides an immediate distinction between late and early transition states for this system and should provide a reasonable test of the Dauben proposals (24).

It is observed from TABLE 19 that the major contribution to the calculated isotope effect is from the zero-point-energy term. This

is the usual result of machine calculations and an entirely expected observation (102). The maximum isotope effect is observed close to the expected symmetrical transition state, where the forces on the hydrogen are equal ($\bar{c}_a$, 0.25 ZN). The inclusion of the bending modes has changed its position to about 0.2 ZN, but as suggested (142), the incorporation of the tunnelling correction restores the maximum calculated effect to that of a simple three-centre model (96,143).

The RBEXC values for this transition state model vary about 8% and are within the range defined by the EtCl model and those considered by Collins and Bowman (144). If there are isotopic vibrations of exceptionally low frequency in the transition state, then it is possible that extensive thermal excitation of the bending modes will give rise to values significantly lower than unity (96). It is gratifying to note that this does not occur in these calculations, in fact, more thermal excitation occurs in the reactants. Thus the RBEXC factor cannot contribute to the observed inverse effects and obscure the interpretation based on zero-point-energy differences.

The dependence of $RATIF$ and $v_{LH}^\ddagger$ on ZN and the observation that they reach a maximum near the maximum isotope effect, is in accord with previous calculations (96,143), and will be dealt with, in more detail, in a later section of this thesis.

Transition State Models 2 and 3

The Lehn postulate (90) of hydride approaching a carbonyl centre from an angle, between 109° and 126° , behind the carbonyl was explored in the next two transition state models. They are similar in geometry to transition state model 1 but now the $H---C=O$ angle is 109° and 126° respectively. These models, the $180^\circ-109^\circ$ and the $180^\circ-126^\circ$,

are illustrated in FIGURE 46.

For these variations of the linear transfer of hydride the same force constants and bond lengths were used as for the 180° - 90° transition state model. Both of these angular variations, however, gave the same isotope effects (ca 1%) as the 180° - 90° case.

FIGURE 16

Transition State Models 2 and 3

Linear Hydride Transfer

The insensitivity of the isotope effect to geometry (145) has been well documented and with hindsight this is perhaps the expected result in these calculations. Since the isotope effects are quite insensitive to the angle of approach of the nucleophile (moment of inertia effects are still quite small, ca. 1%) experimental isotope effects could not lead to a test of the Lehn proposal and no distinction

between these or other linear transfer models is likely using this approach.

The relevant machine parameters for these two models are presented in TABLES 20 and 21 respectively.

TABLE 20

180°-109° Transition State Model 2

<u>ZN</u>	<u>k_H/k_D</u>	<u>RZPE</u>	<u>RBEXC</u>	<u>RATIF</u>	<u>$v_{LH}^\ddagger$</u>
0.125	1.91	1.72	1.09	1.23	-407
0.250	1.84	1.56	1.16	1.35	-615
0.375	1.55	1.29	1.18	1.33	-582
0.500	1.14	0.953	1.18	1.22	-421
0.625	0.815	0.684	1.17	1.12	-263
0.750	0.575	0.488	1.16	1.05	-153
0.875	0.412	0.354	1.15	1.02	-83

TABLE 21

180°-126° Transition State Model 3

<u>ZN</u>	<u>k_H/k_D</u>	<u>RZPE</u>	<u>RBEXC</u>	<u>RATIF</u>	<u>$v_{LH}^\ddagger$</u>
0.125	1.92	1.73	1.10	1.24	-400
0.250	1.84	1.56	1.16	1.36	-617
0.375	1.54	1.29	1.18	1.32	-579
0.500	1.13	0.944	1.18	1.21	-410
0.625	0.799	0.671	1.17	1.10	-252
0.750	0.565	0.478	1.17	1.05	-147
0.875	0.400	0.348	1.15	1.02	-80

Transition State Models 4 and 5

The alternative to the linear transfer is the popular non-linear hydride addition to the carbonyl (18,60). Several non-linear models have been examined; the first two models were the 90° - 90° complexation and the 90° - 90° non-complexation models. The angular nomenclature has its previous meaning and "complexation" means that there is an Al-O bond forming between the aluminium and the carbonyl oxygen simultaneously with the Al-H bond breakage and C-H bond formations. "Non-complexation" means that this bond is not formed. These two models are presented in FIGURE 17.

FIGURE 17

Non-linear Transition State Models 4 and 5

The 90° angle for the C-H-Al moiety was chosen because it represents the extreme for the smallness of this angle while the 180° angle in transition states models 1,2 and 3 represent the maximum for this angle and these two models should provide an upper and lower boundary for the calculated isotope effect at any given value of ZN. An intermediate angle of hydride transfer would be expected to display a k_H/k_D in between these two boundary models.

The bond lengths and forces were those previously defined; in the 90^0-90^0 complexation model the bond forming between the aluminium and carbonyl oxygen is varied from 0 to $3.5 \text{ m dyn/\AA}$ with a linear dependence on ZN. The calculations for these models are summarized in TABLES 22 and 23 respectively and FIGURE 18.

TABLE 22

Model 4 90^0-90^0 Complexation

<u>ZN</u>	<u>k_H/k_D</u>	<u>RZPE</u>	<u>RBEXC</u>	<u>RATIF</u>	<u>$v_{LH}^\ddagger$</u>
0.125	0.869	0.856	1.00	1.07	-117
0.250	0.718	0.686	1.03	1.07	-119
0.375	0.573	0.538	1.05	1.06	-98
0.500	0.466	0.431	1.07	1.03	-73
0.625	0.382	0.352	1.07	1.02	-50
0.750	0.323	0.292	1.09	1.01	-29
0.875	0.277	0.248	1.10	1.01	-13

TABLE 23

Model 5 90^0-90^0 Non-complexation

<u>ZN</u>	<u>k_H/k_D</u>	<u>RZPE</u>	<u>RBEXC</u>	<u>RATIF</u>	<u>$v_{LH}^\ddagger$</u>
0.125	0.867	0.862	0.994	1.05	-106
0.250	0.725	0.693	1.03	1.06	-130
0.375	0.589	0.547	1.07	1.07	-141
0.500	0.491	0.444	1.09	1.06	-129
0.625	0.409	0.365	1.11	1.06	-110
0.750	0.344	0.303	1.11	1.06	-98
0.875	0.293	0.258	1.12	1.05	-70

FIGURE 18

 $90^\circ/90^\circ$ BENT TRANSITION STATE k_H/k_D AS A FUNCTION OF ZN

Clearly, the extreme non-linearity of this hydride transfer has produced a most pronounced decrease on the kinetic isotope effects. The 90° angle of transfer of the hydride causes all the calculated isotope effects to be inverse, however, the possibility does exist that an extremely early transition state would show a small normal effect. It is interesting to note that the concept of an Al-O bond forming during the reaction, or at this method of expressing this interaction has only a small (0-5%) effect on the calculated isotope effect. Experimentally these could not be readily distinguished by the isotope effects alone, especially if the value of ZN is not approximately known.

The 90° - 90° models (models 4 and 5) suffer from a very obvious deficiency, the aluminium is too close to the oxygen for a realistic transition state ($1.31\text{\AA}$). Thus a calculation of a more reasonable non-linear transfer of hydride was considered.

Transition State Models 6, 7 and 8

A new non-linear model was constructed using bond lengths characteristic of the ground states, see FIGURE 19.

FIGURE 19

Construction of Non-linear Model

This led to the C-H-Al angle being 122° ; this angle, in combination with the previously defined transition state geometry led to an acceptable transition state bond length of $2.03 \text{ \AA}$ for the $\text{Al}\cdots\text{O}$ bond distance (ground state value $1.85 \text{ \AA}$). Three variations of this geometric model were considered; $\text{Al}\cdots\text{O}$ complexation, $\text{Al}\cdots\text{O}$ non-complexation and a model in which the aluminium does not complex with the carbonyl oxygen but in which the aluminium-oxygen bond in the $\text{Al}-\text{O}-\text{C}$ moiety is slightly strengthened ($3.3 \rightarrow 3.5 \text{ mdyn/\AA}$) in the transition state. These three transition state models are presented in FIGURE 20 as the $122^\circ-90^\circ$ complexed, $122^\circ-90^\circ$ non-complexed and the $122^\circ-90^\circ$ strengthened models.

FIGURE 20

Transition State Models 6, 7 and 8 - Non-linear Transfer

2

These three variations of this non-linear transition state model span the realm of reasonable possibilities for the motion of the atoms. The expected result of these transition states is to give calculated isotope effect curves intermediate between those of the 180° - 90° and the 90° - 90° models, since they were considered to be the two extremes for the transfer. The tabulated results are presented in TABLES 24 and 25 and graphically in FIGURE 21.

TABLE 24

122° - 90° Complexed Non-linear Transition State Model

<u>ZN</u>	<u>k_H/k_D</u>	<u>RZPE</u>	<u>RBEXC</u>	<u>RATIF</u>	<u>$v_{LH}^\ddagger$</u>
0.125	1.27	1.17	1.07	1.18	-223
0.250	1.20	0.992	1.14	1.28	-376
0.375	1.01	0.830	1.16	1.29	-384
0.500	0.799	0.676	1.16	1.23	-282
0.625	0.616	0.525	1.15	1.15	-177
0.750	0.454	0.398	1.12	1.06	-122
0.875	0.342	0.305	1.10	1.01	- 65

122° - 90° Non-complexed Non-linear Transition State Model

<u>ZN</u>	<u>k_H/k_D</u>	<u>RZPE</u>	<u>RBEXC</u>	<u>RATIF</u>	<u>$v_{LH}^\ddagger$</u>
0.125	1.28	1.20	1.05	1.16	-212
0.250	1.26	1.12	1.12	1.29	-318
0.375	1.06	0.910	1.11	1.29	-332
0.500	0.808	0.692	1.15	1.20	-258
0.625	0.624	0.532	1.16	1.14	-198
0.750	0.479	0.408	1.16	1.10	-142
0.875	0.368	0.317	1.14	1.07	- 86

FIGURE 21

122°-90° BENT TRANSITION STATE

 k_H/k_D AS A FUNCTION OF ZN

TABLE 25

122°-90° Strengthened Non-linear Transition State Model

<u>ZN</u>	<u>k_H/k_D</u>	<u>RZPE</u>	<u>RBEXC</u>	<u>RATIF</u>	<u>$v_{HL}^\ddagger$</u>
0.125	1.35	1.27	1.05	1.19	-275
0.250	1.32	1.17	1.11	1.31	-406
0.375	1.12	0.965	1.14	1.30	-419
0.500	0.846	0.719	1.10	1.23	-334
0.627	0.683	0.578	1.17	1.18	-258
0.750	0.523	0.439	1.18	1.14	-164
0.875	0.384	0.327	1.16	1.08	-103

Very small differences are observed with the three models, the 10% variation between the three models is apparently due to variation in the zero-point-energy term because it parallels the variation in isotope effect more closely than do the other parameters. These small differences do not readily lend themselves to experimental distinction and again point out that this method of expressing concertedness does not drastically affect the isotope effect.

The magnitudes of the calculated isotope effects are dominated by the zero-point-energy contributions and are intermediate in magnitude as previously predicted. Presumably, the models with angles intermediate between 122° and 180° would have k_H/k_D versus ZN curves that lie in between the curves for the 122° and 180° cases. A range of isotope effects may then be observed, at constant ZN or Al-H bond rupture if the angle of transfer changes throughout a series of compounds.

Tunnelling

Throughout these calculations tunnelling corrections to the isotope effect have been ignored. Tunnelling is simply the non-classical passage of a particle through a potential barrier. It has been pointed out that significant corrections to isotope effects will be important only for the hydrogen isotopes (146), this being due to the relatively large mass difference between hydrogen, deuterium and/or tritium. Since the hydrogen tunnels much more easily than deuterium or tritium, its rate constant is larger than in the absence of tunnelling and the isotope effect may be substantially larger.

In machine calculations of this type it is the stretching interaction force constant which determines the value of the imaginary frequency, $\nu_L^\ddagger$, and therefore, the degree of proton tunnelling (109, 142, 143). Since the degree of tunnelling is dependent on the value of $\nu_L^\ddagger$, it is obvious why tunnelling is favoured by high-energy barriers which have high values of $\nu_L^\ddagger$ (109, 147). The simplest treatment of the tunnelling factor that is used in machine calculations of this sort (96, 143) is the expression due to Bell (109),

$$\Gamma = 1 + \frac{u^2}{24} + \frac{u^4}{2880}$$

$$\text{where } u = \frac{h c \nu_L^\ddagger}{kT}$$

It has been noted by More O'Ferrall (44) that the contribution of proton tunneling to the isotope effect has the same dependence on ZN and transition state geometry as does the zero-point-energy term. This means that when the transition state is at its most symmetric, tunneling

will be at its maximum. TABLE 26 is a tabulation of the transition states with the tunnelling corrections for both $v_{LH}^\ddagger$ and $v_{LD}^\ddagger$ and the corrected isotope effects.

TABLE 26
Comparison of Calculated k_H/k_D 's with and without Tunnelling Correction

Transition State	ZN	$v_{LH}^\ddagger$	$v_{LD}^\ddagger$	E_H	E_D	k_H/k_D	Γ^*	k_H/k_D^*
180°-90°	.125	-405	-331	1.17	1.109	1.90	1.06	2.01
	.250	-612	-451	1.39	1.21	1.84	1.15	2.12
	.375	-585	-439	1.36	1.20	1.55	1.13	1.76
	.500	-432	-351	1.19	1.12	1.16	1.06	1.23
	.625	-274	-243	1.07	1.06	0.830	1.01	0.838
	.750	-159	-150	1.03	1.022	0.585	1.01	0.590
	.875	-85	-84	1.007	1.007	0.417	1.00	0.419
180°-109°	.125	-407	-330	1.17	1.10	1.91	1.06	2.03
	.250	-615	-455	1.40	1.21	1.84	1.16	2.13
	.375	-585	-438	1.36	1.20	1.55	1.13	1.76
	.500	-421	-344	1.18	1.12	1.14	1.05	1.20
	.625	-263	-237	1.07	1.06	0.815	1.01	0.823
	.750	-153	-146	1.02	1.02	0.575	1.00	0.575
	.875	-83	-81	1.007	1.006	0.412	1.00	0.412
180°-126	.125	-400	-322	1.16	1.10	1.92	1.06	2.03
	.250	-617	-455	1.40	1.21	1.84	1.16	2.13
	.375	-579	-437	1.35	1.20	1.54	1.13	1.73
	.500	-410	-338	1.17	1.11	1.13	1.05	1.19
	.625	-252	-228	1.06	1.05	0.799	1.01	0.807
	.750	-147	-141	1.02	1.02	0.565	1.00	0.565
	.875	-80	-79	1.006	1.006	0.406	1.00	0.406
90°-90° non-complexed	.125	-106	-102	1.01	1.01	0.867	1.00	0.876
	.250	-130	-122	1.02	1.01	0.725	1.01	0.732
	.375	-141	-132	1.02	1.02	0.589	1.00	0.589
	.500	-129	-122	1.02	1.01	0.491	1.01	0.496
	.625	-117	-111	1.013	1.01	0.409	1.00	0.409
	.750	-98	-93	1.01	1.01	0.344	1.00	0.344
	.875	-70	-67	1.005	1.005	0.293	1.00	0.293
122°-90° complexed	.125	-263	-223	1.05	1.05	1.27	1.00	1.27
	.250	-376	-293	1.14	1.09	1.20	1.05	1.26
	.375	-385	-298	1.15	1.09	1.01	1.06	1.07
	.500	-282	-230	1.08	1.05	0.799	1.03	0.822
	.625	-177	-154	1.03	1.02	0.616	1.01	0.622
	.750	-122	-114	1.02	1.01	0.454	1.01	0.459
	.875	-65	-62	1.004	1.004	0.342	1.00	0.342

Transition State	ZN	$v_{LH}^\ddagger$	$v_{LD}^\ddagger$	r_H	r_D	k_H/k_D	r^*	k_H/k_D^*
122°-90° non-complexed	.125	-212	-183	1.04	1.03	1.28	1.01	1.29
	.250	-318	-247	1.10	1.06	1.26	1.04	1.31
	.373	-332	-259	1.11	1.07	1.06	1.04	1.31
	.500	-258	-214	1.07	1.05	0.808	1.02	0.833
	.625	-198	-174	1.04	1.03	0.624	1.01	0.630
	.750	-142	-129	1.02	1.02	0.479	1.00	0.479
	.875	-86	-81	1.007	1.006	0.368	1.00	0.368
122°-90° strengthened	.125	-275	-230	1.08	1.05	1.35	1.03	1.39
	.250	-406	-311	1.17	1.10	1.32	1.06	1.41
	.375	-419	-323	1.18	1.10	1.12	1.07	1.20
	.500	-334	-290	1.11	1.08	0.846	1.03	0.870
	.625	-258	-220	1.07	1.05	0.683	1.02	0.696
	.750	-184	-164	1.03	1.03	0.523	1.00	0.523
	.875	-103	-96	1.01	1.01	0.384	1.00	0.384

FIGURES 22 and 23 are plots of the isotope effects as a function of ZN without and with Bell tunnelling correction. As predicted, the tunnelling correction reaches its largest value, 16%, at the largest value of $v_{L_0}^\ddagger$ which corresponds to the most symmetrical transition state. For the linear transition state a simple three-centre model calculation gives the point of balance for the stretching forces on the hydrogen at ~ 0.26 ZN. The observed maximum of the uncorrected tunnelling curve is ~ 0.2 ZN whereas for the tunnelling corrected curve (FIGURE 23) the maximum is at ~ 0.25 ; in excellent agreement with the three-centre model. It has been suggested (142) that the tunnelling correction often need only be applied when isotopic bending modes are considered.

The tunnelling corrections do not dramatically change the overall conclusions that may be made from these calculations, which are dealt with at the end of this section. It is clear, however, from FIGURE 22 that geometry and the degree of bond rupture play major roles in the determination of the magnitude of the calculated isotope effects.

FIGURE 22

LATBH TRANSITION STATES

 k_H/k_D AS A FUNCTION OF ZN

FIGURE 23

LATBH TRANSITION STATES

 k_H/k_D AS A FUNCTION OF ZN

TUNNELLING CORRECTED

Non-linear Transition States

The observation that decreasing the angle of hydrogen transfer leads to a substantially lowered isotope effect has been presented by previous workers (96,148-150). More O'Ferrall (95) has discussed the reasons for this observation in some detail and it is gratifying to note that these calculations are in agreement with his conclusions. In order to comprehend why non-linear hydride transfer gives rise to a lowered isotope effect, the arguments of More O'Ferrall will be presented and shown to have good correspondence with the present results. The model chosen by More O'Ferrall is presented in FIGURE 24.

FIGURE 24

In this model the angle β was varied and the isotope effect calculations were done at $ZN = 0.5$ or half hydrogen transfer. As well, for the extreme non-linear cases it was found that the calculated isotope effect was quite insensitive to the extent of hydrogen transfer. These data are collected in TABLE 27. There is a remarkable dependence of k_H/k_D upon the angle of transfer; this is because the factors which control the magnitude of the isotope effect on these different angular transfers are quite different. Analysis of FIGURE 25 (96) indicates that it is impossible, in the non-linear transition states to allow a

TABLE 27

Dependence of k_H/k_D upon β (96)

β	k_H/k_D	$v_{LH}^\ddagger$
180°	7.9	-715
175°	7.8	-715
150°	6.2	-670
120°	3.0	-532
90°	1.7	-319
60°	0.9	-181

FIGURE 25

Comparison of the Forces on a Linear
and a Non-linear Transition State (96)

$v_R^\ddagger$ $v_L^\ddagger$

situation where the forces on the isotopic hydrogen are balanced.

For the linear transition state k_H/k_D is determined, to a large extent by the ZPE change in the high frequency stretching mode in the reactants and this is large at a symmetrical transition state. The maximum isotope effect occurs at this symmetric transition state because the forces which hold the hydrogen are balanced. Accordingly, the hydrogen is not in motion in the $\nu_R^\ddagger$ vibration and thus isotopic replacement is unable to produce a ZPE difference to offset that in the reactants and the maximum isotope effect is observed. As this linear transition state becomes more and more asymmetric (not non-linear) the isotopic sensitivity of the reaction coordinate frequency $\nu_L^\ddagger$ decreases and that of $\nu_R^\ddagger$ increases. This decrease causes the ratio of imaginary frequencies to show a maximum at the symmetric transition state. This $\nu_L^\ddagger$ decrease and $\nu_R^\ddagger$ increase lead to increasing compensation in the transition state for the ZPE changes in the reactant and the isotope effect decreases.

In the non-linear symmetric transition state More O'Ferrall (96) has suggested that the real vibration ($\nu_R^\ddagger$) is a combined bending-stretching mode of such high frequency that it compensates for zero-point-energy differences in the reactants. Thus, the isotope effect for the non-linear transition state will be much smaller than for the linear transfer of hydrogen. As the non-linear transition state becomes asymmetric, no appreciable loss of isotopic sensitivity is observed because of the opposition of $\nu_R^\ddagger$ and $\nu_L^\ddagger$. Thus the isotope effect remains small and the extent of bond rupture has only a mild effect on the isotope effect.

By comparison of the $\nu_R^\ddagger$ and $\nu_L^\ddagger$ frequencies for the various transition states of the present calculations it is possible to quantify More O'Ferrall's comments and show that the agreement between the two works is quite good. Comparison of the $\nu_L^\ddagger$ and $\nu_R^\ddagger$ for a sample of transition states is given in TABLE 28.

TABLE 28

Comparison of $\nu_R^\ddagger$ and $\nu_L^\ddagger$ Frequencies for
Linear and Non-linear Transition States

180°-90° Linear Transition State

<u>ZN</u>	<u>$\nu_R^\ddagger$</u>	<u>$\nu_L^\ddagger$</u>
.125	1003, 920	-405, -330
.250	1143, 1073	-611, -451
.375	1245, 1077	-585, -440
.500	1332, 1087	-432, -350
.625	1401, 1131	-274, -243
.750	1847, 1616	-159, -150
.875	2216, 1734	- 84, - 82

122°-90° Non-complexed Non-linear Transition State

<u>ZN</u>	<u>$\nu_R^\ddagger$</u>	<u>$\nu_L^\ddagger$</u>
.125	1652, 1198	-775, -230
.250	1766, 1311	-406, -311
.375	1978, 1729	-419, -322
.500	2101, 1695	-534, -434
.625	2229, 1705	-258, -219
.750	2378, 1789	-188, -164
.875	2570, 1923	-103, - 95

90°-90° Non-complexed Non-linear Transition State

<u>ZN</u>	<u>$\nu_R^\ddagger$</u>	<u>$\nu_L^\ddagger$</u>
.125	2077, 1775	-106, -101
.250	2290, 1750	-130, -122
.375	2491, 1827	-141, -131
.500	2596, 1902	-129, -122
.625	2707, 1985	-117, -111
.750	2805, 2061	- 98, - 93
.875	2892, 2131	- 70, - 67

FIGURE 26

LATBH TRANSITION STATES

The trends of the $\nu_R^\ddagger$ and $\nu_L^\ddagger$ are in total agreement with those of More O'Ferrall (96,143) and indicate that the calculations are giving correct, qualitative answers. For the linear transition state (180° - 90° case) the $\nu_R^\ddagger$ and $\nu_L^\ddagger$ show the expected dependence on asymmetry. The isotopic dependence of $\nu_R^\ddagger$ decreases until ZN is about 0.25 and then increases as ZN increases; this means that $\nu_R^\ddagger$ is most insensitive at the symmetric transition state. Whereas $\nu_L^\ddagger$ has the opposite behaviour; $\nu_L^\ddagger$ reaches its maximum isotopic dependence at ZN = 0.25 or its symmetric transition state and at the extrema of ZN it has a very small isotopic dependence.

In further perusal of TABLE 28 it is immediately seen that a very high value of $\nu_R^\ddagger$ is present in all values of ZN for the non-linear transition states. For no value of ZN are the isotopic values of $\nu_R^\ddagger$ as close as they are for ZN = 0.25 in the linear transition state. This shows that the forces in the non-linear transition state are never in balance. Increasing the non-linearity of the hydride transfer causes increasingly larger values of $\nu_R^\ddagger$, the composite bending-stretching mode, to appear.

Clearly, the origin of the smaller isotope effects for these non-linear transition state models is due to a composite "stretching-bending" vibration of high enough frequency to offset the zero-point-energy changes from the reactants.

Mechanistic Conclusions

There are several conclusions to be made from these calculations with respect to the mechanism of reduction;

- (1) Complexation between the aluminium and the carbonyl oxygen does not affect the isotope effect substantially enough that this component of the reaction surface might be experimentally probed.
- (2) These calculations show that isotope effects would not provide a test of the Lehn postulate.
- (3) Geometry of the hydride transfer appreciably affects the magnitude of the isotope effect, especially for the first half of Al-H bond breakage.
- (4) Asymmetry of transition state provides for a large change in isotope effect.
- (5) If the Dauben Postulate was operating then a range of isotope effects ranging from primary to inverse would be observed.
- (6) The three transition state variations are distinguishable only if the transition state is symmetrical (i.e. early) where the maximum differences in isotope effect are apparent.
- (7) No ready distinction between transition states is possible if the transition state occurs in the later half of the reaction coordinate.
- (8) A ready distinction between early and late transition states is possible; normal versus inverse effects. For almost all the transition states the isotope effects become inverse near half bond breakage.

In summary then, the interpretation of experimental isotope effects is going to be poor as far as describing the transition state in any exact manner. However, it is important to reiterate that several clear-cut possibilities do exist. If the experimental kinetic isotope

effect is 2.2 then the transition state has linear hydride transfer and the Al-H bond is one-quarter broken. If the isotope effect is between 1.2 and 2.2 then the transfer may still be linear but with Al-H bond rupture lying between 0.1 ZN and 0.4 ZN. However, this value for the isotope effect is also consistent with non-linear hydride transfer if the angle is greater than 122° and less than 180° . Any isotope effect less than 1.2 is consistent with any reasonable angle of transfer somewhere along the reaction coordinate up to one-half transfer.

However, the situation is not as bleak as it may seem. All the isotope effects become inverse between 0.5 and 0.6 hydride transfer and the differences between the isotope effects due to the non-linearity of the transfer become very small. Thus if the effects are inverse then the position of the transition state may be pinned down with reasonable accuracy. But, no determination in the angle of transfer appears possible in this region.

A large scatter in the experimental isotope effects ($2.2 \rightarrow 0.4$) would mean that a variation in transition state was occurring for a series of ketones. Of course, this variation could be due to variations in Al-H bond cleavage angle of hydride transfer or both! A closely bunched set of data would tend to deny the Dauben postulate (24) for these species, since this result would be most consistent with all ketones having the same type of transition state with respect to "lateness" and "earliness".

Heavy Isotope Effect Calculations

Since mechanistic conclusions of geometry would be tenuous based solely on hydrogen isotope effects, and because the Lehn postulate invokes

FIGURE 27

CARBON ISOTOPE EFFECTS

a change of angle at the carbon, it was hoped that isotopic substitution into the carbonyl carbon would provide a means for resolving this problem. Calculations for the various transition states were carried out for C^{12}/C^{14} species to test the feasibility of performing a radio-chemical experiment. If the calculations showed that a large difference in the carbon isotope effects existed for the various transition states then this experiment would provide a promising possibility of distinguishing between geometries.

The geometry and forces used in the previous calculations were also used here, it was necessary to generate new G-matrices for the various transition states since the deuterium is replaced by hydrogen and the carbonyl carbon becomes isotopic.

Unfortunately, the calculations (see FIGURE 27) show that the transition states have quite similar isotope effects, with a considerable overlap of values. Curves of similar shape have been reported earlier by Saunders and coworkers (152-154); no explanation was offered for the shape of the curve, but explanations similar to those from proton isotope effects are much harder to use because the isotopic shifts are smaller and there are many more bonds and changing force constants at this isotopic atom. What is clear, however, is that the carbon isotope effect would not give a clear-cut distinction between geometries.

Previous Experimental Work with LATBH

LATBH has been used in three previous kinetic investigations of the reduction of ketones. The most comprehensive and best documented work was that of Ayres, Kirk, and Sawdaye, who measured the rates of reduction of a series of p,p'-disubstituted benzophenones in THF at 0°C (38). Using a gas-liquid chromatographic technique, they found an acceptable fit with the expected second-order rate expression, in agreement with the previous work of Klein and Dunkelblum (50). A ten-fold excess of hydride was used and the reaction monitored for the first 30% of the reaction. The slope of the resultant Hammett plot was 2.13. This value for ρ is consistent with substantial negative charge being stabilized in the transition state by the adjacent aromatic groups. This large positive value denies the possibility of reduction by a neutral aluminohydride but is consistent with $\text{Al}(\text{OBu}^t)_3\text{H}$ as the reducing species. The reduction of the same benzophenones with AlH_3 gave a value for ρ of 0.89, consistent with little charge separation in the transition state.

Klein et al. (50) determined the rates of reduction of several alkyl cyclohexanones at 30°C by a spectrophotometric method. However, the method of hydride determination and the source of their reagents was not specified. As well, their spectral readings were taken at 285 nm. which gives rise to errors in the rate constants for the more hindered ketones since the wavelength maximum for these ketones is 295 nm.. They did conclude, however, that the reaction

was first order in ketone and LATBH and thus second order overall. It was determined that the reaction was neither diffusion controlled nor mixing controlled, this is important because specific rate constants may then be calculated from the product epimer ratio. On the basis of the similarities of the rate constants for equatorial attack (TABLE 29) they concluded that Product Development Control played no role in these reductions.

TABLE 29

Rates of Equatorial Attack

<u>Ketone</u>	<u>k_e ($M^{-1}s^{-1}$)</u>
0.13
0.075
0.052

Although the rates for equatorial attack are more similar than the rates for axial attack, where a factor of over one hundred was observed, this does not mean that Product Development Control is not important. This concept is discussed more fully in a later section of this thesis.

In a preliminary communication, Calvet and Levisalles (46) reported the optical rotatory dispersion kinetics of a series of 3-ketosteroids. Unfortunately, neither a temperature nor the method of hydride analysis was specified in this work, so direct comparisons with the 3-cholestanone used in this thesis could not be made. Also in this study, substituents at the 1 and 5 position were varied in

a systematic manner to give interesting results. FIGURE 28 is the system that was studied and the specific rate constants for their study are presented.

FIGURE 28

Steroid System Specific Rate Constants

<u>Y</u>	<u>k_a</u> (M ⁻¹ s ⁻¹)	<u>k_e</u> (M ⁻¹ s ⁻¹)
H	1.47	0.14
CH ₃	0.0018	0.0089
F	0.019	0.0240
Cl	0.044	0.0045
CN	0.290	0.2240

These workers conclude that their results are most reconcilable with a transition state that is product-like or at least, not close to reactants as Klein had proposed, and that Product Development Control was important in these reductions.

Competition kinetic isotope effects using LATBH/LATBD were reported by Wigfield and coworkers (53). The highly hindered ketones

used in their study gave inverse isotope effects which they concluded were consistent with either a non-linear hydride transfer, a late transition state or both.

In summary, the information that is known about the LATBH reduction of ketones is as follows:

- (1) The reaction is first order in ketone and in LATBH.
- (2) The transition state has substantial negative character.
- (3) The reaction is neither diffusion nor mixing controlled
- (4) The data concerning Product Development Control is conflicting.

In order that the question of transition state structure be explored it was felt that a comprehensive kinetic study would be the most useful tool. Activation parameters and kinetic isotope effects were considered to be of utmost importance in this regard. However, in order that proper interpretation of the experimental results be possible, several points needed clarification;

- (1) Status of LATBH in tetrahydrofuran.
- (2) Standardization of LATBH solutions.
- (3) Availability and isotopic purity of LATBD.
- (4) The reaction order of ketone and hydride.
- (5) Development of a suitable kinetic technique.

Status of LATBH in Tetrahydrofuran

The mechanism of reduction of ketones by aluminohydride species is not well understood. Since a substituted cyclohexanone is an asymmetric molecule, attack of a larger reducing agent is expected to give a greater proportion of products arising from attack at the least hindered face of the ketone. This is due to

the generality that the steric bulk of the reducing agent is responsible for the degree of stereoselectivity displayed. However, it has often been observed that lithium trimethoxy aluminium hydride (LATMH) is more selective than LATBH (25,155). This observation led several workers to speculate that this was due to a change in mechanism for LATBH (25,156). It was suggested that an equilibrium existed, giving di-tert-butoxy aluminium hydride (ADBH) as the actual reducing agent.

However, this mechanism was nicely discarded by Ashby and coworkers (157). Their infrared measurements showed that the equilibrium concentration of ADBH could not be more than 1%. Since this did not rule out the possibility of very fast reduction by ADBH, ADBH was synthesized and found to have a very different degree of stereoselectivity. Ashby concluded that the disproportionation mechanism is not responsible for the apparent reversal of stereochemistry for LATMH and LATBH.

In a more recent study of this problem Ashby (132) showed that the trisubstituted tert-butyl derivatives had a relatively constant degree of association of 1.0 for most concentrations, whereas for LATMH increasing degrees of association were observed. This increase in association would then mean that LATMH would in fact be larger than LATBH under some conditions and thus give rise to a greater

amount of axial epimer in ketone reductions. This work also shows that LATBH exists in solution as the ion pair and not solvent separated species, as well as being monomeric under most concentration ranges. LATBH is considered to be held together by bridge bonds rather than by electrostatic attraction (132) and this is illustrated in FIGURE 29.

FIGURE 29

Solution Structure of LATBH

Standardization of LATBH¹

Complex metal hydrides, such as lithium aluminium hydride (LAH), are generally analysed titrimetrically by reaction with iodine. The analysis involves two titrations: (a) titration of the iodine solution with thiosulphate, and (b) the addition of a deficient amount of LAH to the same volume of iodine solution as in (a), followed by titration of the remaining iodine with thiosulphate. The difference between the two titrations clearly has equivalence to the quantity of hydride oxidized. Felkin (158) has shown that the following

equation holds.

This equation, in combination with the reaction of iodine with thiosulphate,

establishes the 1:4 equivalence between LAH and thiosulphate.

Direct extrapolation of the I_2 -LAH reaction to LATBH gives the following equation.

This equation in combination with equation 2, clearly implies a 1:1 equivalence between LATBH and thiosulphate. If the original titre of x ml. of thiosulphate to reduce the iodine solution is diminished to z ml. by the prior addition of y ml. of LATBH solution, then the molarity of the LATBH is given by,

$$[\text{LATBH}] = [\text{NaS}_2\text{O}_3] (x-z/y) \quad (4)$$

This equation is equivalent to that suggested by Ayres et al. (159).

In the course of using equation 3 and resulting expressions, however, certain peculiarities led to the consideration of its basis more carefully. In the absence of further experimental detail an alternative reaction seemed equally possible.

This equation, in combination with equation 2, gives a 1:2 equivalence between LATBH and thiosulphate, and, retaining the same designation of the volumes x, y, and z, leads to equation 6.

$$[\text{LATBH}] = [\text{NaS}_2\text{O}_3] (x-z/2y) \quad (6)$$

Equations 4 and 6 clearly differ by a factor of two, and an independent method of quantitative analysis is required to establish which of the two is correct. For this purpose the reaction of LATBH with

cyclohexanone was chosen and the extent of reduction evaluated. This reaction has the twofold advantage that, firstly, it is the reaction that this thesis concerns itself with, and, secondly, that cyclohexanone is known to react in a 1:1 stoichiometry with LATBH (25).

In order to utilize the reduction of cyclohexanone as a measure of LATBH, accurate assay of the extent of reduction is required. This was achieved with two independent methods.

The first of these methods involved gas-liquid chromatography (GLC) determination of the relative amounts of cyclohexanol and cyclohexanone after reaction with a deficient amount of LATBH. With this method the molarity of a LATBH solution is given by

$$[\text{LATBH}] = [\text{ketone}] (b/a) (\% \text{ reduction}/100) \quad (8)$$

where a and b are the volumes (ml.) of the LATBH and ketone solutions respectively. For the GLC system used in this work a significant detector response was measured; the actual percent reduction was thus obtained by multiplying the apparent percent reduction by 0.92.

The second method of analysis was the measurement of unreacted ketone by the absorbance of the $n-\pi^*$ band at the wavelength maximum. This analytical application was somewhat simpler, involving only the initial absorbance and the absorbance after reaction was complete. The molarity of a LATBH solution in this determination is given by

$$[\text{LATBH}] = (A_0 - A_f/\epsilon) (a+b/a) \quad (9)$$

where A_f is the final absorbance value and A_0 is the initial absorbance value, already corrected for the change in volume that will occur on adding the LATBH solution, ϵ is the molar extinction

coefficient, and a and b are the volumes previously indicated. It was found that the GLC and spectral analyses were in close agreement.

Armed with reliable analyses of LATBH solutions, comparisons were made with the apparent analysis given by the iodine titration method using both equations 4 and 6. From the results, summarized in TABLE 30, a number of points are evident.

(1) At low hydride to iodine ratios, equation 5 apparently occurs and the use of equation 6 gives reasonably good agreement with the GLC or spectral analyses. There is still a substantial error, however, due to the small quantity of iodine consumed and the small volume thus being a small difference between two large titres. In fact these ratios were those actually used for the initial kinetic work, and led to the belief that equation 5 was the chemistry involved.

(2) At hydride concentrations comparable to the iodine concentration, equation 3 appears to occur and the use of equation 4 gives the correct analysis of the hydride concentration.

(3) At most hydride:iodine ratios, the true hydride concentration lies between the values obtained using equations 4 and 6. Presumably, this corresponds to LATBH reacting by both equations 3 and 5.

(4) The consequence of point 3 is that the iodine titration method for LATBH is an unreliable and almost useless analytical method. The stoichiometry is variable and unpredictable unless the concentration of LATBH is already known with sufficient accuracy to ensure that conditions for predominance of either equation 3 or equation 5 will be in effect.

TABLE 30

Comparison of Titration, GLC, and Spectral Concentrations of LATBH^a

<u>Titration</u> <u>(equation 4)</u>	<u>Titration</u> <u>(equation 6)</u>	<u>GLC</u>	<u>Spectral</u>	<u>Correct Equation</u>
0.0144	0.0072	0.0074		6
0.0244	0.0122	0.0143		6
0.0394	0.0197	0.0183		6
0.0500	0.0250		0.0321	
0.0532	0.0266	0.0336	0.0344	
0.0554	0.0277	0.0355	0.0351	
0.0572	0.0286		0.0419	
0.0622	0.0311		0.0450	
0.0702	0.0351		0.0424	
0.0704	0.0352		0.0456	
0.0750	0.0375		0.0540	
0.0814	0.0407		0.0537	
0.0868	0.0434		0.0542	
0.0900	0.0450		0.0584	
0.0932	0.0466		0.0650	
0.0980	0.0495		0.0661	
0.1054	0.0527		0.0750	
0.1290	0.0645	0.1250		4
0.1404	0.0702	0.1274		4
0.1722	0.0861	0.1764		4

a [LATBH], moles/litre

These conclusions, although unexpected, are not unreasonable. Even if equation 3 were to occur, the first step of such a process would presumably be equation 5. The second step would be

From the data, therefore, it would appear that equation 10 is viable and the question of whether equation 3 or 5 is appropriate is essentially a question of competition between equations 5 and 10.

Clearly at low hydride to iodine ratios there will always be a predominance of I_2 over HI, equation 10 is effectively eliminated by this concentration effect, and the data will correspond to equations

FIGURE 30
Change of Stoichiometry

EQUATION (4)

III

TITRIMETRIC CONCENTRATION

EQUATION (6)

TITRIMETRIC CONCENTRATION

GLC / SPECTRAL CONCENTRATION

5 and 6. At higher hydride to iodine ratios, more HI will be produced, equation 10 will compete more effectively with equation 5 to the point where equations 3 and 4 accommodate the data. An attempt to illustrate this change of stoichiometry from the 1:1 of equation 5 to the 2:1 of equation 3 is presented in FIGURE 30.

The difference in chemistry between LATBH and LAH is worth considering. Clearly the reduction of HI by LAH competes more effectively with reduction of I_2 than it does in the LATBH case.

One important difference between LAH and LATBH is that LAH has four hydrides while LATBH has one, and it is worth noting that after the reaction of LAH with I_2 , the HI and the modified aluminium species are necessarily produced in the same vicinity. It is possible, therefore, that the efficient reduction of HI to H_2 by LAH is due to this local concentration or solvent cage effect. Such an effect would not be applicable in the LATBH reductions because it is known to be monomeric in solution (132,157). This is illustrated in FIGURE 31.

FIGURE 31

Reactions of LAH and LATBH with I_2

Kinetic Method - Reduction of Ketones by LATBH

General

The kinetic method is based on the spectral kinetic method previously developed for the NaBH_4 reductions (9). The disappearance of the $n-\pi^*$ band of the ketone was followed at about 290 nm., the wavelength being specific for each ketone. The λ_{max} and the molar extinction coefficients for each ketone are collected in TABLE 31. Fortunately THF, LATBH, and the immediate reduction products have no measurable absorbance in this region to obscure the interpretation of the spectral trace. The usual hydride to ketone ratios varied from 0.5 to 2. This range of concentration ratios is certainly more desirable than the huge excesses of hydride used for pseudo-order kinetics in previous studies (38,46,50). This is the first work in which second order kinetics have been stringently tested for this system. Using comparable concentrations of ketone to hydride allows for a more sensitive test of the proposed kinetic scheme. This procedure led to the discrepancy in the standardization procedure that was previously discussed.

The rates of reduction by LATBH are much faster than by NaBH_4 (11) and modifications of the kinetic method were necessary. The ketone solution was injected into a cuvette containing the hydride solution through a specially fitted spectrophotometer cover, the hydride solution had been previously blanked. Simultaneously with this injection, the recorder trace was obtained by activating the recorder. The reproducibility of the injection technique was 2%. This was determined by injecting the ketone solution into a cuvette containing only solvent. The rate of mixing was sufficient since

Extinction Coefficients for Cyclohexanones in THF at

Various Temperatures

λ_{MAX}^a	$\epsilon_{283^\circ\text{K}}^b$	$\epsilon_{292^\circ\text{K}}$	$\epsilon_{298^\circ\text{K}}$	$\epsilon_{305^\circ\text{K}}$
288	15.0	14.9	15.1	14.8
289	15.1	15.0	15.1	15.1
288	15.2	15.1	14.7	14.8
288	15.9	15.6	15.8	15.8
287	16.7	16.5	16.4	16.5
287	17.3	17.2	17.2	17.2
290	18.9	18.8	18.8	18.8
290	17.7	18.0	18.1	17.7
286	18.1	18.2	18.6	18.7
290	18.2	18.3	20.9	18.3
290	19.8	19.8	19.6	19.7
290	15.9	16.5	16.6	16.4
	290	16.1	16.7	16.6	16.6
	295	16.5	16.9	17.0	16.6
	295	14.6	14.6	14.6	14.6

a nm.

b $1 \text{ mole}^{-1} \text{ cm}^{-1}$

the ketone reaches its limiting absorbance within 1.5 seconds, as the reaction time varies from 60 seconds to 30 minutes for the range of ketones studied, the time required for thorough mixing of the solutions is not an important consideration in these results.

Reaction Order - LATBH and 3,3,5- Trimethylcyclohexanone

In any comprehensive kinetic study it is important to know the order of the reaction in order to use the correct rate expression. Although a previous study of the LATBH reduction of cyclohexanones had shown that the order of the reaction was first order in both components (50) by pseudo-order methods, it was deemed necessary to experimentally confirm their findings.

The most obvious method to determine the order of a reaction is to make a direct comparison between rate and concentration. The rate expression for a reaction may be written as

$$-\frac{dx}{dt} = k[A]^a[B]^b \dots\dots$$

where A and B are the components of the reaction, a and b are the experimental exponents, k is the rate constant, and $\frac{dx}{dt}$ is the observed rate. It is convenient to let $-\frac{dx}{dt}$ represent the ketone disappearance since this the measurement upon which the kinetic experiment is based. By holding one component of the reaction constant and varying the other, a series of initial rates is obtained (for reasonable accuracy, only 5-10% of the reaction may be followed (160)).

The experiment may be expressed more conveniently in a

logarithmic manner,

$$\log -\frac{dx}{dt} = \log k + a \log [\text{ketone}] + b \log [\text{LATBH}]$$

A plot of $\log$ (initial rate) as a function of $\log$ (initial ketone concentration), at constant LATBH concentration, gives as the slope the exponent a and as the intercept $\log k + b \log [\text{LATBH}]$. In a similar manner the exponent b for the hydride order may be obtained. Once the values for a and b are known then the rate constant, k , may be evaluated.

The ketone chosen for this study was 3,3,5-trimethylcyclohexanone because it is reduced slowly enough by LATBH to permit a good estimation of the initial rates to be made. The data are summarized in TABLES 32 and 33 and graphically displayed in FIGURES 32 and 33.

TABLE 32

Concentrations and Initial Rates for LATBH Order

<u>[ketone] x 10²</u>	<u>[LATBH] x 10²</u>	<u>(-dx/dt) x 10⁵</u>
2.72	0.443	3.21
	0.660	3.36
	0.866	4.95
	1.055	5.64
$b = 1.03$	1.072	5.87
$k = 0.21 \text{ l mol}^{-1} \text{ s}^{-1}$	1.320	7.55
	1.668	10.78
	2.140	13.32
	2.300	16.00

FIGURE 32

LATBH Order

FIGURE 33

Ketone Order

TABLE 33

Concentrations and Initial Rates for Ketone Order

<u>[ketone] x 10²</u>	<u>[LATBH] x 10²</u>	<u>(-dx/dt) x 10⁵</u>
1.96	1.033	5.19
2.51		6.43
2.57		6.48
4.17		10.21

$$a = 1.10$$

$$k = 0.17 \text{ l mol}^{-1} \text{ s}^{-1}$$

Linear regression analysis of the two plots gave the exponents as 1.10 and 1.03 for the ketone and hydride components respectively. These values are good evidence for the first order nature of each component and provide a rationale for using a second order rate expression to treat the data. The agreement between the rates calculated from the intercepts (average = 0.19) and those from the integrated rate expression (average = 0.17) indicate that the order of the reaction is well represented by a second order process.

Isotopic Purity of LATBD -

Since LATBD is commercially available at a very prohibitive price (\$280.00 for 0.02 moles (161)), it was necessary to prepare this compound via the literature route for the analagous LATBH species (25).

Since the LiAlD_4 used was 99% deuterium, this should mean that the product would also contain 99% deuterium for its active

deuteride. However, recent work in the hydrolysis of borohydride has shown that hydrolysis with D_2O is consistent with a BH_4D^+ intermediate which can lose H_2 as well as the expected HD (92). The possibility that this might occur with the alcoholysis of $LiAlD_4$ seemed a real concern. This could conceivably lower the deuterium content of the LATBD to a very small percentage and obscure the isotope effects that were sought.

By a combination of spectral techniques the percentage deuterium in the synthetic LATBD was demonstrated to be at least 98.5% and the observed kinetic isotope effects were real and not an artefact of isotopic purity. To determine the percentage deuterium in the LATBD required the preparation of a suitable derivative that would allow quantification of the isotope. 4-tert-butylcyclohexanone was reduced with the LATBD in THF and the resulting alcohol analysed for deuterium by nuclear magnetic resonance spectra and by mass spectrometry. Integration of the hydroxy methine proton and comparison to the rest of the integrated spectrum indicated that at least 98% of the C-1 position had been deuterated. In order to further quantify this result, field-ionization mass spectra were obtained (162), (the molecular ion, in an electron impact experiment, for this compound is very small). Mass spectral analysis showed 98.5% deuterium in the sample, thus LATBD must have a deuterium content of at least this value, corresponding well to the 99% deuterium in the starting $LiAlD_4$. This experiment also rules out any $AlHD_4^+$ intermediate in the alcoholysis of $LiAlD_4$.

Comparison of LATBH from Commercial and Synthetic Sources
Rate Identities

As it was necessary to use synthetic LATBD, this required the use of synthetic LATBH to obtain the isotope effects, this would remove any problems associated with comparing rates between reducing agents of different origins which might contain different impurities that could possibly catalyze one reaction and not the other. In order to remove any suspicions as to the identity of the reducing agent and the purity, a comparison between the rates of reduction of several ketones by synthetic and commercial LATBH was undertaken. The results of this study are reported in TABLE 34.

TABLE 34

Comparison of Rates Obtained from Commercial and Synthetic

<u>LATBH</u>		
<u>Ketone</u>	<u>Rate (Commercial)^a</u>	<u>Rate (Synthetic)^a</u>
0.176	0.174
0.096	0.089

^a, l mol⁻¹ s⁻¹

The fact that these rates are close means that there is little doubt as to the identity of the synthetic LATBH, and that comparisons between LATBH and LATBD provide a good value for the isotope effect.

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Kinetic Results

LATBH Reduction Kinetics

A summary of the kinetic results for the LATBH reduction of fifteen cyclohexanones with the temperature dependence of the rate constants and the LATBD results at 298°K are found in TABLE 35. A more comprehensive compilation of the treatment of the raw data, plots of the integrated rate expression, and collection of the rate constants appear in APPENDICES 3 and 4.

Perusal of the data in TABLE 35, at a constant temperature (e.g. 298°K), shows the same general dependence of rate of reduction on structure as did a NaBH_4 study of the same ketones (11,49,51). With the rate of reduction of cyclohexanone taken as a standard, the effect of alkyl substitution may be explored. A methyl group in the 4 position slightly augments the rate, quite possibly by a small ring distortion (49). The rates of reduction of ketones with substitution in the three position are slower than cyclohexanone and the four substituted species. Although 3-cholestanone has two substituents in the four position and only one in the three position it has a rate of reduction comparable to 3-methylcyclohexanone itself. This apparent anomaly is probably due to ring distortions, caused by the ring junction, cancelling the four substituent effect to give a rate comparable to 3-methylcyclohexanone.

The rate of reduction of the 2-alkylcyclohexanones decreases dramatically as the substitution at this position increases. This has been attributed to steric (165), inductive (49), and torsional (30) considerations. These rates parallel those of the NaBH_4

Compiled Rates of Reduction for LATBH and LATBD

Ketone	283°K ^{a,d}	292°K ^{a,d}	298°K ^{a,d}	305°K ^{a,d}	$k_D^{b,d}$	k_H/k_D^b
1.91	2.40	3.31	4.88	3.46	0.96
2.43	2.87	4.39	5.93	4.49	0.98
1.90	2.35	3.42	4.56	3.65	0.94
1.47	1.84	2.80	3.37	3.13	0.90
1.94	2.56	3.12	2.72	0.94
0.985	1.29	1.71	2.42	1.77	0.97
0.576	0.745	1.06	1.36	1.12	0.95
0.471	0.654	0.875	1.08	1.02	0.86
0.277	0.371	0.455	0.753	0.466	0.98
0.0368	0.0683	0.0708	0.118	0.0818	0.98
0.00383	0.00498	0.00712	0.00560	0.89
0.0734	0.127	0.175	0.207	0.168	1.04
0.0753	0.127	0.174	0.208	0.167	1.04
0.0394	0.0627	0.0894	0.106	0.0951	0.94
0.0966	0.123	0.159	0.161	0.77

a. 1 mol⁻¹s⁻¹

b. 298°K

d. average error 5-9%

reductions quite closely (11,49) and it is likely that the same factors play dominant roles in both systems. Substitution of axial alkyl groups into the three and five position of cyclohexanone causes a marked decrease in the rate of reduction of these compounds. 3,3-Dimethyl and 3,3,5-trimethylcyclohexanone have identical rate constants under all conditions; this means that an equatorial three methyl group has a negligible effect on the rate of equatorial attack. In contrast, the introduction of another axial methyl group at C-5 decreases the rate further, this important result is discussed in greater detail in a later section of this thesis.

Since the differences in rates for 4-methylcyclohexanone and 2-tert-butylcyclohexanone are a factor of almost 10^3 the possibility of complexation being the rate-determining step is remote. It would be expected that the rates of complexation between LATBH and this series of ketones would be quite similar and this would then be reflected in the rate constants. This result makes the interpretation of the isotope effects much simpler since the only reasonable mechanism remaining is the rate-limiting hydride transfer process.

It has been suggested that steroids offer a more conformationally rigid system for reduction studies and are preferable to the more flexible monocyclic systems (46). While this point is conceded, the availability of quantities of mono-ketonic steroids of high purity with the variety of substitution necessary to probe the transition state is quite poor. It is likely that the conclusions regarding transition state geometry and position on the reaction coordinate for these classes of compounds would be similar, if not the same.

Experimental Kinetic Isotope Effects

To complement the theoretical calculation of the isotope effects, the experimental isotope effects using LATBD were determined at 298°K. These values are summarized in TABLE 35 and presented in more detail in APPENDICES 3 and 4. Surprisingly, from the point of view of the Dauben postulate, the experimental kinetic isotope effects are quite constant and vary from 1.04 to 0.77 (the error on these isotope effects averages about 0.08) with the average of the fifteen isotope effects being 0.94 ± 0.13 . With the isotope effects being so close to unity there is a temptation to conclude that hydride transfer is not rate-determining, however, the formation of a complex has already been ~~dismissed~~. Thus these isotope effects are consistent with hydride transfer being the rate controlling step if the transition state for this ~~process~~ lies between 0.4 and 0.7 along the reaction coordinate. This is illustrated in FIGURE 34. These values of the isotope effect are consistent with hydride transfer occurring with an angle of transfer between 180° and 122°. Although it is disappointing that no firm conclusions can be made on the geometry of the transition state, what is clear, however, is that the transition states are closely clustered at half hydride transfer. This result is clearly at odds with the proposal of a variable transition state, which is supposed to account for the change of product ratio as steric hindrance about the carbonyl increases.

The concept of the transition state being at half-transfer of the hydride receives considerable support from the ρ value of 2.13 determined by Ayres and coworkers (38). The large value of ρ implies

FIGURE 34

POSITION OF
LATBH TRANSITION STATE

that the transition state contains a good deal of negative charge. A large value for ρ is also consistent with considerable rehybridization at the carbonyl carbon, the kinetic results of Calvet and Levisalles (46) support this point since they note that their results are not consistent with the reactant-like transition state proposed by Klein (50) but with a structure that resembles products because of the large differences in equatorial attack for their ketones.

The concept of a "central" transition state for this reducing species has important ramifications on the concept of Product Development Control which will be dealt with in a separate section of this thesis.

Activation Parameters

The exploration of a reaction mechanism is rarely complete without activation parameters. Little is known about these parameters for the complex metal hydride reduction of ketones. The most extensive work has been on the NaBH_4 reductions of ketones (15,47) and recently, parameters for LiAlH_4 and NaAlH_4 reductions of aromatic ketones have been reported (166). The entropies of activation for these species, albeit for different ketones, indicate that NaBH_4 transition states are more ordered than LiAlH_4 , which in turn, are more ordered than NaAlH_4 ones. It has been suggested that the difference between LiAlH_4 and NaAlH_4 is in the counter-ion carbonyl association in the transition state; in turn it is clear that for NaBH_4 reductions in 2-propanol, the solvent can play a role similar to that of the Li^+ and can account for the very high entropy of activation in this system.

FIGURE 35
Arrhenius Plots

The activation parameters were calculated from the rates of reduction at several temperatures by constructing a plot of $\ln(k/T)$ as a function of T^{-1} . The slope of this plot is $\Delta H^\ddagger/R$ and the intercept is $\Delta S^\ddagger/R - \ln k_B/h$, where $\Delta H^\ddagger$ is the enthalpy of activation, R is the gas constant, $\Delta S^\ddagger$ is the entropy of activation, k_B is the Boltzmann constant, and h is Planck's constant (167).

The rate constants are found in TABLE 35, the Arrhenius plots in FIGURE 35, and TABLE 36 is the tabulation of the activation parameters calculated by least squares analysis of the Arrhenius plots.

The Arrhenius plots are quite interesting since they appear to be nearly parallel for all the ketones. This startling result is borne out by examination of the activation parameters, TABLE 36. All of the ketones have similar slopes but varying degrees of entropy contributions. The major barrier to this reaction is, in fact, entropy. As well, the reduction is apparently controlled by these changes of entropy. That the reaction is controlled by these changes is not immediately obvious from TABLE 36. The construction of an isokinetic plot (172), by plotting $\Delta H^\ddagger$ as a function of $\Delta S^\ddagger$, shows that several lines are defined by the data (see FIGURE 36). One line for the unhindered ketones (predominately axial attack), one for the 2-alkyl ketones, another for the hindered ketones (predominately equatorial attack), and the possibility of another line for the highly hindered, 2-alkyl ketones. The slopes of these lines lead to the isokinetic temperature, β . When β is less than the working temperature then the reaction is said to be entropy controlled (172). All the lines in FIGURE 36 have β less than 270°K and are thus considered to be entropy dominated. The validity of isokinetic

Activation Parameters

	$\Delta G^\ddagger$ a	$\Delta H^\ddagger$ a	$\Delta S^\ddagger$ b
16.7 ± 1.3	6.71 ± 0.39	-33.4 ± 3.1
16.5 ± 1.4	6.61 ± 0.46	-33.2 ± 3.2
16.7 ± 1.2	6.42 ± 0.35	-34.4 ± 3.0
16.8 ± 1.3	6.22 ± 0.36	-35.6 ± 3.0
16.8 ± 1.1	5.84 ± 0.28	-36.9 ± 2.7
17.0 ± 1.1	6.40 ± 0.26	-35.7 ± 2.7
17.4 ± 1.1	6.30 ± 0.26	-37.2 ± 2.7
17.4 ± 1.0	6.20 ± 0.24	-37.9 ± 2.6
17.8 ± 1.5	6.91 ± 0.46	-36.5 ± 2.4
18.9 ± 1.2	8.22 ± 0.31	-35.7 ± 2.9
20.5 ± 0.9	7.80 ± 0.16	-42.6 ± 2.4
18.5 ± 1.2	7.66 ± 0.34	-36.2 ± 3.0
18.5 ± 1.2	7.50 ± 0.31	-36.7 ± 2.9
18.9 ± 1.1	7.35 ± 0.27	-38.6 ± 2.8
18.6 ± 1.1	6.18 ± 0.16	-41.7 ± 3.1

a Kcal/mole

b cal/degree mole

FIGURE 36

Isokinetic Plots

plots is not defended (173,174,175), since the errors on this particular plot tend to nullify any quantitative arguments that might be made. However, the lines that do arise in this plot are consistent with different interactions being met in the transition state for axial and equatorial attack.

The entropies of activation become increasingly more negative as the steric hindrance about the carbonyl increases. This entropy increase may be interpreted as being due to increasing degrees of order or due to a transition state which is subjected to increasing amounts of steric strain. This latter possibility is certainly consistent with a transition state in which hybridization has advanced to a point where secondary steric interactions begin to control the reaction. This is illustrated in FIGURE 37.

FIGURE 37

Secondary Steric Interactions

Product Development Control

Dauben, Fonken, and Noyce (24) presented two postulates for the rationalization of the stereochemical outcome of the hydride reduction of cyclic ketones, "a steric postulate involving competitive attacks from a favoured (unhindered) or an unfavoured (hindered) side which for simplicity can be termed steric approach control" (SAC) and "an energy consideration involving the relative stability of the possible products and which can be termed product development control" (PDC). When these postulates are applied to the reduction of cyclohexanones, then it is clear that SAC applies to hindered ketones and PDC to unhindered ketones. The concept of PDC has been heavily criticized in recent years (19,27-32).

Brown and Deck (25) proposed, in 1965, that the Dauben nomenclature be replaced with the terms "steric strain control" (SSC) and "product stability control" (PSC), thereby avoiding the confusion about kinetic and thermodynamic processes when the reactions under consideration are obviously kinetically controlled. This nomenclature serves to focus attention on the actual epimeric transition states and not on the reaction coordinate itself. Eliel and Senda (19) felt a further clarification of terms was necessary. SAC or SSC was referred to as "the steric strain involving the incoming nucleophile in the transition state" and PDC or PSC was "the difference in strain energy between the transition state and the ground state". Eliel also showed that an axial methyl group in the 3-position slows down the rate of axial attack but not the rate of equatorial attack. PDC would be expected to decrease the rate of equatorial attack if an axial 3 methyl group were present.

Early in 1977, Ashby and Noding (32) provided an elegant method showing that PDC was not operative for LiAlH_4 reductions. They studied the reduction of 7-Norbornanone and exo-2-methyl-norbornanone by LiAlH_4 . Their experiment is outlined in FIGURE 38.

FIGURE 38

Reduction of Norbornanone Derivatives

The 7-norbornanone is symmetric to attack from both directions a and b, the exo-2 methyl system is reduced exclusively from direction c to give the syn alcohol. When equimolar amounts of these two ketones are reduced with a deficient amount of LAH, twice as much 7-norbornol is produced in comparison to the syn alcohol. If PDC were operating, then, this ratio would have been greater than 2:1 since the exo-2-methyl would impede the rate of reduction from direction c. Since the exo-2-methyl group has no effect on the rate of reduction, they concluded PDC plays no role in LiAlH_4 reductions. They also noted, that the same behaviour was observed for LiBH_4 , LiGaH_4 , NaAlH_4 , and NR_4AlH_4 species.

Product Development Control has undergone a major overhaul of definition since the original definition of Dauben, the modern version of this concept bears little resemblance to its forbearer.

What Product Development Control has come to mean in the last several years is summarized below;

Product Development Control may be considered to play an important role in hydride reductions if, factors on the face of the carbonyl, opposite to the face of hydride attack, decrease the rate of reduction.

With this more concise definition of PDC it is possible to explore the possibility of PDC occurring in LATBH and NaBH_4 reductions of ketones. The rates of reduction for axial and equatorial attack of several cyclohexanones by LATBH are presented in TABLE 37.

TABLE 37

Rates for Axial and Equatorial Attack by LATBH

<u>Ketone</u>	k_{ax}^a	k_{eq}^a
3.91	0.483
2.38	0.420
0.019	0.155
0.089

$a. 1 \text{ mol}^{-1} \text{ s}^{-1}$

From this data it is clear that substituents on the same face of the molecule as the hydride attack dramatically decrease the

rate, witness k_{ax} , this is Steric Approach Control. The substituents on the face of the molecule opposite to the direction of hydride attack also cause a decrease in the rate of reduction, k_{eq} . The introduction of an axial methyl group at C-3 decreases the rate of reduction, from cyclohexanone, by a factor of three and another axial methyl group at C-5 decreases the rate by almost a factor of two again. Clearly then, this can only be due to PDC.

The concept of PDC operating for the LATBH reduction of ketones gathers strength from several sources. The kinetic isotope effects are consistent with a transition state which has progressed to half-way along the reaction coordinate. As well, the ρ value of Ayres and coworkers (38) is consistent with a transition state in which a large degree of rehybridization of the carbonyl carbon has occurred. The results of Calvet and Levisalles (46), in which they find that an axial C-5 methyl group decreases the rate of equatorial attack by a factor of fifteen, are also consistent with a transition state where hybridization has progressed to a large degree.

Since the reduction of ketones by NaBH_4 has a more positive ρ value (47) than does the LATBH reduction of ketones this would mean that the transition state for the NaBH_4 reductions would be later than the LATBH one, and thus in the later half of the reaction coordinate. If this were true, PDC would be expected to play an even larger role in these reductions. The rates of reduction of several ketones by NaBH_4 in 2-propanol are presented in TABLE 38. These data are taken from reference 164.

TABLE 38

Ketone	Rates of Reduction by NaBH_4	
	k_{ax}^a	k_{eq}^a
765	125
520	85
10.5	11.3
1.92

$a \text{ l mol}^{-1} \text{ s}^{-1} \times 10^4$

The rates of reduction for equatorial attack parallel those of the LATBH example quite closely except there are much greater differences between individual members of the table. PDC plays a more important role in these reductions than previously suspected (19) and, in fact, plays a larger role in NaBH_4 reductions than in the LATBH case, this being consistent with NaBH_4 having a later transition state than LATBH and being in the later half of the reaction coordinate. TABLE 39 compares the rates of equatorial attack for NaBH_4 and LATBH compared to the rate of reduction of 4-tert-butylcyclohexanone. This table shows that the interactions met in the transition state for equatorial attack are much more pronounced in the NaBH_4 system.

TABLE 39

Comparison of Equatorial Rates of Reduction for NaBH₄ and LATBH

<u>Ketone</u>	<u>LATBH k_{eq}</u>	<u>NaBH₄ k_{eq}</u>
1.00	1.00
0.87	0.68
0.32	0.09
0.18	0.015

TABLE 40 presents data to show that the LiAlH₄ transition state is earlier than the LATBH transition state which in turn is earlier than the NaBH₄ transition state. The ρ values order the reducing agents in the same order as the isotope effects do, if a smaller isotope effect can be interpreted to mean that the reaction is further along the reaction coordinate. Although LiAlH₄ and NaBH₄ isotope effects are complicated by secondary effects, the major contribution in these systems is undoubtedly the primary isotope effect. The isotope effect calculations presented earlier should also be a good approximation for the LiAlH₄ system, this puts the transition state for this species in the earlier half of the reaction coordinate.

The entropies of activation, which are a measure of the order of the system, become increasingly negative across the table. A later transition state should show increased order over an earlier one and

this is apparently observed in these reductions. Product Development Control does not operate for the LiAlH_4 reductions (or at least not in the 7-norbornanone system) whereas it becomes increasingly important in the LATBH and NaBH_4 systems, this means that the LiAlH_4 transition state is earlier than the LATBH transition state which is earlier than the NaBH_4 transition state.

TABLE 40

Comparison of Reducing Agents

<u>Parameter</u>	<u>LiAlH_4</u>	<u>LATBH</u>	<u>NaBH_4</u>
ρ	1.95 (40)	2.13 (38)	3.06 (47)
k_H/k_D	1.27 (166)	0.94	0.65 (20)
$\Delta S^\ddagger$	-26 (166)	-37	-42 (11)
PDC	NO	YES	YES

Conclusions

The results of the experimental work on LATBH are summarized below;

(1) The reduction of ketones by LATBH was confirmed to be second order overall, first order in each component.

(2) The standardization procedure for LATBH based on the reaction of LiAlH_4 with iodine is unsuitable.

(3) The kinetic isotope effects using LATBH and LATBD are closely clustered around 0.94 ± 0.13 , this is consistent with the transition state being just passed half hydride transfer.

(4) No firm conclusions regarding the geometry of the transition state can be made from the isotope effects, except that the carbonyl has undergone a major change in hybridization by the time the transition state is reached.

(5) The reaction is dominated by entropy considerations, which provide most of the barrier to reduction. Entropy tends to increase as the steric hindrance increases about the carbonyl or as the amount of equatorial attack increases.

(6) The enthalpies of activation tend to offset increases of entropy and several isokinetic lines are obtained. Different interactions in the transition state give rise to these lines.

(7) Product Development Control is important in LATBH and NaBH_4 reductions.

(8) The transition state for LiAlH_4 is earlier than for LATBH which in turn is earlier than for the NaBH_4 reduction of ketones.

Experimental

General

Melting points (uncorrected) were taken on a Fisher-Johns apparatus. A Perkin-Elmer 237B Infrared Spectrophotometer and a Beckman Model 25 UV/VIS Spectrometer were used for the infrared and ultraviolet spectra respectively. Proton magnetic resonance spectra were obtained on a Varian T-60 Spectrometer, proton spectra with deuterium decoupling were obtained at the University of Ottawa on a Varian HA-100 instrument. Carbon-13 magnetic resonance spectra were performed on a Varian XL-100 Spectrometer. Gas-liquid chromatography was performed on a Hewlett-Packard F and M Scientific 402 High Efficiency Gas Chromatograph fitted with six-foot glass columns or on a Perkin-Elmer 990 Gas Chromatograph equipped with an Infotronics CRS-208 Electronic Integrator. Mass spectra were obtained at the University of Windsor on a Field- Ionization Mass Spectrometer. Slopes of various linear relationships were obtained via least squares programmes in the University Xerox Sigma-9 computer and the kinetic data were evaluated by the programme HOPE (see APPENDIX 5).

Reagents

Tetrahydrofuran (Fisher) and diglyme (Ansol) were distilled from Lithium Aluminium Hydride (Ventron) under nitrogen immediately before use. Benzene (Fisher) and 2-propanol (Fisher) were distilled under nitrogen and stored over molecular sieves (4Å). All other reagents were used without further purification, care being taken to keep the hydride reagents dry. All ketones were commercially available or were

oxidized from the corresponding alcohols by the Brown procedure (168). All ketones were purified by vacuum distillation or vacuum sublimation except for 3-cholestanone which was used as received (Sigma). The 3,3,5,5-tetramethyl-4-acetyl-cyclohexanone was a gift from Roure-Bertrand et Fils Ltee. (France) and was sublimed before use. All ketones were greater than 99% pure by GLC analysis, except for 2,6-dimethyl-cyclohexanone and menthone which contained 4% and 6% of their epimers (164).

Alcohol Oxidation

The procedure of Brown was followed for the oxidation of the alcohols to the corresponding ketones (168). Stock solution of the oxidizing solution was prepared as below:

100g. (0.33mol.) of $\text{Na}_2\text{Cr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$ were dissolved in 300ml. of distilled water. To this was added, cautiously, with stirring, 136 g. of 98% sulphuric acid (1.34 mol.) and then diluted to 500 ml. with distilled water.

A sample oxidation follows;

To 15.6 g. of 4-tert-butylcyclohexanone (0.10 mol.) in 50 ml. of Mallinkrodt ether in an ice bath 50.0 ml. of the above oxidizing solution was added dropwise over 40 minutes. The solution was magnetically stirred for a total of one hour and diluted with water. The solution was extracted with ether (3x50 ml.) and backwashed with water (3x50 ml.), dried (MgSO_4) and rotary evaporated to give 13.66 g. (90%) of crude 4-tert-butylcyclohexanone which was purified by sublimation (50°C., 1.5 Torr.).

Standardization of NaBH_4 Solutions

Standard KIO_3 Solution (169)

2.645 g. (0.01236 mol.) of dried KIO_3 (2 hours at 120°C) was dissolved in 1000.0 ml. of distilled water.

$$N(\text{KIO}_3) = \text{Molarity} \times 6$$

Preparation of $\text{Na}_2\text{S}_2\text{O}_3$ Solution (169)

27 g. of $\text{Na}_2\text{S}_2\text{O}_3$ was added with 0.1 g. of Na_2CO_3 to one litre of distilled water which had been cooled after boiling for twenty minutes to remove dissolved carbon dioxide. The solution was stored in a dark, glass bottle.

Preparation of Starch Solution (169)

A paste, made of 2 g. of soluble starch and 10 mg. of HgI_2 in 30 ml. of water, was dissolved in one litre of hot water and stored in a dark glass bottle.

Preparation of NaBH_4 Solutions

0.331 g. of NaBH_4 was stirred overnight in 100 ml. of solvent; 2-propanol or diglyme. The solution was gravity filtered and standardized by the procedure that follows.

Standardization of $\text{Na}_2\text{S}_2\text{O}_3$ Solutions

25.0 ml. of standard KIO_3 solution was pipetted into a 250 ml. erlenmeyer flask. Approximately 1-2 g. of KI was added and swirled until dissolution was complete. Upon addition of 10 ml. of 1 M. HCl the dark red colour of I_2 appeared. This solution was titrated immed-

ately titrated with $\text{Na}_2\text{S}_2\text{O}_3$ until a light yellow coloured solution was obtained. The addition of 5 ml. of starch solution gave the characteristic blue-black starch-iodine complex which was titrated to the colourless endpoint.

$$N(\text{Na}_2\text{S}_2\text{O}_3) = N(\text{KIO}_3)(\text{ml. of KIO}_3) / (\text{ml. of Na}_2\text{S}_2\text{O}_3)$$

Standardization of NaBH_4 Solutions (170)

To 25.0 ml. of standard KIO_3 , 1-2 g. of KI was dissolved. 1.0 ml. of the NaBH_4 solution was added and let sit for five minutes. Addition of the acid, $\text{Na}_2\text{S}_2\text{O}_3$, and starch solution was identical to the $\text{Na}_2\text{S}_2\text{O}_3$ standardization.

$$M(\text{NaBH}_4) = \frac{N(\text{KIO}_3)(\text{ml. of KIO}_3) - N(\text{Na}_2\text{S}_2\text{O}_3)(\text{ml. of Na}_2\text{S}_2\text{O}_3)}{8 (\text{ml. of NaBH}_4)}$$

Standardization of LATBH Solutions

Preparation of LATBH Solutions

0.254 g. of LATBH (0.001 mol.) was stirred for several hours in 50 ml. of dry tetrahydrofuran (THF) and then transferred to 12 ml. screw-cap centrifuge tubes. The solutions were centrifuged for 10 min.

Preparation of Iodine Solutions (158)

1.7301 g of iodine (0.00688 mol.) was stirred in 100.0 ml. of dry benzene for twenty-four hours before use (to ensure that all of the I_2 had dissolved)

Titrimetric Analysis for LATBH (158)

5.0 ml. of the LATBH solution was pipetted into an iodine flask containing 10.0 ml. of the iodine solution. The flask was stoppered and swirled periodically (ca. two minutes). 15 ml. of glacial acetic acid was added and the solution titrated with the standardized thiosulfate solution to the starch-iodine endpoint. A blank following the same procedure was run, omitting the hydride solution.

Gas-Liquid Chromatographic Analysis for LATBH

To 5.0 ml. of a stock cyclohexanone solution (0.05416 M. in THF), 5.0 ml. of the hydride solution was added and the vessel stoppered. After two days (the time required for reaction is usually only 2-3 minutes) at room temperature the solution was treated with 1 M. HCl (1 ml.), extracted with ether (2x2 ml.) and analyzed by GLC. After correcting for detector response the concentration of hydride available for reduction was calculated. The GLC analyses were performed on a Hewlett-Packard Fand M gas chromatograph equipped with a QF-1(5%) column. Carrier gas flow was 4 ml./min., oven 86°C., injector and manifold 200°C. The retention times for cyclohexanone and cyclohexanol were 2.9 and 5.8 min. respectively. Peak areas were determined electronically with an Infotronics CRS-208 electronic integrator.

Spectral Determination of LATBH

To 2.0 ml. of hydride solution in a cuvette, which had been fitted with a cover, 1.0 ml. of ketone solution was injected. Simultaneously with injection the chart recorder was activated and the reaction trace obtained. The limiting absorbance was (A_f) was observed after several minutes. The initial concentration of the ketone solution was divided

by three to allow for dilution, this gives rise to A_0 .

$$M(\text{LATBH}) = A_0 - A_f / \epsilon$$

Temperature Control of Kinetic Experiments

Solutions of ketone, hydride, and solvent were thermostated, in a GCA / Scientific Precision Circulating System 254 bath, for at least 30 minutes before use. The Beckman Model 25 UV/VIS Spectrophotometer was capable of maintaining an internal running temperature of 25.0°C. or 32°C. For kinetic work at 19°C. a Koldwave Air Conditioner (10K BTU) was successful in lowering the room temperature to 16°C. and it was found that the internal running temperature of the spectrophotometer held constant at $19 \pm 1^\circ\text{C}$. A cold room, courtesy of Professor Tsai, was used for the 10°C. kinetics. The temperature of the cold room was originally 4°C. but gradually warmed to 6°C. while the experiments were being set up. The internal running temperature of the spectrometer under these conditions was $10 \pm 1^\circ\text{C}.$

Experiments on the Mechanism of the NaBH_4 Reduction of Ketones

Alkoxy Group Exchange in NaB(OR)_4 Species

The following experiment is typical;

0.250 g. of NaB(OMe)_4 was stirred in 50 ml. of 2-propanol, suction filtered through a fine sintered glass filter and stirred for twenty-four hours at room temperature. About 80% of the solvent was removed by vacuum evaporation at room temperature or until precipitation of the product had occurred, 10 ml. of dry benzene was added and the mixture

centrifuged for five minutes. This was repeated 5-6 times after the supernatant benzene was removed. The addition of benzene caused an apparent coagulation or gelling of the NaB(OR)_4 species. The remaining benzene was removed on a vacuum line. The solid residue was dissolved in 0.5 ml. of D_2O and the nuclear magnetic resonance spectra recorded. The resultant alcohol was extracted from the D_2O with ether, dried over MgSO_4 , and analyzed by GLC on a Carbowax 3000 column. The identity of the alcohols was confirmed by peak enhancement using authentic samples.

Photochemical Catalysis of NaBH_4 Reductions of Ketones in Diglyme

A typical procedure follows;

1.30 g. of 3,3,5,5-tetramethylcyclohexanone (0.0084 mol.) was dissolved in 50 ml. of dry diglyme containing 1.27 g. of NaBH_4 (0.033 mol.).

The solution was divided among two flasks; one for the photochemical experiment and the other for the control (dark) reaction. The 25 ml. aliquot was photolyzed in a (W-K)² low pressure lamp (Nuclear Supplies) at 254 nm in a quartz vessel for 25 minutes. The solution was removed from the reactor, acidified with 1 M HCl (100 ml.), extracted with ether (3x25 ml.), and backwashed with ice-water (4x50 ml.) to remove excess diglyme. The solvent was removed by rotary evaporation after drying (Na_2SO_4) to yield a white solid which recrystallized from petroleum ether (30-60) at 0°C.. The spectral and physical properties were in accord with an authentic sample of 3,3,5,5-tetramethylcyclohexanol. Less than 1% reduction had occurred in the non-photolyzed reaction. This shows that the reaction observed is not due to a thermal reaction nor to a reaction that occurs on workup.

Kinetics of Reduction by NaBH_4 in Diglyme, Catalyzed by Pr^iOH

A solution of 2-propanol in diglyme of desired molarity was prepared (0.5 to 13 M.). To one half of this solution was added enough NaBH_4 to give a solution of about 0.06 M., which was stirred for one hour, gravity filtered and standardized. The ketone solution was made by dissolving a weighed quantity of ketone into the remaining mixed solvent. These solutions were thermostated at 25.0°C for thirty minutes. 1.0 ml. of the hydride solution was pipetted into a cuvette and the spectrophotometer blanked at 290 nm.. 1.0 ml. of the ketone solution was added and the cell inverted three times and then quickly placed in the thermostated spectrophotometer. Time zero was taken as the time of half addition of the ketone solution. The times and absorbance readings were recorded at appropriate times, the rate constants were evaluated using the programme HOPE, found in APPENDIX 5. For solutions with very low alcohol concentrations $\text{NaB(OPr}^i)_4$ tended to precipitate out and it was necessary to conduct these kinetics using larger volumes of solutions (20 ml. total). A small aliquot was filtered into the cuvette just before a reading was required. The data for this experiment may be found in APPENDIX 1.

Solvent Isotope Effects and Sodium Isopropoxide Catalysis

A solution of NaBH_4 in 2-propanol or 2-propanol-OD was filtered and standardized. 1.0 ml. of this solution was placed in a cuvette containing either sodium isopropoxide in 2-propanol or 2-propanol-OD, depending on which experiment was being performed. The cuvette was placed in the spectrophotometer and blanked at the appropriate wavelength for the ketone studied. 1.0 ml. of the ketone solution was added and the cuvette inverted three times, the recorder was activated

at half addition of the ketone solution. Points taken from the decay trace were used to calculate the rate constants. For the reactions with sodium isopropoxide the cuvette contents were poured into 10 ml. of 1 M. HCl, extracted with ether (3x5 ml.), dried (MgSO_4) and analyzed by GLC on a Qf-1 (5%) column.

Recovery of Unreacted NaBH_4 , Investigation of Disproportionation

A typical experiment follows;

0.25 g. of NaBH_4 (0.0066 mol.) and 0.75 g. of NaBD_4 (0.018 mol.) were stirred magnetically, each in 25 ml. of 2-propanol. These solutions were standardized after gravity filtration. Appropriate volumes of the two solutions were combined and to this was added a 1 ml. solution of ketone whose concentration would give 50% oxidation of the borohydride species present in the solution. This solution was stirred magnetically for 2 hours in the case of cyclohexanone and 2 days for 3,3,5,5-tetramethylcyclohexanone. The solvent was removed on the rotary evaporator and the solid residue taken up in D_2O . The proton spectrum of the mixed borohydride species was obtained by refluxing 2.0 g. of NaBH_4 in 50 ml. of D_2O for 48 hours. The spectra reproduced in this thesis are of the second, lowest field portion of the quartet produced by the boron-11 nucleus. This avoids the problem of interference by isopropoxide in dilute samples.

Experiments on the Mechanism of Reduction of Ketones by LATBH

Preparation of Synthetic LATBH and LATBD (25)

3.98 g. of LiAlH_4 (0.105 mol.) was stirred magnetically for three hours, at room temperature, in 200 ml. of Mallinkrodt ether. This grey suspension was filtered through 30 g. of Celit 545 on medium sintered glass filter under aspirator pressure. The clear filtrate was stirred at 0°C . and tert-butanol with 2% ether (to prevent the alcohol from crystallizing) was added dropwise over one hour. Intense foaming of the solution signaled the near-end of the reaction. Several more drops of tert-butanol resulted in the precipitation of LATBH from solution as a fine, white powder. The LATBH was collected in a fine sintered glass filter under aspirator pressure, washed with ether (3x 20 ml.) and then evacuated for 20 hours at room temperature.

Yield: 12.1 g. (45% based on all LiAlH_4)

Infrared: (Al-H) 1750 cm^{-1} (liquid cell, in THF), 1750 cm^{-1} (KBr disc), 1760 cm^{-1} (lit. 132)

Spectral Kinetic Method for LATBH Reduction of Ketones

A solution of centrifuged LATBH in THF was equilibrated at the appropriate temperature for thirty minutes before use. 2.0 ml. of the hydride solution was pipetted into a 3 ml. quartz cuvette in the spectrometer. A cuvette cover, which had a hole for the delivery of the ketone solution, was taped on. The tape was punctured with a Pasteur pipette and the spectrometer cover closed. The solution was zeroed at the appropriate wavelength of the ketone to be studied, with the manual baseline control. To a 1.0 ml. volumetric flask the ketone solution was added to the mark and removed with a Pasteur pipette.

This ketone solution was injected through a special spectrophotometer cover into the cuvette containing the hydride solution. Simultaneously, with this injection the chart recorder was activated and the reduction trace obtained. Zero time was taken as the time the ketone was injected and the chart recorder activated. The concentration of the ketone was calculated gravimetrically and checked by taking the absorbance of the ketone solution before reduction. The molar extinction coefficient of the ketone was used to calculate the ketone concentration at various times in the reduction. The hydride concentration was calculated from the reduction of several unhindered ketones by the spectral method previously discussed. The data were treated by plotting $\ln(a-x)/(b-x)$ against time, where a is the initial ketone concentration, b is the initial hydride concentration, and x is the concentration of the product alcohol at time t . The slope of this plot is equal to $k(a-b)$, where k is the second order rate constant, this was computed by the programme HOPE (APPENDIX 5)

Product Ratios of Ketones Reduced by LATBH

A typical determination follows;

0.101 g. of 3-methylcyclohexanone was dissolved in 3 ml. of dry THF and thermostated at 25.0°C.. To this was added 20 ml. of a standardized LATBH solution, the hydride to ketone ratio was usually 2:1. This was thoroughly mixed and let sit for twenty-four hours. The solution was quenched with 20 ml. of 1 M. HCl and extracted with ether (5x10 ml.), dried (Na_2SO_4) and rotary evaporated to yield an oil (0.098 g.). GLC analysis led to the product ratios in TABLE 41, the retention times of the various alcohols on the appropriate columns are listed in TABLE 41.

TABLE 41

GLC Conditions and Product Ratios for LATBH Reductions at 298°K

	Column	Oven ^a	Retention Times ^b		Axial % ^d	Equat % ^d
			Axial	Equat
TCEP	100	9.5	10.9	15	85
TCEP	100	29.7	40.9	10	90
TCEP	100	9.3	10.6	14	86
^c	XE-60	246	14.8	16.5	7	93
TCEP	50	35.1	36.6	23	77
TCEP	100	12.2	14.1	36	64
TCEP	100	12.4	14.1	34	66
TCEP	80	7.5	8.2	45	55
TCEP	100	16.5	21.2	38	62
TCEP	100	15.6	17.8	58	42
TCEP	100	10.1	14.1	11	89

^a °C
^b minutes
^d ± 1%

Kinetics of Reduction with 3,3,5,5-tetramethyl-4-acetyl-cyclohexanone and LATBH/LATBD.

The kinetic analysis of the title compounds posed a difficulty which was not satisfactorily overcome. This compound has two ketone functionalities, cyclic and acyclic, only the ring ketone is reduced under these conditions (164), the acetyl ketone remaining intact. The kinetic experiment is based on a spectral method and the observed extinction coefficient is due to both of these ketones. The problem lies in dividing up the extinction coefficient into the two components. Actually, the problem is quite complex because the conformation of the starting diketone is unknown in THF solution (12).

Thus the extinction coefficient measured for the starting diketone reflects this equilibrium and has four contributions from the four ketones. The simple assumption of dividing the extinction coefficient into two equal parts does not reflect the subtle differences that alkyl substituents are known to play on the system. The approach to the problem was to allow the diketone to reduce as far as possible under the conditions of a normal kinetic experiment. An approximate extinction coefficient was estimated from this change in absorbance. This value was the lowest measured for the ketones in this study and probably reflects incomplete reduction. The rates of reduction are high when compared to the analogous 3,3,5,5-tetramethylcyclohexanone and may be due to this extinction coefficient.

The effect of these approximations on the kinetic results for this ketone may be estimated. It is likely that, of the activation parameters, only the entropy of activation will undergo a significant change. The enthalpy of activation will not be significantly different and the kinetic isotope effect should remain the same since the same approximations were made for each isotope.

APPENDIX 1

Data for Kinetics of Reduction by NaBH_4 of Ketones in DiglymeCatalyzed by Pr^iOH

$[\text{Ketone}]^a$	$[\text{NaBH}_4]^a$	$[\text{Pr}^i\text{OH}]^a$	$k \times 10^4{}^b$	r^c
0.02182	0.1451	0.503	2.99	0.999
0.02307	0.0926	0.670	4.94	0.993
0.01028	0.0384	0.740	6.80	0.997
0.01898	0.0947	0.968	9.19	0.998
0.01534	0.0836	1.188	12.90	0.995
0.01761	0.0741	1.400	16.42	0.992
0.01932	0.1296	1.605	21.74	0.994
0.01535	0.0292	2.183	41.33	0.992
0.01898	0.0292	2.183	35.42	0.990
0.07428	0.0350	2.620	46.70	0.999
0.01658	0.0350	2.620	51.51	0.998
0.02818	0.0454	3.396	66.87	0.999
0.01582	0.0454	3.396	67.41	0.995
0.07956	0.0246	4.332	85.15	0.996
0.05038	0.0649	4.332	112.7	0.996
0.04452	0.0581	6.500	138.0	0.999
0.03925	0.0974	6.500	157.2	0.999
0.01875	0.1157	8.730	169.0	0.999
0.01289	0.1591	8.730	159.7	0.999
0.03046	0.0775	8.730	179.7	0.999
0.03105	0.1299	8.730	181.1	0.999
0.00791	0.1907	10.400	228.0	0.999
0.01875	0.0930	10.400	247.3	0.999
0.02783	0.1560	10.400	243.4	0.999
0.01763	0.1401	10.400	235.0	0.999
0.01582	0.1949	13.10	733.0	0.999

a mole/litre

b $\text{l mol}^{-1}\text{s}^{-1}$

c Correlation coefficient

APPENDIX 2

Kinetic Data for the Reduction of Ketones in PrⁱOD by NaBH₄Cyclohexanone

<u>Solvent</u>	<u>[Ketone]</u> ^a	<u>[NaBH₄]</u> ^a	<u>k x 10⁴</u> ^b	<u>r</u> ^c
Pr ⁱ OH	0.01954	0.01795	716.0	0.999
Pr ⁱ OH	0.04446	0.01795	787.0	0.999
Pr ⁱ OH	0.03069	0.01795	686.0	0.999
Pr ⁱ OD	0.02861	0.00788	346.0	0.997
Pr ⁱ OD	0.02670	0.00788	356.0	0.998

3,3,5-Trimethylcyclohexanone

<u>Solvent</u>	<u>[Ketone]</u> ^a	<u>[NaBH₄]</u> ^a	<u>k x 10⁴</u> ^b	<u>r</u> ^c
Pr ⁱ OH	0.02424	0.01533	21.6	0.998
Pr ⁱ OH	0.02424	0.01533	23.7	0.999
Pr ⁱ OD	0.01046	0.01853	15.3	0.998

a moles/litre

b l mol⁻¹s⁻¹

c Correlation coefficient

APPENDIX 3

Sample Kinetic Data for LATBH and LATBD Reductions ofCyclohexanone at 298°K.

[Ketone]^a = 0.03775, [LATBH]^a = 0.0351, ϵ = 15.1, see FIGURE 39

Time ^c	Absorbance	a-x	b-x	$\ln(a-x/b-x)b/a$
2.4	0.460	0.03046	0.02782	0.01821
3.6	0.430	0.02848	0.02583	0.02487
4.8	0.393	0.02603	0.02338	0.03457
6.0	0.361	0.02391	0.02126	0.04466
7.2	0.336	0.02225	0.01960	0.05398
8.4	0.314	0.02079	0.01815	0.06349
9.6	0.292	0.01934	0.01669	0.07454
10.8	0.272	0.01801	0.01536	0.08628
12.0	0.255	0.01689	0.01424	0.09784
13.2	0.241	0.01596	0.01331	0.10870
14.4	0.230	0.01523	0.01258	0.11826
15.6	0.218	0.01444	0.01179	0.12991
16.8	0.208	0.01377	0.01113	0.14077
18.0	0.199	0.01318	0.01053	0.15160
19.2	0.190	0.01258	0.00993	0.16358

[Ketone]^a = 0.03775, [LATBD]^a = 0.0341, ϵ = 15.1, see FIGURE 40

Time ^c	Absorbance	a-x	b-x	$\ln(a-x/b-x)b/a$
2.4	0.462	0.03060	0.02696	0.02525
3.6	0.430	0.02828	0.02484	0.03535
4.8	0.393	0.02603	0.02239	0.04923
6.0	0.362	0.02397	0.02034	0.06325
7.2	0.337	0.02232	0.01868	0.07661
8.4	0.311	0.02060	0.01696	0.09303
9.6	0.293	0.01940	0.01577	0.10629
10.8	0.275	0.01821	0.01457	0.12151
12.0	0.262	0.01735	0.01371	0.13398
13.2	0.248	0.01642	0.01279	0.14907
14.4	0.235	0.01556	0.01192	0.16494
15.6	0.224	0.01483	0.01120	0.18004
16.8	0.215	0.01424	0.01060	0.19373
18.0	0.206	0.01364	0.01000	0.20884
19.2	0.197	0.01305	0.00941	0.22560

a moles/litre, b l mol⁻¹ cm⁻¹, c seconds

FIGURE 39

Second Order Rate Plot

FIGURE 40

Second Order Rate Plot

Sample Kinetic Data for LATBH and LATBD Reductions of
3,3,5,5,-Tetramethylcyclohexanone at 298°K.

[Ketone]^a = 0.01825, [LATBH]^a = 0.04404, ϵ = 17.6^b, see FIGURE 41

Time ^c	Absorbance	a-x	b-x	$\ln(a-x/b-x)b/a$
12	0.308	0.01757	0.04336	-0.02256
24	0.293	0.01671	0.04250	-0.05255
36	0.280	0.01597	0.04176	-0.08033
48	0.265	0.01512	0.04090	-0.11468
60	0.254	0.01449	0.04028	-0.14162
72	0.247	0.01409	0.03988	-0.15960
84	0.236	0.01341	0.03919	-0.19209
96	0.225	0.01284	0.03862	-0.22091
108	0.216	0.01232	0.03811	-0.24835
120	0.207	0.01181	0.03759	-0.27735
132	0.198	0.01129	0.03708	-0.30805
144	0.190	0.01084	0.03662	-0.33691
156	0.182	0.01038	0.03617	-0.36738
168	0.176	0.01004	0.03583	-0.39140
180	0.170	0.00970	0.03548	-0.41648

[ketone]^a = 0.01825, [LATBD]^a = 0.03020, ϵ = 17.6^b, see FIGURE 42

Time ^c	Absorbance	a-x	b-x	$\ln(a-x/b-x)b/a$
12	0.315	0.01797	0.02991	-0.00626
24	0.305	0.01740	0.02934	-0.01927
36	0.295	0.01683	0.02877	-0.03297
48	0.286	0.01631	0.02826	-0.04595
60	0.277	0.01580	0.02775	-0.05959
72	0.270	0.01540	0.02735	-0.07069
84	0.262	0.01495	0.02689	-0.08394
96	0.252	0.01438	0.02632	-0.10141
108	0.245	0.01398	0.02592	-0.11430
120	0.239	0.01363	0.02558	-0.12580
132	0.233	0.01329	0.02524	-0.13776
144	0.226	0.01289	0.02484	-0.15231
156	0.220	0.01255	0.02450	-0.16534
168	0.215	0.01226	0.02421	-0.17662
180	0.210	0.01198	0.02393	-0.18830

a moles/litre, b l mol⁻¹cm⁻¹, c seconds

FIGURE 4I

Second Order Rate Plot

FIGURE 42

Second Order Rate Plot

APPENDIX 4

Cumulative Reduction Data for LATBH and LATBD Kinetics

Ketone	$^{\circ}\text{K.}$	[Ketone] ^a	[LATBH] ^a	k ^b	r ^c	$k_{\text{ave.}}$ ^d
305	0.05284	0.03114	4.71	0.999	4.88 $\pm$ 0.57
		0.03074	0.02526	4.41	0.999	
		0.03074	0.02526	5.52	0.999	
	298	0.03775	0.03510	3.32	0.999	3.31 $\pm$ 0.08
		0.03775	0.03510	3.34	0.999	
		0.03808	0.02500	3.17	0.999	
		0.03861	0.02500	3.40	0.998	
		0.06536	0.03173	3.36	0.999	
		0.06536	0.03173	3.32	0.999	
		0.03848	0.03173	3.23	0.999	
	292	0.06177	0.03893	2.49	0.994	2.40 $\pm$ 0.18
		0.06177	0.03893	2.60	0.998	
		0.5158	0.02534	2.20	0.999	
		0.5158	0.02534	2.31	0.999	
	283	0.04247	0.02462	1.93	0.997	1.91 $\pm$ 0.03
		0.04247	0.02462	1.89	0.999
305	0.03245	0.03114	5.51	0.999	5.93 $\pm$ 0.32
		0.03245	0.03114	6.05	0.996	
		0.03417	0.02526	5.88	0.999	
		0.03417	0.02526	6.28	0.998	
	298	0.02987	0.0351	4.28	0.999	4.39 $\pm$ 0.16
		0.02987	0.0351	4.46	0.999	
		0.03033	0.0250	4.57	0.999	
		0.03914	0.0317	4.24	0.998	
	292	0.03775	0.03894	3.12	0.999	2.87 $\pm$ 0.18
		0.03775	0.03894	2.84	0.999	
		0.03404	0.02534	2.82	0.999	
		0.03404	0.02534	2.69	0.999	
	283	0.03411	0.02462	2.42	0.999	2.43 $\pm$ 0.01
		0.03411	0.02462	2.44	0.999	

Ketone

°K.

[ketone]^a[LATBH]^ab
kc
rd
k_{ave}

305

0.02615
0.026150.03114
0.031144.66
4.460.998
0.999

4.56 ±0.14

298

0.03156
0.03156
0.02939
0.033040.03510
0.03510
0.03510
0.030393.71
3.45
3.25
3.280.999
0.999
0.998
0.996

3.42 ±0.18

292

0.03722
0.03722
0.02947
0.029470.03893
0.03893
0.02543
0.025432.29
2.34
2.38
2.390.999
0.999
0.999
0.999

2.35 ±0.05

283

0.03638
0.036380.02462
0.024622.07
1.720.999
0.999

1.90 ±0.25

305

0.03215
0.03215
0.03108
0.031080.03114
0.03114
0.02526
0.026253.93
3.29
3.30
2.960.996
0.999
0.999
0.999

3.37 ±0.41

298

0.04911
0.04911
0.03525
0.03525
0.03411
0.034110.03510
0.03510
0.02500
0.02500
0.03173
0.031732.92
2.96
2.78
2.79
2.77
2.590.999
0.996
0.998
0.997
0.999
0.998

2.80 ±0.13

292

0.02919
0.02919
0.03544
0.035440.03893
0.03893
0.02534
0.025341.86
1.85
1.85
1.790.999
0.999
0.999
0.998

1.84 ±0.03

283

0.03252
0.032520.02462
0.024621.49
1.440.998
0.999

1.47 ±0.04

Ketone	$^{\circ}\text{K.}$	[Ketone] ^a	[LATBH] ^a	$\frac{b}{k}$	$\frac{c}{r}$	k_{ave}^d
305	0.01762	0.03114	3.18	0.999	3.12 $\pm$ 0.21
		0.01762	0.03114	3.30	0.999	
		0.01729	0.02526	3.19	0.999	
		0.01729	0.02526	2.82	0.999	
	298	0.02573	0.03510	2.72	0.999	2.56 $\pm$ 0.14
		0.02573	0.03510	2.58	0.999	
		0.02451	0.02500	2.65	0.999	
		0.02263	0.03173	2.48	0.994	
		0.02263	0.03173	2.36	0.999	
	292	0.02451	0.03893	1.86	0.999	1.94 $\pm$ 0.07
		0.02745	0.02534	1.98	0.998	
		0.02745	0.02534	1.99	0.999	
	283	0.02397	0.02462	1.74	0.999	2.42 $\pm$ 0.31
	305	0.03025	0.03114	2.64	0.990	
		0.03292	0.02526	2.20	0.999	
	298	0.03279	0.03510	1.72	0.999	
		0.03279	0.03510	1.75	0.999	
		0.03227	0.02500	1.86	0.994	
		0.03227	0.02500	1.54	0.991	
		0.03779	0.03173	1.82	0.999	
		0.03779	0.03173	1.58	0.997	
	292	0.03294	0.03893	1.26	0.999	
		0.03294	0.03893	1.26	0.999	
		0.03375	0.02534	1.32	0.999	
		0.03375	0.02534	1.30	0.999
283	0.03235	0.02462	969	0.999	0.985 $\pm$ 0.03
		0.03235	0.02462	0.01	0.999	

Ketone	°K.	[Ketone] ^a	[LATBH] ^a	^b k	^c r	^d k _{ave}
305	0.02842	0.03114	1.39	0.999	1.36 ±0.10
		0.02842	0.03114	1.48	0.999	
		0.02498	0.02526	1.23	0.999	
		0.02498	0.02526	1.30	0.999	
	298	0.02896	0.03510	0.982	0.997	1.06 ±0.12
		0.02480	0.02500	0.921	0.999	
		0.02480	0.02500	1.12	0.999	
		0.02832	0.02500	1.19	0.999	
	292	0.02810	0.03893	0.800	0.999	0.745 ±0.047
		0.02810	0.03893	0.759	0.999	
		0.02690	0.02534	0.729	0.999	
		0.02690	0.02534	0.690	0.999	
	283	0.02422	0.02462	0.563	0.999	0.576 ±0.018
		0.02422	0.02462	0.589	0.999
305	0.02498	0.03114	1.09	0.999	1.08 ±0.07
		0.02498	0.03114	1.16	0.999	
		0.01895	0.02526	1.08	0.999	
		0.01895	0.02526	1.00	0.999	
	298	0.02678	0.03893	0.775	0.999	0.875 ±0.104
		0.02678	0.03893	0.840	0.999	
		0.02286	0.02500	1.04	0.997	
		0.02048	0.03173	0.814	0.999	
		0.02048	0.03173	0.903	0.999	
	292	0.02679	0.03510	0.652	0.999	0.654 ±0.035
		0.02679	0.03510	0.670	0.999	
		0.02324	0.02534	0.688	0.999	
		0.02324	0.02534	0.606	0.997	
	283	0.02614	0.02462	0.480	0.998	0.471 ±0.013
		0.02614	0.02462	0.462	0.998	

Ketone	°K.	[Ketone] ^a	[LATBH] ^a	^b k	^c r	^d k _{ave}
305	0.02984	0.03114	0.777	0.999	
		0.02984	0.03114	0.787	0.998	
		0.02529	0.02526	0.791	0.994	
		0.02529	0.02526	0.656	0.999	
	0.753 ±0.065					
	298	0.02667	0.04404	0.433	0.999	
		0.02667	0.04404	0.455	0.999	
		0.02324	0.02500	0.467	0.998	
		0.02718	0.03173	0.477	0.999	
		0.02718	0.03173	0.478	0.999	
0.01517		0.03601	0.433	0.998		
0.01517		0.03601	0.442	0.998		
0.455 ±0.02						
292	0.02777	0.03893	0.364	0.999		
	0.02777	0.03893	0.359	0.998		
	0.02686	0.02534	0.403	0.997		
	0.02686	0.02534	0.359	0.996		
0.371 ±0.02
283	0.02770	0.02462	0.277	0.999	
	305	0.01981	0.03114	0.132	0.999	
		0.01981	0.03114	0.132	0.999	
		0.01948	0.02526	0.101	0.999	
		0.01948	0.02526	0.105	0.999	
	0.118 ±0.017					
	298	0.01671	0.03510	0.0749	0.998	
		0.01671	0.03510	0.0714	0.997	
		0.01848	0.03173	0.0940	0.999	
		0.01848	0.03173	0.0925	0.999	
		0.02071	0.03070	0.0727	0.999	
		0.02071	0.03070	0.0735	0.998	
	0.0798 ±0.010					
	292	0.02073	0.03893	0.0673	0.998	
		0.02073	0.03893	0.0719	0.999	
		0.02385	0.02534	0.0675	0.999	
		0.02385	0.02534	0.0665	0.999	
	0.0683 ±0.002					
	283	0.02075	0.02462	0.0368	0.999	

Ketone	°K.	[Ketone] ^a	[LATBH] ^a	k ^b	r ^c	k _{ave} ^d
305	0.02457	0.03114	0.225	0.999	0.208 ±0.015
		0.02457	0.03114	0.216	0.999	
		0.02256	0.02526	0.193	0.999	
		0.02256	0.02526	0.197	0.999
298	0.02681	0.04404	0.165	0.999	0.174 ±0.008
		0.02917	0.02500	0.165	0.999	
		0.02856	0.03173	0.177	0.999	
		0.02856	0.03173	0.189	0.999	
		0.01359	0.04001	0.177	0.999	
		0.01359	0.04001	0.173	0.999	
		0.01329	0.03600	0.179	0.999	
		0.01329	0.03600	0.171	0.999
292	0.01800	0.03893	0.123	0.999	0.127 ±0.003
		0.01800	0.03893	0.126	0.999	
		0.02233	0.02534	0.128	0.999	
		0.02233	0.02534	0.129	0.999
283	0.02571	0.02462	0.0754	0.999	0.0753 ±0.0002
		0.02571	0.02462	0.0751	0.994
310	0.01727	0.05330	0.121	0.997	0.106 ±0.01
	305	0.02431	0.03114	0.117	0.999	
		0.02431	0.03114	0.111	0.999	
		0.02444	0.02526	0.100	0.999
298	0.02444	0.2526	0.0959	0.999	0.0894 ±0.004
		0.01825	0.03510	0.0919	0.999	
		0.01825	0.03510	0.0913	0.999	
		0.02310	0.02500	0.0867	0.999	
		0.02310	0.02500	0.0847	0.999	
		0.01905	0.03173	0.0809	0.999	
		0.01905	0.03173	0.0922	0.999	
		0.01055	0.04001	0.0887	0.999	
		0.01055	0.04001	0.0917	0.999	
		0.01410	0.03600	0.0869	0.999	
		0.01410	0.03600	0.0886	0.999	
		0.01410	0.03600	0.0886	0.999
292	0.02656	0.03893	0.0642	0.999	0.0627 ±0.001
		0.02656	0.03893	0.0626	0.999	
		0.02233	0.02534	0.0622	0.999	
		0.02233	0.02534	0.0620	0.999	

Ketone	°K.	[Ketone] ^a	[LATBH] ^a	^b <u>k</u>	^c <u>r</u>	^d <u>k_{ave}</u>
283	0.02571	0.02462	0.0411	0.996	0.0394 ±0.002
		0.02571	0.02462	0.0377	0.993	
	305	0.00847	0.03114	0.168	0.999	0.159 ±0.013
		0.00847	0.03114	0.150	0.999	
	298	0.00870	0.03070	0.112	0.998	0.123 ±0.016
		0.00870	0.03070	0.121	0.999	
		0.01986	0.04001	0.146	0.998	
		0.01986	0.04001	0.112	0.999	
	292	0.00753	0.03893	0.107	0.999	0.0966 ±0.008
		0.00753	0.03893	0.0969	0.997	
		0.00959	0.02534	0.0886	0.999	
		0.00959	0.02534	0.0940	0.997	

LATBD Reductions at 298°K.

Ketone	^a [Ketone]	^a [LATBD]	^b k	^c r	^d k _{ave}
0.03775	0.03411	3.27	0.999	3.46 ± 0.15
	0.03775	0.03411	3.30	0.999	
	0.03808	0.02499	3.57	0.999	
	0.03808	0.02499	3.64	0.999	
	0.06536	0.02092	3.40	0.999	
	0.04967	0.04070	3.46	0.994	
	0.04967	0.04070	3.59	0.993
0.02987	0.03411	4.26	0.999	4.49 ± 0.32
	0.02987	0.03411	4.96	0.996	
	0.03033	0.02499	4.58	0.996	
	0.03914	0.02092	4.13	0.998	
	0.04258	0.04070	4.27	0.991	
	0.04258	0.04070	4.71	0.999
0.03073	0.03411	3.65	0.998	3.66 ± 0.15
	0.02881	0.02499	3.59	0.999	
	0.02881	0.02499	3.89	0.999	
	0.03437	0.02092	3.56	0.998	
	0.03238	0.04070	3.77	0.998	
	0.03238	0.04070	3.47	0.999
0.05139	0.03411	2.90	0.999	3.13 ± 0.27
	0.05139	0.03411	3.24	0.991	
	0.03689	0.02499	3.40	0.995	
	0.03689	0.02499	2.80	0.997	
	0.03258	0.04070	3.32	0.999
0.02598	0.03411	2.59	0.996	2.72 ± 0.16
	0.02598	0.03411	2.84	0.999	
	0.02457	0.02499	2.83	0.999	
	0.02457	0.02499	2.77	0.999	
	0.02226	0.02092	2.84	0.999	
	0.02226	0.02092	2.45	0.998
0.03279	0.03411	1.72	0.999	1.77 ± 0.16
	0.03279	0.03411	1.75	0.999	
	0.03227	0.02499	1.61	0.997	
	0.03517	0.02092	1.99	0.998	

Ketone	[Ketone] ^a	[LATBD] ^a	<u>k</u> ^b	<u>r</u> ^c	<u>k_{ave}</u> ^d
0.02888	0.03411	1.05	0.999	1.12 ±0.08
	0.03279	0.03411	1.06	0.999	
	0.02473	0.02499	1.07	0.999	
	0.02473	0.02499	1.11	0.998	
	0.02824	0.02092	1.22	0.999	
	0.02824	0.02092	1.23	0.998
0.02674	0.03411	0.858	0.997	1.02 ±0.15
	0.02674	0.03411	0.845	0.999	
	0.02282	0.02499	0.974	0.999	
	0.02282	0.02499	1.14	0.997	
	0.02044	0.02092	1.17	0.999	
	0.02044	0.02092	1.15	0.995
0.02666	0.03411	0.390	0.997	0.466 ±0.073
	0.02666	0.03411	0.397	0.995	
	0.02715	0.02499	0.566	0.992	
	0.01516	0.05001	0.489	0.999	
	0.01516	0.05001	0.489	0.999
0.01679	0.03411	0.0792	0.998	0.0818 ±0.006
	0.01679	0.03411	0.0756	0.999	
	0.02095	0.02092	0.0896	0.999	
	0.02095	0.02092	0.0828	0.999
0.02473	0.03411	0.00490	0.999	0.00555 ±0.0005
	0.02473	0.03411	0.00612	0.999	
	0.01128	0.05001	0.00567	0.998	
	0.01128	0.05001	0.00549	0.999
0.02506	0.03411	0.165	0.999	0.168 ±0.009
	0.02550	0.02499	0.177	0.998	
	0.02550	0.02499	0.178	0.999	
	0.01506	0.04004	0.160	0.999	
	0.01506	0.04004	0.155	0.999	
	0.01121	0.05001	0.167	0.999	
	0.01121	0.05001	0.173	0.998
0.02849	0.02092	0.166	0.999	0.167 ±0.005
	0.02849	0.02092	0.163	0.991	
	0.01361	0.04004	0.164	0.999	
	0.01361	0.04004	0.169	0.999	
	0.01355	0.05001	0.164	0.999	
	0.01355	0.05001	0.175	0.999	

Ketone	^a [Ketone]	^a [LATBD]	^b k	^c r	^d k _{ave}
0.01818	0.03411	0.0894	0.999	0.0951 ± 0.0046
	0.01818	0.03411	0.0917	0.999	
	0.02557	0.02499	0.1037	0.999	
	0.01051	0.04004	0.0969	0.999	
	0.01051	0.04004	0.0963	0.999	
	0.01278	0.05001	0.0948	0.999	
	0.01278	0.05001	0.0926	0.999
0.00870	0.04070	0.164	0.998	0.161 ± 0.004
	0.00870	0.04070	0.164	0.999	
	0.01230	0.04004	0.157	0.999	
	0.01230	0.04004	0.163	0.994	
	0.01020	0.05001	0.163	0.997	
	0.01020	0.05001	0.154	0.999	

a moles/litre

b $\text{l mol}^{-1} \text{s}^{-1}$

c correlation coefficient

d mean rate of reduction with standard deviation
 $\text{l mol}^{-1} \text{s}^{-1}$

APPENDIX 5

Computer Programme Hope

This is a general programme for determining the rate of reduction of a ketone by a hydride reducing species, based on a spectral method. The data required are the number of data pairs, the initial absorbance value, the initial hydride concentration and the ketone extinction coefficient. After the time and absorbance data (maximum of 50 each) are read in, the least squares slope and least squares intercept are calculated. The rate constant and the correlation coefficient are also outputted. The programme and sample data are found on the next two pages of this appendix.


```

C SECOND ORDER KINETICS PROGRAMME-- HOPE---
  DIMENSION TIME(50),ABSORB(50),X(50),Y(50),SUM(50)
  REAL KETONE
  OUTPUT "ENTER THE NUMBER OF DATA PAIRS, THE INITIAL"
  OUTPUT "ABSORBANCE, THE HYDRIDE CONCENTRATION, AND"
  OUTPUT "THE KETONE EXTINCTION COEFFICIENT. ALL ON"
  OUTPUT "THE SAME LINE SEPARATED BY COMMAS."
  READ(105,10) N,A,B,EXTINC
  A=A/EXTINC
  KETONE = A
  HYDRID = B
  OUTPUT KETONE, HYDRID
10  FORMAT(F10.7,F10.7,F10.7,F10.7)
  OUTPUT "ENTER THE KINETIC READINGS;TIME,ABSORB"
  OUTPUT "ONE SET OF DATA TO A LINE."
  DO60I=1,N
  READ(105,12) TIME(I),ABSORB(I)
60  CONTINUE
  OUTPUT "      TIME          A-X          B-X          SUM"
  DO66I=1,N
  AX=ABSORB(I)/EXTINC
  XX=A-AX
  BX=B-XX
  TERM=(B*AX)/(A*BX)
  SUM(I)=ALOG(TERM)
  PRINT(108,50) TIME(I),AX,BX,SUM(I)
50  FORMAT(1X,F10.5,1X,F10.5,1X,F10.5,1X,F10.5)
66  CONTINUE
12  FORMAT(F10.8,F10.8)
  SUMX=0
  SUMY=0
  SUMXY=0
  SSQX=0
  SSQY=0
  AB=A-B
  DO65I=1,N
  X(I)=TIME(I)
  Y(I)=SUM(I)
  SQX=X(I)**2
  SQY=Y(I)**2
  XY=X(I)*Y(I)
  SUMX=SUMX+X(I)
  SUMY=SUMY+Y(I)
  SUMXY=SUMXY+XY
  SSQX=SSQX+SQX
  SSQY=SSQY+SQY
65  CONTINUE
  AN=N
  B=SUMXY-((SUMX*SUMY)/AN)
  C=SSQX-((SUMX**2)/AN)
  D=SSQY-((SUMY**2)/AN)
  E=SQRT(C*D)
  SLOPE=B/C
  YCEP=(SUMY-(SUMX*SLOPE))/AN
  COEF=B/E
  RATE=SLOPE/AB
  OUTPUT AB
  OUTPUT COEF,YCEP,SLOPE
999 OUTPUT RATE
  END

```

!FLAG HOPE

WITH>

ENTER THE NUMBER OF DATA PAIRS, THE INITIAL
ABSOBANCE, THE HYDRIDE CONCENTRATION, AND
THE KETONE EXTINCTION COEFFICIENT. ALL ON
THE SAME LINE SEPARATED BY COMMAS.

715.0,0.416,0.04404,16.6

KETONE = 2.506023E-02

HYDRID = 4.404000E-02

ENTER THE KINETIC READINGS; TIME, ABSORB
ONE SET OF DATA TO A LINE.

712.0,0.375

724.0,0.350

736.0,0.320

748.0,0.296

760.0,0.274

772.0,0.255

784.0,0.240

796.0,0.224

7108.0,0.209

7120.0,0.195

7132.0,0.184

7144.0,0.174

7156.0,0.165

7168.0,0.156

7180.0,0.147

TIME	A-X	B-X	SUM
12.00000	.02259	.04157	-.04604
24.00000	.02108	.04006	-.07813
36.00000	.01928	.03826	-.12159
48.00000	.01783	.03681	-.16103
60.00000	.01651	.03549	-.20159
72.00000	.01536	.03434	-.24067
84.00000	.01446	.03344	-.27463
96.00000	.01349	.03247	-.31437
108.00000	.01259	.03157	-.35546
120.00000	.01175	.03073	-.39772
132.00000	.01108	.03006	-.43398
144.00000	.01048	.02946	-.46962
156.00000	.00994	.02892	-.50416
168.00000	.00940	.02838	-.54132
180.00000	.00886	.02784	-.58146

AB = -1.897977E-02

COEF = -.999829

YCEP = -7.174492E-03

SLOPE = -3.204279E-03

RATE = .168826

STOP

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