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STEREOCHEMISTRY AND MECHANISM OF KETONE REDUCTIONS BY HYDRIDE REAGENTS

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INTRODUCTION

The puzzle of stereochemistry and mechanism in the reduction of ketones by hydride reducing agents is a quarter of a century old. From the outset it has been an intriguing problem and a challenge to ingenuity, both in the creating of speculative ideas on the origin of the variable stereoselectivity, and in the devising of experiments to probe the questions of mechanism and transition state structure.

The stereochemical phenomenon that has been of interest concerns mainly the reduction of 6-membered ring ketones. The stereochemical distinction between the products is illustrated in Fig. 1, and the question of which isomer predominates, and by how much, under a variety of circumstances, is the matter which has defied rigorous understanding for so long.

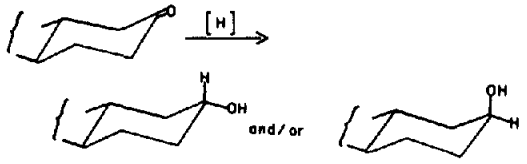
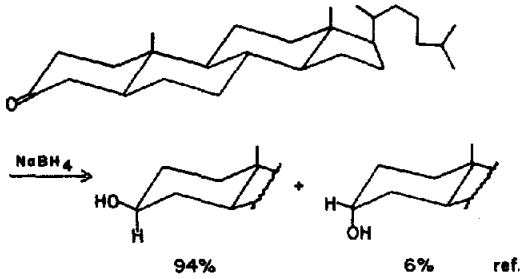
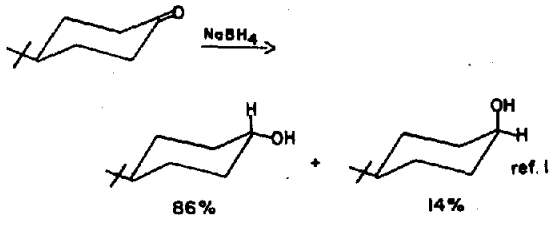


Fig. 1. The stereochemically different products in reduction of cyclohexanones. (Substituted cyclohexanone required to avoid product interconversion by conformational ring flip.)

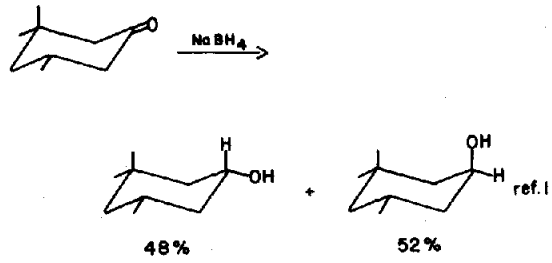
The two main variables affecting the stereochemical product ratio are the structure of the cyclohexanone and the nature of the hydride reducing agent. A few examples follow. Reduction of a 3-ketosteroid (e.g. cholestan-3-one), as representative of an unhindered ketone in a commonly encountered molecular environment, by sodium borohydride, gives a 94% predominance[1] of axial attack, yielding the equatorial alcohol.



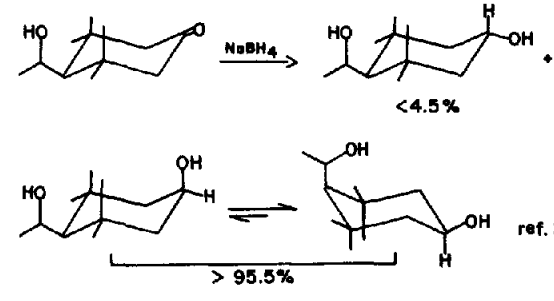
A similar example in the simple cyclohexanone series is reduction of 4-t-butylcyclohexanone by the same reductant, giving an 86% predominance[1] of *trans*-4-t-butylcyclohexanol.



This stereoselectivity is dramatically attenuated, however, by the introduction of axial substituents at the C-3 and C-5 positions. Reduction by sodium borohydride of, for example, 3,3,5-trimethylcyclohexanone, shows that the stereoselectivity not only is eliminated, but even slightly inverted, by the introduction of the axial Me group.[1] (Reduction of 3-methylcyclohexanone shows that the stereochemical effect of an equatorial methyl group is minor.[1])



Introduction of a second axial Me group pushes the stereochemistry to the opposite end of the spectrum to that of the unhindered ketone. Reduction of 4 - hydroxyethyl - 3,3,5,5 - tetra - methylcyclohexanone by sodium borohydride gives at least a 95.5% predominance of the epimer which corresponds to initial equatorial attack of borohydride.[2]



Other cases of highly hindered ketones that are reduced to give high stereoselectivities in favour of the axial alcohol include the 11-ketosteroids.[3]

This general picture of stereoselectivity has been known for a long time. The summary of Barton[4] that "reduction (of cyclohexanones) with sodium borohydride or lithium aluminum hydride in general affords the equatorial epimer if the ketone group is not hindered, the polar (axial) epimer if it is hindered or very hindered" is still valid† today.

In addition to the structure of the cyclohexanone, the nature of reducing agent is also a variable that determines the stereochemistry of the reduction. Less attention was originally paid to this variable, probably because the two oldest and commonest reducing agents—sodium borohydride and lithium aluminum hydride—although quite different in overall chemical reactivity, reduce many cyclohexanones with rather similar stereoselectivities.

HISTORICAL BACKGROUND

The stereochemical puzzle described above arose naturally around 1950 as a result of two major developments in organic chemistry. Instigated by World War II, research commenced in the United States in 1941 to search for volatile compounds of uranium. One of the most remarkable consequences of this military decision was the incidental discovery, in 1943, of sodium borohydride by the research group headed by H. I. Schlesinger aand including H. C. Brown.[5] A decade passed before this, and related, work was reported in full in the open literature[6] and in that interval a paper by S. W. Chaikin and W. G. Brown appeared, reporting the far-reaching result that sodium borohydride is an excellent and selective reducing agent for aldehydes and ketones.[7] These authors also reported semi-quantitative work leading to the conclusions that all four hydrogens of sodium borohydride are available for reduction. Since 1950, sodium borohydride has been used in ever-increasing amounts for aldehyde, ketone, and other reductions, and today there can be few organic chemists who have not themselves handled this ubiquitous reagent.

At the same time, another major development in organic chemistry was occuring. In 1950, Barton published the famous paper on conformational analysis, pointing out the importance of the chair conformation of 6-membered rings, and the distinction between axial and equatorial bonds.[8] The combination of these two developments in organic chemistry led naturally to the question of whether reduction of cyclohexanones by sodium borohydride would display stereoselectivity or whether a 50:50 mixture of axial and equatorial alcohols would be formed (Fig. 1).

RATIONALIZATIONS OF STEREOCHEMISTRY

In the last 20 years, a number of ingenious suggestions have been made to account for the crucial stereochemical observations: (a) preferential axial attack of the hydride reagent in the reduction of unhindered cyclohexanones and (b) the changes of stereoselectivity to preferential equatorial attack of the reagent in the reduction of hindered cyclohexanones. The main features of these rationalizations are as follows.

1. *Product Development Control–Steric Approach Control (Dauben, Fonken and Noyce 1956[9])*

The first rationalization of the variable stereoselectivity in the reduction of cyclohexanones by hydride reducing agents was that of Dauben, Fonken and Noyce in 1956[9] in a highly quoted paper in which the concepts of Product Development Control and Steric Approach Control were introduced. Product Development Control was a concept applying to the formation of the *most stable* (equatorial) alcohol in the reduction of non-hindered cyclohexanones. Steric Approach Control applied to the preferential equatorial attack on hindered ketones, to give the axial alcohol. The original descriptions of these two terms were somewhat vague and it has never been completely clear what was meant. Steric Approach Control was described as "a steric postulate involving competitive attacks from a favoured (unhindered) or an unfavoured (hindered) side". The description for Product Development Control was "an energy consideration involving the relative stability of the possible products". Clearly the essence of this rationalization is the point that if the dominating factor is the ease of attack of the reducing agent, then equatorial attack will occur, and the axial alcohol will result (Steric Approach Control), whereas if the dominating factor is the stability of the product, then the equatorial alcohol will be formed.

Although these terms may be subject to various ways of interpretation, one interpretation of product development control must certainly be discarded. This is the notion, that still occasionally persists,[10] that product development control has to do with thermodynamic control (i.e. product equilibrium). This is certainly not the case. No evidence for any product equilibration (change of stereochemistry) has ever been presented, and experiments designed specifically to test such equilibration (in $NaBH_4$ reductions) have failed to detect it.[11]

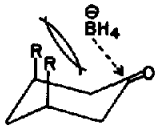
The most usual interpretation of Steric Approach Control and Product Development Control is in terms of transition states, and this certainly leads to a plausible hypothesis, subject to experimental test, whether or not this is what the original authors[9] have in mind. Thus if the transition state is *reactant-like* (Steric Approach Control), the effect of product stability on the two diastereomeric transition states (axial vs equatorial attack) would be minimal, and the product ratio would presumably be controlled by the ease of approach to the carbonyl group, thus leading to equatorial attack and formation of the axial alcohol. On the other hand, if the transition state were product-like (Product Development Control), then the more stable diastereomeric transition state would presumably be that leading to the more stable product (equatorial alcohol), and thus one would obtain the *thermodynamically more stable product for purely kinetic reasons.*

If one accepts this interpretation of product development control and steric approach control, it requires that unhindered ketones are reduced through a product-like transition state, and hindered ketones are reduced through a reactant-line transition state. This requirement would be necessary for all reducing agents that give the typical stereochemical results. This transition state vari-

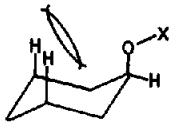
†For Tables of stereoselectivities in reductions of ketones by $NaBH_4$, see Ref. 1, and references therein.

ability is a factor that is experimentally tangible and will be further discussed in a later section.

In the past decade, the concept of product development control has not been very widely accepted; on the other hand, the concept of steric approach control—i.e. interaction of the incoming reagent with bulky groups at



Steric Approach Control Interactions

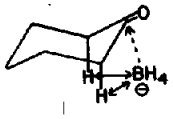


Product Development Control Interactions

C-3 and C-5 of the cyclohexanone ring has really never been challenged. For this reason, the later rationalizations, accepting steric approach control, have all been aimed at alternatives to product development control—i.e. reasons for the intrinsic preference for axial attack on unhindered cyclohexanones, not involving a product—like transition state.

2. *Effect of the axial hydrogens at* C-2 *and* C-6 (*Richer*, 1965[12])

In this rationalization of predominant axial attack in unhindered cyclohexanones, the steric significance of the axial hydrogens at C-2 and C-6 is considered. The point is made that the carbonyl is not symmetrically placed between the equatorial and axial hydrogens at C-2 and C-6; in fact the CO group is almost eclipsed by the equatorial hydrogens. Thus in axial attack an incoming group (at 90° to the CO group) is not encumbered by the equatorial hydrogens at C-2 and C-6, but in equatorial attack (at 90° to the CO group) the incoming group might be significantly hindered by the axial hydrogens at C-2 and C-6.

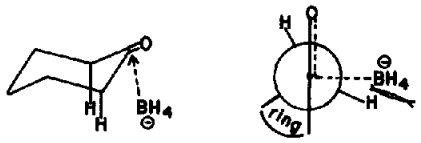


Steric Repulsion

This rationalization is thus based solely on steric strain, with various product ratios arising as a result of the balance between the effects of axial substituents at C-2 and C-6 (hindering equatorial attack) and axial substituents at C-3 and C-5 (hindering axial attack).

3. *Torsional strain* (*Cherest and Felkin* 1968[13])

The key feature of this rationalization again involves axial hydrogens at C-2 and C-6 of the cyclohexanone. Instead of *steric* interaction between these hydrogens and the incoming reagent, however, the point is made that the incoming group, approaching the CO group at 90°, is virtually eclipsed with these hydrogens. The proposal is made, therefore[14] that "torsional strain involving partial bonds (in transition states) represents a substantial fraction of the strain between fully-formed bonds, even when the degree of bonding is quite low". The rationalization for preferential axial attack, therefore, is the torsional strain developing in equatorial attack between the forming C–H bond and the axial C–H bonds of C-2 and C-6.

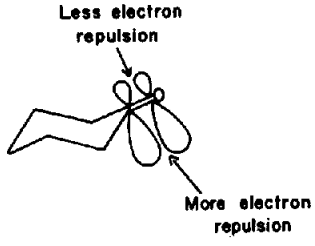


Torsional Strain (Eclipsing)

It is noteworthy that of all the rationalizations, the Felkin proposal appears to have received the widest acceptance.

4. *Orbital interaction* (*Klein*, 1973, 1974[15,16])

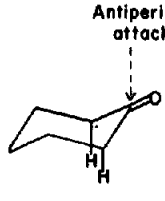
An entirely different rationalization for predominant axial attack on unhindered cyclohexanones (by nucleophiles—predominant equatorial attack for attack by electrophiles) was put forward by Klein in 1973.[16,16] In this rationalization, the orbital interaction of the p orbitals of the CO group with the σ orbitals of the β C–C bonds (C2–C3; C6–C5) is considered. This interaction is considered to give rise to unsymmetrical electron density on the two faces of the CO group, with higher electron density on the "equatorial" face.



The predominance of axial attack, therefore, is attributed to less electron–electron repulsion between the π bond electrons and the incoming nucleophile when attacking from this direction.

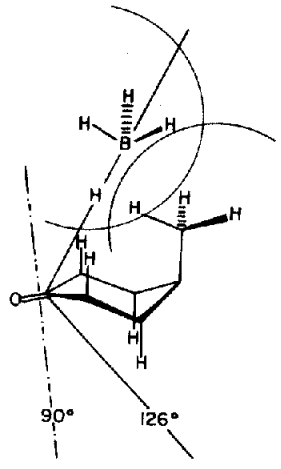
5. *Antiperiplanarity of the axial hydrogens at* C-2 *and* C-6 (*Anh et al.* 1976, 1977[17,18])

Anh *et al.*[17,18] have performed *ab initio* (STO-3G) calculations on various geometries of transition states for nucleophilic attack on CO groups, particularly in relation to assessing the merits of suggested models for asymmetric induction in acyclic systems. The results support the Felkin model,[14] however the reason for this preference, according to the calculations, is the favourable consequences of achieving antiperiplanarity between the new bond being formed and other bonds in the substrate. Extending these results to reduction of cyclohexanones, interaction with the C-2 and C-6 axial hydrogens clearly becomes possible. In axial attack, antiperiplanarity is clearly achievable, and can be improved by flattening the ring, whereas in equatorial attack this is not possible. The Felkin rationalization[13] therefore becomes modified such that axial attack is a favoured process (due to antiperiplanarity) rather than equatorial attack being disfavoured (due to torsional strain).



6. *Steric effect of the axial hydrogen at* C-4 (*Wigfield and Gowland*, 1977[19])

In this rationalization, the point is made that there are in fact three axial hydrogens (C2, C4, C6) that a nucleophile attacking in a equatorial sense might encounter, whereas there are only two axial hydrogens (C3, C5) to hinder axial attack. Based on mechanistic evidence for $NaBH_4$ reductions, which suggested an acyclic mechanism,[19,20] molecular models involving attack at 126°, rather than 90°[21] were inspected. These suggested that the steric influence of the axial hydrogen at C-4 might be as severe as those at C-2 and C-6, and that a simple, purely steric, rationalization of preferential axial attack might be the interaction with three axial hydrogens for equatorial attack, vs interaction with only two axial hydrogens in axial attack.



7. *Quantum calculation of electrostatic potential around the carbonyl group* (*Royer*, 1978[22])

CNDO calculations of a lithium-complexed cyclohexanone give rise to a disymmetric electrostatic potential around the carbonyl group.[22] Axial attack, in this rationalization, is favoured as a result of this electrostatic potential.

MECHANISTIC ASPECTS

From the above summary of stereochemical rationalizations, it is clear that the stereoselectivity may be explained in a wide variety of ways. Almost without exception, however, these rationalizations have a serious shortcoming in common. This shortcoming is the fact that the rationalizations are conceived and developed in isolation from any consideration of the reaction mechanism. In the absence of such knowledge, studies aimed at discovering the origin of stereoselectivity in these reductions cannot proceed beyond the hypothesis stage. In order to proceed beyond the hypothesis or rationalization stage, and endeavour to develop a rational explanation, it is clear that the reaction mechanism(s) and the transition state(s) involved must be considered. In view of the diversity of reducing agents involved, it does not follow that there is one common mechanism, or consequently, one common explanation of stereoselectivity. The group of seven rationalizations tends to encourage the notion that such an explanation does exist; in fact, in view of the possibility of mechanistic variation, this notion may well be a myth.

This mechanistic review will focus on sodium borohydride reductions, with mention of other reducing agents where appropriate; this format is, at present, essentially unavoidable since a good deal more attention has so far been paid to sodium borohydride reductions than to other hydride reducing agents.

Stoichiometry of reduction

Sodium borohydride contains four hydrogens. In 1949 Chaikin and Brown[7] stated that "semiquantitative observations... leave no doubt that four moles of the aldehyde or ketone react with one of borohydride...". It is not clear on which aldehyde(s) or ketone(s) this work was carried out and this, as far as we know, is the only published evidence supporting the generally held view that all four hydrogens are utilized in all reductions. In contrast, and very interestingly, it has recently been shown that reduction of cyclohexanone with tetrabutylammonium borohydride proceeds only to 75%.[23] However, there is no doubt that most ketones are reduced with this 4:1 stoichiometry, and, with possible reservations about reduction of very hindered ketones,[24] the following equation appears generally valid.

$$NaBH_4 + 4\ \begin{matrix} R_1 \\ \diagdown \\ \diagup \\ R_2 \end{matrix} C{=}O \xrightarrow{H_3O^{\oplus}} 4\ \begin{matrix} R_1 \\ \diagdown \\ \diagup \\ R_2 \end{matrix} CHOH. \qquad (1)$$

This equation raises the following important question.

The question of disproportionation

The question of how the presumably sequential transfer of four hydrogens occurs was first addressed by Garrett and Lyttle who, in the first kinetic study of the reaction (on 3α - hydroxy - 11α - acetoxypregnan - 20 - one)[25] noted that the data were consistent with a simple second order process with a 4:1 stoichiometry.

$$\text{i.e. } \frac{dx}{dt} = k(A-x)(B-4x) \qquad (2)$$

where A = initial $[NaBH_4]$, B = initial [ketone] and x = amount of sodium borohydride consumed at time t, giving an integrated rate equation of

$$\log\frac{(A-x)}{(B-4x)} = \frac{(4A-B)kt}{2.303} - \log\frac{B}{A}. \qquad (3)$$

This simple result is, in fact, remarkable; a process involving four successive transfers with comparable rate constants will generally give rise to very complex kinetics. Thus the absence of complication, although most agreeably welcome, does place severe constraints on interpretation and is mechanistically highly significant. Garrett and Lyttle suggested two possible interpretations. The first of these was sequential transfer of hydrides as indicated below (eqns 4–7), with a rate-determining first step to conform with the observed kinetics.

$$\overset{\ominus}{B}H_4 + \begin{matrix} \diagdown \\ \diagup \end{matrix} C{=}O \xrightarrow{k_1} H_3\overset{\ominus}{B}{-}O{-}\underset{\diagdown}{\overset{\diagup}{CH}} \qquad (4)$$

$$H_3\overset{\ominus}{B}-O-\underset{\diagdown}{\overset{/}{CH}} + \underset{\diagup}{\overset{\diagdown}{C=O}} \xrightarrow{k_2} H_2\overset{\ominus}{B}-(-O-\underset{\diagdown}{\overset{/}{CH}})_2 \quad (5)$$

$$H_2\overset{\ominus}{B}-(-O-\underset{\diagdown}{\overset{/}{CH}})_2 + \underset{\diagup}{\overset{\diagdown}{C=O}} \xrightarrow{k_3} H\overset{\ominus}{B}-(-O-\underset{\diagdown}{\overset{/}{CH}})_3 \quad (6)$$

$$H\overset{\ominus}{B}-(-O-\underset{\diagdown}{\overset{/}{CH}})_3 + \underset{\diagup}{\overset{\diagdown}{C=O}} \xrightarrow{k_4} \overset{\ominus}{B}-(-O-\underset{\diagdown}{\overset{/}{CH}})_4. \quad (7)$$

The alternative suggestion made by Garrett and Lyttle again involved the same initial rate-determining first step, followed by hydrolysis of the intermediate alkoxyborohydride, i.e.

$$H_3\overset{\ominus}{B}-O-\underset{\diagdown}{\overset{/}{CH}} \xrightarrow{H_2O} H_3\overset{\ominus}{B}OH + HO-\underset{\diagdown}{\overset{/}{CH}} \quad (8)$$

with subsequent (rapid) reduction steps being effected by $H_3\overset{\ominus}{B}OH$, $H_2\overset{\ominus}{B}(OH)_2$, and $H\overset{\ominus}{B}(OH)_3$. This suggestion avoided the necessity of proposing intermediates with several large steroid molecules attached to boron. For reductions carried out in the usual solvent-2-propanol-, the parallel suggestion would be alcoholysis rather than hydrolysis, and this can now be discarded, at least for the final step of the reduction (reduction by $H\overset{\ominus}{B}(OR)_3$) in view of our recent finding that exchange of secondary alkoxy groups on boron is extremely slow under conditions usually employed for borohydride reductions.[20] The original proposal of Garrett and Lyttle (described by these workers only as a "postulate"), although reinforced by a similar study by Brown *et al.*[26] on several more ketones, appears to have become generally accepted as the mechanism for sequential hydride transfer.

This sequential mechanism, however, contains a serious obstacle for stereochemical rationalization. For it postulates not a single reducing agent but four different ones, and each must be responsible for a quarter of the product molecules if the condition $k_2, k_3, k_4 \gg k_1$ is to be met. Since it is most improbable that all of these four reducing agents would have the same stereoselectivity, the concept of "*the* stereoselectivity of sodium borohydride" is a rather meaningless term, being, if the sequential mechanism is correct, an average of these four differing stereoselectivities.

At first sight the sequential mechanism also appears to impose a grave limitation on the value of kinetic studies to shed light on the origin of stereoselectivity. This limitation is the point that whereas stereoselectivity studies represent the average of all four steps, kinetic studies refer to transfer of only the first hydride—the rate determining step. Brown and Muzzio noted this problem in 1966,[27] and in 1970 Rickborn and Wuesthoff devised experimentation to assess the differential stereoselectivity of these intermediate reducing agents.[28] This involved an extrapolation technique to obtain an estimate of the stereochemical product ratio at 0% reduction and at 100% reduction. Although differences are obtained, the magnitude of the differences is surprisingly small (~15% or less, especially for reduction of hindered ketones. Table 1 indicates this point for reduction of 3,3,5-trimethylcyclohexanone and comparison with the stereoselectivity difference between $LiAlH_4$ and $LiAl(OBu^t)_3H$.

Although it is difficult to assess the question of whether these small differences in stereoselectivity in sodium borohydride reductions constitute evidence for or against the sequential mechanism, the smallness of these differences (stereoselectivities at 0% and 100% reaction) do tend to minimize the difficulty of comparing kinetic and stereochemical results. Wigfield and Phelps have used the values of these differences to defend the practice of subdividing observed rate constants of reduction into their axial (k_{ax}) and equatorial (k_{eq}) components by using the experimental product ratio—at least for the purposes of obtaining activation parameters for axial and equatorial attack respectively.[1,29]

In contrast to the sequential mechanism (eqns 4–7), the alternative mechanism is complete or partial disproportionation of the alkoxyborohydride intermediates. Complete disproportionation is shown in eqns (9)–(11) (equations left unbalanced for the sake of simplicity).

$$(RO)\overset{\ominus}{B}H_3 \longrightarrow \overset{\ominus}{B}H_4 + (RO)_2\overset{\ominus}{B}H_2 \quad (9)$$

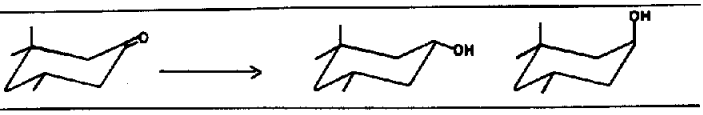
$$(RO)_2\overset{\ominus}{B}H_2 \longrightarrow \overset{\ominus}{B}H_4 + (RO)_3\overset{\ominus}{B}H \quad (10)$$

$$(RO)_3\overset{\ominus}{B}H \longrightarrow \overset{\ominus}{B}H_4 + (RO)_4\overset{\ominus}{B}. \quad (11)$$

It has been known through some of the earliest investigations of Schlesinger, Brown *et al.* that alkoxyborohydrides were prone to disproportionation. For example, reaction of diborane and sodium methoxide yields not sodium methoxyborohydride, as might have been expected, but the complete disproportionation products instead (eqns 12, 13).[28,30]

$$B_2H_6 + 2NaOCH_3 \not\longrightarrow 2\overset{\oplus}{Na}\overset{\ominus}{B}H_3(OCH_3) \quad (12)$$

Table 1. Reduction of 3,3,5-trimethylcyclohexanone



Reagent used		Stereochemical product ratio		Reference
$NaBH_4$/2-propanol/0°	a) 0% reaction	41.9	58.1	28
	b) 100% reaction	38.3	61.7	28
$LiAlH_4$/ether/0°		42.	58.	45
$LiAl(OBu^t)_3H$/THF/0°		4.	96.	45

$$2B_2H_6 + 3NaOCH_3 \longrightarrow 3NaBH_4 + B(OCH_3)_3. \quad (13)$$

In fact, of the alkoxyborohydrides, only the trialkoxyborohydrides appear to have reasonable stability, and only in THF solution.[31]

Despite this knowledge, the possibility of disproportionation of intermediates playing a role in sodium borohydride reductions has been given surprisingly little attention. The question is of critical importance to the understanding of stereochemistry. In contrast to the sequential mechanism, in which four different reducing agents would be involved, the complete disproportionation mechanism would involve reduction by $NaBH_4$ only—the intermediate alkoxyborohydrides disproportionating back to $NaBH_4$ rather than acting as a reducing agent. The disproportionation mechanism, therefore, would greatly simplify the understanding of stereochemistry, even though the mechanism itself is somewhat more involved than the sequential mechanism (eqns 4–7).

In addition to the complete disproportionation mechanism (eqns 9–11), there is also the possibility of partial disproportionation, i.e. disproportionation of some, but not all, of the intermediate alkoxyborohydride intermediates.

Recently we have shown that the existing evidence, both kinetic and stereochemical, does not offer distinction between the sequential and the disproportionation mechanisms.[32] Based on the work of Kreevoy on borohydride hydrolysis,[33] an NMR spectroscopy test for the disproportionation of the monoalkoxyborohydride intermediate involved in the reduction of ketones was devised. This test utilized a mixture of $NaBH_4$ and $NaBD_4$ followed by analysis to determine whether any isotopically mixed species, $NaBH_4D_{4-n}$, had been formed. The test was conclusively negative, and establishes that the *monoalkoxyborohydride intermediate* in borohydride reductions of ketones *does not disproportionate*, but reduces a second molecule of ketone to produce the dialkoxyborohydride. Equations 4 and 5 of the sequential mechanism (but not necessarily eqns 6 and 7),† are therefore established.‡

The significance of this result to stereoselectivity is the following. Equation 4 shows that the first ketone molecule (of the four eventually reduced; i.e. 25%) is reduced by $NaBH_4$ itself. The establishment of eqn (5) shows that the second ketone molecule (a further 25%) is reduced by $NaBH_3(OR)$. The remaining two ketone molecules (the last 50%) are reduced by some combination of $NaBH_3(OR)$, $NaBH_2(OR)_2$ and $NaBH(OR)_3$, depending on the extent of disproportionation of the latter two species. Complete disproportionation is ruled out, but the sequential mechanism (eqns 4–7), with its stereochemical complexities, is not yet experimentally established. For a full understanding of stereoselectivity, this point requires settling.

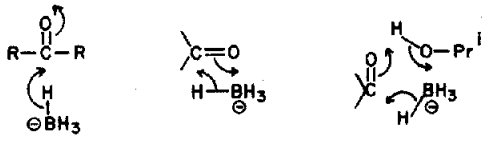
†Equation (7) is, of course, generally believed. At the risk of suggesting heresy, we should like to point out that we have been unable to find any compelling experimental evidence that the species $NaBH(OR)_3$ is not actually a 50:50 mixture of $NaBH_2(OR)_2$ and $NaB(OR)_4$. Some experimental evidence (e.g. Ref. 29, especially p. 6897 and Table V) actually seems to fit the latter formulation better.

‡These equations will undergo a significant revision in the following section, but the sequential-disproportionation distinction will remain unaltered.

This problem of disproportionation is one that is less serious for the understanding of stereoselectivites of other reducing agents. For reduction by reducing agents possessing only one active hydrogen (e.g. $LiAl(OBu^t)_3H$, Selectride reducing agents,[34] the problem does not exist at all, since there is only one step in the reduction. For reduction by $LiAlH_4$ the question must clearly be considered, especially as there is evidence for disproportionation of intermediates.[35,36] There is, however, a striking difference in the kinetic behaviour of $NaBH_4$ and $LiAlH_4$. In $NaBH_4$ reductions, transfer of the first hydride is rate-determining (slowest); in $LiAlH_4$ reductions, transfer of the first hydride is fastest. The consequence of this result is that 1:1 ketone:hydride kinetics can be measured,[36] and, provided an excess of $LiAlH_4$ is used, most or all of the ketone molecules will be reduced by $LiAlH_4$ itself, thus essentially removing the disproportionation problem. If a 1:4 hydride:ketone mole ratio is employed, then clearly the disproportionation problem is relevant.

Mechanism of reduction (transition state geometry)

Even though, as indicated above, one cannot specify the structure of the reducing agent in $NaBH_4$ reductions for any step except the first and second, this is sufficient to raise another tangible, yet fundamental question. What is the gross transition state geometry for the transfer of any individual hydride? Three quite different geometries are to be found in the literature,[20] and these are depicted below.



(A) (B) (C)

Mechanism (C) differs from mechanism (B) by the incorporation of a molecule of hydroxylic solvent, whereas the role of solvent in mechanism (A) could be either (i) to protonate the carboxyl oxygen, or, (ii) to become bonded to the potentially electron-deficient boron, or, (iii) to do both of these (two molecules of solvent) or (iv) to do neither. Clearly the steric interactions arising from mechanisms (A) (with its variations), (B), and (C) will be quite different, and thus the question of which is correct constitutes a crucial aspect of understanding the stereoselectivity in these reactions.

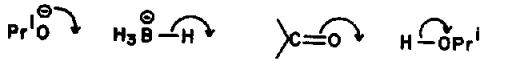
Until recently there was little experimental evidence bearing on this point. Within the last 2 years, however, two new facts have emerged. In the first of these we have exploited the fact that mechanisms (B) and (C) predict different pre-hydrolysis products, according to whether the newly-formed alcohol or the alcoholic solvent respectively becomes attached to boron as an alkoxy group. We have shown that under the reaction conditions exchange of such alkoxy groups on boron is extremely slow, and that the tetraalkoxyborohydride product has alkoxy groups exclusively derived from solvent attached to boron.[20] This evidence is clearly incompatible with the four-centre mechanism (B), at least in so far as the final step (eqn 7) of reduction is concerned.

The second, and most direct, piece of evidence is the kinetic role of hydroxylic solvent. By performing reduc-

tions in dry diglyme with 2-propanol added not as solvent, but as the third reagent, it appears that the kinetic order with respect to 2-propanol is a surprising 1.5.[19] Thus the overall kinetic order of the reaction is 7/2, i.e.

$$\text{Rate} = k[\text{ketone}][\overset{\ominus}{B}H_4][Pr^iOH]^{3/2}. \qquad (14)$$

This evidence is certainly not compatible in any obvious way with either of the cyclic mechanisms (B) or (C), and at once focusses attention on the variations of the acyclic mechanism (A). It is worth noting that an acyclic mechanism is also more satisfactory from the point of view of the Baldwin Rules;[37] the cyclic mechanisms being disfavoured 4-*endo-tet* (mechanism B) or 6-*endo-tet* (mechanism C) processes with respect to boron. Of the various possible acyclic mechanisms, we have suggested[19] that the following arrangement appears best in accord with the available experimental evidence, although this is a tentative suggestion at the present time. It is intriguing that in non-hydroxylic solvents sodium



borohydride reductions are dramatically accelerated by irradiation, and this may be the photochemically-allowed 4-centre mechanism (B).[38]

The finding that the tetraalkoxyborohydride product has alkoxy groups derived from solvent, and that the ketone is reduced to the free alcohol requires that the overall equation for borohydride reduction of ketones is represented as in (15).

$$NaBH_4 + 4(\rangle C{=}O) + 4ROH \text{ (solvent} \longrightarrow 4(\rangle CHOH) + NaB(OR)_4. \qquad (15)$$

This formulation necessitates modification of eqns (4)–(7), in order to take into account the participation of alcoholic solvent in the reaction mechanism. Equations (4)–(7) thus become eqns (16)–(19) respectively.

$$\overset{\ominus}{B}H_4 + \rangle C{=}O + ROH \longrightarrow H_3\overset{\ominus}{B}(OR) + \rangle CHOH \qquad (16)$$

$$H_3\overset{\ominus}{B}(OR) + \rangle C{=}O + ROH \longrightarrow H_2\overset{\ominus}{B}(OR)_2 + \rangle CHOH \qquad (17)$$

$$H_2\overset{\ominus}{B}(OR)_2 + \rangle C{=}O + ROH \longrightarrow H\overset{\ominus}{B}(OR)_3 + \rangle CHOH \qquad (18)$$

$$H\overset{\ominus}{B}(OR)_3 + \rangle C{=}O + ROH \longrightarrow \overset{\ominus}{B}(OR)_4 + \rangle CHOH. \qquad (19)$$

To reiterate the point made in the previous section, eqns (16) and (17) can be regarded as established; the relative role of eqns (18) and (19) vs disproportionation remains unknown.

The geometrical arrangement of atoms in reductions by other hydride reducing agents remains unknown. No information on the cyclic–acyclic nature of the transition state in $LiAlH_4$ reductions is currently available. Perhaps the most important point to make is that the reaction mechanism for $LiAlH_4$ reductions must be quite different than that for $NaBH_4$ reductions. This conclusion follows from the fact that $LiAlH_4$, and many other reductions are conducted in non-hydroxylic solvent, and thus there can be no question of any participation of hydroxylic solvent in the mechanism.

Extent of hydride transfer at the transition state

Another vital question in the gaining of a sufficiently close picture of the transition state for stereoselectivities to be understood, is that of whereabouts on the reaction coordinate it occurs. In contrast to the two questions already raised, this one has frequently been a matter of active speculation. Unfortunately the number of ways of tackling this question are of course, extremely limited, as well as being somewhat speculative, and most approaches have not been definitive. The current evidence may be summarized as follows.

1. *The Hammond postulate.* A considerable body of opinion among organic chemists considers the reduction of ketones by sodium borohydride to proceed through an early, or reactant-like, transition state. This opinion is held, in part, because of application of the Hammond postulate[39] to this reaction, the latter being considered to be highly exothermic. In point of fact, there is not a single piece of evidence in the literature pertaining to the exothermicity of reduction of cyclohexanones by sodium borohydride. At this time, however, we can report that the enthalpy of reduction of cyclohexanone by sodium borohydride is -50.0 ± 0.3 kcal/mole.[40] This value, of course, represents the total enthalpy of all four reduction steps, and therefore, making the assumption that all four steps contribute equally, gives a value of -12.5 kcal/mole for the enthalpy of each individual step. Thus the reaction is, in fact, far less exothermic than has generally been supposed, and the conclusion of an early transition state is, as a consequence, far less obvious. Wipke and Gund have also concluded that the transition state is not obviously reactant-like, even based on the much higher value of ΔH (-128 kcal/mole) reported for the reduction of acetone.[41]

2. *Stereoselectivity.* In general it has been found much easier to rationalize stereochemical product ratios on the assumption of an early transition state than on a late one. Product development control in fact,[9] is the only rationalization with an implication[42,43] of a later transition state, and product development control has, in the past decade, not enjoyed great popularity.[44–46] This circumstance, together with the Hammond postulate consideration mentioned above, constitute the basis for the opinion that the transition state is early. It is a weak basis.

3. *Quantitation of the Hammond postulate.* If the Hammond postulate is taken literally, and further, that the simplistic viewpoint is taken that the energy change is proportional to the change of position, n, along the reaction co-ordinate (on a scale from 0 to 1), then the position of the transition state on the reaction co-

ordinate, n†, is given by,[47]

$$n^{\dagger} = \frac{\Delta G^{\dagger}}{2\Delta G^{\dagger} - \Delta G_0} \quad (20)$$

Although this equation cannot be utilized directly because there are no available values of ΔG_0, the corresponding enthalpy equation can be employed, now that the value of ΔH_0 for cyclohexanone reduction is known.[40] The combination of $\Delta H^{\dagger} = 6.4$ kcal/mole[29] and $\Delta H_0 = 12.5$ kcal/mole, gives the value of $n^{\dagger} = 0.25$. Thus on this enthalpy basis, an early, but not very early, transition state is indicated. However, while there are insufficient data to use the free energy relationship (eqn 20), one can, in fact, be quite certain that it will indicate a considerably later transition state than this. Firstly, the activation entropy is very substantially negative[1,29] causing $\Delta G^{\dagger}$ to be of *greater* magnitude than $\Delta H^{\dagger}$. Secondly, although the reaction entropy is unknown, and likely to remain so, it is almost certainly negative, since the reaction involves overall loss of translational freedom; thus ΔG_0 will be of *smaller* magnitude than ΔH_0. Using the modest figure of -15 e.u. for $\Delta S°$, thus giving $\Delta G°$ as -8 kcal/mole, together with the known figure of 18.9 kcal/mole, for $\Delta G^{\dagger}$[1] the value of $n^{\dagger}$ rises to 0.41. Thus the literal use of the Hammond postulate, using the best available figures, supports not the idea of a very early transition state, but a transition state closely approaching the midpoint between reactants and products.

4. *Linear free energy relationships.* The rates of substituted acetophenones by sodium borohydride have been measured and give a substantial ρ value of 3.06.[48] While this value in isolation is of limited use, it is complemented by the fact that cyanide addition to substituted benzaldehydes has a *smaller* ρ value of +2.33, yet has a Brönsted exponent of 0.74.[49,50] Thus one is led to the conclusion that borohydride reduction of acetophones must have $\alpha > 0.74$, or a late transition state in the final quarter of the reaction co-ordinate.

These results are not, however, without interpretative difficulties. Firstly there is the question of how good a model substituted acetophenones are for other, aliphatic, ketones, and in particular, cyclohexanones. Secondly, the reputation of the Brönsted exponent as an indicator of transition state structure has been sadly tarnished by the demonstration of exponents outside the range 0 to 1.[51] Nevertheless the ρ value interpretation does not now rest solely on Brönsted exponents, and will be discussed further (parts 8, 9 of this section).

5. *Kinetic isotope effects.* The difficulty of using primary kinetic isotope effects ($NaBH_4$ vs $NaBD_4$) lies in the presence of the four hydrogens. If the first step is indeed the only kinetically important one, then this step has one primary and three secondary isotope effects. Since the observed isotope effects are actually inverse (0.59–0.77)[42,43] the three secondary effects may outweigh the primary effect, but about the only firm conclusion that may be drawn is that, for the primary effect itself to be so outweighed, it must be very small. This could be the result of a very early, or very late, or a non-linear transition state, all of which[52,53] are known to give rise to diminished isotope effects.

In an ingenious effort at overcoming these interpretative difficulties, Pasto and Lepeska[54] have measured the tritium isotope effects which avoids the secondary isotope effect ambiguity due to the tracer quantity of tritium. Unfortunately this approach runs into the difficulty of the sequential reactions, and once again is inconclusive. In common with the deuterium isotope effects,[42,43] the tritium isotope effects are small and rather insensitive to ketone structure (3.21–3.81).

6. *The Brönsted relationship.* The obstacle to the setting up of a Brönsted relationship (eqn 21)

$$\delta\Delta G^{\dagger} = \alpha\delta\Delta G_0 \quad (21)$$

by comparison of the kinetic and thermodynamic parameters of reduction of a series of ketones is clearly the total lack of any information regarding values of ΔS_0 or ΔG_0. In view of the clouds hanging over the interpretation of α, already alluded to,[51] efforts to obtain such values for this purpose would be of questionable wisdom. However, since values of ΔH_0 are more easily obtained, and values of $\Delta H^{\dagger}$ are already known,[1,29] the corresponding enthalpy relationship (eqn 22) may be investigated. In an effort to pursue this line, attempts to

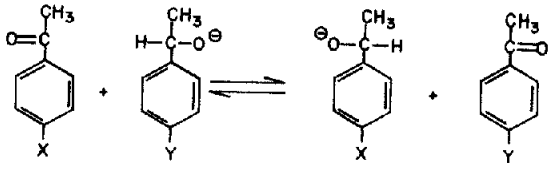
$$\delta\Delta H^{\dagger} = \alpha\delta\Delta H_0 \quad (22)$$

measure values of ΔH_0 were made,[40] but difficulty was encountered in obtaining values for any except four very quickly reduced cyclohexanones. The apparent value of α emerging from these four values and eqn (22) was 0.02; however, the scatter was such that the results are experimentally, as well as theoretically,[51] meaningless.

7. *Isokinetic plots.* The dissection of activation parameters[55] into the axial attack and equatorial attack components allows the comparison of isokinetic plots for hindered and unhindered ketones, and also of individual axial and equatorial attack on the same series of ketones. This has been done, and the results turn out to be quite striking.[1] Both for axial and equatorial attack, there is a sharp difference between the reduction of hindered and unhindered ketones, although there does not appear to be a great deal of difference between axial and equatorial attack on either series of ketones. These results appear to indicate some sort of mechanistic change between hindered and unhindered ketone reductions, although clearly it is one to which isotope effects are not particularly sensitive.

8. *Further significance of the Hammett rho value: reduction by alkali-metal alkoxides.* In part 4 of this section, the large negative rho value of $NaBH_4$ reductions of aromatic ketones was discussed. In 1976 Burnett and Kirk[56] presented strong evidence supporting the idea[50] that this value implies a product-like transition state, removing the necessity of the conclusions resting on the wobbly Brönsted exponent.

In this work the reduction of acetophenones by alkali-metal alkoxides of 1-phenylethanols was studied and the rho value measured. These values ranged from 1.45 to 1.75, depending on the nature of the metal cation, values considerably smaller than the value reported (3.06) for $NaBH_4$ reductions.[48] Because of the near local symmetry in the metal alkoxide reduction, the transition state is presumably at or near the mid-point of the reaction



coordinate; the rho value of 1.45–1.75 thus corresponds to this mid-way transition state and the larger rho value of the borohydride reduction implies a transition state considerably further along the reaction coordinate than the mid-point. A product-like transition state is clearly indicated, at least for the sodium borohydride reductions of these aromatic ketones.

9. *Kinetic isotope effects in reductions by* $LiAl(OBu^t)_3H$. Although, as indicated above (part 5 of this section), interpretation of kinetic isotope effects in sodium borohydride reductions was non-conclusive, this approach on other reducing agents holds the promise of considerably more success. A study on reduction by $LiAl(OBu^t)_3H$ and $LiAl(OBu^t)_3D$ has recently been completed.[57,58] The reactions of this reducing agent are considerably simpler than those of $NaBH_4$, particularly since, having only one active hydrogen, the problems of sequential reactions and secondary isotope effects are eliminated. The reagent has also been shown to be unaffected by the complications of association, which affect some reducing agents.[59]

Calculations of kinetic isotope effects were made for various transition state geometries of reduction (cyclic and acyclic mechanisms), and the spectrum of degrees of hydride transfer from highly reactant-line to highly product-like.[57] These values were compared with experimentally observed kinetic isotope effects determined both from mass spectra (competition experiments),[60] and from direct kinetics.[57,61] Experimental kinetic isotope effects are clustered around $k_H/k_D = 0.95$ with a few values above unity and very hindered ketones more inverse ($k_H/k_D \sim 0.8$). Regardless of whether the reduction mechanism is cyclic or acyclic, these results indicate that most ketones are reduced through a similar type of transition state in terms of the degree of hydride transfer, and the values are consistent with calculation only if the transition state for $LiAl(OBu^t)_3H$ reductions is close to the mid-point of the reaction coordinate.

The mid-point transition state in $LiAl(OBu^t)_3H$ reductions, as well as being interesting itself, is directly relevant to sodium borohydride reductions. Since the rho value for $LiAl(OBu^t)_3H$ reductions is known,[62] it provides a second check on the significance of the large rho value from sodium borohydride reductions. Once again, since the rho value for $LiAl(OBu^t)_3H$ reductions (2.13) is substantially smaller than that for $NaBH_4$ reductions (3.06), and the $LiAl(OBu^t)_3H$ transition state appears to be at the mid-point of the reaction coordinate,[57] the conclusion is reached that the transition state in $NaBH_4$ reductions is product-like.[63] Analysis of kinetic isotope effects, rho values, and entropies of activation seems to support the idea that a spectrum of transition states occur, with $NaBH_4$ reductions product-like, $LiAlH_4$ reductions reactant-like, and $LiAl(OBu^t)_3H$ reductions near the mid-point.[63]

This variation of transition state structure as a function of *reducing agent*, but the apparent *lack* of variation of transition state structure as a function of *ketone structure*, is an important consideration in making an assessment of the rationalizations of stereoselectivity in cyclohexanone reductions.

The role of the metal cation

The mechanistic role of the metal cation, if any, is another essential question in the understanding of the reduction mechanism. One has only to look at the different reactivity between $LiBH_4$ and $NaBH_4$[64] to appreciate the vital nature of the cation (a reactivity difference, incidentially, that is also paralleled in the aluminohydride series[36]). The use of crown ethers and other compounds that form strong complexes with metal ions has been a valuable approach in this regard. In 1973 Matsuda and Koida showed that dibenzo-18-crown-6 halted ketone reductions by sodium borohydride in (the rather unusual medium of) refluxing toluene.[65] Similar experiments have been done by Pierre and Handel,[66] who found, nevertheless, that crown ethers do *not* affect $NaBH_4$ reductions carried out in methanol. While studies of this type have not been done with 2-propanol, the normal solvent for reduction, it is likely that the results would be similar to those of methanol, and suggests that the sodium ion does not play any part in the mechanism of sodium borohydride reductions under these normal conditions. These studies, actually, confirm and complement much earlier work by Brown and Ichikawa who demonstrated a negligible rate increase in reductions by sodium borohydride in 2-propanol by the addition of sodium iodide.[67] In contrast, addition of lithium ion causes marked accelerations.[67] This evidence is consistent with the evidence for solvent participation in $NaBH_4$ reductions.[19,20]

It seems clear, therefore, that in the sodium borohydride/2-propanol reductions of ketones, the metal ion does not play any significant mechanistic role. This is an important difference between these reductions and those of the aluminohydride series, those with $LiBH_4$, and, for that matter, $NaBH_4$ reductions in non-hydroxylic solvents. In these cases, all the evidence from similar types of experiments[65–67] indicates that the cation plays a crucial role in the mechanism, presumably by complexation with the carbonyl oxygen. Another, more subtle, role that the metal cation may play which can affect the stereoselectivity, is to change the position of conformational equilibrium in a conformationally mobile cyclohexanone. There is evidence for this in such systems as $LiAlH_4$ in tetrahydrofuran.[68,69]

Intermediate complex formation

Aside from the complexation of the cation, in some reductions, with the CO group, mentioned above, there is no evidence of which we are aware for intermediate complex formation such as boron or aluminum complexing with the CO oxygen, which might cause non-rate-determining hydride transfer. Indeed it does not seem possible to write any such structures that would possess reasonable stability. At the present time, therefore, any mechanisms other than a straightforward one-step hydride transfer appear to be an unnecessary and unwarrented over-complication of these already rather complex reactions. In this respect it is interesting to note the difference between reductions with $NaBH_4$ and hydrolysis of $NaBH_4$ (i.e. reduction of ketones vs reduction of water). In the latter case the reaction appears to proceed by initial addition of a proton to give BH_5.[33]

Activation parameters

The activation parameters for both axial and equatorial attack of borohydride on a wide variety of cyclohexanones of different substitution patterns have been reported[1,29] and allow a greater insight into the origin of stereoselectivity. Overall (i.e. undissected) activation enthalpies are small and vary from 5.4 to 11.1 kcal/mole;

activation entropies are large and negative and vary from -36.4 to -48.4 e.u.

Examination of dissected rate constants and activation parameters reveal the following points.

1. Axial attack is very sensitive to steric hindrance, with rate constants being reduced from 800×10^{-4} l mole^{-1} sec^{-1} to $0{\cdot}5 \times 10^{-4}$ l mole^{-1} sec^{-1} as a result of increasing substitution. Equatorial attack is also impeded, but to a leseer extent (100×10^{-4} l mole^{-1} sec^{-1} also to $0{\cdot}5 \times 10^{-4}$ l mole^{-1} sec^{-1}). The observed attenuation and inversion of stereoselectivity is thus a simple consequence of this differential sensitivity.

2. There is a very large entropy barrier; indeed entropy represents at least 50% and sometimes as much as 70% of the free energy barrier.

3. Despite entropy being a more significant component of the free energy barrier than enthalpy, examination of the trends in the activation parameters reveal that changes in rate and stereoselectivity arise clearly due to the variation of *enthalpy*. The reaction is therefore enthalpy controlled and this conclusion makes the generation of stereochemical rationalizations more straight-forward. The variation of entropy opposes that of enthalpy (i.e. more hindered ketones are reduced with a more favourable entropy of activation) in the usual compensating (isokinetic) manner. The conclusions of enthalpy control is also evident from the values of the apparent isokinetic temperatures, which all lie well above the temperatures used for rate measurements.

Although kinetics and activation parameters for $LiAlH_4$ reductions have recently been determined, these measurements have so far been on hindered aromatic ketones,[36,70] and it has not yet been possible to make kinetic measurements on the very fast reduction of cyclohexanones. Kinetics of reduction of cyclohexanones by $LiAl(OBu^t)_3H$ have been measured,[58,61] and give values of $\Delta H^{\ddagger}$ 5.8–8.2 kcal/mole and values of $\Delta S^{\ddagger}$ -33 to -42 e.u.

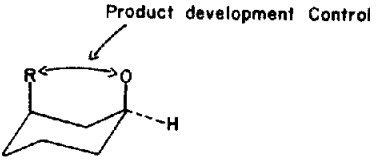
CRITICAL ASSESSMENT OF STEREOCHEMICAL RATIONALIZATION IN THE LIGHT OF MECHANISTIC AND OTHER EXPERIMENTAL DATA

1. *Product Development Control–Steric Approach Control*

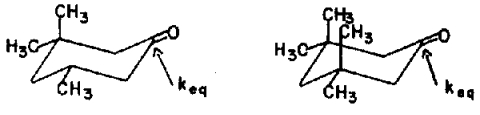
The lack of variation of kinetic isotope effect as a function of ketone structure in reductions by $LiAl(OBu^t)_3H$ and $LiAl(OBu^t)_3D$, even though the observed values lie on a steep (and therefore sensitive) portion of the calculated kinetic isotope effect-reaction coordinate profile, suggests similar degrees of hydride transfer in the transition states for reduction of different ketones.[57] A similar lack of variation of kinetic isotope effect is observed in sodium borohydride reductions.[42,43] These observations are not consistent with the interpretation of Steric Approach Control and Product Development Control in terms of variable transition states (reactant-like and product-like respectively).

Nevertheless, the individual concepts may both be relevant to particular circumstances. Steric Approach Control has never been seriously questioned, and indeed the conclusion that an axial bulky group on C-3 or C-5 must offer steric resistance to incoming axial substituents at C-1 seems unavoidable. Whether or not this is a concept that would be relevant in sodium borohydride reductions, in which a product-like transition state is indicated, is a matter that will receive further development.

Product Development Control, on the other hand, has received far less acceptance. It will not, presumably, be relevant for reductions involving reactant-like transition states, and, if the conclusion that $LiAlH_4$ proceeds via a reactant like transition state is correct,[63] it is a concept of little importance to these reductions. Sodium borohydride, in contrast, appears to involve a product-like transition state,[50,56,57] and it is therefore of considerable interest to devise experimentation specifically to test product development control. Following the experiments of Ashby and Noding,[71] who demonstrated the lack of product development control in the reduction of bicyclic ketones by $LiAlH_4$, the reductions by $NaBH_4$ have been re-examined.[63] Resistance of an axial 3- or 5-Me group to equatorial attack on C-1 is presumably only possible for a product-like transition state in which the nearly-formed



alcohol oxygen is already approaching the axial position and therefore experiencing steric repulsion from the Me group. Comparison, therefore, of rates of equatorial attack on 3,3,5-trimethycyclohexanone and 3,3,5-tetramethylcyclohexanone, represent a measure of this effect which can be regarded as a manifestation of product development control.



This rate ratio is, in fact, available both for $LiAl(OBu^t)_3H$ reductions and $NaBH_4$ reductions. In contrast to the lack of effect in $LiAlH_4$ reductions,[71] the rate ratio for $LiAl(OBu^t)_3H$ reductions is 1.8, and that for $NaBH_4$ reductions 5.8.[63] These values suggest the onset of product development control in $LiAl(OBu^t)_3H$ reductions and substantial product development control in $NaBH_4$ reductions, conclusions that are in harmony with the idea of $LiAlH_4$ reductions involving reactant-like transition states, $LiAl(OBu^t)_3H$ reductions having a transition state near 50% hydride transfer, and $NaBH_4$ reductions involving a product-like transition state.

One of the most powerful objections to product development control is the finding of Eliel and Senda[45] that kinetic stereospecificity (of the transition state) often exceeds the axial-equatorial equilibrium of the products themselves. As already mentioned, product development control cannot be a relevant factor in reductions involving reactant-like transition states, and several reducing agents (such as $LiAlH_4$, $LiAl(OBu^t)_3H$) have high and very similar (90%) stereoselectivities on such unhindered ketones as 4-t-butylcyclohexanone, strongly suggesting some other factor inducing the preferential axial attack. In this connection, the lower stereoselectivity of $NaBH_4$ reductions, for which product development control could be a contributing factor, appears to be a significant observation.

We conclude that both steric approach control and product development are still useful concepts in reaching an understanding of cyclohexanone reduction

stereoselectivity. Steric Approach Control appears to have relevance to $LiAlH_4$ and probably other reductions (reactant-like transition state); Product Development Control may be a significant factor in $NaBH_4$ reductions, which, in contrast, appear to involve a product-like transition state. The crucial limitation of the concepts is that, unlike their original formulation, *both* concepts cannot apply to reductions involving a *single* reducing agent. In other words, the *change* from one to the other to explain variation of stereoselectivity as a function of ketone structure (for a single reducing agent) is not in accord with mechanistic experimental evidence.

2. *Other rationalizations*

The other rationalizations (Nos. 2–7) have all originated in attempts to circumnavigate product development control as an explanation for the apparent intrinsic preference for axial attack on unhindered cyclohexanones. All of them require a reactant-like transition state. Rationalizations 2 (Richer), 3 (Felkin), 5 (Anh's reinterpretation of Felkin), and 6 (Wigfield) demand this by virtue of requiring the carbonyl carbon to have sp^2 bond angles for the explanations to be valid. Rationalizations 4 (Klein) and 7 (Royer) are concerned with the approach of the reducing agent before very much bonding has occurred, and thus also require a reactant-like transition state. With this in mind, it is clearly of importance to make distinction between reducing agents whose reactions proceed through a reactant-like transition state and those whose reactions proceed through a product-like transition state. If the experimental results indicating that sodium borohydride reductions proceed through a product-like transition state[50,56,57] are interpreted correctly, it follows that *none* of these rationalizations can represent the key factor in sodium borohydride reductions. An explanation needs to be developed involving a product-like transition states, and we offer such an explanation in the next section of this review.

Other reductions, such as $LiAlH_4$ reductions, appear to involve a reactant-like transition state, and for these reductions a more careful analysis of the relative merits of the existing rationalizations is required. In the reduction of hindered ketones, in which steric factors are almost certainly involved in controlling stereochemistry, a wide variety of stereoselectivities is observed depending on the nature (size) of the reducing agent. In contrast, there is a striking constancy to the extent of preferential axial attack on unhindered ketones, many reagents reducing, for example, 4-t-butylcyclohexanone with close to 90% axial attack. In view of this lack of variation as a function of the nature of the reducing agent (e.g. $LiAlH_4$ vs $LiAl(OBu^t)_3H$), it seems improbable that the intrinsic preference for axial attack on unhindered ketones can be purely steric in origin. On these grounds we reject Rationalizations 2 (Richer) and 6 (Wigfield) as being of key significance in controlling stereoselectivity. Rationalization 4 (Klein) also seem dubious. Not only has there been experimental evidence that does not appear to be in accord with this type of orbital control,[72,73] but also it has been pointed out to us[74,75] that the extent of 2s character in the π frontier orbital required for this rationalization seems too small to be significant.

We are left with the Felkin torsional strain rationalization (Rationalization 3), either unmodified or in its modified form (Anh, Rationalization 5) in which antiperiplanarity rather than torsional strain is regarded as the key factor; and also Rationalization 7 (Royer). We have no significant criticism of either. The Royer rationalization is probably too new to have been subjected to searching analysis. The Felkin–Anh idea, however, has not only survived (the torsional strain version) a decade, but also is wide in its application, being relevant in general to nucleophilic attack on acyclic ketones as well as this particular cyclohexanone problem. It is unfortunate that different theoretical ideas (e.g. Felkin–Anh vs Royer) are often difficult to distinguish experimentally.

CONCLUSIONS REGARDING THE ORIGIN OF STEREOSELECTIVITY

Table 2 summarizes some of the experimental evidence available for $NaBH_4$ reductions in 2-propanol, with comparison with $LiAlH_4$ reductions.

This Table emphasizes the point that in almost every mechanistic aspect these reductions are completely different, and thus the futility of searching for all-encompassing explanation of stereoselectivity should be evident. Each reducing agent should be individually assessed.

$NaBH_4$ *reductions. Steric repulsion in product-like transition states: a new rationalization*

At this stage, having reviewed the available experimental evidence, we wish to put forward suggestions as

Table 2. Comparison of mechanistic features of $NaBH_4$ and $LiAlH_4$ reductions

	$NaBH_4/Pr^iOH$	$LiAlH_4$/ethereal solvent
1.	Stereochemical Product Ratio arises from sequential reduction of at least two, and probably four different reducing species.	If $LiAlH_4$ is in excess, reduction is by $LiAlH_4$ alone.
2.	Mechanism probably acyclic.	Mechanism unknown.
3.	Mechanism involves participation of hydroxylic solvent.	Hydroxylic solvent absent.
4.	Transition state product-like.	Transition state probably reactant-like.
5.	Kinetic evidence for product development control.	Kinetic evidence for lack of product development control.
6.	Metal cation not involved in mechanism.	Metal cation essential for reduction.

to what appear to be the key factors involved in controlling stereochemistry of reduction of cyclohexanones, based on the currently available evidence. The mechanistic evidence on sodium borohydride reductions is summarized in Table 2, and we select out two key pieces of information—an acyclic mechanism, and a product-like transition state. Whatever the exact details of the mechanism may be, therefore, the key features of the mechanism may be represented as shown in Fig. 2, for axial and equatorial attack on both hindered (3-axial substituent) and unhindered cyclohexanones.

A product-like transition state involves essentially (or close to) sp^3 hybridization at the CO carbon, with the appropriate tetrahedral geometry of the O atom and the incoming hydride. The major difference between the product-like *transition state* and the *product* itself, lies in the significant positioning of the rest of the borohydride molecule. In view of the acyclic mechanism, it is likely that this position is defined by a 180° angle of C(1)-H-B. The relevant transition states for consideration are therefore as shown in Fig. 2.

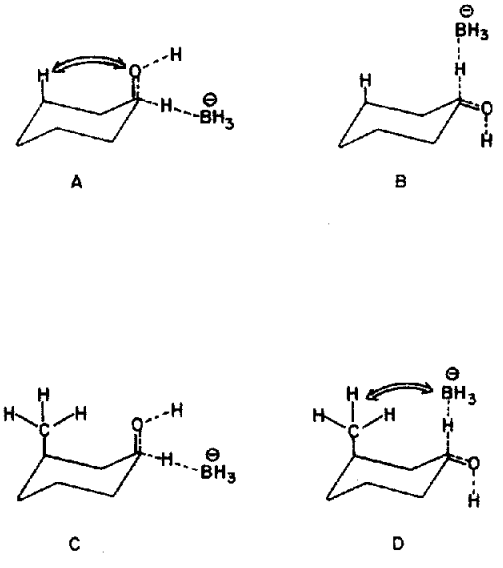


Fig. 2. Rationalization of stereochemistry in $NaBH_4$ reductions. Unhindered cyclohexanones: transition state B favoured over transition state A because of developing steric interaction between O and C-3, C-5 axial H's in A. Hindered cyclohexanones: transition state C preferred over transition state D because of steric repulsion between axial CH_3 groups at C-3, C-5 and the borohydride molecule in D.

(a) *Reduction of unhindered ketones* (A *vs* B). The rationale for the preference of transition state B over transition state A (preferential axial attack) is essentially that of product development control. The significant factor is the steric interaction between the forming axial OH group, and the axial hydrogens C-3 and C-5 (A). The incorporation of the rest of the borohydride molecule does not adversely affect transition state B since the axial groups at C-3 and C-5 (hydrogens) do not reach up far enough to interact.

(b) *Reduction of hindered ketones* (C *vs* D). A contrasting situation is seen in the reduction of hindered ketones (C vs D). Transition state C is destabilized with respect to A because of the HO...CH_3 interaction; this is in accord with the kinetic evidence discussed previously for product development control.[63] Far more serious, however, is the previously overlooked interaction between the axial Me groups at C-3 and C-5 with the remainder of the borohydride molecule in transition state D. (In the absence of mechanistic evidence, of course, it is not obvious that such a geometry would pertain, and thus the interaction be significant). Molecular models indicate this to be a serious steric interaction and we suggest that this may be a key factor in the reversal of stereochemistry in reducing hindered vs non-hindered cyclohexanones by $NaBH_4$. With respect to this hypothesis there are three points to be made:

(i) It is possible to rationalize stereoselectivity in $NaBH_4$ reductions purely by a consideration of steric factors involved in product-like transition states.

(ii) This is the only explanation for $NaBH_4$ reductions which is compatible with available experimental data.

(iii) The explanation, although related to product development control, differs from it in the incorporation of the remainder of the borohydride molecule. This is especially critical in considering the reduction of hindered cyclohexanones.

Factors governing stereoselectivity in $LiAlH_4$ *reductions*

The stereochemical factors in $LiAlH_4$ reductions appear to be two-fold. Firstly there is an intrinsic preference for axial attack. From our assessment of the rationalizations offered for this phenomenon, the most likely cause of this appears to be the Felkin–Anh factor of antiperiplanarity between the incoming nucleophile and the axial hydrogens at C-2 and C-6. Thus (Fig. 3), reactant-like transition state F (axial attack) is preferred over transition state E (equatorial attack). This intrinsic factor is modified by steric interactions the nucleophile may encounter approaching the carbonyl group, and thus, in the reduction of hindered cyclohexanones, transition state G (equatorial attack) is preferred over transition state H (axial attack). This control, in the reduction of hindered cyclohexanones by $LiAlH_4$, is steric approach control.

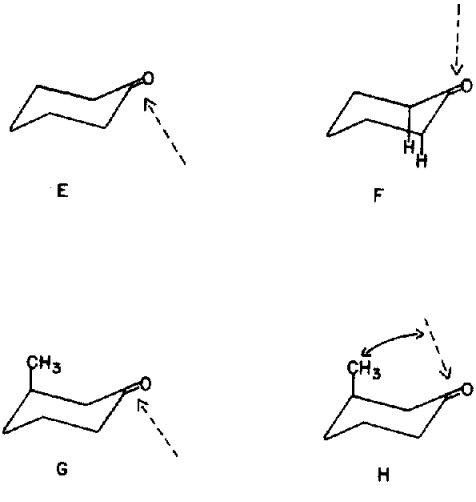


Fig. 3. Rationalization of stereochemistry in $LiAlH_4$ reductions. Unhindered cyclohexanones: transition state F favoured over transition E due to favourable antiperiplanarity in F. Hindered cyclohexanones: transition state G favoured over transition state H due to steric approach control.

SYNTHETIC ASPECTS

As well as endeavouring to get to the root of the cause of stereoselectivity in cyclohexanone reductions, two other aspects are of particular concern to synthetic organic chemistry. These are (a) prediction of the stereochemical outcome in particular reductions and (b) experimental manipulations possible to achieve the maximum yield of the desired stereoisomer.

Stereoselective synthesis. This problem is, to a large degree, satisfactorily solved. Since reduction of unhindered cyclohexanones normally gives predominantly the equatorial alcohol and reduction of hindered cyclohexanones the axial alcohol, the principal problem is obtaining axial alcohols from unhindered cyclohexanones and equatorial alcohols from hindered cyclohexanones.

The first of these problems, obtaining axial alcohols from unhindered cyclohexanones, has essentially been solved by the development of a range of new, and highly hindered, reducing agents by Brown *et al.* L-Selectride ($Li(2\text{-}Bu)_3BH$),[34] for example, almost[76] always results in formation of the axial alcohol. 4-t-Butylcyclohexanone is reduced by L-Selectride to give 96.5% of the axial alcohol.[34] The second problem, that of obtaining equatorial alcohols from hindered cyclohexanones, can usually be solved by equilibration of the axial-equatorial alcohol product mixture. Eliel and Schroeter have shown that Raney Nickel is particularly effective at this equilibration, although aluminum alkoxides can also be used.[77] Some examples of these reactions are shown below.

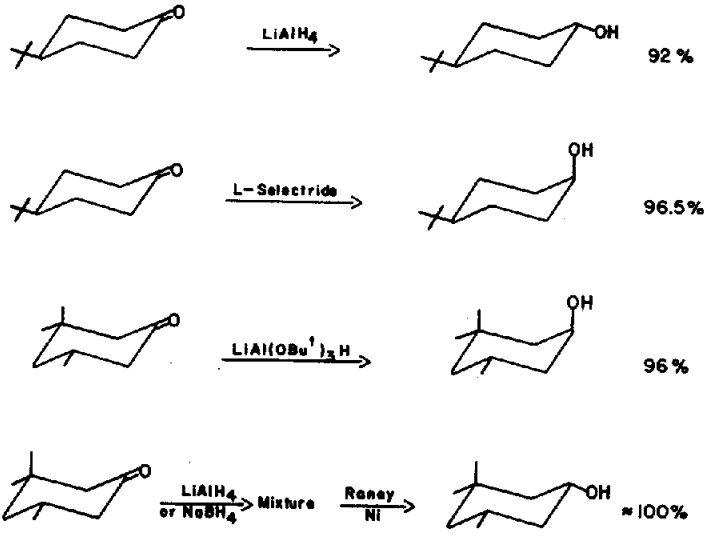
Quantitative prediction of stereochemistry. Although the Barton generalization of stereochemical trends was put forward in 1953,[4] no apparent progress was made for twenty years towards converting this qualitative generalization to a quantitative predictive instrument. In view of the mechanistic diversity involved in these reductions, however, this is not surprising, and clearly the search for a global predictive formula is likely to be as fruitless as a search for a global rationalization of stereoselectivity.

Recently, however, two approaches to quantitative prediction of stereochemistry have been reported. In one of these,[78] we have developed a purely empirical approach for $NaBH_4$ reductions based on experimentally determined activation parameters. Activation enthalpy increments are defined for substituents at all the possible positions around the cyclohexanone ring; these are summed, and the result put into a simple formula to take into account the differential isokinetic behaviour that hindered and non-hindered cyclohexanone reductions exhibit. The agreement between calculated and experimental axial:equatorial alcohol product ratios is generally within a few per cent.

The other approach is considerably more complex. Wipke and Gund[41] have developed a calculation based on the ground-state properties of the ketone to generate what is termed a congestion function. This function may be used to calculate axial/equatorial product ratios, but in some cases needs a correction based on torsional state effects to give the "torsion-corrected" congestion. Use of this parameter to calculate stereochemical product ratios gives agreement between experimental and calculated ratios in many cases within 10%. The approach does not take into consideration mechanistic differences between reductions with different reducing agents, and thus it is likely that this level of agreement is as good as can be expected.

CONCLUSIONS

Although the mechanistic picture of $NaBH_4$ reductions is far from complete, and that for $LiAlH_4$ and other reductions almost non-existent, sufficient data exist to reach the conclusion that, in almost every aspect, the mechanisms involved in these two reductions are quite different. This being the case, it is no longer justified to expect that one global explanation of stereoselectivity covering reductions with all the common reducing agents will be found. Such a search or expectation is almost certainly futile. A logical division may be made between those reductions which appear to involve reactant-like transition states (e.g. $LiAlH_4$), and those which appear to involve product-like transition states (e.g. $NaBH_4$), and further subdivisions may subsequently be required. There is no evidence at present to suggest that variation of ketone structure causes substantial change in the nature of the transition state. *Sodium Borohydride reductions* appear to be rationalized simply and adequately by the *steric interactions involved in the product-like transition state*—a concept that is a development of, but clearly distinguished from, product development control. *Lithium aluminum hydride* (and



probably many other) reductions appear to require the *combination of two counteracting effects*—(a) a *steric factor* (Steric Approach Control) favouring equatorial attack if bulky axial groups are present at C-3 and C-5 and (b) *some other* (*non-steric*) *factor* which provides an intrinsic preference for axial attack. At the present time, the strongest candidates for the identity of this factor appear to be either the Felkin–Anh Rationalization based on either torsional strain or the need for antiperiplanarity, or possibly, the very recent Royer rationalization. Twenty-five years after the original stereochemical observations[4] a rational understanding of the factors behind this stereochemical puzzle appears to be developing.

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