# ASYMMETRIC INDUCTION IN ADDITIONS <br> TO SOME ASYMMETRIC ALDEHYDES AND KETONES 

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This is to certify that the thesis entitled

## ASYMMETRIC INDUCTION IN ADDITIONS TO SOME ASYMMETRIC ALDEHYDES AND KETONES presented by

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# ABSTRACT <br> ASYMMETRIC INDUCTION IN ADDITIONS TO SOME ASYMMETRIC ALDEHYDES AND KETONES 

By
Richard Nelson Nipe

The model for asymmetric induction proposed by Karabatsos (1) predicts not only the major diastereomer, but also the diastereomeric ratio as well. The predictions from the model are based on the interactions of the carbonyl oxygen with the large and medium groups on the asymmetric center. To test the validity of this model under a variety of conditions (nucleophile, temperature, and solvent), the reactions of 2-methylbutanal-2-d; 2,3,3-trimethylbutanal-2-d; 3-methyl-2-pentanone-1,1,1,3- $\underline{d}_{4}$; and 3,4,4-trimethyl-2-pentanone-1,1,1- $\underline{d}_{3}$ were carried out with lithium aluminum deuteride and lithium aluminum hydride in ether, sodium borodeuteride in tetrahydrofuran and isopropyl alcohol, methyllithium in ether, methylmagnesium iodide and bromide in ether, and methylmagnesium chloride in tetrahydrofuran. The ratios of the isotopically related diastereomers were determined by integration of their nmr spectra. The ratios of the 3,4,4-trimethyl-2-pentanols ( $\underline{d}_{0}$ and 2- $\underline{d}_{1}$ ) were
determined by separation on a six foot Carbowax column and integration of the peak areas.

In contrast to earlier data, the values of $\Delta \Delta G_{A B}^{\neq}$calculated according to the Curtin-Hammett principle (2) were not

$$
\Delta \Delta G_{A B}^{\ddagger}=-R T \ln (A / B)
$$

constant with temperature. Accordingly, values for $\Delta \Delta H_{A B}^{\ddagger}$ were calculated from plots of $\ln \frac{A / B}{T}$ versus $1 / T$ and were found to agree with the values calculated by the Karabatsos model. The $\Delta \Delta S_{A B}^{\ddagger}$ was shown to control the stereospecificity of the reactions.

The conclusions drawn from this study are: 1) the stereospecificity in reactions of 1,2-asymmetric inductions can be controlled by $\Delta \Delta H_{A B}^{\ddagger}$ or $\Delta \Delta S_{A B}^{\ddagger}$; 2) the $\Delta \Delta H_{A B}^{\ddagger}$ predicted by the model and those found experimentally agree well;
3) stereospecificity depends on the attacking species, although its exact dependence is difficult to predict;
4) the increase in effective steric bulk of the attacking reagent increases stereospecificity.

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# ASYMMETRIC INDUCTION IN ADDITIONS TO SOME ASYMMETRIC ALDEHYDES AND KETONES 

By<br>Richard Nelson Nipe

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## TABLE OF CONTENTS

Page
LIST OF TABLES ..... vi
LIST OF FIGURES ..... vii
INTRODUCTION. ..... 1
RESULTS AND DISCUSSION. ..... 11
A. Errors Involved in Calculations of Thermo- dynamic Parameters ..... 11
B. The Relation Between Activation Parameters and Stereospecificity ..... 21
C. The Contributions of Nucleophile and Solvent. ..... 23
D. Conclusion. ..... 25
EXPERIMENTAL. ..... 26
A. General Procedures ..... 26
B. Preparation of 2-Methylbutanal-2-d. ..... 27
C. Nmr Studies of 2-Methyl-1-butanol-2,0-d2 ..... 28
D. Additions to 2-Methyl-1-butanol-1,2-d 2 ..... 28
E. Nmr Solvent Studies of 2,3-Dimethyl-2-pent- anol. ..... 29
F. Preparation of 3-Methyl-2-pentanone- $1,1,1,3$ - $_{4}$ ..... 30
G. Additions to 3-Methyl-2-pentanone-1,1,1,3-d ${ }_{4}$. ..... 31
H. Preparation of 2,3,3-Trimethylbutanoic Acid ..... 32
I. Preparation of 2,3,3-Trimethylbutyryl Chloride. ..... 33
J. Preparation of 3,4,4-Trimethyl-2-pentanone. . ..... 34
K. Preparation of 3,4,4-Trimethyl-2-pentanone- 1,1,1- den $_{3}$ ..... 35
L. Additions to 3,4,4-Trimethyl-2-pentanone. ..... 35
M. Additions to 3,4,4-Trimethyl-2-pentanone- 1,1,1- d $_{3}$. ..... 36
N. Preparation of 2,3,3-Trimethyl-1-butanol ..... 36
O. Preparation of 2,3,3-Trimethylbutanal ..... 38
P. Preparation of 2,3,3-Trimethylbutanal-2-d ..... 40
Q. Additions to 2,3,3-Trimethylbutanal ..... 41
R. Additions to 2,3,3-Trimethylbutanal-2-d ..... 41
BIBLIOGRAPHY. ..... 44

## LIST OF TABLES

Table Page
I. Additions to 2-Methylbutanal and 2-Methyl- butanal-2-d. ..... 12
II. Additions to 3-Methyl-2-pentanone and 3-Methyl- 2-pentanone-1,1,1,3-- 4 $_{4}$ ..... 13
III. Additions to 3,4,4-Trimethylpentanone and 3,4,4- Trimethylpentanone-1,1,1- $\underline{d}_{3}$ ..... 14
IV. Additions to 2,3,3-Trimethylbutanal and 2,3,3- Trimethylbutanal-2-d ..... 15
V. The Activation Parameters of the Reactions in Tables I-IV. ..... 16
VI. List of Solvents Used to Resolve the Diastereo- topic Methyl Groups of 2;3-Dimethyl-2-pentanol. ..... 30

## LIST OF FIGURES

Figure Page1. The nmr spectrum of $30 \%$ solutions of 2,3,3-trimethyl-1-butanol in acidic methylenechloride. . . . . . . . . . . . . . .372. The neat nmr spectrum of 2,3,3-trimethyl-butanal39
3. The nmr spectrum of 2,3,3-trimethyl-1-butanol-1,2-d2 obtained in the reaction of 2,3,3-tri-methylbutanal-2-d with sodium borodeuteride at $-70^{\text {in tetrahydrofuran . . . . . . . . . . . . } 42 ~}$

## INTRODUCTION

The recognition that the arrangement of atoms in space is three dimensional rather than two dimensional represented a major change in the theory of molecular structure. J. H. van't Hoff (1), who advanced this concept in 1875, explained the differences between isomeric compounds which are identical by elemental analysis and react in a similar manner, but are different in their interactions with plane polarized light. This configurational theory proposed that a molecule can be defined by stating not only the number of covalent bonds by which the atoms are attached, but also stating the geometrical arrangement of the atoms. This theory can be partially justified by the fact that all observations of science to date are consistent with it.

A second important concept used in the development of the theory of asymmetric induction was steric bulk. Both Hofmann (2), who reported that no reaction occurred between methyl iodide and dimethylmesitylamine and Meyer (3), who reported that steric hindrance retarded the esterification and hydrolyse of ortho-disubstituted benzoic acid showed how the outcome of a reaction can be determined by the spacial arrangements of the reactants. A further development
involved showing that restricted rotation in biphenyls could result in optical resolution. Both Kenner et al. (4) and Turner et al. (5) showed that 6,6'-dinitrobiphenic acid could be resolved into enantiomers. These concepts of the conformational effects and steric interactions form the basis of the arguments used to interpret the observed results of asymmetric induction.

Asymmetric induction represents any reaction in which unequal amounts of two possible enantiomers or diastereomers are formed due to asymmetry present in reactant, reagent, catalysts, or solvent molecules. In 1952, Cram and Elhafez (6) introduced a model for asymmetric induction shown below.

"Cram's model" for asymmetric induction was derived empirically, based on the role of steric interactions in determining the major diastereomeric product. The argument used was that the carbonyl oxygen when complexed with a metallic atom of the attacking reagent, became the largest group in the molecule. Therefore, it would be in the most stable
conformation when placed between the small and medium groups. The attack of the reagent to give the major isomer A would be past the small group, $s$, and the attack to give the minor product, past the medium group, M. This model is thus based on the assumption that the magnitude of the steric interactions between the incoming group and the $s$ group and those between the incoming group and the $M$ group determine the product ratio. This rule is applied to kinetically controlled reactions in which the groups attached to the asymmetric center do not complex with the attacking reagent. The kinetic versus thermodynamic control of these reactions has led to the coining of two terms (7): "steric approach control" and "product development control". These terms have been used to describe additions to cyclohexanone systems. They represent the two possible extremes on the reaction coordinate: first, a transition state that resembles the starting materials with little change in bonding orders, and second, a transition state in which extensive bond breaking has occurred.

A simple empirical model, proposed by Karabatsos (8), predicts not only the major diastereomer in 1,2-asymmetric induction, but also the semiquantitative ratio of the diastereomers ( $A / B$ ). In this model, which correctly focuses attention to transition states rather than ground states, several assumptions are made: a) little bond making or breaking has occurred in the diastereomeric transition states,
b) the two low energy transition states that determine product stereospecificity have the smallest group adjacent to the incoming reagent, and c) the diastereomeric ratios can be evaluated from the relative magnitudes of the calculated interactions between the carbonyl group and the group that eclipses it at the asymmetric carbon atom.

Considering the first assumption, one concludes that the transition states in the additions to aldehydes and ketones would resemble the ground state conformations found by nmr. The conformation having an alkyl or aryl group eclipsing the carbonyl oxygen was found to be more stable than that having a hydrogen eclipsing the carbonyl group (9). Three possible transition states, I-III, can be drawn leading to one diastereomeric product, A:


I


II


III

Referring to the second assumption, the approach of the reagent would be less hindered while moving past the small group than past either the medium or large group, i.e.,
structure $I$ would be favored over either II or III as the low energy transition state. Other interactions which would contribute to the greater stability of $I$ versus II or III are $R^{\prime} \leftrightarrow S$ and $R \leftrightarrow S$ interactions in $I$ versus $R^{\prime} \leftrightarrow M$ and $R \leftrightarrow M$ in II and the much larger $R^{\prime} \leftrightarrow L$ and $R \leftrightarrow L$ interactions in III. The non-bonded interactions between carbonyl oxygen and the eclipsing group, as mentioned in assumption $c$, would also favor I over II and III. For example, when s is hydrogen, $M$ is methyl, and $L$ is ethyl, $I$ is favored over II by $-100 \mathrm{cal} / \mathrm{mole}$ and over III by $-800 \mathrm{cal} / \mathrm{mole}$.

These same arguments can be applied to predict the low energy transition state leading to the other diastereomeric product, B. Of the three structures, IV-VI, structure V


R


R


R

VI
would be the low energy transition state leading to the other diastereomer.

The next step was to determine which of these two low energy diastereomeric transition states led to the major
and which to the minor product.


R


R

I

The interactions of $R^{\prime} \leftrightarrow s, R \nleftarrow s$, and $R^{\prime} \nleftarrow R$ would cancel each other in both $I$ and $V$; to a first approximation, $R \leftrightarrow L$ and $R^{\prime} \leftrightarrow M$ in $I$ might counterbalance the corresponding interactions $R \nleftarrow M$ and $R^{\prime} \leftrightarrow L$ in $V$, thus leaving $O \leftrightarrow M$ and $O \leftrightarrow L$ as the interactions from which one might calculate the relative stabilities of $I$ and $V$. The evaluation of these interactions is available from nmr studies on carbonyl compounds (9) and therefore allows a semiquantitative prediction of the magnitude of the diastereomeric product ratio. The difference in the free energy of the diastereomeric transition states is related to the diastereomeric ratio by the following equation:

$$
\Delta \Delta G_{A B}^{\ddagger}=-R T \ln A / B
$$

This equation represents an application of the Curtin-Hammett principle (10) to these systems. The results found in the
literature correlated well with the calculated results from this model (8).

The model as just explained seems to offer the best starting point for further investigations of asymmetric induction. There are several factors which have not been evaluated and which can affect the success of the model: 1) the differences in free energy of the two diastereotopic transition states due to entropy effects of the two transition states, 2) the degree of bond making and breaking which marks the transition states, 3) the differences in the gauche nonbonded interactions in the transition states, and 4) the differences in solvation energies of the diastereomeric transition states.

In planning an experiment on asymmetric induction, the effects of these four unknown factors should be minimized or hopefully be amenable to evaluation. In any system, the differences in entropy of a given reaction can be found from the changes in the free energy of the diastereomeric transition states with temperature. Secondly, the degree of bond making and breaking has been suggested previously to explain the product distribution in acyclic (11), monocyclic (7), and bicyclic (12) ketones. To determine the extent of bond making and breaking in the relevant diastereotopic transition states, experiments should be chosen in which the conformational energy differences of the reactants and the energy differences of the diastereomeric products are known (13).

Since the differences in energies of most diastereomers are not known, a system must be chosen in which these differences are known a priori. The use of isotopically related groups would reduce the differences in energy of diastereomeric products to a minimum because these would be due only to secondary isotope effects. Since the energies of the two products would be equal, the diastereomeric product ratio expected with extensive bond breaking and making would approach unity. At the other extreme, if very little bond making or breaking has occurred at the transition states, the diastereomeric ratio would reflect the differences in conformational energy of the carbonyl substrates.

Thirdly, differences in conformational energy in the transition states are partially due to nonbonded interactions between groups attached to the carbonyl carbon, the incoming reagent, and the carbonyl oxygen. Since the gauche interactions of the diastereomeric transition states cannot be estimated exactly, the differences should be minimized in the cases where the isotopically related diastereomers are formed.


I


V

In $I$, the gauche interactions are $R^{\prime} \leftrightarrow s, R \nleftarrow S, R^{0} \leftrightarrow M$, and $R \leftrightarrow L$, and in $V, R^{\prime} \leftrightarrow S, R \nleftarrow S, R \not M M$, and $R^{\prime} \nprec L$. Since $R$ and $R^{\prime}$ are isotopically related, the interactions (save that $R^{\prime}$ is bound to a metal atom) are similar and could lead to a very small energy difference. The main energy difference between $I$ and $V$ would thus arise from the nonbonded interactions of $M \leftrightarrow 0$ o_versus $L \nleftarrow 0$.

The final factor, i.e.., the contribution of solvation to the energies of the two diastereomeric transition states, is expected to be quite complex. It is uncertain what types of interactions the solvent has with all species present. However, judging from cases of asymmetric induction in optically active solvents, one may state that the contribution of solvent to the differences in the free energies of the two diastereomeric transition states is probably small and of the order of 50-100 cal/mole (14).

In several examples in the literature the effect of reagents on the stereospecificity of reactions has been reported $(15,16)$. In these experiments, the stereospecificity varies with the halogen atom of the Grignard reagent and with the alkyllithium reagents. This effect has been studied in a systematic way by Karabatsos and Althuis (13). Some of their results are given in the discussion section in Table $V$. In continuing the work on asymmetric induction, the purpose of this study was to consider the effects of temperature, reagent, and solvent on the stereospecificity of
nucleophilic additions to 2-methylbutanol-2-d_1, 3-methyl-2-pentanone-1,1,1,3- $\underline{d}_{4}, 2,3,3-t r i m e t h y l b u t a n a l-2-\underline{d}_{1}$, and 3,4,4-trimethyl-2-pentanone-1,1,1-d $\mathbf{d}_{3}$. Since the diastereotopic groups are magnetically nonequivalent, the analysis of the diastereomeric alcohols was carried out by using nmr (16).

## RESULTS AND DISCUSSION

The results of the reactions of lithium aluminum deuteride, sodium borodeuteride, methyllithium, methylmagnesium iodide, bromide, and chloride with 2-methylbutanal-2-d, 3-methyl-2-pentanone-1,1,1,3- $\underline{d}_{4}, 2,3,3-t r i m e t h y l b u t a n a l-2-\underline{d}_{1}$, and 3,4,4-trimethyl-2-pentanone-1,1,1- $\underline{d}_{3}$ are summarized in Tables I-IV respectively. Also included in these tables are literature results from reduction or addition reactions to similar compounds. Table $V$ includes results from the calculations of the $\Delta \Delta G_{A B^{\prime}}^{\ddagger} \Delta \Delta H_{A B^{\prime}}^{\ddagger}$ and $\Delta \Delta S_{A B}^{\neq}$for the metal hydride and methyl Grignard additions to the aldehydes and ketones listed above.

## A. Errors Involved in Calculations of Thermodynamic Parameters

The errors in the thermodynamic parameters stem from the errors inherent in the calculation of the percentages of isomers $A$ and $B$. Since the errors in the $A / B$ ratios were taken as $+1 \%$, a ratio $A / B$ of $60 / 40$ would not exceed the range of 61 to 59 for $A$ and 39 to 41 for $B$. These errors were in all cases larger than the precision of the measurements made by nmr integration or by cutting and weighing either nmr or
Table I.--Additions to 2-Methylbutanal and 2-Methylbutanal-2-d.

| Substrate | Nucleophile | Temp | Solvent | $\%$ | Yield | Ratio $A / B^{a}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |

$$
\begin{aligned}
& \mathrm{a}_{\text {The ratios }} A / B \text { of the diastereomeric } 2-\text { methyl-1-butanol-1,2- } d_{2} \text { were determined by the } \\
& \text { integration of peak } A \text { at } 5.94 \tau \text { and peak } B \text { at } 5.90 \tau \text { in } 20 \% \text { isopropyl alcohol solutions. } \\
& \mathrm{b}_{\text {The }} \Delta \Delta G_{A B}^{\ddagger} \text { values are given in cal/mole. } \\
& \mathrm{C}_{\text {These data can be found in reference } 19 .}
\end{aligned}
$$

13
Table II.--Additions to 3-Methyl-2-pentanone and 3-Methyl-2-pentanone-1,1,1,3- $\mathbf{A}_{4}$.

| Substrate | Nucleophile | Temp. | Solvent | \% Yield | Ratio $A / B^{\text {a }}$ | $\Delta \Delta G_{\text {AB }}^{\ddagger} \mathrm{b}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | MeMgI | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | Ether | $\begin{aligned} & 85 \\ & 80 \\ & 90 \end{aligned}$ | $\begin{aligned} & 54.9 / 45.1 \\ & 53.6 / 46.4 \\ & 52.9 / 47.1 \end{aligned}$ | $\begin{array}{r} -110 . \pm 10 \\ -90 . \pm 10 \\ -50 . \pm 7 \end{array}$ |
|  | MeMgBr | $\begin{array}{r} 35^{\circ} \\ 0 \\ -70^{\circ} \end{array}$ | Ether | $\begin{aligned} & 90 \\ & 85 \\ & 80 \end{aligned}$ | $\begin{aligned} & 54.5 / 45.5 \\ & 54.9 / 45.1 \\ & 53.0 / 47.0 \end{aligned}$ | $\begin{gathered} -100 . \pm 10 \\ -110 . \pm 10 \\ -50 . \pm 6 \end{gathered}$ |
|  | MeMgCl | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | Tetrahydrofuran | $\begin{aligned} & 85 \\ & 70 \\ & 75 \end{aligned}$ | $\begin{aligned} & 51.4 / 48.6 \\ & 54.4 / 45.6 \\ & 52.8 / 47.2 \end{aligned}$ | $\begin{aligned} & -50 . \pm 7 \\ & -90 . \pm 10 \\ & -50 . \pm 7 \end{aligned}$ |
|  | MeLi | $\begin{array}{r} 35^{\circ} \\ 0 \\ -70^{\circ} \end{array}$ | Ether | $\begin{aligned} & 75 \\ & 90 \\ & 95 \end{aligned}$ | $\begin{aligned} & 56.9 / 43.1 \\ & 57.5 / 42.5 \\ & 58.0 / 42.0 \end{aligned}$ | $\begin{aligned} & -170 . \pm 15 \\ & -180 . \pm 15 \\ & -130 . \pm 13 \end{aligned}$ |
|  | LiAlH4 ${ }^{\text {c }}$ | $\begin{array}{r} 35^{\circ} \\ 0 \\ -70 \end{array}$ | Ether | -- | $\begin{aligned} & 49.0 / 51.0 \\ & 48.5 / 51.5 \\ & 51.5 / 48.5 \end{aligned}$ | $\begin{array}{r} 36 \\ 32 \\ -16 . \end{array}$ |

[^0]Table III.--Additions to 3,4,4-Trimethylpentanone and 3,4,4-Trimethylpentanone-1,1,1-d $\mathbf{A}_{3}$

| Substrate | Nucleophile | Temp . | Solvent | \% Yield | Ratio $\mathrm{A} / \mathrm{B}^{\text {a }}$ | $\Delta \Delta G_{A B}^{\ddagger} \mathrm{b}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | $\mathrm{LiAld}_{4}$ | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | Ether | $\begin{aligned} & 90 \\ & 85 \\ & 95 \end{aligned}$ | $\begin{aligned} & 54.1 / 45.9 \\ & 51.8 / 48.2 \\ & 38.5 / 61.5 \end{aligned}$ | $\begin{array}{r} 100 . \pm 10 \\ 40 . \pm 10 \\ -190 . \pm 15 \end{array}$ |
|  | $\mathrm{NaBD}_{4}$ | $\begin{array}{r} 66^{\circ} \\ 0^{\circ} \end{array}$ | Tetrahydrofuran | $\begin{aligned} & 60 \\ & 40 \end{aligned}$ | $\begin{aligned} & 51.9 / 48.1 \\ & 48.1 / 51.9 \end{aligned}$ | $\begin{array}{r} 50 . \pm 10 \\ -40 . \pm 10 \end{array}$ |
|  | $\mathrm{NaBD}_{4}$ | $\begin{array}{r} 20^{\circ} \\ -70^{\circ} \end{array}$ | Isopropyl alcohol | $\begin{aligned} & 55 \\ & 85 \end{aligned}$ | $\begin{aligned} & 58.4 / 41.6 \\ & 47.1 / 52.9 \end{aligned}$ | $\begin{aligned} & 200 . \pm 20 \\ & -50 . \pm 10 \end{aligned}$ |
|  | MeMgCl | $\begin{array}{r} 66^{\circ} \\ 0^{\circ} \end{array}$ | Tetrahydrofuran | $\begin{aligned} & 98 \\ & 95 \end{aligned}$ | $\begin{aligned} & 70.3 / 29.7 \\ & 74.9 / 25.1 \end{aligned}$ | $\begin{array}{ll} -580 . & \pm 40 \\ -590 . & \pm 45 \end{array}$ |
|  | MeMgBr | $\begin{array}{r} 35^{\circ} \\ 0 \end{array}$ | Ether | $\begin{aligned} & 85 \\ & 90 \end{aligned}$ | $\begin{aligned} & 73.6 / 26.4 \\ & 76.7 / 23.3 \end{aligned}$ | $\begin{aligned} & -630 . \pm 55 \\ & -650 . \pm 60 \end{aligned}$ |
|  | MeMgI | $\begin{array}{r} 35^{\circ} \\ 0 \end{array}$ | Ether | $\begin{aligned} & 90 \\ & 70 \end{aligned}$ | $\begin{aligned} & 72.1 / 27.0 \\ & 74.0 / 26.0 \end{aligned}$ | $\begin{aligned} & -580 . \pm 45 \\ & -570 . \pm 40 \end{aligned}$ |
|  | MeLi | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | Ether | $\begin{aligned} & 85 \\ & 75 \\ & 70 \end{aligned}$ | $\begin{aligned} & 73.7 / 26.3 \\ & 75.7 / 24.3 \\ & 83.8 / 16.2 \end{aligned}$ | $\begin{aligned} & -630 . \pm 55 \\ & -620 \cdot \pm 55 \\ & -660 . \pm 70 \end{aligned}$ |
|  | Me 2 Mg | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \end{array}$ | Ether | $\begin{aligned} & 99 \\ & 80 \end{aligned}$ | $\begin{aligned} & 66.9 / 33.1 \\ & 86.3 / 13.7 \end{aligned}$ | $\begin{aligned} -430 \cdot & \pm 30 \\ -1000 . & \pm 140 \end{aligned}$ |

[^1]Table IV.--Additions to 2,3,3-Trimethylbutamal and 2,3,3-Trimethylbutanal-2-d.

| Substrate | Nucleophile | Temp. | Solvent \% | Yield | Ratio $A / B^{\text {a }}$ | $\Delta \triangle G_{A B}^{\ddagger}{ }^{\text {b }}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | LiAld $_{4}$ | $\begin{array}{r} 35^{\circ} \\ 0 \\ -70^{\circ} \end{array}$ | Ether | $\begin{aligned} & 90 \\ & 75 \\ & 95 \end{aligned}$ | $\begin{aligned} & 73.3 / 26.7 \\ & 76.0 / 24.0 \\ & 86.2 / 13.8 \end{aligned}$ | $\begin{aligned} & -620 . \pm 50 \\ & -630 . \pm 55 \\ & -740 . \pm 108 \end{aligned}$ |
|  | $\mathrm{NaBD}_{4}$ | $\begin{array}{r} 66^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | Tetrahydrofuran | $\begin{aligned} & 75 \\ & 80 \\ & 90 \end{aligned}$ | $\begin{aligned} & 53.9 / 46.1 \\ & 60.0 / 40.0 \\ & 77.0 / 23.0 \end{aligned}$ | $\begin{aligned} & -110 . \pm 10 \\ & -220 . \pm 15 \\ & -490 . \pm 45 \end{aligned}$ |
|  | $\mathrm{NaBD}_{4}$ | $\begin{array}{r} 82^{\circ} \\ 0 \\ -70^{\circ} \end{array}$ | Isopropyl alcohol | $\begin{aligned} & 85 \\ & 80 \\ & 85 \end{aligned}$ | $\begin{aligned} & 60.2 / 39.8 \\ & 71.1 / 28.9 \\ & 75.5 / 24.5 \end{aligned}$ | $\begin{aligned} & -290 \cdot \pm 20 \\ & -490 \cdot \pm 40 \\ & -450 . \pm 40 \end{aligned}$ |
|  | MeMgCl | $\begin{array}{r} 66 \\ 0 \\ -70 \end{array}$ | Tetrahydrofuran | $\begin{aligned} & 60 \\ & 90 \\ & 85 \end{aligned}$ | $\begin{aligned} & 77.1 / 22.9 \\ & 93.3 / 6.7 \\ & 93.9 / 6.1 \end{aligned}$ | $\begin{aligned} & -1580 . \pm 180 \\ & -1430 . \pm 200 \\ & -1100 . \pm 180 \end{aligned}$ |
|  | MeMgBr | $\begin{array}{r} 35^{\circ} \\ 0 \\ -70^{\circ} \end{array}$ | Ether | $\begin{aligned} & 85 \\ & 95 \\ & 98 \end{aligned}$ | $\begin{aligned} & 93.4 / 6.6 \\ & 92.6 / 7.4 \\ & 95.9 / 4.1 \end{aligned}$ | $\begin{aligned} & -1620 . \pm 250 \\ & -1370 . \pm 180 \\ & -1270 . \pm 300 \end{aligned}$ |
|  | MeMgI | $\begin{array}{r} 35^{\circ} \\ 0 \\ -70^{\circ} \end{array}$ | Ether | $\begin{aligned} & 95 \\ & 90 \\ & 80 \end{aligned}$ | $\begin{aligned} & 89.1 / 10.9 \\ & 80.6 / 19.4 \\ & 86.0 / 14.0 \end{aligned}$ | $\begin{array}{r} -1290 . \pm 120 \\ -770 . \pm 80 \\ -730 . \pm 80 \end{array}$ |

[^2]Table V.--The Activation Parameters of the Reactions in Tables I-IV.

| Substrate | Nucleophile (Solvent) | Temp - | $\Delta \Delta G_{A B}^{\ddagger} a$ | $\Delta \Delta H_{A B}^{\ddagger} \mathbf{b}$ | $\Delta \Delta S_{A B}^{\neq c}$ | Average $\Delta \Delta S_{A B}^{\mp}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | $\stackrel{\text { LiAld }}{4}^{(\text {Ether })}$ | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | $\begin{aligned} -90 . & \pm 10 \\ -40 . & \pm 5 \\ 20 . & \pm 4 \end{aligned}$ | -270. $\pm 470$ | $\begin{aligned} & -0.6 \\ & -0.8 \\ & -1.4 \end{aligned}$ | $-1.0 \pm 2.1$ |
|  | $\begin{gathered} \mathrm{NaBD}_{4} \\ (\mathrm{THF}) \end{gathered}$ | $\begin{array}{r} 66^{\circ} \\ 0 \\ -70^{\circ} \end{array}$ | $\begin{aligned} & -310 . \pm 20 \\ & -210 . \pm 15 \\ & -100 . \pm 10 \end{aligned}$ | -360. $\pm 400$ | $\begin{aligned} & -0.1 \\ & -0.5 \\ & -1.3 \end{aligned}$ | $-0.7 \pm 2.4$ |
|  | $\stackrel{\mathrm{NaBD}_{4}}{(\mathrm{i}-\mathrm{PrOH})}$ | $\begin{array}{r} 82^{\circ} \\ 0 \\ -70 \end{array}$ | $\begin{aligned} -220 . & \pm 15 \\ -100 . & \pm 10 \\ -80 . & \pm 9 \end{aligned}$ | -420. $\pm 380$ | $\begin{aligned} & -\Theta .6 \\ & -1.2 \\ & -1.7 \end{aligned}$ | -1.1 $\pm 2.3$ |
|  | MeMgI (Ether) | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | $\begin{array}{r} -110 . \\ -90 . \\ -50 . \end{array} \pm 10$ | -400. $\pm 470$ | $\begin{aligned} & -1.0 \\ & -1.2 \\ & -1.7 \end{aligned}$ | $-1.3 \pm 2.1$ |
|  | MeMgBr <br> (Ether) | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | $\begin{gathered} -100 . \pm 10 \\ -110 . \pm 10 \\ -50 . \pm 6 \end{gathered}$ | -430. $\pm 470$ | $\begin{aligned} & -1.1 \\ & -1.2 \\ & -1.9 \end{aligned}$ | -1.4 $\pm 2.1$ |
|  | $\begin{aligned} & \text { MeMgCl } \\ & (\mathrm{THF}) \end{aligned}$ | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | $\begin{aligned} & -50 . \pm 7 \\ & -90 . \pm 10 \\ & -50 . \pm 7 \end{aligned}$ | -460. $\pm 470$ | $\begin{aligned} & -1.3 \\ & -1.4 \\ & -2.0 \end{aligned}$ | $-1.6 \pm 2.1$ |
|  | MeLi (Ether) | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | $\begin{aligned} & -170 . \pm 15 \\ & -180 . \pm 15 \\ & -130 . \pm 13 \end{aligned}$ | -540. $\pm 470$ | $\begin{aligned} & -1 \cdot 2 \\ & -1 \cdot 3 \\ & -2 \cdot 0 \end{aligned}$ | $-1.5 \pm 2.1$ |
|  | $\underset{\text { (Ether) }}{\mathrm{LiAlH}_{4}}$ | $\begin{array}{r} 35^{\circ} \\ 0 \\ -70^{\circ} \end{array}$ | $\begin{array}{r} 36 \\ 32 \\ -16 \end{array}$ | -610. $\pm 470$ | $\begin{aligned} & -2.1 \\ & -2.4 \\ & -2.9 \end{aligned}$ | $-2.5 \pm 2.1$ |

Table V.--(cont'd.)

| Substrate | Nucleophile (Solvent) | Temp | $\Delta \Delta G_{\text {AB }}^{\ddagger}$ | $\Delta \Delta H_{\text {AB }}^{\ddagger}$ | $\Delta \Delta S_{A B}^{\ddagger} \mathrm{C}$ | $\begin{aligned} & \text { Average } \\ & \Delta \Delta S_{A B}^{+} \end{aligned}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | $\stackrel{\text { LiAld }}{4}^{(\text {Ether })}$ | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | $\begin{aligned} & -620 . \pm 50 \\ & -630 . \pm 55 \\ & -740 . \pm 108 \end{aligned}$ | $-1390 \pm 470$ | $\begin{aligned} & -2.5 \\ & -2.8 \\ & -3.2 \end{aligned}$ | -2.8 $\pm 2.1$ |
|  | ${\underset{(T H F)}{\mathrm{NaBD}_{4}}}^{(\mathrm{THF}}$ | $\begin{array}{r} 66_{0}^{\circ} \\ 0 \\ -70 \end{array}$ | $\begin{aligned} & -110 . \pm 10 \\ & -220 . \pm 15 \\ & -490 . \pm 45 \end{aligned}$ | -1580. $\pm 400$ | $\begin{aligned} & -4.3 \\ & -5.0 \\ & -5.3 \end{aligned}$ | $-4.9 \pm 2.4$ |
|  | $\begin{aligned} & \mathrm{NaBD}_{4} \\ & \text { ( }-\mathrm{PrOH}) \end{aligned}$ | $\begin{array}{r} 82^{0} \\ 0 \\ -70 \end{array}$ | $\begin{aligned} & -290 . \pm 20 \\ & -490 . \pm 40 \\ & -450 . \pm 40 \end{aligned}$ | -1210. $\pm 380$ | $\begin{aligned} & -2.6 \\ & -2.6 \\ & -3.7 \end{aligned}$ | $-3.0 \pm 2.3$ |
|  | $\begin{aligned} & \text { MeMgCl } \\ & (\mathrm{THF}) \end{aligned}$ | $\begin{array}{r} 66^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | $\begin{aligned} & -1580 . \pm 180 \\ & -1430 . \pm 200 \\ & -1100 . \pm 180 \end{aligned}$ | -900. $\pm 400$ | $\begin{aligned} & 2.0 \\ & 1.9 \\ & 1.0 \end{aligned}$ | $1.6 \pm 2.4$ |
|  | $\begin{gathered} \mathrm{MeMgBr} \\ \text { (Ether) } \end{gathered}$ | $\begin{array}{r} 35^{\circ} \\ 0 \\ -70 \end{array}$ | $\begin{aligned} & -1620 . \pm 250 \\ & -1370 . \pm 180 \\ & -1270 . \pm 300 \end{aligned}$ | -1100. $\pm 470$ | $\begin{aligned} & 1.7 \\ & 1.0 \\ & 0.8 \end{aligned}$ | $1.2 \pm 2.1$ |
|  | MeMgI (Ether) | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70^{\circ} \end{array}$ | $\begin{array}{r} -1290 . \pm 120 \\ -770 . \pm 80 \\ -730 . \pm 80 \end{array}$ | -1240. $\pm 470$ | $\begin{array}{r} 0.1 \\ -1.7 \\ -2.5 \end{array}$ | -1.4 $\pm 2.1$ |
|  | $\begin{gathered} \text { LiAld }_{4} \\ \text { (Ether) } \end{gathered}$ | $\begin{array}{r} 35^{\circ} \\ 0^{\circ} \\ -70 \end{array}$ | $\begin{array}{r} 100 . \pm 10 \\ 40 . \pm 10 \\ -190 . \pm 15 \end{array}$ | -1250. $\pm 470$ | $\begin{aligned} & -4.4 \\ & -4.7 \\ & -5.2 \end{aligned}$ | $-4.8 \pm 2.1$ |
|  | $\begin{gathered} \mathrm{NaBD}_{4} \\ (\mathrm{THF}) \end{gathered}$ | ${ }_{0}^{66}$ | $\begin{array}{r} 50 . \pm 10 \\ -40 . \pm 10 \end{array}$ | -1060. $\pm 560$ | $\begin{aligned} & -3.3 \\ & -3.7 \end{aligned}$ | $-3.5 \pm 2.3$ |
|  | $\stackrel{\mathrm{NaBD}_{4}}{(\mathrm{i}-\mathrm{PrOH})}$ | $\begin{array}{r} 20^{\circ} \\ -70 \end{array}$ | $\begin{aligned} & 200 . \pm 20 \\ & -50 \pm 10 \end{aligned}$ | -1080. $\pm 360$ | $\begin{aligned} & -4.4 \\ & -5.1 \end{aligned}$ | $-4.7 \pm 2.1$ |

18
Table V.--(cont'd.)

vpc peaks. The error in calculating the differences in enthalpies of activation was determined (17) by using expression 1. The symbols in the expression are defined as follows:

$$
\begin{equation*}
\delta=2 R \frac{T^{\prime} T}{T^{\prime}-T} \alpha \tag{1}
\end{equation*}
$$

$\delta$ is the error in $\Delta \Delta H_{A B}^{\neq}$in cal/mole, $R$ is the universal gas constant, $T^{\prime}$ and $T$ are the temperatures at the extreme of the temperature range used in the calculations for $\Delta \Delta H_{A B^{\prime}}^{\ddagger}$ and $\alpha$ represents the maximum fractional error in the ratios. The maximum fractional error for all data was assumed to be 0.1. This estimate includes an error in the $\Delta \Delta G_{A B}^{\neq}$due to $\pm 2^{\circ}$ in the temperature.

The formula for the error in the differences in the entropies of activation for the diastereomeric transition states is given below:

$$
\begin{equation*}
\sigma=\delta\left[\frac{1}{T}+\frac{T^{\prime}-T}{2 R^{\prime} T}\right] \tag{2}
\end{equation*}
$$

In this expression, $\sigma$ is defined as the error in the entropy of activation; $\delta$, the error in the enthalpy of activation as calculated in expression (1); and $T$ and $T$ ', the temperature extremes of the measurement of the diastereomeric ratios. The results of these calculations are given in Table $V$. The errors generally observed in the literature in similar cases would indicate that the errors in vpc and ir analysis are of the same magnitude as the values found for nmr. Nmr and vpc analysis for the diastereomeric alcohols
from the reduction of $3,4,4$-trimethyl-2-pentanone with lithium aluminum deuteride'at $35^{\circ}$ agreed within experimental error. The value of $\Delta \Delta G_{A B}^{\neq}$found by nmr integrations was $+93 \pm 9 \mathrm{cal} / \mathrm{mole}$ whereas the value of $\Delta \Delta G_{A B}^{\ddagger}$ found by vpc was $+100 \pm 10 \mathrm{cal} / \mathrm{mole}$. Similar agreement between vpc and nmr analysis was also found in another system by Karabatsos and Zioudrou (18). Because many investigators ignore the temperature dependence of the ratios, it is difficult to compare the diastereomeric ratios found in the literature with ours. In most cases reported in the literature the reaction temperatures were estimated from the description of the experimental procedure.

The absolute configuration of the products formed in the reduction and addition reactions studied in this work has not been proven. Previous results in the literature for which the absolute configuration $(5,19)$ of the diastereomers has been proven, find the major product to be consistent with that predicted by the Karabatsos model. In the case of the reduction of $2,3,3$-trimethylbutanal with lithium aluminum deuteride, the nmr of the resultant diastereomeric alcohols proves that the major diastereomer is indeed the one predicted by the Karabatsos model. Figures $A$ and $B$, on the following page, represent the most stable conformations of, respectively, the major and minor diastereomers predicted by the model. The proton labeled $H_{A}$ on the major diastereomer A of $2,3,3$-trimethyl-1-butanol-1,2- $\underline{d}_{2}$ would give a different


A


B
nmr splitting pattern than the proton, $H_{B}$, on the minor diastereomer $B$. In the major isomer $A$, the coupling constants, $J_{H-D_{1}}$ and $J_{H-D_{2}}$, would be expected to be approximately equal and of the order of 1.5 Hz . This would give a quintet in the $n m r$. In the minor diastereomer, the dihedral angle $\left(\phi_{B}\right)$ between $H$ and $D_{2}$ is approximately $60^{\circ}$. On the basis of the Karplus relationship (20) between the coupling constant and the dihedral angle, one would predict a much smaller coupling constant for $J_{H-D_{2}}$ than 1.5 Hz . The absorption signal for the minor stereoisomer $\left(H_{B}\right)$ in the nmr is quite broad whereas that for the major diastereomer ( $H_{A}$ ) appears as a well resolved quintet. Thus, at least in this case, the major diastereomer has the absolute configuration predicted by the model.

## B. The Relation Between Activation Parameters and Stereospecificity

The Karabatsos model applies only to cases where $\Delta \Delta G_{A B}^{\ddagger}$ is controlled solely by the differences in the enthalpies
of activation $\left(\Delta \Delta H_{A B}^{\ddagger}\right)$. In cases where $\Delta \Delta S_{A B}^{\neq}$contributes significantly to $\Delta \Delta G_{A B^{\prime}}^{\ddagger}$ the model should not be valid. In the twenty reactions studied by Karabatsos and Althuis $(13,21)$, only one system showed an appreciable temperature dependence of the $\Delta \Delta G_{A B}^{\neq}$that was outside experimental error. This led to the conclusion that $\Delta \Delta S_{A B}^{\neq}$contributions in those systems were negligible.

The values of $\Delta \Delta H_{A B}^{\ddagger}$ were calculated for the two systems studied by Karabatsos and Althuis. In the first system with phenyl, methyl, and hydrogen on the asymmetric center, the average $\Delta \Delta H_{A B}^{\ddagger}$ value was $-1400 \pm 500 \mathrm{cal} / \mathrm{mole}$ and in the second system with phenyl, isopropyl, and hydrogen on the asymmetric center, the average $\Delta \Delta H_{A B}^{\ddagger}$ was $-1550 \pm 500 \mathrm{cal} / \mathrm{mole}$. The value of $-1400 \pm 500 \mathrm{cal} / \mathrm{mole}$ for $\Delta \Delta H_{A B^{\prime}}^{\ddagger}$ as well as the experimental $\Delta \Delta G_{A B}^{\ddagger}$ value, in the first system is actually larger than the $\Delta \Delta H_{A B}^{\ddagger}$ value of $-600 \mathrm{cal} / \mathrm{mole}$ calculated by the model. The same is true for the $\Delta \Delta H_{A B}^{\ddagger}$ values in the second system where the average $\Delta \Delta H_{A B}^{\ddagger}$ is $-1550 \pm 500 \mathrm{cal} / \mathrm{mole}$ compared to the calculated value of $-200 \mathrm{cal} / \mathrm{mole}$. It should be emphasized, however, that many of these $\Delta \Delta H_{A B}^{\ddagger}$ values were calculated from results obtained only at two temperatures.

There appears to be better agreement between $\Delta \Delta H_{A B}^{\neq}$calculated for the model and the actual $\Delta \Delta H_{A B}^{\ddagger}$ as found in the two systems studied in this work. In the first system, with ethyl, methyl, and hydrogen groups on the asymmetric center, the average value of $\Delta \Delta H_{A B}^{\ddagger}$ calculated from a plot of $\ln \left(\frac{A / B}{T}\right)$
versus $1 / \mathrm{T}$ was $-400 \pm 400 \mathrm{cal} / \mathrm{mole}$. The value of $\Delta \Delta H_{A B}^{\ddagger}$ can be said to agree in sign and order of magnitude with the $-100 \mathrm{cal} / \mathrm{mole}$ value of $\Delta \Delta H_{A B}^{\ddagger}$ expected from the model. In the second system, with $t$ - butyl, methyl, and hydrogen groups on the asymmetric center, the average $\Delta \Delta H_{A B}^{\ddagger}$ found from the same plot was $-1250 \pm 400 \mathrm{cal} / \mathrm{mole}$. This value of $\Delta \Delta H_{A B}^{\ddagger}$ agrees well with the value of $-1,100 \mathrm{cal} / \mathrm{mole}$ calculated from the model.

Enthalpy control of the reactions at the given temperature range means that $\Delta \Delta G_{A B}^{\ddagger}$ and $\Delta \Delta H_{A B}^{\ddagger}$ values agree in sign. Referring to Table $V$, it is obvious that this is not always so. A small difference of a few entropy units could change the values of $\Delta \Delta G_{A B}^{\neq}$from a negative value ( $\Delta \Delta H_{A B}^{\neq}$control) to a positive value ( $\Delta \Delta S_{A B}^{\ddagger}$ control). This positive value for $\Delta \Delta G_{A B}^{\ddagger}$ would represent the predominant formation of the diastereomer opposite to that predicted by the model. This is evident in several entries in the tables. The product stereospecificity is thus controlled by the differences either in the enthalpy or in the entropy of activation.

## C. The Contributions of Nucleophile and Solvent

From the study of the reagent as a combination nucleophile and solvent system, the following general observations can be made. The bulkier the nucleophile, the higher the stereospecificity. Dauben (7) explained the differences in product ratios obtained from sodium borohydride and lithium aluminum
hydride reductions of cyclohexanones by concluding that in more polar solvents sodium borohydride is effectively a larger attacking species. One would have anticipated, therefore, that sodium borohydride in isopropyl alcohol would be more stereospecific than lithium aluminum hydride in ether. Furthermore, since tetrahydrofuran is a more polar solvent than ether, the stereospecificity should have been lower in the latter solvent. However, such is not the case. It is true in one case, but not in two other cases (Tables I, III, and IV). In view of the findings that $\Delta \Delta S_{A B}^{\neq}$may control the stereospecificity of many of these reactions, it is not surprising that such generalizations prove to be inadequate.

The results with methyl Grignard reagents and methyllithium do not follow the trends observed in previous work $(15,21)$. For example, it was found that methylmagnesium chloride was more stereospecific than methylmagnesium bromide, which in turn was more stereospecific than methylmagnesium iodide. In this work, methylmagnesium bromide was found to be more stereospecific than methylmagnesium iodide, which in turn was found to be more stereospecific than methylmagnesium chloride. It should be pointed out that in the previous wark $(13,21)$ where the aforementioned stereospecificity was found, one of the groups attached to the asymmetric carbon atom was phenyl.

## D. Conclusion

This study on 1,2-asymmetric induction in reactions of metal hydrides and methyl Grignard reagents with 2-methylbutanal, 2-methyl-2-pentanone, 2,3,3-trimethylbutanal, and 3,4,4-trimethyl-2-pentanone has shown that product stereospecificity may be controlled by either $\Delta \Delta S_{A B}^{\ddagger}$ or $\Delta \Delta H_{A B}^{\ddagger}$. The role of nucleophile, solvent, and reagent concentration is still not well understood. The halogen of the Grignard reagent does affect the stereospecificity of some reactions, but it does so in an unpredictable manner. The correlation between the $\Delta \Delta H_{A B}^{\ddagger}$ predicted by the Karabatsos model and the $\Delta \Delta H_{A B}^{\ddagger}$ found from plots of $\ln \left(\frac{A / B}{T}\right)$ versus $1 / T$ was good.

## EXPERIMENTAL

## A. General Procedures

The general apparatus used in the reduction, Grignard, and methyllithium reactions consisted of a 50 ml threenecked flask fitted with mechanical stirrer, condenser, thermometer, and addition funnel. The reaction temperatures were maintained at $-70^{\circ}$ with dry ice and isopropyl alcohol bath, $0^{\circ}$ with ice and water, or $35^{\circ}$ with an oil bath.

Prepared solutions of methylmagnesium chloride, methylmagnesium bromide, and methyllithium were obtained from Alpha Inorganics, Inc. The solutions of methylmagnesium iodide were prepared from methyl iodide obtained from Aldrich Chemical Company and from "Mallinckrodt" magnesium. When a solvent other than that supplied in the prepared reagents was used, the Grignard reagent was evaporated to dryness under vacuum and the desired solvent was added.

The nmr spectra were recorded on either a Varian A-60 or HA-100 nmr spectrometer and the ratios of the diastereotopic protons were determined by cutting and weighing, measuring with a planimeter, multiplying the measured peak height times the width at half-peak height, or by integrating the area with the nmr. The average values obtained were
rounded off to the nearest percent. The concentrations of the solutions used in the $n m r$ spectra are expressed as volume percents. All boiling and melting points are uncorrected.
B. Preparation of 2-Methylbutanal-2-d

Forty-six grams ( 0.53 mole) of freshly distilled 2 -methylbutanal was placed in a 250 ml flask fitted with condenser, drying tube and a magnetic stirrer. Anhydrous potassium carbonate was added to 100 ml of $90 \%$ deuterium oxide until the pH 11 was reached (using pH paper as an indicator). The deuterium oxide and aldehyde were then heated at reflux for eighteen hours. The pH of the solution was checked periodically and more potassium carbonate was added to maintain the pH 11. After cooling the reaction mixture to room temperature, the organic layer was separated from the aqueous layer and dried with molecular sieves. The organic layer was then treated successively with 20 ml of $99.9 \%$ deuterium oxide and two portions of 10 ml of $99.9 \%$ deuterium oxide. The organic layer was fractionated and yielded 21 g (45\%) of 2-methyl-butanal-2-d boiling at $87-9^{\circ}, n_{D}^{25}=1.3876$. The multiplet nmr absorption of the undeuterated species centered at $7.7 \tau$ disappeared and the aldehydic proton was reduced to a broad singlet $(\tau=0.3)$. In addition to the broad singlet, the nmr consisted of a singlet at 8.9 т ( 3 H ), a complex triplet centered at $9.06 \tau(3 \mathrm{H})$, and a multiplet at $8.4 \tau$ (2 н) .

## C. Nmr Studies of 2-Methyl-1-butanol-2,0-den

2-Methyl-1-butanol-2,0-d 2 was prepared by the reduction with lithium aluminum hydride ( $0.4 \mathrm{~g}, 0.011 \mathrm{~mole}$ ) in 100 ml ether of 2 -methyl-butanal-2-d ( $3.0 \mathrm{~g}, 0.035$ mole) over a ten minute period. The reaction mixture was then stirred for one hour and after the solution was cooled, 1 ml of deuterium oxide was added. The resulting precipitate was filtered from the ether solution of the alcohol which was dried with sodium sulfate and distilled, yielding $0.7 \mathrm{~g}(23 \%)$.

The spectrum of the alcohol showed an AB system with the center peaks separated by 0.5 Hz and the two outer bands separated by $37 . \mathrm{Hz}$. The difference in chemical shifts for the $A$ and $B$ protons of the $A B$ system was found from the equation: $\Delta \delta_{A B}=((1-4)(2-3))^{\frac{1}{2}}$. By using the above values, $\Delta \delta_{A B}$ was calculated to be 4.3 Hz . The value measured from the neat spectrum of the reaction of 2-methyl-butanal-2-d and lithium aluminum deuteride was 4.4 Hz . The nmr spectrum of 2-methyl-1-butanol consisted of the AB system centered at $6.63 \tau(2 \mathrm{H}), \mathrm{a}$ singlet at $9.1 \tau(3 \mathrm{H})$, a complex triplet at $9.0 \tau(3 \mathrm{H})$, and a multiplet centered at $8.7 \tau$.
D. Additions ta 2-Methyl-1-butanol-1,2-de

A solution of 1.0 g (11 mmoles) of 2-methylbutanal in 5 ml ether was added to a stirred solution of 0.13 g (3 mmoles) of lithium aluminum deuteride and 20 ml ether. The temperature was maintained at 35,0 , or $-70^{\circ}$. The reduction
was repeated with sodium borodeuteride in tetrahydrofuran at 66,0 , and $-70^{\circ}$ and in isopropyl alcohol at 82, 0 , and $-70^{\circ}$. In each reaction, after stirring for three hours, the excess deuteride was destroyed by the dropwise addition of 0.3 ml of water and 0.3 ml of $5 \%$ sodium hydroxide. The ether was filtered to remove the granular salts, then passed over a six foot Carbowax column and collected in a nmr tube (75 to $95 \%$ yields). By using the $20 \%$ isopropyl alcphol solutions, the ratios of the diastereomeric products were obtained on the Varian HA-100. The peaks from the nmr signal centered at $5.92 \tau$ were cut and weighed. These results are reported in Table $I$ along with other values from the literature.

## E. Nmr Solvent Studies of 2,3-Dimethyl-2-pentanol

The 2,3-dimethyl-2-pentanol was prepared from the addition of $10 \mathrm{~g}(0.1$ mole) of freshly distilled 3-methyl-2pentanone (City Chemical, Corporation No. M1538) to methylmagnesium iodide prepared from 3.7 g magnesium in 150 ml ether and $21.3 \mathrm{~g}(0.15 \mathrm{~mole})$ of methyl iodide. After the initial reaction had ceased, 100 ml of $10 \%$ ammonium chloride solution was added. The ether layer was separated, extracted with two portions of 30 ml water and 50 ml saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The ether was removed by distillation and the residue was fractionated, yielding $10.1 \mathrm{~g}(87 \%)$ of the product, bp
$153-5^{\circ}$. The nmr of this alcohol was determined in the neat and in sixteen solvents.

Table VI.--List of Solvents Used to Resolve the Diastereotopic Methyl Groups of 2,3-Dimethyl-2-pentanol.

| Solvent | Concentrations <br> $(\%$ by volume $)$ |
| :--- | :---: |
| Neat |  |
| Pyridine | 100 |
| Dimethylsulfoxide | 20,10 |
| Benzonitrile | 20,10 |
| Methylene bromide | 20,10 |
| Chloroform | 20,10 |
| Carbontetrachloride | 20,10 |
| Methylene chloride | 20,10 |
| Methylene iodide | 20 |
| Benzene | 20 |
| Toluene | 20,10 |
| Nitrobenzene | 20 |
| Chlorobenzene | 20,10 |
| Indene | 20,10 |
| Thiophene | 20 |
| Acetonitrile | 20 |
| N-methylpyrrole | 20 |

$$
\text { F.; } \frac{\text { Preparation of } 3 \text {-Methyl }-2-}{\text { pentanone }-1,1,1,3-\underline{d}_{4}}
$$

A mixture of 3 -methyl-2-pentanone ( $20 \mathrm{~g}, 0.2$ mole) and 25 ml of pH 12 deuterium oxide (95\%) was heated at reflux for fourteen hours. The reaction mixture was cooled and the ketone was separated and dried with calcium chloride. The ketone was treated successively with two portions of 25 ml of $95 \%$ deuterium oxide, 15 ml of $99 \%$ deuterium oxide, and with two portions of 5 ml deuterium oxide. The crude

3-methyl-2-pentanone-1,1,1,3- $\underline{d}_{4}$ was dried over calcium chloride and distilled, bp 116-7 ${ }^{\circ}$, yielding $12.2 \mathrm{~g}(59 \%)$ of pure ketone. The $n m r$ consisted of a doublet at $8.97 \tau(3 \mathrm{H})$, a triplet centered at $9.15 \tau(3 \mathrm{H})$ and a multiplet centered at $8.48 \tau(2 \mathrm{H})$.

## G. Additions to 3-Methyl-2-

 pentanone-1,1,1,3- $\underline{\alpha}_{4}$A solution of 1.0 g ( 9.6 mmoles) of 3 -methyl-2-pentanone-$1,1,1,3-\underline{d}_{4}$ in 5 ml solvent was added over a ten to fifteen minute period to a stirred solution of 15 mmoles of organometallic reagent diluted with 15 ml ether. The Alpha Inorganics prepared solutions of organo-metallics used in these additions were: methylmagnesium iodide in ether, methylmagnesium bromide in ether, methylmagnesium chloride in tetrahydrofuran, and methyllithium in ether. The reaction mixture was maintained at the desired temperature with an appropriate bath. It was allowed to stand for a period of three to eight hours, then 2 ml of $10 \%$ ammonium chloride was added. The organic layer was filtered from the precipitated inorganic salts with a sintered glass funnel, and dried with anhydrous sodium sulfate. After the solvent was distilled, the residue was collected from a six foot Carbowax column. The yields of alcohols estimated from the vpc traces varied from $70 \%$ to 95\%. The resulting diastereomeric alcohols were analyzed in $20 \%$ pyridine solutions on the Varian HA-100. The ratios were calculated by multiplying the peak height times the width of
the peak at half height. The diastereotopic ratios and corresponding $\Delta \Delta G_{A B}^{\ddagger}$ values are summarized in Table II.
H. Preparation of 2,3,3-Trimethylbutanoic Acid

In this preparation, 100 g (1.02 moles) of $2,3,3$-tri-methyl-1-butene and sodium borohydride (19.4 g, 0.46 mole) in 500 ml of tetrahydrofuran were placed in a 3 l . threenecked flask fitted with condenser, mechanical stirrer, and addition funnel. The solution was cooled in an ice bath. Then, boron trifluoride etherate ( $97 \mathrm{~g}, 0.68$ mole, 86 ml ) was added over two hours. After the addition was complete, and the solution warmed to room temperature, stirring was continued for an additional three hours. The excess sodium borohydride was decomposed with 100 ml of water and the solvent was removed by rotary evaporation. The organoborane was dissolved in 500 ml of diethyl ether. The oxidation of the organoborane with a chromic acid solution followed.

The chromic acid solution consisted of 904 g (3.04 moles)
of sodium dichromate-dehydrate and 676 ml of concentrated sulfuric acid diluted to $2,500 \mathrm{ml}$ with water. During the addition of the chromic acid solution, the reaction mixture was held between $10^{\circ}$ and $20^{\circ}$ with a water ice bath. After the addition was complete, the reaction was stirred for two hours. The ether layer was separated and the aqueous solution was successively extracted with three portions of 700 ml of ether. The combined ether extracts (about 2 l.) were
washed with 500 ml of water and 300 ml of saturated sodium chloride. The acid was then extracted from the ether layer with saturated sodium carbonate solution until the aqueous layer was at pH 11 (using pH paper). The basic layer was diluted with water until the acid salt dissolved. The ether layer was separated and the aqueous layer was extracted twice with 500 ml of diethyl ether. The aqueous solution of sodium 2,3,3-trimethylbutanate was then acidified with concentrated sulfuric acid until the pH of the aqueous solution reached three. During this addition the solution was cooled with ice. The aqueous solution was extracted with 1.51 . of diethyl ether in three portions. The combined ether extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. After removing the diethyl ether by rotary evaporation, the residue was fractionally distilled, yielding $64.8 \mathrm{~g}(66 \%)$ of $2,3,3$-trimethylbutanoic acid, bp 208-10 $0^{\circ} \mathrm{mp} 42-5^{\circ}$.

## I. Preparation of 2,3,3-Trimethylbutyryl Chloride

In a three-necked 250 ml round-bottomed flask fitted with stirrer, condenser, and addition funnel, 57.7 g (0.44 mole) of 2,3,3-trimethylbutanoic acid was mixed with 78.6 g (0.66 mole) of thionyl chloride. The reaction mixture was stirred for one hour and heated at reflux for an additional hour. Then, the excess thionyl chloride was distilled off
and the residue fractionally distilled, yielding 55.7 g ( $85 \%$ ) , bp $150-3^{\circ}$.
J. Preparation of 3,4,4-Trimethyl-2-pentanone

A three molar solution of Alpha Inorganic methylmagnesium bromide ( $190 \mathrm{ml}, 0.57$ mole) was placed in a 500 ml threenecked round-bottomed flask fitted with stirrer, condenser, and a glass stopper. To this ice-cold solution was added 53.4 g ( 0.29 mole) of anhydrous cadmium chloride. The solution was stirred an additional hour after the ice bath was removed. After distilling off the ether, 260 ml of anhydrous thiophene-free benzene was added and an additional 50 ml of distillate was collected. The benzene solution of dimethylcadmium was cooled in an ice bath and 55.7 g ( 0.38 mole) of 2,3,3-trimethylbutyryl chloride was added at a rate to maintain reflux. Ten minutes after addition was complete, the solution was heated at reflux for one hour. The benzene solution was poured into 300 ml of ice and water. Sulfuric acid (10\%) was added until the solids dissolved and two clear layers formed. The benzene layer was separated and the aqueous layer was extracted with 200 ml of benzene. The benzene extracts were combined and dried over anhydrous magnesium sulfate. The benzene was removed by distillation and 3,4,4-trimethyl-2-pentanone was fractionated, yielding 29.9 g (62\%), bp 143-6 ${ }^{\circ}$. The nmr spectrum consisted of a singlet at $7.93 \tau(3 \mathrm{H})$, a singlet at $9.1 \tau(9 \mathrm{H})$, a doublet centered at $9.0 \tau(3 \mathrm{H})$, and a quartet centered at $7.52 \tau(1 \mathrm{H})$.

## K. Preparation of $3,4,4$-Trimethyl-2-pentanone-1,1,1- $\underline{d}_{3}$

In a 100 ml flask equipped with condenser, drying tube, and a Teflon-covered magnetic stirring bar was placed 10 g (0.078 mole) of $3,4,4$-trimethyl-2-pentanone and 30 ml of pH 11 deuterium oxide ( $99.7 \%$ ). The mixture was heated at $100^{\circ}$ for twelve hours, then cooled and separated. The organic layer was dried over molecular sieves. This process was repeated twice with 30 ml of $99.7 \%$ deuterium oxide and twice with 20 ml of $99.7 \%$ deuterium oxide. The resulting ketone was distilled, bp 144-6. yielding $6.3 \mathrm{~g}(62 \%)$. The nmr spectrum consisted of a quartet centered at $7.1 \tau(1 \mathrm{H})$, a singlet at $9.04 \tau(9 \mathrm{H})$, and a doublet centered at $9.0 \tau(3 \mathrm{H})$.

## L. Additions to 3,4,4-Trimethyl-2-pentanone

In a typical addition of metal deuterides to 3,4,4-trimethyl-2-pentanone, $1.0 \mathrm{~g}(7.6 \mathrm{mmoles})$ of ketone in 2 ml of solvent (diethyl ether, tetrahydrofuran or isopropyl alcohol) was added to a solution of $0.089 \mathrm{~g}(2.1$ mmoles) of metal deuteride in 16 ml of solvent. The lithium aluminum deuteride reductions were carried out in diethyl ether, while tetrahydrofuran or isopropyl alcohol were used as solvents in the sodium borodeuteride reductions. The additions were kept at constant temperature during and following the reaction (six to twelve hours). They were quenched by adding 0.18 ml of water and 0.18 ml of $5 \%$ sodium hydroxide solution. The inorganic salts were removed by filtration and the
solvent by distillation. The 3,4,4-trimethyl-2-pentanol-2-d was collected from a six foot Carbowax column. The diastereomeric ratios taken from the nmr of these alcohols are summarized in Table III.
M. Additions to 3,4,4-Trimethyl-2-pentanone-1,1,1- $\underline{d}_{3}$

In a typical experiment, $1.0 \mathrm{~g}(7.6 \mathrm{mmoles})$ of $3,4,4-$ trimethyl-2-penanone-1,1,1-d $d_{3}$ and 2 ml of solvent (diethyl ether or tetrahydrofuran) was added to 10.0 mmole of Alpha Inorganics prepared organometallic reagent in 10 ml solvent. The corresponding reagents and solvents used were methylmagnesium bromide and iodide in ether, methyllithium in ether, and methylmagnesium chloride initetrahydrofuran. The reaction mixtures were held at constant temperatures during the additions and for six to twelve hours afterwards. The reactions were quenched with 0.4 ml of $10 \%$ ammonium chloride solution. The inorganic salts were filtered and the solvent removed by distillation. The 2,3,3,4-tetramethyl-2-pentanol-$1,1,1-d_{3}$ was purified by vpc (six foot Carbowax column). The ratios of the diastereotopic methyl groups at $8.78 \tau$ and $8.92 \tau$ are summarized in Table III.

## N. Preparation of 2,3,3-Trimethyl-1-butanol

In a 3 l. three-necked flask fitted with stirrer, condenser, and addition funnel, 100 g (1.02 moles) of 2,3,3-trimethyl-1-butene and $15.7 \mathrm{~g}(0.413 \mathrm{~mole})$ of sodium

borohydride were mixed in 500 ml anhydrous diglyme (distilled from lithium aluminum hydride). The reaction mixture was cooled during the addition of boron trifluoride etherate ( $70 \mathrm{ml}, 79 \mathrm{~g}, 0.55 \mathrm{~mole}$ ). The excess sodium borohydride was destroyed with 80 ml of water. The oxidation of the organoborane was accomplished by using 300 ml of 3 N sodium hydroxide and $120 \mathrm{ml}(176 \mathrm{~g}, 5.2 \mathrm{moles})$ of $30 \%$ hydrogen peroxide. After the addition was complete, 1 l. of pentane was added, and the aqueous layer was separated. The pentane solution was extracted six times with water until no diglyme was present in the vpc of the pentane layer. This pentane solution of the alcohol was distilled and yielded 85.5 g (73\%) of 2,3,3-trimethyl-1-butanol, bp 159-61 ${ }^{\circ}$, literature bp $161-2^{0}(740 \mathrm{~mm})$.

## 0. Preparation of 2,3,3-Trimethylbutanal

The 2,3,3-trimethylbutanal was prepared by oxidation of 2,3,3-trimethylbutanol with bis (pyridinium) chromic (VI) oxide. The bis (pyridinium) chromic (VI) oxide was prepared in methylene chloride and used immediately upon formation. In a 6 l. Erlenmeyer flask, to a solution of 190 ml (2.4 moles) of pyridine (dried over potassium hydroxide) and 51. of anhydrous methylene chloride was added 120 g ( 1.2 moles) of Fisher chromic trioxide, N.F.X. grade. The chromic trioxide was finely powdered with a ball mill. The chromic trioxide was added in small portions with vigorous stirring.


The solution was yellow at the beginning of the addition, but turned gradually to a dark red by the end of the addition. The reagent was allowed to stand for thirty minutes. Then, the $2,3,3$-trimethylbutanol was added in one portion (23.2 9 , 0.12 mole). As the solution was stirred, it turned black. The reaction mixture was stirred several times during the following hour, it was filtered through glass wool and finally divided into two portions. Each portion was cooled with ice and washed with 500 ml of $10 \%$ hydrochloric acid. The organic layer was dried with molecular sieves and filtered through a sintered glass filter with a mat of $100-200$ mesh Florisil. The clear solution was then distilled and the residue was fractionated on a Nester-Faust spinning band column, yielding $26.4 \mathrm{~g}(58 \%), \mathrm{bp} 126-9^{\circ}$, vpc pure, D.N.P. mp $125-7^{\circ}$, literature $126-7^{\circ}$.

## P. Preparation of 2,3,3-Trimethylbutanal-2-d.

Ten grams (0.088 mole) of 2,3,3-trimethylbutanal was treated with one 25 ml portion of pH 11 deuterium oxide ( $80 \%$ ), and three 25 ml portions of pH 11 deuterium oxide (99.9\%). Between each exchange the mixtures were heated at reflux for six hours. The aldehyde and aqueous layers were separated with a separatory funnel after the aqueous layer was saturated with sodium chloride. The aldehyde was dried after each step of the exchange with molecular sieves. The residue was fractionated, yielding 6.3 g ( $62 \%$ ).

## Q. Additions to 2,3,3-Trimethylbutanal

In a typical experiment, $0.5 \mathrm{~g}(4.4$ mmoles) of $2,3,3-$ trimethylbutanal and 2 ml of solvent was added to 6.0 mmoles of Alpha Inorganics prepared Grignard or methyllithium reagents in 6 ml of solvent. The corresponding reagents and solvents used were methyllithium, methylmagnesium bromide or iodide in ether, and methylmagnesium chloride in tetrahydrofuran. The reaction mixtures were held at constant temperature in a bath during and after the addition (six to twelve hourst. The reactions were quenched with 0.25 ml of $10 \%$ ammonium chloride solution. After filtering the inorganic salts with a sintered glass funnel, the solvent was removed by distillation. The diastereomeric 3,4,4-trimethyl-2pentanols were purified by vpc (six foot Carbowax column) and their diastereomeric ratios obtained from the integration of the vpc traces. These ratios are summarized in Table III.
R. Additions to 2,3,3-Trimethylbutanal-2-d

A solution of $0.1 \mathrm{~g}(2.3$ mmoles) of metal deuteride was dissolved in 16 ml of solvent and the mixture was stirred at the boiling point of the solvent, cooled at $0^{\circ}$ in an ice bath, or held at $-70^{\circ}$ with a dry ice isopropyl alcohol bath. The solvent used for the lithium aluminum deuteride reductions was ether; and that for the sodium borodeuteride reductions, tetrahydrofuran or isopropyl alcohol. After the solutions had been stirred for an additional six to twelve hours,
the reactions were quenched with 0.2 ml of water and 0.2 ml of $5 \%$ sodium hydroxide. The inorganic salts were filtered and the solvent removed by distillation. The 2,3,3-tri-methylbutanol-1,2-d2 was purified by vpc. The ratios of the diastereomers were determined by peak integration of the nmr (6.22 $\tau$ and $6.73 \tau)$. The results are given in Table IV.

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[^0]:    $\mathrm{a}_{\text {The ratios }} \mathrm{A} / \mathrm{B}$ of the diastereomeric 2,3-dimethyl-2-pentanols-1,1,1,3-d $\mathbf{d}_{4}$ were determined by the integration of peak $A$ at $8.81 \tau$ and peak $B$ at $8.80 \tau$ in $20 \%$ pyridine solu-
    
    $\mathrm{b}_{\text {The }} \Delta \Delta \mathrm{G}_{\mathrm{AB}}^{\ddagger}$ values are given in cal/mole.
    $C_{\text {These data can be found in reference } 19 .}$

[^1]:    $a_{\text {The }}$ ratios $A / B$ of the diastereomeric 3,4,4-trimethyl-2-pentanol-2-d were determined by integration of the vpc peaks on a six foot Carbowax column. Peak $\bar{A}$ had a retention time The ratios $A / B$ of the
    $\stackrel{4}{0}$ diastereomeric $2,3,4,4-t e t r a m e t h y l-2-p e n t a n o l-1,1,1-d_{3}$ were determined by integration of
    the major isomer $A$ at $8.78 \tau(2-$ methyl group) and isomer $B$ at $8.92 \tau$. $b_{\text {The }} \Delta \Delta G_{A B}^{\ddagger}$ values are given in cal/mole.

[^2]:    The ratios of the diastereomeric 2,3,3-trimethyl-1-butanols were determined by the integration of the nmr with the major peak $A$ at $6.73 \tau$ and the minor peak $B$ at $6.22 \tau$. The ratios of the diastereomeric 3,4,4-trimethyl-2-pentanols were determined by the integra-
     tion time of 4.0 minutes and the minor peak $B$ had a retention time of 5.9 minutes.
    $\mathrm{b}_{\text {The }} \Delta \Delta \mathrm{G}_{\mathrm{AB}}^{\ddagger}$ values are given in cal/mole.

