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CONFORMATIONAL ANALYSIS AND ORGANIC REACTION
MECHANISMS: STUDIES IN ASYMMETRIC INDUCTION AND
HYDROGEN BONDING SYSTEMS

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PREVIEW

CONFORMATIONAL ANALYSIS AND ORGANIC REACTION MECHANISMS:
STUDIES IN ASYMMETRIC INDUCTION AND
HYDROGEN BONDING SYSTEMS

by

Alan E. Sopchik

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In Partial Fulfillment of Requirements
For the Degree of Doctor of Philosophy

Major: Chemistry

Under the Supervision of Dr. C. A. Kingsbury

Lincoln, Nebraska

July, 1981

TITLE

**CONFORMATIONAL ANALYSIS AND ORGANIC REACTION MECHANISMS:
STUDIES IN ASYMMETRIC INDUCTION AND
HYDROGEN BONDING SYSTEMS**

BY

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PREVIEW

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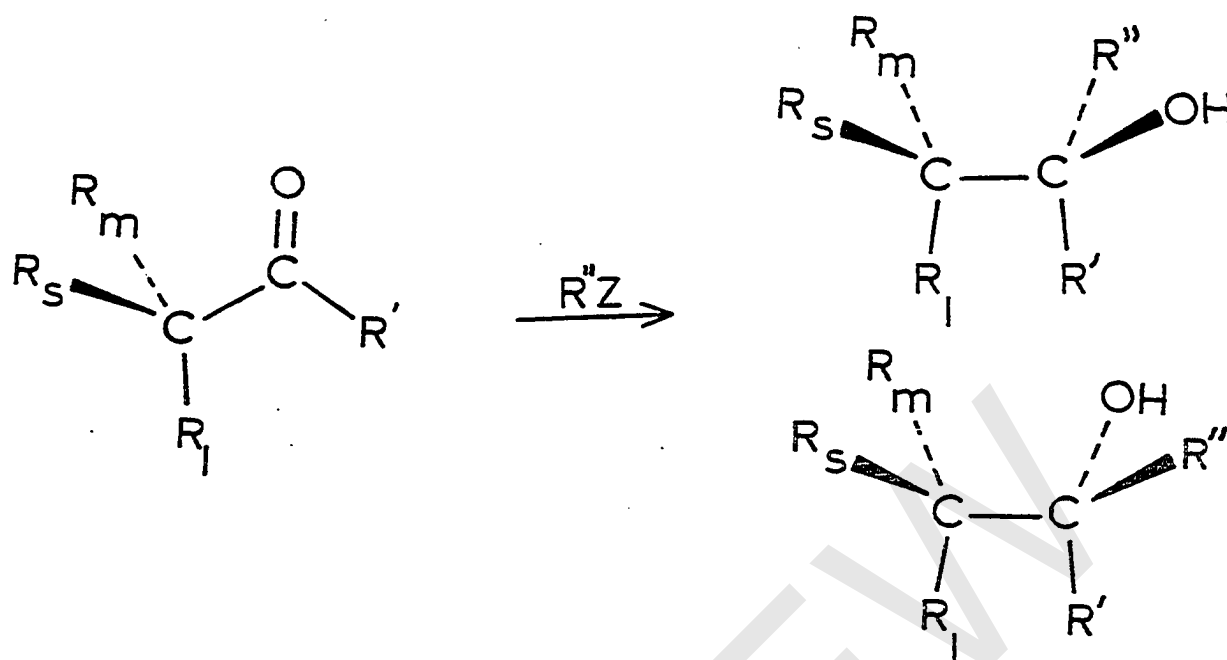
Part I

ASYMMETRIC INDUCTION:
COMPARISON OF CYCLIC AND ACYCLIC SUBSTRATES
IN ASYMMETRIC HYDRIDE REDUCTION

INTRODUCTION

Models for the metal hydride reduction of cyclic and acyclic ketones and aldehydes have, over the past 20 years, caused considerable disagreement between workers in this field. It was not until nearly 10 years after the discovery of the metal hydride reducing agent lithium aluminum hydride¹ that what is now considered a classic paper by Cram and Abd Elhafez² appeared in the literature discussing the first proposed model for ketone and aldehyde reduction. The model enjoyed success because it could at the time explain relatively accurately the observed isomer ratios found for not only hydride reductions but also Grignard additions to acyclic aldehydes and ketones. Although the model was successful, it was entirely empirical in nature and because of this fact the correctness of his theory remained unsettled.

Cram's original proposal or "Cram's rule", used to predict the product ratios of what is termed "1,2-asymmetric addition"³ states."⁴ In noncatalytic (kinetically controlled) reactions (1,2-asymmetric addition), that diastereomer will predominate which would be formed by the approach of the entering group (R'' of the reagent $R''Z$) from the less hindered side of the double bond when the rotational conformation of the C-C bond is such that the double bond is flanked by the two least hindered bulky groups (R_s and R_m , where R_s is a "small" group and R_m is a "medium" size group) attached to the asymmetric center. For the reaction:



The Newman projection, Figure 1, showing the approach of $R''Z$ leading to the predominant product as predicted by Cram is shown below:

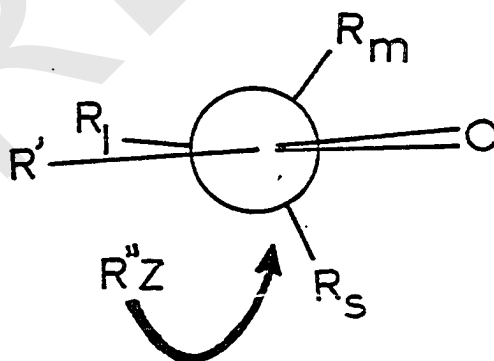


Figure 1. Newman projection of 1,2-asymmetric addition as proposed by Cram.

Some time after publication of Cram's rule certain discrepancies appeared in the literature which, although they did not disprove the validity of Cram's model, did suggest that certain improvements may be needed. Based on information concerning the conformational preferences of large and medium size groups (e.g. phenyl and methyl) from work on acyclic systems, Karabatsos⁵ proposed a modification of Cram's model as shown below (Figure 2).

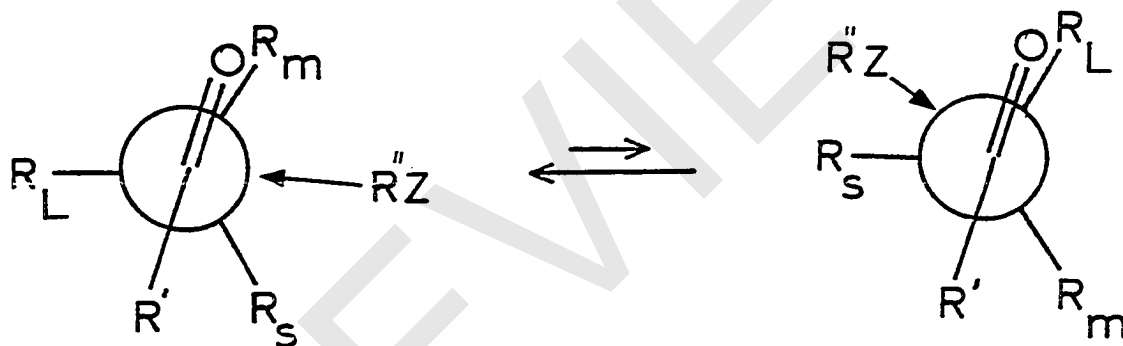


Figure 2. Diagram of the Karabatsos modification of Cram's Rule.

The model differs from that of Cram's only in the conformation of R_L and R_m leading to erythro and threo products (for acyclic ketones and aldehydes) but is similar in that the reagent $R''-Z$ approaches the carbonyl over the smallest group. The model

has the medium size group (R_m) or the large group (R_L) eclipsed with the carbonyl, in Cram's model they are gauche. In 1968, Cherest, Felkin and Prudent⁶ suggested an alternate model to those discussed above. It was felt that a revision was necessary, for the Karabatsos and Cram model could not adequately explain changes in specificity found when R' (the group α to the carbonyl) and hydride sizes were changed.⁷ The Karabatsos model, based on thermodynamic properties of specific group interactions, does not successfully predict changes in product ratios as demanded by Karabatsos's system. Felkin's model (Figure 3), which was the first to attempt a rationalization of 1,2 asymmetric addition for both cyclic as well as acyclic ketones and aldehydes, was formulated on four basic premises which are listed below. (1) The transition state for these reactions is reactant-like. (2) Torsional strain involving partial bonds in the transition state represent a substantial fraction of the strain between fully formed bonds even when the degree of bonding is quite low. (3) The important transition state interaction involves R'' (of the reagent $R''-Z$, see Figure 3) and R' rather than the interactions of the groups on the chiral center. (4) Polar effects stabilize those transition states in which the separation between R'' and the electronegative groups is greatest and destabilize others.

Although this model could explain the effect of R' which previous models could not, it was less successful than the Karabatsos model for explaining the effect of $R_L = \text{phenyl}$. Phenyl has a greater steric influence than most large alkyl groups such

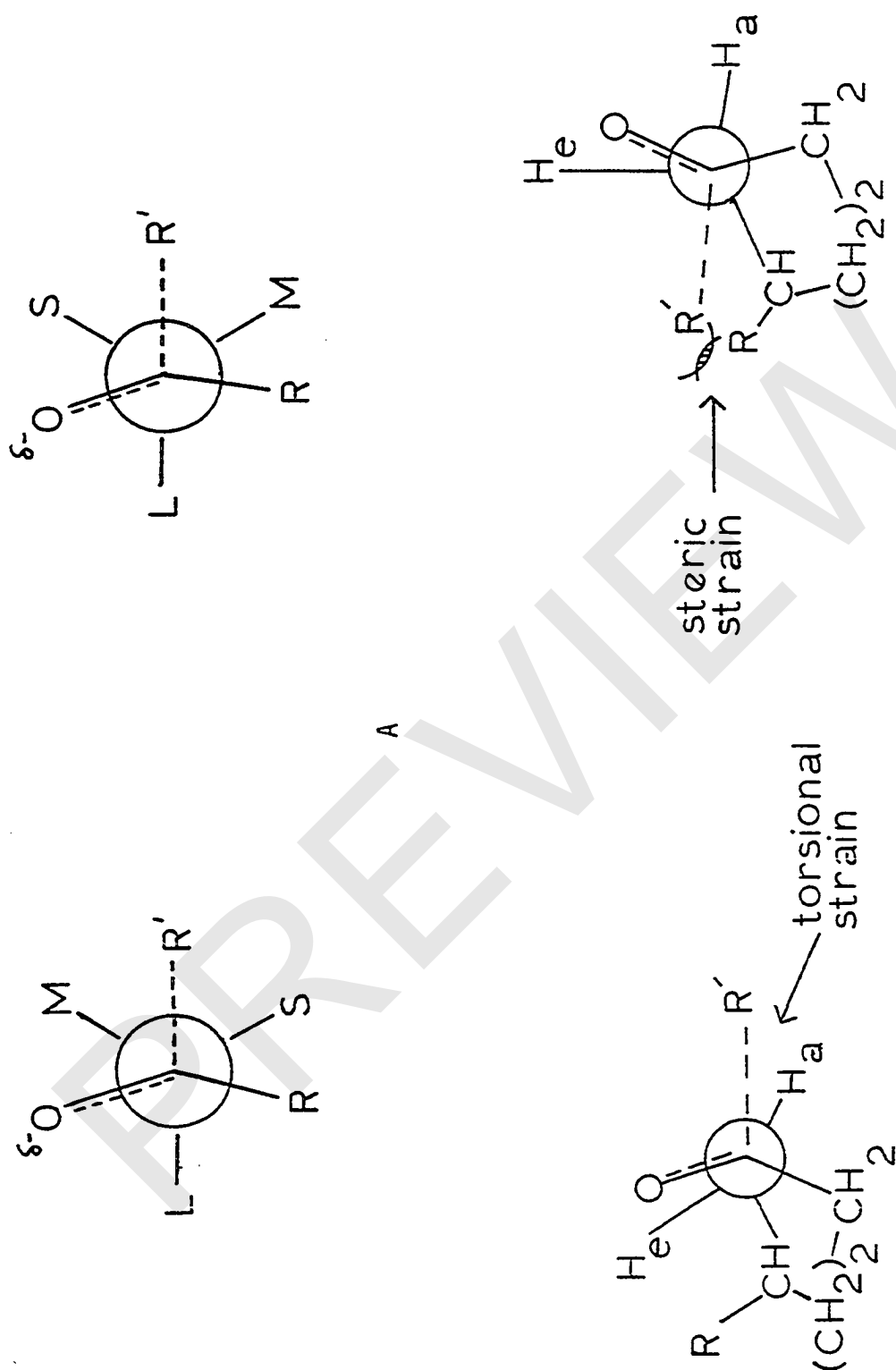


Figure 3. Felkin's models for acyclic hydride reduction (A) and cyclic hydride reduction (B).

as isopropyl and in many instances tertiary butyl. Felkin's model relied on a weak argument concerning the relative polarity of phenyl versus alkyl groups to explain this effect. Although he was not entirely successful his model was nevertheless an improvement on previous attempts.

Subsequently, other rationales have been used to clarify the perplexing question as to what are the factors that influence observed product ratios in both acyclic and cyclic reduction with most of the activity in the present literature focusing on cyclic systems.

Early work on cyclic systems includes that of Dauben et al.⁸ who proposed "steric approach control" and "product development control" which was later remodified by Brown⁹ who made slight variations and renamed the theory "steric strain control" and "product stability control." Both authors' arguments are however essentially the same. Although the steric approach control argument, which is as the name implies a pure steric argument of group interaction which controls initial approach of reagent $R''-Z$, is still in some respects valid, the product development and product stability control arguments presented by both authors has been shown to be in doubt by several authors¹⁰ as to its applicability.

In another work with cyclic ketones, a rationale using pure steric interactions was used by Richer¹¹ to explain the product distribution from the reduction of variously substituted cyclohexanones with lithium tri-tert-butyl aluminum hydride. Although

his data are consistent with present data with the use of this reagent, his explanations lack the depth to describe the full picture of all factors responsible for stereoselective reductions.

Along these same lines, a publication by Marshall¹² appeared the same year as Richer also rationalizing the reduction data of cyclic ketones. Marshall's argument, although steric in origin, was that of kinetic differences between topside (axial attack) and bottom (equatorial attack) approach of hydride. It was thought that by using molecular models it could be shown that since approach by reagent $R^{\prime\prime}Z$ was perpendicular to the carbonyl group to effect maximum overlap of forming orbitals in the transition state,¹³ there would be greater steric interaction with the 2,6 axial positions than the 3,5 axial positions (Figure 4). The distance from a line drawn perpendicular to the planar $C=O$ was shorter for the 2,6 interaction than the 3,5 positions hence a greater steric interaction for "bottom side" attack.

On this basis alone, Marshall concluded that in the transition state smaller hydrides could approach closer to the ketone than could larger hydrides and hence have more bond formation and faster reaction with respect to equatorial attack and an overall greater amount of topside axial approach. Again, this argument cannot be used as the sole rationale. Also along these same lines, Elie¹⁴ demonstrated that there was indeed a difference in rates and energetics for axial and equatorial approach in cyclic ketones. Using competitive rates of reduction for substituted cyclohexanones vs. a suitable standard, the fastest route was observed to give the

predominant product all other factors being constant. It was also indicated by one author¹⁵ that although the overall reaction was

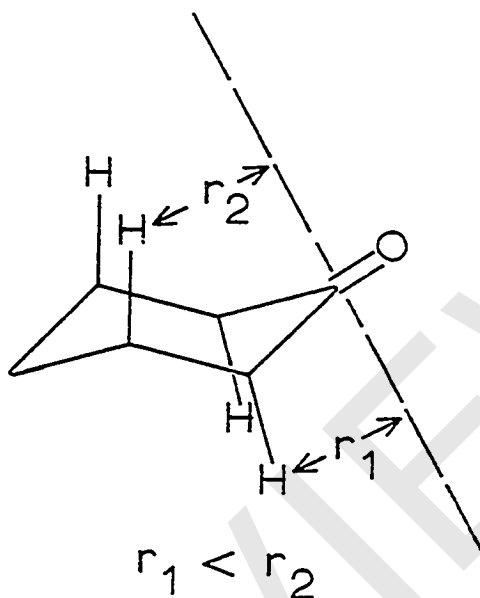


Figure 4. Steric interactions as a result of perpendicular approach of hydride as proposed by Marshall. Line drawn is perpendicular to carbonyl and represents path of hydride for a 90° approach to plane of carbonyl.

entropy dominated the differences in reactivity between pairs of compounds was in fact enthalpy dominated.

Until this point only the nature of the ketone was of primary importance, the nature of the hydride other than size was neglected. It was normally assumed that in all cases the hydride was in a monomeric state. Recent work by Ashby¹⁶ indicated that this was not the case. Experiments using a conductance technique

on ethereal and tetrahydrofuran (THF) solutions of alkyl and alkoxy alumino and borohydrides demonstrated that in actuality the hydrides existed as ion aggregates or several molecules of hydride associated in a tight complex that was solvent and concentration dependent. Also demonstrated conclusively was the important fact that alkoxy substituted hydrides do indeed exchange intermolecularly with other hydrides and that in cases such as tri-tert.-butyl aluminum hydrides the actual reducing agent may be the tri, di, mono or unsubstituted species formed by exchange. This was shown also to be the case for methoxyborohydrides as well.

Other work concerning the nature of the hydride concerns the importance of the metal cation in hydride reduction of ketones. It had been previously suspected¹⁷ that the cation (typically Li^+ , Na^+ , K^+) played a role in directing stereochemistry in that in some cases it was observed that small product ratio changes could be observed by changing from say NaBH_4 to LiBH_4 .¹⁸ It is believed by these workers that prior complexation of the metal cation with the ketone activates the carbon making it more electrophilic and that the electronegativity and size of the cation interact in some cases to such an extent with the ketone that it has been postulated¹⁹ to be the cause of proposed conformational ring flipping to alleviate excess steric interaction present with α substituted ketones prior to hydride transfer.

In related work Doyle²⁰ has postulated a "complexation induced conformational perturbation" argument also based on metal cation or Lewis acid complexation with the carbonyl oxygen.

Doyle's argument is also steric in origin and states that the ring will adopt a conformation to alleviate to the greatest extent any steric interactions present which he states results in a "ring flattening" effect at and around the carbonyl center.

Perhaps a more direct approach to determine more clearly the nature of the transition state and to gain important information concerning the extent of bond formation or cleavage, i.e., the position of the transition state along the reaction coordinate, is the use of deuterium isotope effects. However, there is to be found as much disagreement in the literature concerning the interpretation of data using this technique as that using product ratios as discussed previously. Problems in interpretation arise concerning the point as to where particular values for k_H/k_D ratios reflect the position of the transition state on the reaction coordinate, i.e., whether they are product-like or reactant-like in nature. Based on the Hammond postulate that exothermic reactions are reactant-like and the exothermicity (~ 130 kcal/mole) of borohydride reductions, Wheeler²¹ postulated reactant-like transition states as do Laszlo and Welvant²² based on their interpretation of secondary isotope effects. Primary and secondary isotope effects were also used by Geneste and Lamaty²³ on cyclic and acyclic ketone borohydride reductions but their interpretation was one of a late transition state (product-like). These authors claim that the Hammond postulate was not pertinent to these reactions and that the values of k_H/k_D (~ 0.9) could be best

interpreted by a product-like transition state with a tetrahedral "carbonyl" in a four centered configuration (Figure 5).

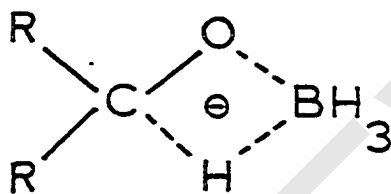


Figure 5. Four centered cyclic transition state for borohydride ketone reduction as envisioned by Geneste and Lamaty.

In earlier work by these same authors, it was proposed that the hyperconjugative effect or "any other phenomenon with conjugative character" was the determining factor for both cyclic and acyclic borohydride deuterium isotope effects and that inductive effects, basicity differences between H and D compounds, and steric differences were all unimportant.

Parallel work with primary isotope effects has also aroused some controversy. Although Davis²⁴ found "small but normal"

primary isotope effects for the hydrolysis of H and D sodium borohydride as did Wigfield and Phelps²⁵ for the reduction of ketones with borohydride, subsequent work by the later authors²⁶ found in a few select cases an inverse primary isotope effect, Figure 6.

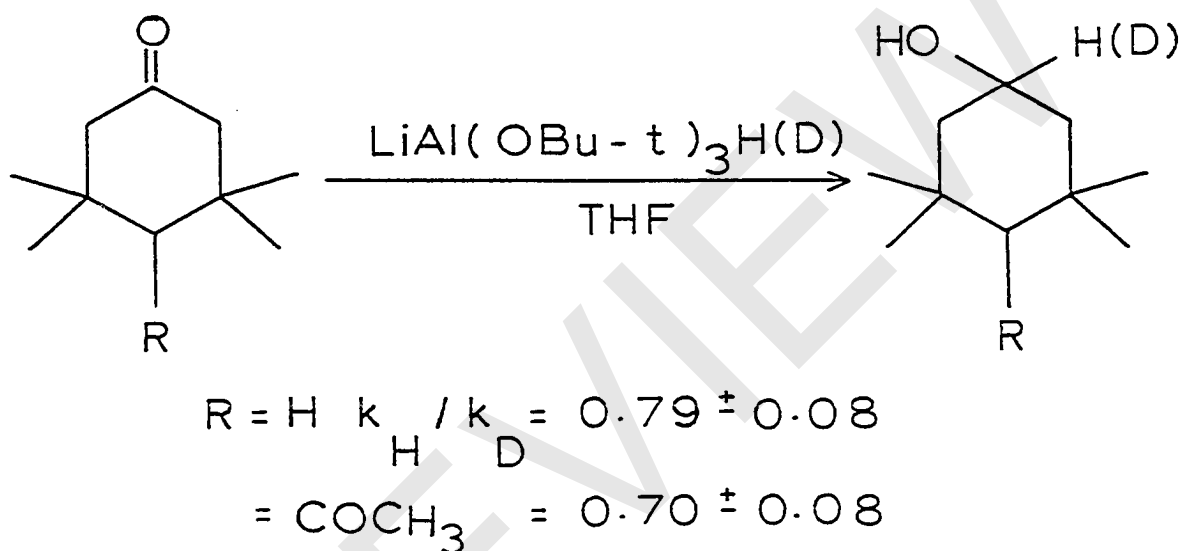


Figure 6. Inverse isotope effects found in the $\text{LiAl}(\text{O-tert. Bu})_3\text{H(D)}$ reduction of sterically hindered ketones as found by Wigfield and Phelps.

These authors, based on the above observations, implied that the transition state should resemble products, supporting the interpretations of Geneste and Lamaty.

In view of all the above mentioned difficulties in deriving an adequate model describing stereoselectivities found in cyclic