FACTORS AFFECTING ASYMMETRIC INDUCTION IN ADDITIONS TO 2,3-DIMETHYLBUTANAL AND 3,4-DIMETHYL-2-PENTANONE

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This is to certify that the

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FACTORS AFFECTING ASYMMETRIC INDUCTION
IN ADDITIONS TO 2,3-DIMETHYLBUTANAL
AND 3,4-DIMETHYL-2-PENTANONE

presented by

Theodosios C. Christodoulidis

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

G. J. Karabatsos
Major professor

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ABSTRACT

FACTORS AFFECTING ASYMMETRIC INDUCTION IN ADDITIONS TO 2,3-DIMETHYLBUTANAL AND 3,4-DIMETHYL-2-PENTANONE

by

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Several models have been developed that predict the course of asymmetric induction in additions to carbonyls directly bonded to asymmetric centers. The Karabatsos model[1] makes not only qualitative predictions, as the others do, but also quantitative predictions as well. The model was tested by analysis of the products obtained from additions to 3,4-dimethyl-2-pentanone of lithium aluminum hydride in ether and tetrahydrofuran, and of sodium borohydride in 2-propanol; additions to 2,3-dimethylbutanal of methylmagnesium iodide in ether, methylmagnesium bromide in ether and tetrahydrofuran, methylmagnesium chloride in tetrahydrofuran and methyllithium in ether. Besides the nucleophiles, other variables were also controlled (solvent, temperature, and concentration of reactants). The ratio A/B of the diastereomeric alcohols, determined by vpc and nmr, was used to calculate the differences in the free energies of the diastereomeric transition states.

$$\Delta\Delta G^{\ddagger}_{AB} = -RT \ln A/B$$

From the $\Delta\Delta H^{\ddagger}_{AB}$ and $\Delta\Delta S^{\ddagger}_{AB}$ values, obtained by plotting ln A/B versus 1/T, we concluded that most of the reactions were enthalpy controlled. Their stereoselectivities depended on the nature of the attacking nucleophiles. They were independent of concentrations of the nucleophiles and the polarities of the solvents. The experimental results agreed fairly well with those predicted by the Karabatsos model.

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1. G. J. Karabatsos, *J. Am. Chem. Soc.*, **89**, 1367 (1967).

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TO MY PARENTS

ACKNOWLEDGMENTS

The author wishes to express his appreciation to Professor G. J. Karabatsos for his guidance during the course of this investigation.

Financial assistance from the Michigan State University Chemistry Department, and from the National Institutes of Health is gratefully acknowledged.

Tyger! Tyger! burning bright

In the forests of the night,

What immortal hand or eye

Dare frame thy fearful symmetry?

William Blake

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INTRODUCTION

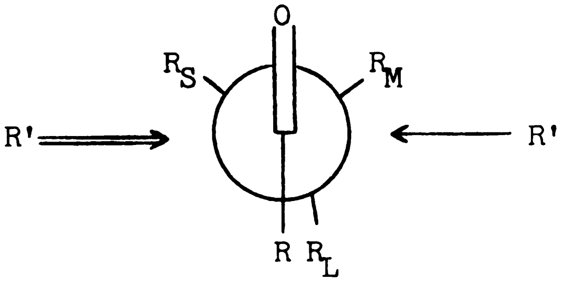
The problem of asymmetric induction started at the end of the last century with the classic work of Emil Fischer on the synthesis of D-glucose.[1] As early as 1904, W. Markwald gave the following definition of asymmetric synthesis.[2] "Asymmetrische Synthesen sind solche, welche aus symmetrisch constituirten Verbindungen unter intermediärer Benutzung optisch-activen Stoffe, aber unter Vermeidung jedes analytischen Vorganges, Optisch-active Substanzen erzeugen."

A more inclusive definition than that of Markwald's is: Asymmetric synthesis is a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts. That is to say, an asymmetric synthesis is a process which converts a prochiral unit into a chiral unit so that unequal amounts of stereoisomeric products result.[3]

Recently Y. Izumi proposed the division of asymmetric synthesis into enantioselective syntheses and diastereoselective syntheses.[4]

From the pioneering work of McKenzie,[5] Erlenmeyer and P. Ritchie, we come to the work of Prelog[6] who reinvestigated McKenzie's work and tried to rationalize the asymmetric induction by assuming steric interactions among the possible reacting conformers.

In the early 1950's Cram and Abd Elhafez published a paper in which they formulated a rule of steric control of asymmetric induction.[7] "In non-catalytic reactions of the type shown (formulas), that diastereomer

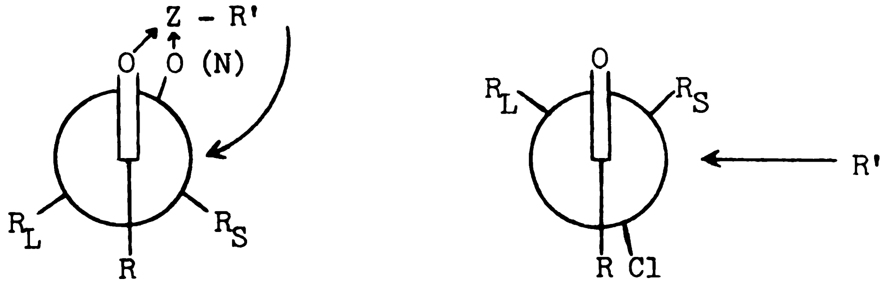


I

Figure 1. The open chain model. Steric bulk is $R_S<R_M<R_L$

will predominate which would be formed by the approach of the entering group from the least 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 bulky groups attached to the adjacent asymmetric center."[7] This empirical model was fairly successful but very soon, after its publication, exceptions to it were reported.

Two more models were developed in 1959, dealing with the discrepancies of the open chain model. These were Cram's rigid model II[8], and Cornforth's dipolar model [9] III, depicted in Figure 2.



II

III

Figure 2. The rigid model II, and the dipolar model III.

For the kinetically controlled asymmetric reactions $\Delta\Delta G^{\circ} = 0$ but $\Delta\Delta G^{\ddagger} \neq 0$, as illustrated in Figure 3. These reactions are stereoselective and the degree of stereoselectivity depends on the energy difference between the two diastereomeric transition states.

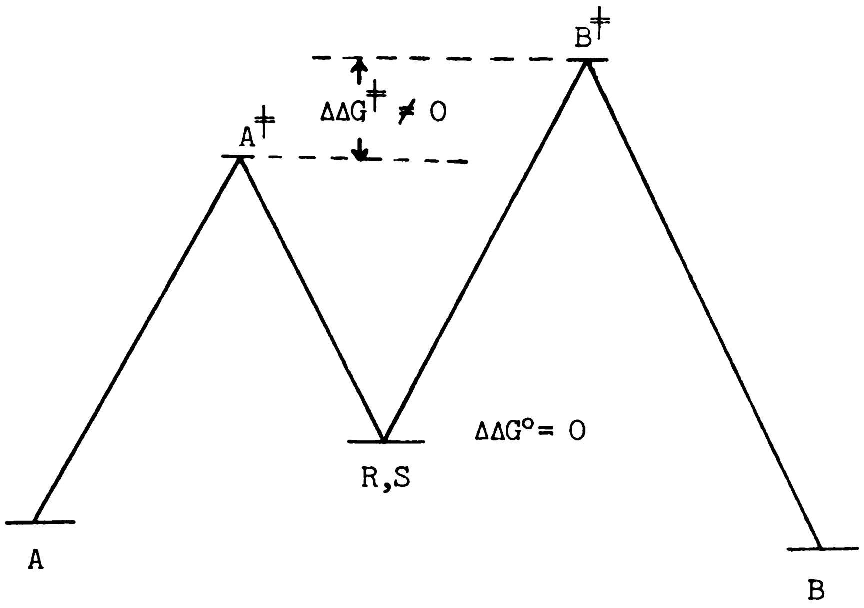
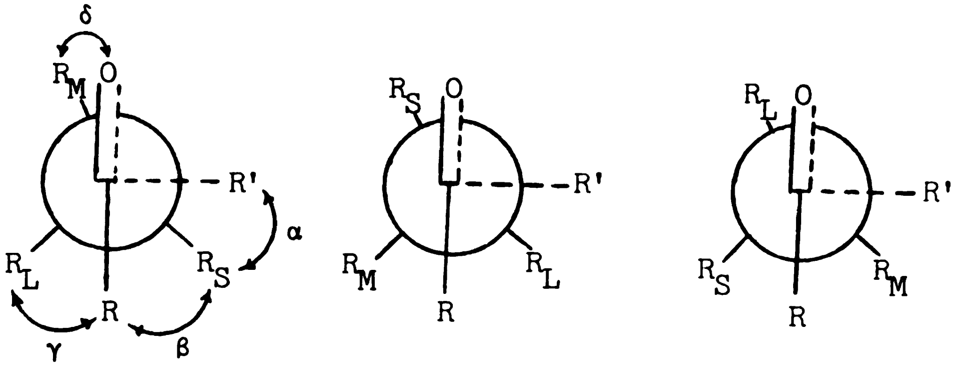


Figure 3. Energy relationship in the production of diastereomers A and B. Transition states are indicated as $A^{\ddagger}$ and $B^{\ddagger}$.

Quantitatively the per cent stereoselectivity Θ is defined as $\Theta = 100\,(A-B)/(A+B)$, where A and B are the diastereomers formed. Thus, the greater the $\Delta\Delta G^{\ddagger}$ is, the greater the Θ; and if $\Delta\Delta G^{\ddagger}$ is zero, then Θ is zero.

In 1967 Karabatsos[10] suggested a semiempirical model on the basis of which approximate quantitative predictions could be made. In devising the model he assumed the following: (i) "Little bond breaking and making has occurred at the transition states. Consequently, the arrangement of the groups of the asymmetric carbon atom with respect to the carbonyl group is similar to that about sp^2 - sp^3 carbon - carbon bond." (ii) "The diastereomeric transition states that control product stereospecificity have the smallest group closest to the incoming bulky group R'."



IV V VI

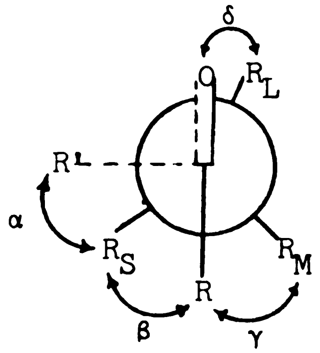
Figure 4. Transition states leading to the diastereomer A.

Considering the three transition states depicted in Figure 4, Karabatsos arrived at the conclusion that transition state IV should be the most stable. This conclusion was based on the evaluation of the following interactions in each conformer.

Conformer	Interactions			
	α	β	γ	δ
IV	$R' \leftrightarrow R_S$	$R \leftrightarrow R_S$	$R \leftrightarrow R_L$	$R_M \leftrightarrow O$
V	$R' \leftrightarrow R_L$	$R \leftrightarrow R_L$	$R \leftrightarrow R_M$	$R_S \leftrightarrow O$
VI	$R' \leftrightarrow R_M$	$R \leftrightarrow R_M$	$R \leftrightarrow R_S$	$R_L \leftrightarrow O$

Interactions α_{IV} and β_{IV} in IV are energetically more favorable than α_V and γ_V in V. $\gamma_{IV} \cong \beta_V$ and cancel each other out. From nmr and microwave data it is known that interaction δ_{IV} favors conformer IV over V.[11] Thus, IV ought to be more stable than V.

From a comparison of IV and VI it is evident that interaction γ_{IV} is energetically less favored than β_{VI}. However, α_{IV} and δ_{IV} are favored over the corresponding α_{VI} and γ_{VI}. Hence, IV ought to be more stable than VI. Repeating the same process for the analogous three transition states leading to diastereomer B, we find VII to be the most stable transition state. Now, we have to compare the energetically favored diastereomeric transition states IV and VII. α_{IV} and δ_{IV} are the interactions favoring IV over VII, and γ_{VII} is the interaction favoring VII. From these interactions only the $(R \leftrightarrow O)$, or δ, is evaluable spectroscopically.[11] For example, $(Me \leftrightarrow O) - (iPr \leftrightarrow O)$ is expected to be about -400 cal/mole. The other gauche interactions, $\alpha - \gamma$, are unpredictable. Karabatsos used the values he obtained for the δ interactions from nmr data to predict the free energy difference of the two diastereomeric transition states and from these the product ratio A/B. The experimental $\Delta\Delta G^{\ddagger}_{AB}$ were obtained by using the Curtin-Hammett principle.[12]



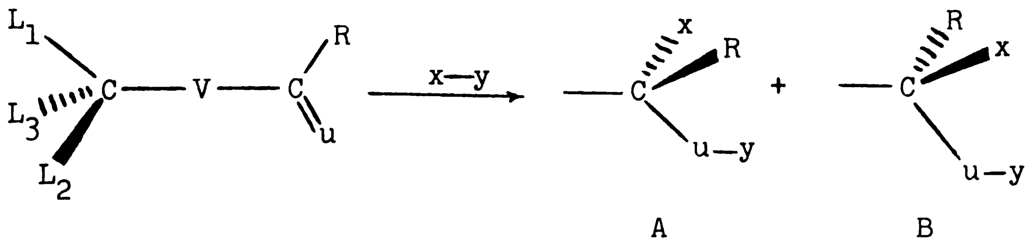
VII

$$\Delta\Delta G^{\ddagger}_{AB} = -RT\ln A/B \qquad (1)$$

These predictions were made with the understanding that the experimental $\Delta\Delta G^{\ddagger}_{AB}$ values, for a given chiral center, will vary as long as the groups R and R' will vary in size. The model does not take into account the extent of bond breaking and making in the transition states, any differences in solvation, or any differences in the entropies of the two transition states. Recent investigations in these laboratories,[14] on 3-methoxy-2-butanone and 3-phenyl-2-butanone, revealed that the above factors are important.

Noting that both previous compounds studied in these laboratories contained polar groups, we decided to study 2,3-dimethylbutanal and 3,4-dimethyl-2-pentanone. The fact that the chiral centers of these two compounds do not contain any polar groups makes them excellent substrates to test the Karabatsos model.

Before discussing the results obtained in this investigation a few words about the "stereochemical analogy model" introduced by E. Ruch and I. Ugi[13] are in order. This mathematical model, based on group theory, allows one to make quantitative predictions as outlined below. The authors assumed that all ligands are achiral, or that their chirality does not interfere with the stereochemistry of the reaction. The product ratio A/B is given by the concentration ratio of the transition states, since the reaction is kinetically controlled. The stereoselectivity of the reaction



is defined as in eq. 2, which represents a linear free energy relationship. The polynomial is a product of the ligand parameters $\lambda_1, \lambda_2, \lambda_3$.

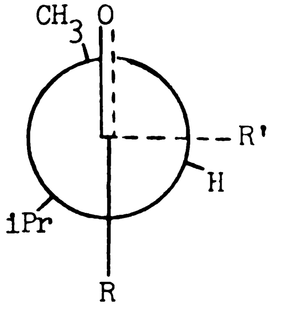
$$\delta \ln C_{RR}/C_{SR} = \rho(\lambda_1-\lambda_2)(\lambda_2-\lambda_3)(\lambda_3-\lambda_1) \qquad (2)$$

There is no stereoselectivity when two or more of the ligands, L_n, become equal. The ratio C_{RR}/C_{SR} is the concentration ratio of the diastereomeric reaction products. A nomenclature factor δ, being equal to +1 for the R-sequence and to -1 for the S-sequence, was introduced, to use the Cahn, Ingold and Prelog R,S nomenclature.[15] From experimental data,[17] they calculated the λ values of nine ligands and the ρ values of two reactions.[16] This method is of limited value though, since the λ and ρ values vary with different reactions. Also, it cannot be used in cases of adjacent chiral centers, thus excluding the large number of 1,2-asymmetric inductions, where the Karabatsos model can be used to make quantitative predictions.

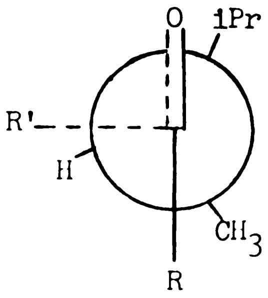
RESULTS AND DISCUSSION

The results of the additions of lithium aluminum hydride and sodium borohydride to 3,4-dimethyl-2-pentanone are summarized in Table I. Those of the additions of methylmagnesium iodide, methylmagnesium bromide, methylmagnesium chloride and methyllithium to 2,3-dimethylbutanal, are presented in Table II.

The above mentioned reactions were carried out at various substrate concentrations, solvents, and temperatures. The transition states leading to the diastereomeric product ratio A/B are depicted below (VIII, IX).



VIII



IX

When R=H and R'= $-CH_3$, the predominant diastereomer is the erythro-3,4-dimethyl-2-pentanol (R-R and S-S mixture).

TABLE I. The effect of temperature on asymmetric inductions of 3,4-dimethyl-2-pentanone.[a,b]

Run	Nucleophile	Solvent	Conc.[c]	Temp. °C	A : B[d]	$\Delta\Delta G^{\ddagger e}_{AB}$
1	$LiAlH_4$	Ether	0.7	35	56.6 : 43.4	-164 ± 24
2	$LiAlH_4$	Ether	0.1	35	61.3 : 38.7	-282 ± 42
3				22	61.7 : 38.3	-278 ± 42
4				2	64.5 : 35.5	-328 ± 49
5				-22	67.7 : 32.3	-371 ± 56
6				-69	78.0 : 22.0	-530 ± 80
7	$LiAlH_4$	Ether	0.05	35	61.5 : 38.5	-288 ± 43
8				22	63.0 : 37.0	-312 ± 47
9				1.5	65.0 : 35.0	-336 ± 50
10				-22	68.0 : 32.0	-373 ± 56
11	$LiAlH_4$	THF	0.1	66	59.0 : 41.0	-244 ± 37
12				35	60.0 : 40.0	-247 ± 37

TABLE I (Continued)

Run	Nucleophile	Solvent	Conc.[c]	Temp. °C	A : B[d]	$\Delta\Delta G^{\ddagger e}_{AB}$
13	$LiAlH_4$	THF	0.1	22	63.0 : 37.0	-310 ± 46
14				2	65.2 : 34.8	-345 ± 52
15				-10	66.5 : 33.5	-357 ± 53
16				-22	66.4 : 33.6	-340 ± 51
17	$NaBH_4$	iPrOH	0.25[f]	43	61.0 : 39.0	-270 ± 40

[a] In runs 1-6 we used the 3,4-dimethyl-2-pentanone-1,1,1,3-$\underline{d}_4$.

[b] Reactions were carried out at 2.09 : 1 nucleophile/ketone ratio.

[c] Moles of nucleophile/l of solvent.

[d] *Threo*/*Erythro* ratio of diastereomeric 3,4-dimethyl-2-pentanols.

[e] Cal/mole.

[f] Reaction was carried out at 1.984 : 1 nucleophile/ketone ratio.

TABLE II. The effect of temperature on asymmetric inductions of 2,3-dimethylbutanal[a]

Run	Nucleophile	Solvent	Conc.[b]	Temp. °C	A : B[c]	$\Delta\Delta G^{\ddagger}_{AB}$[d]
18	CH_3MgI	Ether	0.1	35	74.0 : 26.0	-640 ± 96
19				22	75.0 : 25.0	-648 ± 97
20				1.5	76.6 : 23.4	-648 ± 97
21				-22	78.3 : 21.7	-642 ± 96
22	CH_3MgI	Ether	0.05	35	77.4 : 22.6	-754 ± 113
23				21	77.8 : 22.2	-735 ± 110
24				1.5	78.5 : 21.5	-707 ± 106
25				-22	80.5 : 19.5	-710 ± 106
26	CH_3MgBr	THF	0.1	66	80.7 : 19.3	-967 ± 145
27				38	81.4 : 18.6	-913 ± 137
28				22	81.8 : 17.2	-880 ± 132
29				1.5	82.0 : 18.0	-827 ± 124

TABLE II (Continued)

Run	Nucleophile	Solvent	Conc.[b]	Temp. °C	A : B[c]	$\Delta\Delta G^{\ddagger d}_{AB}$
30	CH_3MgBr	Ether	0.1	35	79.0 : 21.0	-824 ± 124
31				22	79.4 : 20.6	-792 ± 119
32				1.5	79.5 : 20.5	-740 ± 111
33				-21	80.0 : 20.0	-692 ± 104
34	CH_3MgBr	Ether	0.05	35	80.3 : 19.7	-858 ± 128
35				22	80.0 : 20.0	-814 ± 122
36				1.5	80.8 : 19.2	-784 ± 117
37				-21	81.0 : 19.0	-728 ± 109
38	CH_3MgCl	THF	0.1	66	77.0 : 23.0	-814 ± 122
39				37	79.3 : 20.7	-827 ± 124
40				21	80.0 : 20.0	-810 ± 121
41				2	81.2 : 18.8	-802 ± 120

TABLE II (Continued)

Run	Nucleophile	Solvent	Conc.[b]	Temp. °C	A : B[c]	$\Delta\Delta G^{\ddagger}_{AB}$[d]
42	CH_3Li	Ether	0.1	35	73.0 : 27.0	-608 ± 91
43				21.5	72.0 : 28.0	-547 ± 82
44				1	74.5 : 25.5	-584 ± 87
45				-22	75.0 : 25.0	-549 ± 82
46	CH_3Li	Ether	0.05	35	72.0 : 28.0	-581 ± 87
47				21.5	71.5 : 28.5	-535 ± 80
48				1	76.5 : 23.5	-643 ± 96

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[a] Reactions were carried out at 1.875 : 1 nucleophile/aldehyde ratio.

[b] Moles of nucleophile/l of solvent.

[c] *Erythro*/*Threo* ratio of diastereomeric 3,4-dimethyl-2-pentanols.

[d] Cal/mole.

TABLE III. Asymmetric induction of some selected carbonyl systems.

Substrate	Nucleophile	Solvent	Temp. °C	$\Delta\Delta G^{\ddagger}_{AB}$ exp.	Calc.	Ref.
$iPrCD(C_6H_5)CHO$	$LiAlD_4$	Ether	35	-520	-200	21
	$NaBD_4$	THF	66	-300	-200	21
	$NaBD_4$	iPrOH	26	-450	-200	21
$iPrCD(C_6H_5)COCD_3$	MeMgl	Ether	25	-140	-200	21
	MeMgBr	Ether	35	-380	-200	21
	MeMgCl	THF	66	-710	-200	21
$CH_3(C_6H_{11})CHCHO$	MeMgl	Ether	35	-380	-300	22
	MeLi	Ether	0	-110	-300	22
$CH_3CD(C_2H_5)CHO$	$LiAlD_4$	Ether	35	-90	-100	23
	$NaBD_4$	iPrOH	0	-100	-100	23

When R= $-CH_3$ and R'=H, the threo alcohol (R-S and S-R mixture) predominates. Verification of the above assignments will be given later in Section E. Table III contains asymmetric induction results of some selected carbonyl systems.

A. Calculation of Activation Parameters.

The difference in the free energies of activation of the two diastereomeric transition states was calculated by using the Curtin-Hammett principle,[12]

$$\Delta\Delta G^{\ddagger}_{AB} = -RT\ln A/B$$

where A/B is the ratio of the diastereomeric products A and B, R is the ideal gas constant, and T is the absolute temperature (Tables I - VI). The errors in $\Delta\Delta G^{\ddagger}_{AB}$ values were calculated as follows: The maximum deviation in the temperature of ±2° was taken into account together with the maximum possible fractional error in the ratio A/B which ranged from 2-8%. This error was obtained by integrating eight times the areas under the appropriate signals in the nmr and vpc tracings.

The equation given above was combined with

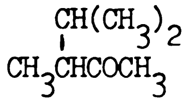
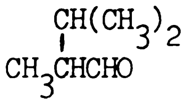
$$\Delta\Delta G^{\ddagger}_{AB} = \Delta\Delta H^{\ddagger}_{AB} - T\Delta\Delta S^{\ddagger}_{AB}$$

to give:

$$\ln A/B = -\Delta\Delta H^{\ddagger}_{AB}/RT + \Delta\Delta S^{\ddagger}_{AB}/R$$

By plotting ln A/B vs. 1/T (Figures 5-7) we obtained the various $\Delta\Delta H^{\ddagger}_{AB}$ and $\Delta\Delta S^{\ddagger}_{AB}$ values. The values and the errors reported in Table VII were calculated by using the KINFIT computer program of Dye and Nicely.[18]

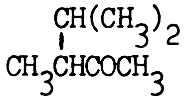
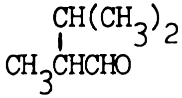
TABLE IV. The effect of nucleophile on asymmetric inductions of 2,3-dimethylbutanal and 3,4-dimethyl-2-pentanone.

Substrate	Run #	Nucleophile	A : B	$\Delta\Delta G^{\ddagger}_{AB}$
 $CH_3\overset{CH(CH_3)_2}{\overset{\vert}{C}}HCOCH_3$	8	$LiAlH_4$[a]	63.0 : 37.0	-312 ± 47
	17	$NaBH_4$[b]	61.0 : 39.0	-270 ± 40
 $CH_3\overset{CH(CH_3)_2}{\overset{\vert}{C}}HCHO$	18	CH_3MgI[c]	74.0 : 26.0	-640 ± 96
	30	CH_3MgBr[c]	79.0 : 21.0	-824 ± 124
	39	CH_3MgCl[d]	79.3 : 20.7	-827 ± 124
	42	CH_3Li[c]	73.0 : 27.0	-608 ± 91

[a] 0.05 in ether at 22°. [b] 0.025 M in iPrOH at 43°.

[c] 0.1 M in ether at 35°. [d] 0.1 M in THF at 37°.

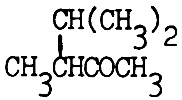
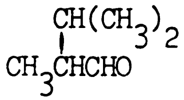
TABLE V. The effect of nucleophile concentration on asymmetric inductions of 2,3-dimethylbutanal and 3,4-dimethyl-2-pentanone.

Substrate	Run #	Nucleophile	Conc.	A : B	$\Delta\Delta G^{\ddagger}_{AB}$
 $\begin{array}{l} CH(CH_3)_2 \\ \vert \\ CH_3CHCOCH_3 \end{array}$	1	$LiAlH_4$[a]	0.7	56.6 : 43.4	-164 ± 24
	2		0.1	61.3 : 38.7	-282 ± 42
	7		0.05	61.5 : 38.5	-288 ± 43
 $\begin{array}{l} CH(CH_3)_2 \\ \vert \\ CH_3CHCHO \end{array}$	19	CH_3MgI[b]	0.1	75.0 : 25.0	-648 ± 97
	23		0.05	77.8 : 22.2	-735 ± 110
	31	CH_3MgBr[b]	0.1	79.4 : 20.6	-792 ± 119
	35		0.05	80.0 : 20.0	-814 ± 122
	43	CH_3Li[b]	0.1	72.0 : 28.0	-547 ± 82
	47		0.05	71.5 : 28.5	-535 ± 80

[a] In ether at 35°

[b] In ether at 22°

TABLE VI. Solvent effects on asymmetric inductions of 2,3-dimethylbutanal, and 3,4-dimethyl-2-pentanone.

Substrate	Run #	Nucleophile[a]	Solvent	A : B	$\Delta\Delta G^{\ddagger}_{AB}$[b]
 $CH_3\overset{\overset{CH(CH_3)_2}{\vert}}{C}HCOCH_3$	3	$LiAlH_4$	Ether	61.7 : 38.3	-278 ± 42
	13		THF	63.0 : 37.0	-310 ± 46
 $CH_3\overset{\overset{CH(CH_3)_2}{\vert}}{C}HCHO$	31	CH_3MgBr	Ether	79.4 : 20.6	-792 ± 119
	28		THF	81.8 : 17.2	-880 ± 132

[a] 0.1 M in solvent at 22°.

[b] Cal/mole.

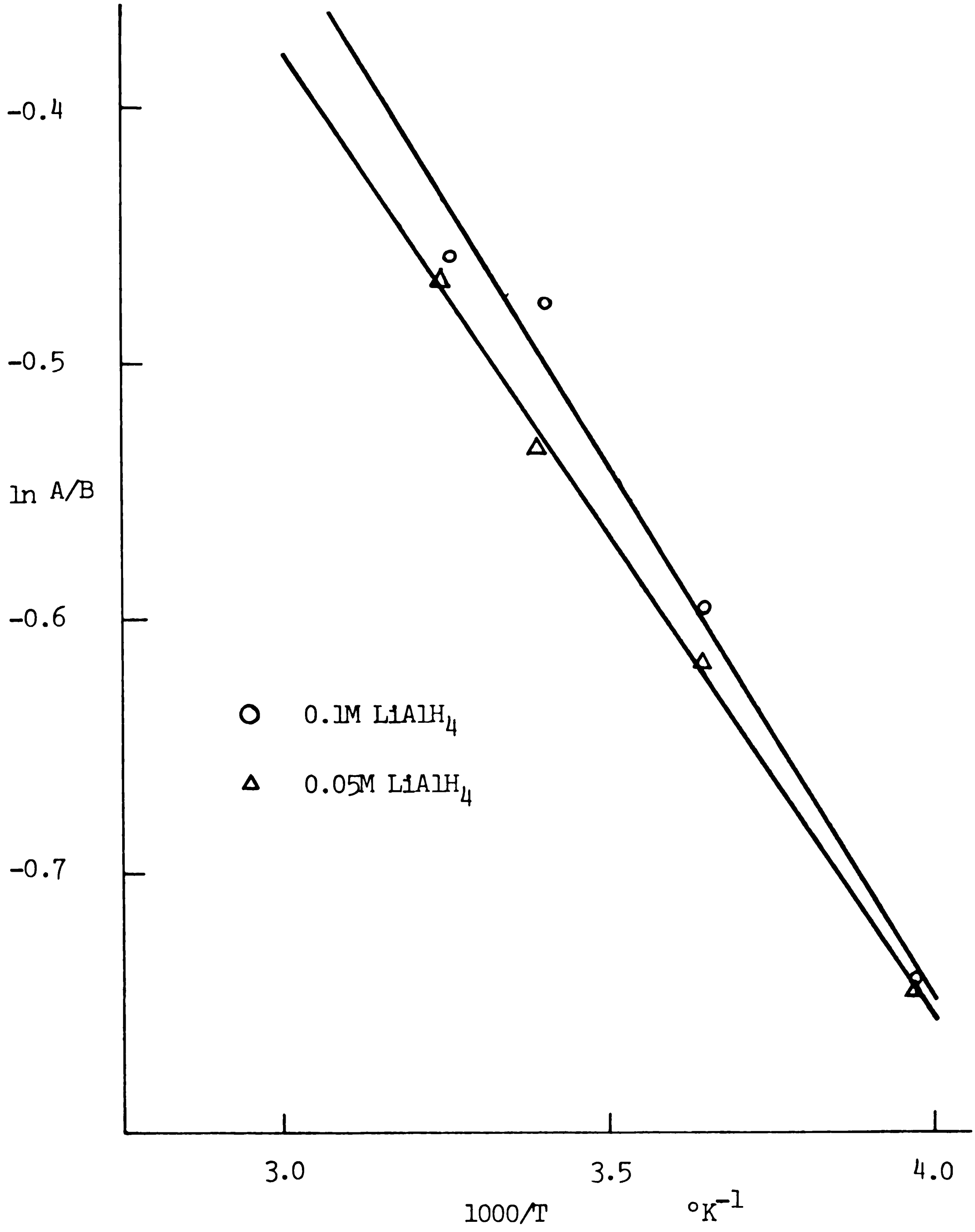


Figure 5. Activation Parameter Plots of the Reaction of 3,4-Dimethyl-2-pentanone with $LiAlH_4$ in ether.

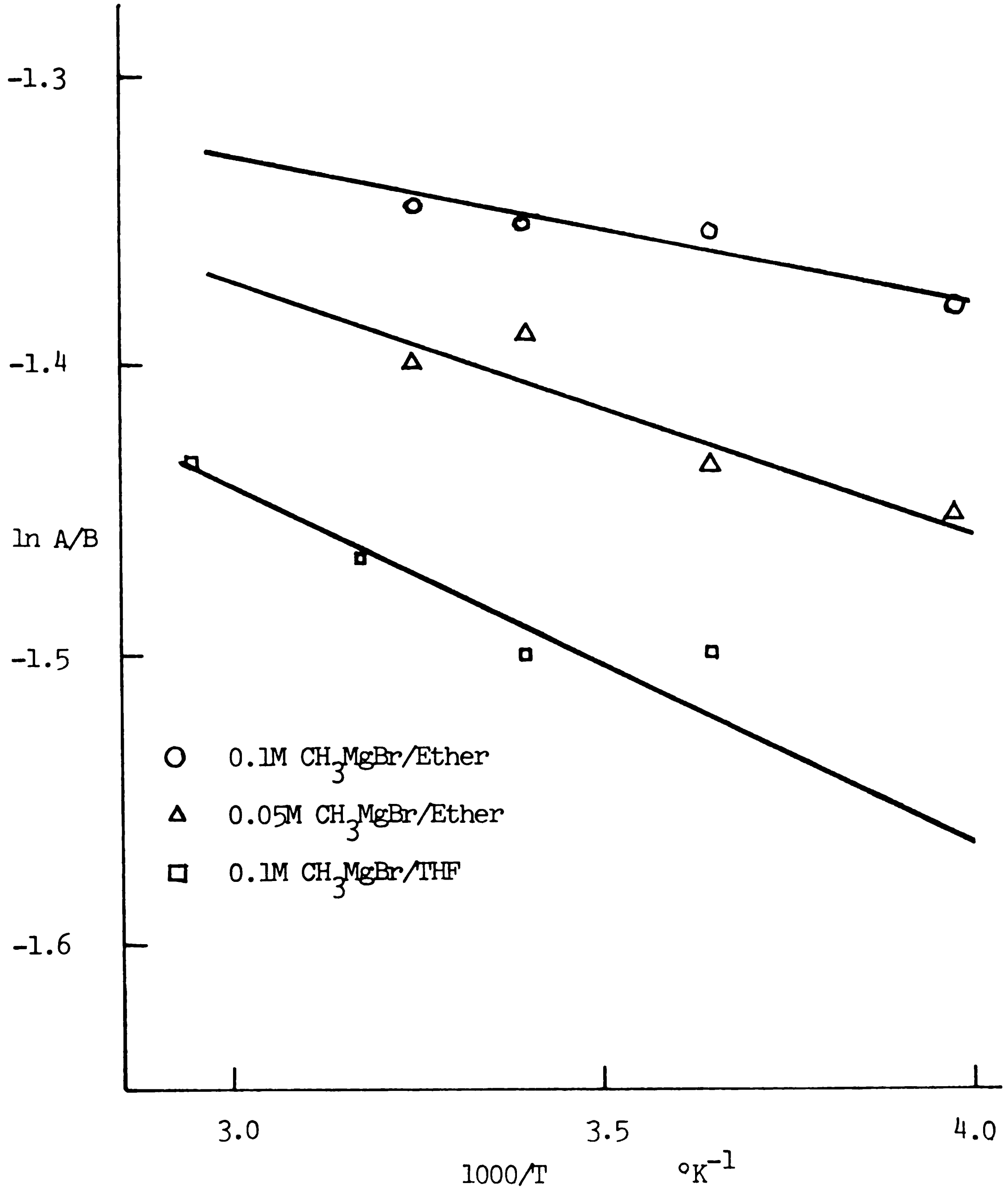


Figure 6. Activation Parameter Plots of the reactions of 2,3-Dimethylbutanal with CH_3MgBr in ether and THF.

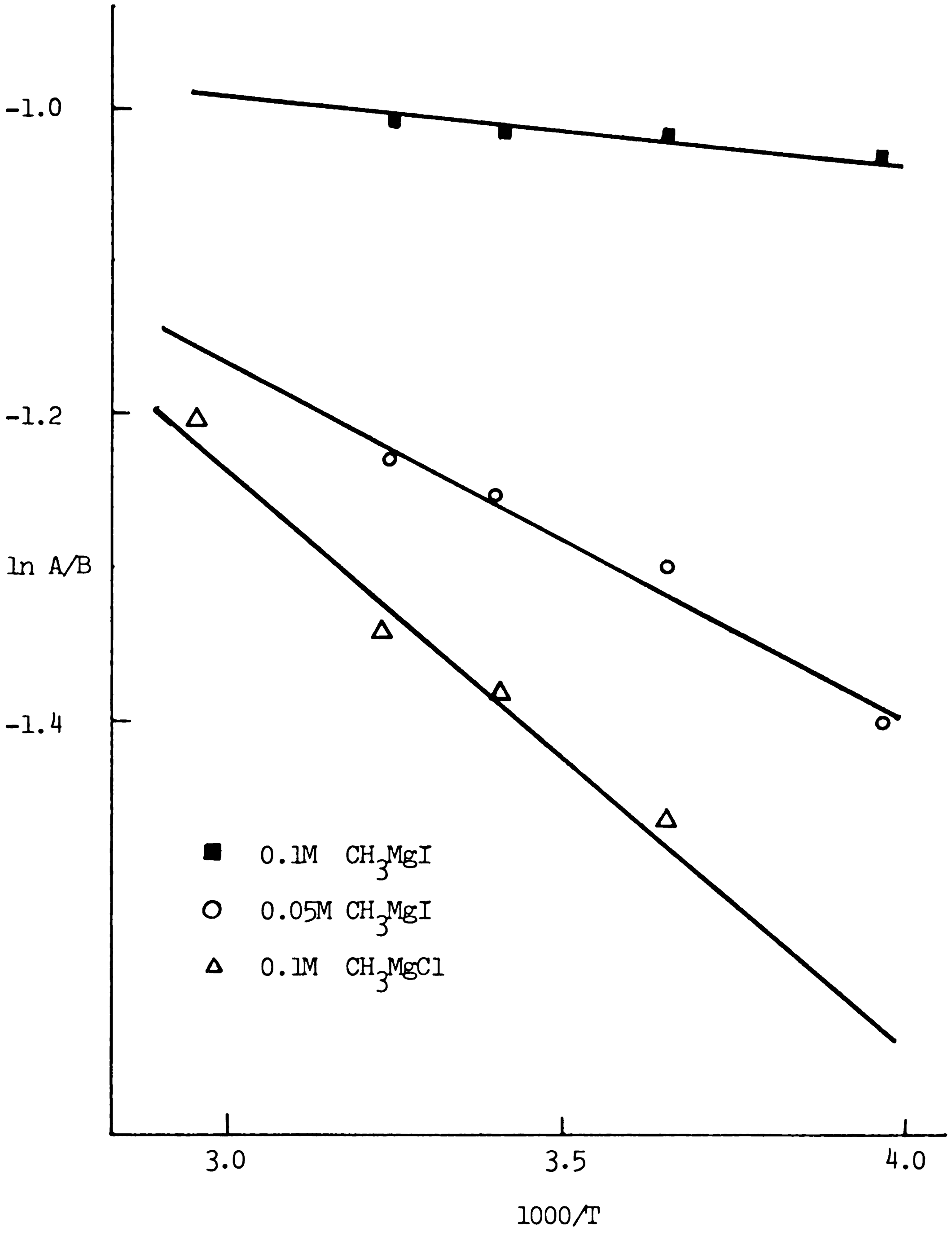
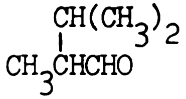
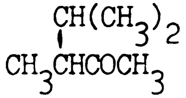


Figure 7. Activation Parameter Plots of the Reactions of 2,3-Dimethylbutanal with CH_3MgI in Ether and CH_3MgCl in THF.

TABLE VII. $\Delta\Delta H^{\ddagger}_{AB}$ and $\Delta\Delta S^{\ddagger}_{AB}$ values for the reactions reported in Tables I and II.

Substrate	Nucleophile	Solvent	Conc.	$\Delta\Delta H^{\ddagger a,b}_{AB}$	$\Delta\Delta S^{\ddagger c}_{AB}$
 $CH_3\overset{\overset{CH(CH_3)_2}{\vert}}{C}HCHO$	CH_3MgBr	Ether	0.1	-100 ± 22	2.37 ± .10
			0.05	-165 ± 60	2.23 ± .21
		THF	0.1	-234 ± 42	2.17 ± .14
	CH_3MgI	Ether	0.05	-510 ± 82	0.76 ± .30
			0.1	-630 ± 35	0.04 ± .12
	CH_3MgCl	THF	0.1	-667 ± 63	0.49 ± .22
	CH_3Li	Ether	0.1	-383 ± 177	0.67 ± .63
 $CH_3\overset{\overset{CH(CH_3)_2}{\vert}}{C}HCOCH_3$	$LiAlH_4$	THF	0.1	-660 ± 102	-1.22 ± .36
		Ether	0.05	-740 ± 20	-1.45 ± .08
			0.1	-790 ± 80	-1.70 ± .25

[a] Cal/mole.

[b] $\Delta\Delta H^{\ddagger}_{AB}$ is predicted by the Karabatsos model to be -400 cal/mole.

[c] In e.u.

B. Effect of Nucleophile.

Grignard Reagents.

The reactions of 2,3-dimethylbutanal with methyl Grignard reagents revealed stereoselectivity in the following order (runs 18, 30, 39, Table IV).

$$CH_3MgCl \cong CH_3MgBr > CH_3MgI$$

This order is probably due to the combination of two effects.[19] First, the increase of the steric effect in going from methylmagnesium chloride to methylmagnesium iodide; and, secondly, the corresponding decrease of the inductive effect of the halogens. Why the effect should be as found, however, is not understood, as the mechanism of the Grignard addition to aldehydes and ketones is not completely known. Smith,[24] in spectroscopic and kinetic studies of the reaction of methylmagnesium bromide with 2,4-dimethyl-4'-methylmercaptobenzophenone in diethyl ether, obtained data below ca. 0.3M methylmagnesium bromide that were consistent with complex formation followed by first-order conversion to product. The proposed mechanism was:

$$\text{ketone} + \text{Grignard} \underset{}{\overset{K}{\rightleftarrows}} \text{complex} \xrightarrow{k} \text{product} \qquad (4)$$

At concentrations above ca. 0.3M the mechanism was found to be faster than predicted on this basis. Billet and Smith[25] studied the reaction of 4-methylmercaptoacetophenone in ether with methylmagnesium bromide at 25°. The pseudo-first-order rate constant for the reaction was found to increase from 0.3 to 1.3 sec^{-1} with an increase in the Grignard concentration from 0.05 to 0.6M. The following scheme involving dimerization of the methylmagnesium bromide was proposed for the reaction of 4-methylmercaptoacetophenone with methylmagnesium bromide.

$$K + G_1 \xrightleftharpoons{K_1} C_1 \xrightarrow{k_1} P$$

$$2\ G_1 \xrightleftharpoons{K_2} G_2$$

$$K + G_2 \xrightleftharpoons{K_3} C_2 \xrightarrow{k_3} P$$

"It is of interest to note that, as with the previous example,[24b] to the extent that this scheme represents the actual chemical system, the complex containing the dimeric Grignard yield product ca. ten times faster than the complex between ketone and monomeric Grignard. Thus, the formation of a more reactive complex between the ketone and the dimeric Grignard can account for the observed pseudo-first-order rate constant being larger than predicted on the basis of the scheme outlined in eq. 4."[25]

The composition of Grignard reagents has been extensively studied. Recently Parris and Ashby[20] came out in support of the Schlenk type equilibrium of the Grignard compounds.

$$R_2Mg + MgX_2 \xrightleftharpoons{K} 2\ RMgX$$

The equilibrium constant K, determined by nmr temperature studies, was found to change with R, halogen, and solvent. In diethyl ether bromides and iodides were monomeric at concentrations between 0.05 and 0.1M. At concentrations between 0.3 and 1M increasing association to dimers occurred. In tetrahydrofuran, regardless of the nature of the halogen involved, only monomers were found.

To make sure that monomeric Grignards were the attacking species, we used concentrations in the range of 0.05 to 0.1M (Tables II and IV). The stereoselectivity of methylmagnesium iodide (run 19 *vs.* 23) and methylmagnesium bromide (run 31 *vs.* 35), Table V, remained the same despite the change in concentration from 0.05 to 0.1M.

Methyllithium. The mechanism of the addition of organolithium reagents to carbonyl compounds was found to be first-order in each reactant, second-order overall.[26]

$$\text{ketone} + \text{RLi} \xrightleftharpoons{\text{Fast}} \text{complex} \xrightarrow{\text{Slow}} \text{products}$$

The mechanism is believed to involve the formation of 1:1 coordination complex between the carbonyl compound and the organolithium in a fast and reversible step, followed by a rate determining step to give product.

The observation of ^{13}C -^{7}Li spin-spin coupling in ether and tetrahydrofuran, defines the structure of the methyllithium tetramer in these solutions.[28]

The additions of methyllithium to 2,3-dimethylbutanal gave smaller $\Delta\Delta G^{\ddagger}_{AB}$ values than those of the Grignards (run 42 *vs.* 18, 30, 39, Table IV). Furthermore, as was the case with the Grignards, no change in stereoselectivity was observed with increase in methyllithium concentration from 0.05 to 0.1M (run 47 *vs.* 43, Table V).

Metal Hydrides. The formation of alkoxyaluminum hydrides in the reduction of carbonyl compounds, and their interference with the mechanism of the reduction, has been extensively studied. Eliel[29] proposed that alkoxyaluminum hydrides were not involved in the reduction of 3,3,5-

trimethylcyclohexanone with lithium aluminum hydride, but that, as soon as they formed, they disproportionated to lithium aluminum hydride and lithium aluminum tetraalkoxide. Thus, the lithium alumunum hydride was the only effective reducing agent throughout the reduction. Furthermore, it is known that alkoxyaluminum hydrides are less effective reducing agents than AlH_4^-.

Sodium borohydride reductions of aldehydes and ketones in isopropyl alcohol exhibit simple second-order kinetics, first-order in borohydride and first-order in the carbonyl derivative.[30]

Lithium aluminum hydride reduction of 3,4-dimethyl-2-pentanone revealed no change in stereoselectivity in the range 0.05 to 0.1M (run 7 vs. 2, Table V), and only a slight decrease in the range 0.1 to 0.7M (run 2 vs. 1). Sodium borohydride was less stereoselective than lithium aluminum hydride (run 17 vs. 8, Table IV).

C. Solvent Effects.

Solvent can play an important role in the stereoselectivity of reactions. Solvation of the transition states usually takes place through hydrogen bonding, ion-ion, ion-dipole, or dipole-dipole interactions. The more polar solvents stabilize the more polar transition states.[14a]

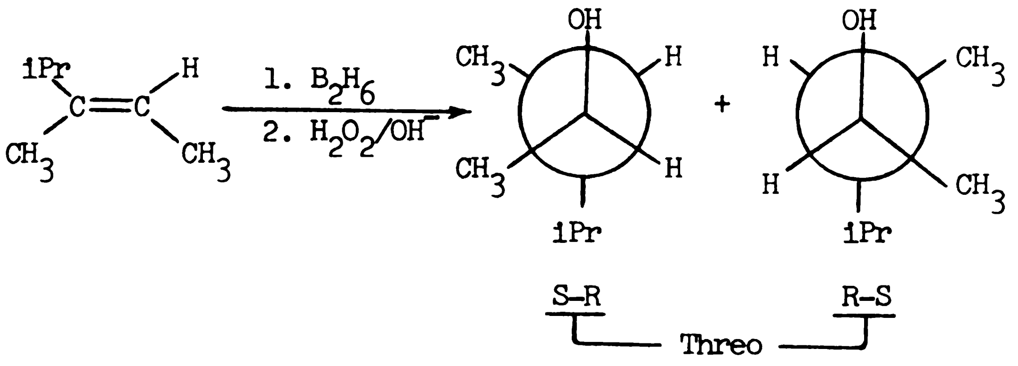
Changing the solvent from ether to tetrahydrofuran, in the reactions of 3,4-dimethyl-2-pentanone with lithium aluminum hydride and 2,3-dimethylbutanal with methylmagnesium bromide (runs 3 vs. 13 and 31 vs. 28, Table VI), did not alter the stereoselectivity of the reactions. Thus, the greater stereoselectivity in tetrahydrofuran than in ether, observed in the reactions of 3-methoxy-2-butanone,[14a] was not observed here. The suggested greater solvation of the hydride species in tetrahydrofuran than in ether,[29] and the effect of increased solvent polarity,[14a] were of minor importance. Since both 2,3-dimethylbutanal, and 3,4-dimethyl-2-pentanone contain no polar groups, besides the carbonyl group, it is not surprising to find that the population of the two transition states VIII and IX remained unaffected with a change in solvent. Solutions of methylmagnesium chloride in ether, and methylmagnesium iodide in tetrahydrofuran were not studied, because the former disproportionates in ether at room temperature, and the latter is unstable in tetrahydrofuran.[20]

D. Entropy Effects.

In the reductions of 3,4-dimethyl-2-pentanone with lithium aluminum hydride, both $\Delta\Delta H^{\ddagger}_{AB}$ and $\Delta\Delta S^{\ddagger}_{AB}$ had the same, negative sign (Table VII). The $\Delta\Delta H^{\ddagger}_{AB}$ and $\Delta\Delta S^{\ddagger}_{AB}$ had opposite signs in the reaction of 2,3-dimethylbutanal with methyl Grignards and methyllithium. The methylmagnesium iodide, methylmagnesium chloride and methyllithium additions were enthalpy controlled. The entropy was positive and small, ranging from 0.04 to 0.76 e.u. Only the Reaction of methylmagnesium bromide in ether and tetrahydrofuran is an exception, as it is entropy controlled. These findings are in concert with the restrictions placed on the Karabatsos model, namely that entropy differences between the two diastereomeric transition states must be negligibly small. Thus, our findings differ from those obtained in the additions of methyllithium, lithium aluminum hydride, and methylmagnesium iodide to 3-phenyl-2-butanone-1,1,1,3-d_4,[14b] and methyl Grignard and metal hydride reductions of 3-methoxy-2-butanone-1,1,1,3-d_4,[14a] which were entropy controlled. They also differ from those obtained in the reductions of 3-methyl-2-pentanone and 3,4,4-trimethyl-2-pentanone with metal hydrides, in which cases entropy differences caused an inversion of the diastereomeric product ratio A/B.[23]

E. Configurational Studies.

In order to prove that the stereochemistry of the 3,4-dimethyl-2-pentanols is as predicted by the Karabatsos model, we independently synthesized one of the two alcohols. Pure *threo*-3,4-dimethyl-2-pentanol was prepared by hydroboration of *trans*-3,4-dimethyl-2-pentene,[27] according to the equation:



We were unable to detect any *erythro*-3,4-dimethyl-2-pentanol, or 2,3-dimethyl-3-pentanol in the reaction product. The pure *threo*-3,4-dimethyl-2-pentanol matched the major diastereomeric alcohol A produced from the reaction of 3,4-dimethyl-2-pentanone with metal hydrides, and the minor diastereomeric alcohol B obtained from the methyl Grignard and methyllithium additions, to 2,3-dimethylbutanal. Thus, the stereochemistry was found to be as predicted by the Karabatsos model.

F. Conclusions.

This study of the additions to 2,3-dimethylbutanal and to 3,4-dimethyl-2-pentanone showed that the nucleophile concentration and the solvent polarity do not affect the stereoselectivity of the reactions. The experimental results closely paralleled those predicted by the Karabatsos model. Any discrepancies, from the predictions, were not very significant. Small discrepancies are to be expected, however, since the model's predictions are based on the measurable R↔O interactions. The other, gauche, interactions in the transition state, being unmeasurable, are disregarded.

It would appear that the extension of the model to other chemical systems, e.g. imines, seems very promising.

EXPERIMENTAL

A. General

In the asymmetric induction studies, the apparatus consisted of a three-necked flask equipped with a thermometer, a magnetic stirrer, condenser, and a septum cap. The system was closed by placing a balloon at the top of the condenser and was flushed with nitrogen.

All solvents used were distilled from lithium aluminum hydride, placed in flame dried flasks, closed with septum caps, and stored under nitrogen. The necessary amounts of solvent and reagents were introduced into the reaction flask with syringes. The temperatures of the reaction mixtures were controlled with carbon tetrachloride-dry ice, tert-amyl alcohol-dry ice, water-ice, or water baths (for -22°, -12°, 1°, 22° respectively). The higher temperatures, 35° in ether and 60° in tetrahydrofuran, were controlled by refluxing the solvent. This method introduced a maximum deviation in temperature of ± 2°.

Reagents: Solutions of methylmagnesium bromide (3.0M) in ether and methylmagnesium chloride (3.16M) in tetrahydrofuran (THF) were obtained from Alfa Inorganics Inc. Solutions of methyllithium (2.4M) in ether, lithium aluminum hydride (2.14M) in THF, and lithium aluminum hydride (4.4M) in ether were obtained from Foot Mineral Company. A solution of methylmagnesium bromide (3.0M) in THF was prepared from the ether solution by removing the ether under vacuum and adding anhydrous THF.

B. Preparation of 3,4-Dimethyl-2-pentanone

To a cooled suspension (-5 to 0°) of 26g (0.137 mole) of copper (I) iodide, prepared according to Kauffman and Pinnell,[31] in 100ml of ether, was added 100ml of methyllithium, 2.4M in ether (Alfa). A solution of 7.9g (0.080 mole) of 3-methyl-2-penten-2-one (Aldrich) in 50ml of ether was added over a period of 15 min. to the lithium dimethyl cuprate suspension, by using the procedure of House and Fischer, Jr.[32] After 15 min. of stirring, the mixture was quenched with an aqueous solution (pH 8-9) of ammonium chloride-ammonia. The ether layer was washed three times with aqueous ammonium chloride solution and was dried over anhydrous magnesium sulfate. Upon removal of the solvent and distillation, a fraction of 5.3g (58% yield) of 3,4-dimethyl-2-pentanone was collected: bp 130-134°. Literature value:[33] bp 128-133° at 719mm. Vapor phase chromatograms were taken on an Aerograph A90-P3, by using a 20% Carbowax DMCS, Chromosorb W, 20 ft. column, He pressure 21 psi, and column temperature 130°. The ketone was 96% pure, and had a retention time of 15 min. Nmr spectra (40mg of ketone in 0.250ml of carbon tetrachloride with 12mg of $Eu(FOD)_3$) were obtained with a Varian A 56/60D spectrometer. The spectrum consisted of a quartet centered at δ 1.07, a doublet centered at δ 1.23, a multiplet centered at δ 1.80, a multiplet centered at δ 2.34 and a singlet at δ 2.34 (ratios, 6.0 : 3.0 : 1.0 : 1.0 : 3.0, respectively).

Mass spectrum showed most abundant peaks at:

m/e	R.A.[34]	m/e	R.A.	m/e	R.A.
39	10.5	55	12.4	72	38.8
41	17.5	57	8.0	99	7.3
43	100.0	71	7.9	114	6.7

C. Preparation of 3,4-Dimethyl-2-pentanone-1,1,1,3-$\underline{d}_4$

In a 50ml round-bottomed flask equipped with a magnetic stirrer, a condenser, and closed at the top with a calcium chloride drying tube, was placed four grams (0.035 mole) of 3,4-dimethyl-2-pentanone together with 15ml of 90% deuterium oxide. The mixture was refluxed at 100° for one day. The pH of the deuterium oxide was maintained at 10 by using a few drops of lithium deuteroxide. The same treatment of the ketone was repeated two more times with 99.5% deuterium oxide, and refluxed for two days. After extraction with ether, the ether layer was dried over anhydrous magnesium sulfate and distilled. The fraction boiling at 131-134° was collected to give 3.2g (80% yield). The nmr spectrum of a 20% solution of this ketone in benzene (Figure 8-B), exhibited a quartet centered at δ 0.73, a singlet at δ 0.87, and a multiplet centered at δ 1.77 (ratios, 6.0 : 3.0 : 1.0, respectively).

D. Additions to 3,4-Dimethyl-2-pentanone-1,1,1,3-$\underline{d}_4$

1. Addition of Methylmagnesium Bromide.

In the apparatus described previously (Section A) were placed 20ml of anhydrous ether and 4ml of methylmagnesium bromide (3.0M solution in ether). While maintaining a temperature of 35°, a solution of 0.64g (5.42 mmoles) of 3,4-dimethyl-2-butanone-1,1,1,3-$\underline{d}_4$ in 1.8ml of ether was added by means of a syringe. After stirring for three hours the mixture was quenched with a 10% ammonium chloride-ammonia solution (pH 9). The ether layer was separated, washed twice with 15ml of water and dried over anhydrous magnesium sulfate. The ether was removed by distillation and the crude 2,3,4-trimethyl-2-pentanol-1,1,1,3-$\underline{d}_4$ was further purified

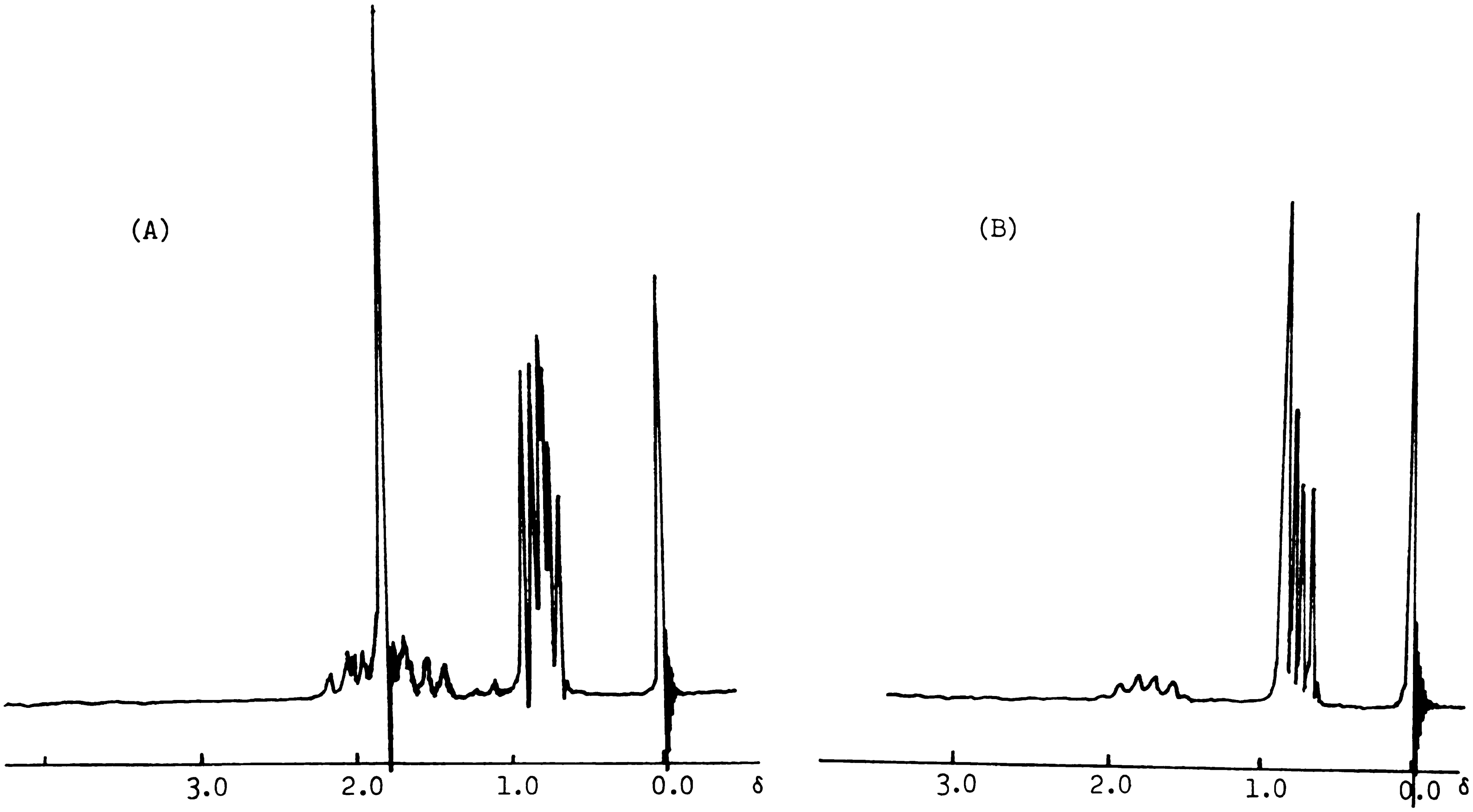


Figure 8. N.M.R. spectra of 20% solution of (A) 3,4-dimethyl-2-pentanone and (B) 3,4-dimethyl-2-pentanone-1,1,1,3-$\underline{d}_4$, in benzene.

by vpc (6 ft. x 1/4 inch, column, Chromosorb W). The nmr spectrum of a 14% solution of the alcohol in pyridine (Figure 9) showed a multiplet centered at δ 0.97, a singlet of unresolved diastereotopic methyl protons at δ 1.32, a multiplet centered at δ 2.25, and a singlet at δ 4.85.

2. N.M.R. Solvent Studies of 2,3,4-Trimethyl-2-pentanol-1,1,1,3-$\underline{d}_4$

Since the nonequivalence of the diastereotopic methyl protons, H_A and H_B, at δ 1.32, was not observed with the pyridine solution (Figure 9), the following solvents were used in an attempt to resolve the diastereotopic protons: Carbon tetrachloride, chloroform, dimethyl sulfoxide, benzene, chlorobenzene, toluene, phenol, nitrobenzene, formamide, dimethyl formamide, acetonitrile, hexamethyl phosporoamide, $\underline{t}$-butyl alcohol, acetone-$\underline{d}_6$, and carbon tetrachloride/Eu(FOD)$_3$. These efforts, to find a suitable solvent to resolve the diastereotopic H_A and H_B, remained fruitless.

3. Additions of Lithium Aluminum Hydride and Sodium Borohydride

The procedure described previously (Section D-1) was followed for additions of lithium aluminum hydride to the carbonyl compounds. A solution of 0.6ml (2.84 mmoles) of lithium aluminum hydride (4.4M) in ether was diluted with ether to concentration of 0.1M (runs 2-6) or 0.05M (runs 7-10). A second solution of 0.2ml (1.26 mmoles) of 3,4-dimethyl-2-pentanone-1,1,1,3-$\underline{d}_4$ in 0.5ml of ether was added slowly, with fast stirring, to the hydride solution at the appropriate temperature. The same procedure was used for runs 11-16, with only the solvent being changed from ether to THF. In run 17, a 0.025M solution of sodium borohydride in isopropyl alcohol was used.

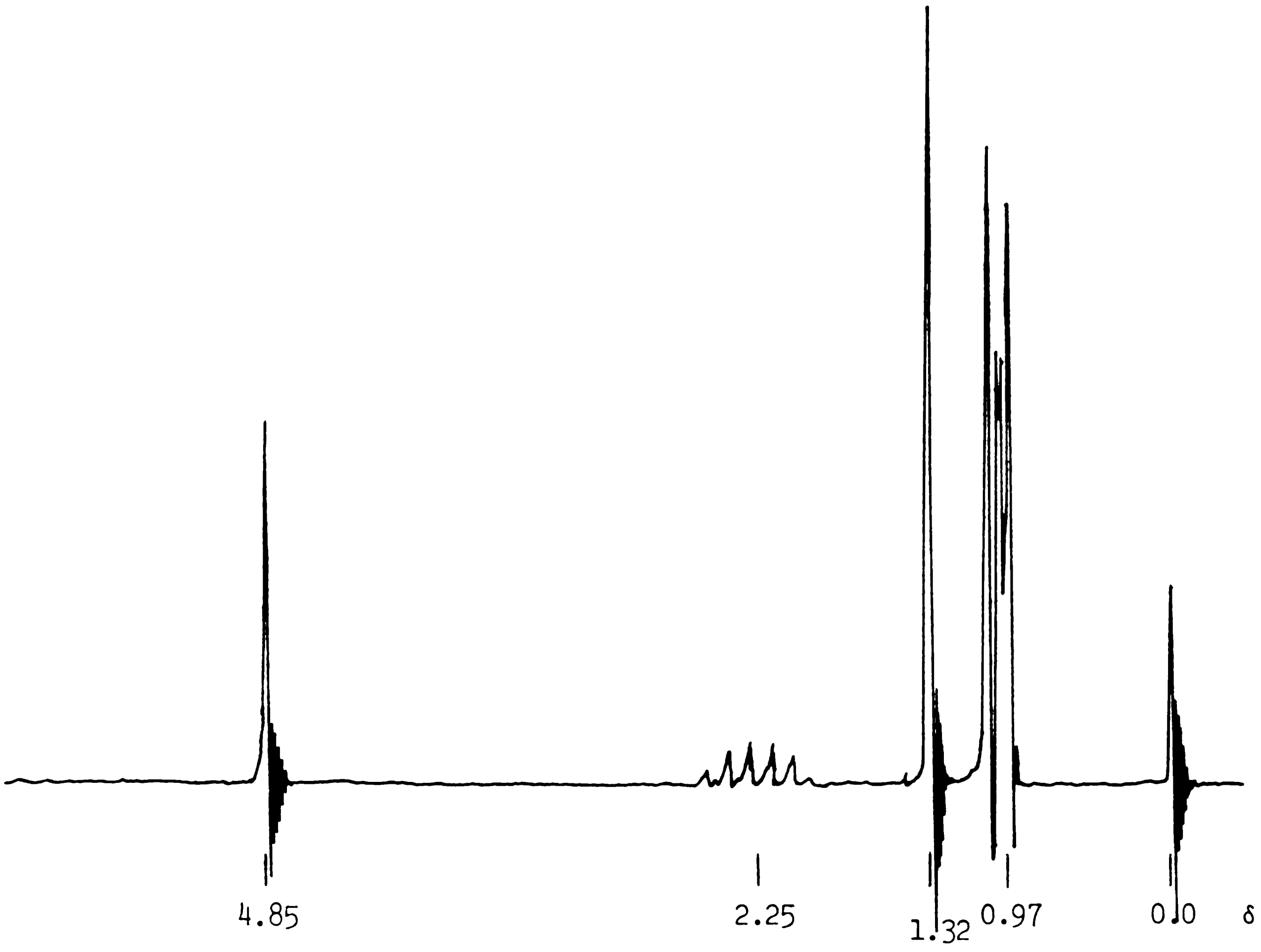


Figure 9. N.M.R. Spectrum of 14% Solution of 2,3,4,-Trimethyl-2-pentanol-1,1,1,3-$\underline{d}_4$ in pyridine.

4. N.M.R. and V.P.C. Studies of 3,4-Dimethyl-2-pentanol and 3,4-Dimethyl-2-pentanol-1,1,1,3-$\underline{d}_4$

A solution of 3,4-dimethyl-2-pentanol-1,1,1,3-$\underline{d}_4$ in pyridine showed the nonequivalent diastereotopic protons H_A and H_B, $-C\underline{H}(OH)-CD_3$, as two singlets at δ 3.84 and 3.97 (Figure 10). Quantitative measurements were made by integrating the area under these two singlets. In the case of 3,4-dimethyl-2-pentanol the ratio A/B (threo/erythro) was determined by integrating the area under the two doublets, centered at δ 1.25 and δ 1.29, of the diastereotopic methyl protons $-CH(OH)\underline{CH_3}$ (Figure 11).

Ratios A/B, calculated by vpc, were in good agreement with those obtained from the nmr measurements. Vapor phase chromatograms were taken on an Aerograph, by using a Carbowax DMCS, Chromosorb W, 20 ft. column, He pressure 20 psi and column temperature 130°. The erythro-3,4-dimethyl-2-pentanol had a retention time of 27 min. and the threo-3,4-dimethyl-2-pentanol a retention time of 30 min.

E. Preparation of 2,3-Dimethylbutanal

According to the procedure of Freeman et.al,[35] a solution of 42.08g (0.5 mole) of 2,3-dimethyl-1-butene (Chemical Samples Co.) in 600ml of freshly distilled dichloromethane (Matheson-Colleman) was placed in a three-necked 2-l flask equipped with an addition funnel, a mechanical stirrer and a drying tube. The temperature of the solution was kept between 1-4° by using an ice-water bath. To it was added, dropwise through the funnel, a solution of 80.6g (0.52 mole) of freshly distilled chromyl chloride (Alfa) in 400ml of dichloromethane. The mixture was allowed to stand in the cooling bath, with stirring, for one hour.

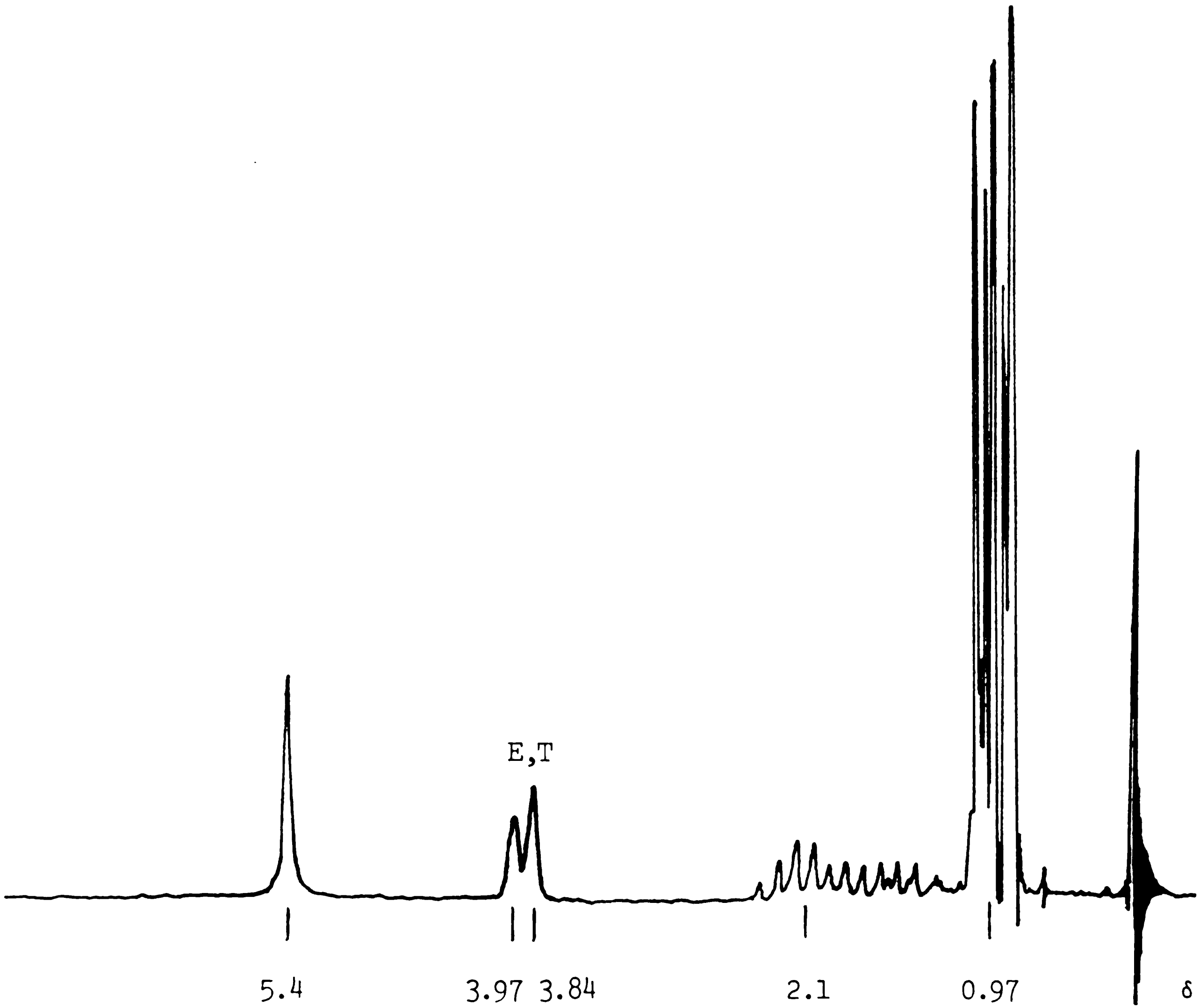


Figure 10. N.M.R. Spectrum of 3,4-Dimethyl-2-pentanol-1,1,1,3-$\underline{d}_4$ in pyridine. (E = <u>Erythro</u>; T = <u>Threo</u>).

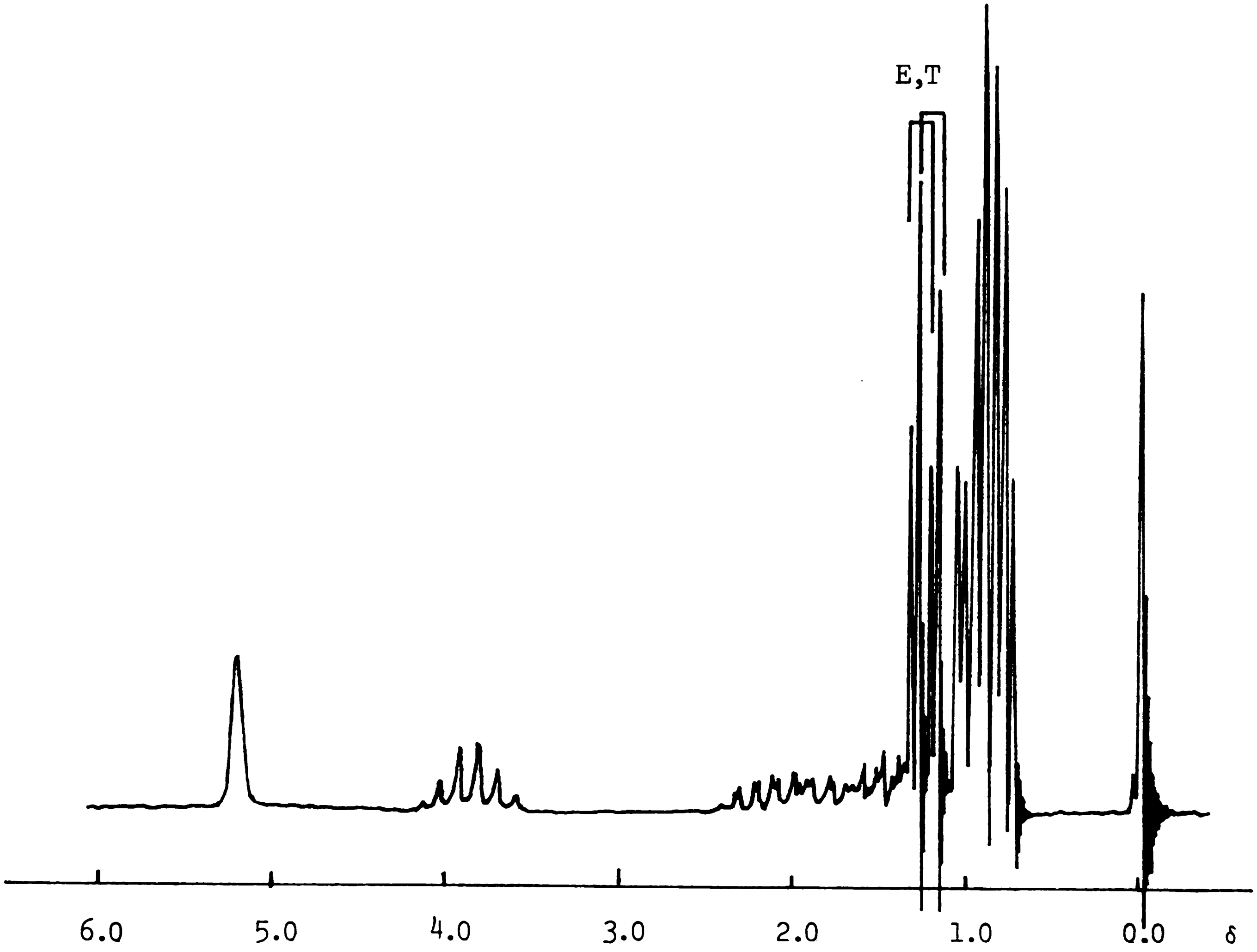


Figure 11. N.M.R. Spectrum of 18% solution of 3,4-Dimethyl-2-pentanol in pyridine. (E = Erythro; T = Threo).

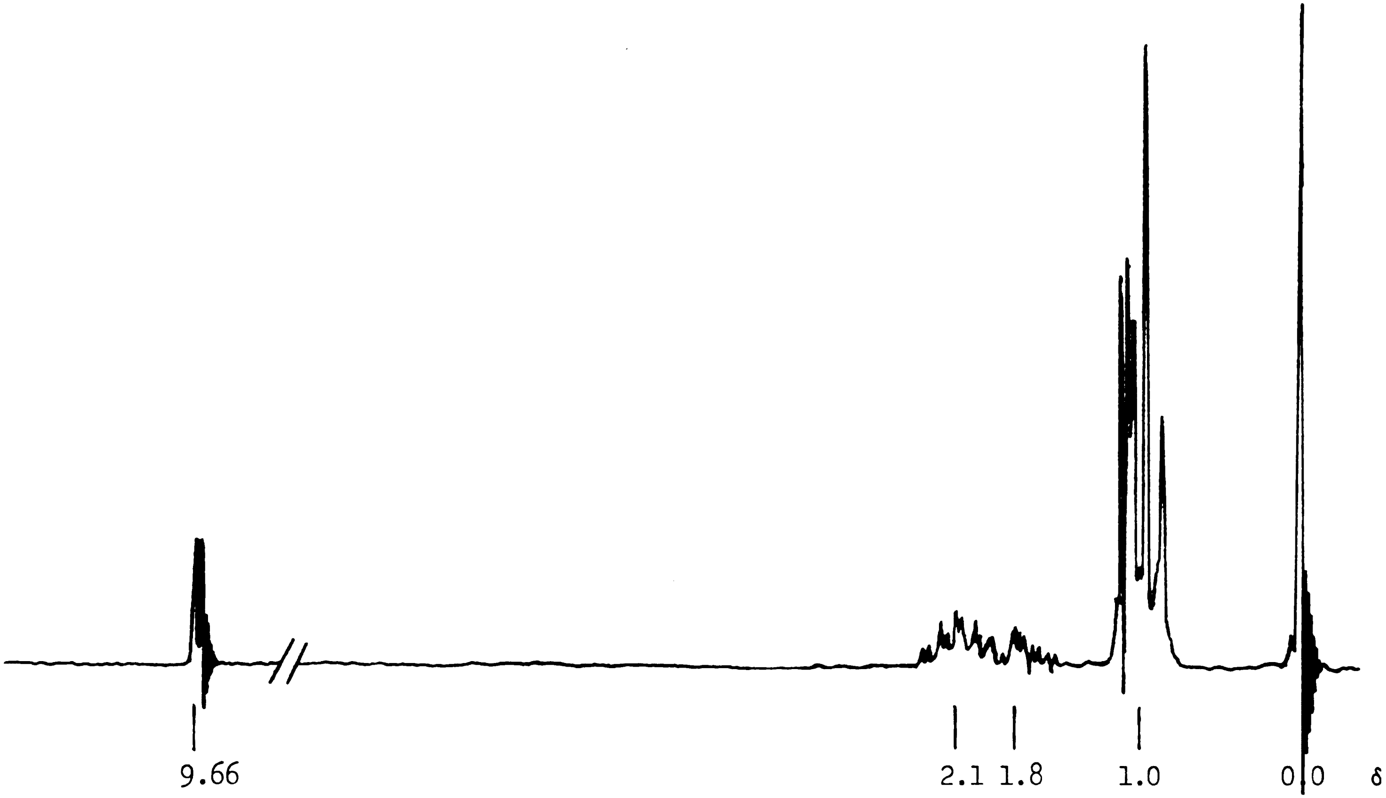


Figure 12. N.M.R. Spectrum of 30% solution of 2,3-Dimethylbutanal in carbon tetrachloride

Zinc dust, 41.8g (0.64 mole), was added and the mixture was stirred for an additional 30 min. after which 350ml of ice-water was added. The mixture was steam distilled, and the dichloromethane layer was separated from the aqueous one, washed with water, dried over anhydrous magnesium sulfate and filtered. The solvent was removed by distillation through a short Vigreaux column, and the residue was transferred to a smaller flask and redistilled. The distillate was further purified <u>via</u> vpc, yielding 8.0g (16%) of pure 2,3-dimethylbutanal: bp 114-116°. Literature value: 110-112°,[36] 112-114°.[37] Vapor phase chromatograms were taken on an Aerograph A90-P3, with a 20% Carbowax DM-CS, Chromosorb W, 20 ft. column, He pressure 21 psi and column temperature 130°. The retention time was 10' 30". Nmr of 30% solution in carbon tetrachloride (Figure 12) consisted of a multiplet centered at δ 1.0, a multiplet centered at δ 1.8, a multiplet centered at δ 2.1, and a doublet centered at δ 9.66 (ratios, 9.0 : 1.0 : 1.0 : 1.0, respectively).

F. Additions of Methyl Grignards to 2,3-Dimethylbutanal

A typical addition of methyl Grignards to 2,3-dimethylbutanal was as follows: In an apparatus, described in Section A, was placed 29ml of ether together with 1ml (3 mmoles) of methylmagnesium bromide (3.0M in ether). A solution of 0.2ml (0.16g, 1.6 mmoles) of 2,3-dimethylbutanal in 0.5ml of ether was injected. The temperature of the solution was maintained at 35° with an oil bath. After stirring for two hours, the reaction mixture was quenched with a 10% solution of ammonium chloride-ammonia solution (pH 9). The ether layer was separated, dried over anhydrous magnesium sulfate and removed by distillation.

The ratio A/B (erythro/threo) of the diastereomeric 3,4-dimethyl-2-pentanols was determined by vpc, as described in Section D-4.

G. Preparation of Threo-3,4-Dimethyl-2-pentanol

In a 50ml two-necked round-bottomed flask equipped with a magnetic stirrer, a septum cap, a condenser closed at the top with a balloon and under nitrogen atmosphere, was placed a mixture of 0.34g (9.0 mmoles) sodium borohydride in 15ml THF. Trans-3,4-dimethyl-2-pentene, 2.94g (0.030 mole), was introduced into the reaction flask, through the septum cap, with a syringe. The mixture was stirred and 1.51ml (1.7g, 0.012 mole) of freshly distilled boron trifluoride-ether solution in 2ml of THF was added drop-wise over a period of one hour. The temperature was maintained at 25°. After the addition was over, the mixture was kept at 25° for an additional hour. The excess diborane was decomposed with water followed by oxidation with 3.2ml of 3N sodium hydroxide and drop-wise addition of 3.2ml of 30% solution of hydrogen peroxide. The resulting mixture was saturated with sodium chloride and the THF layer was separated, dried over anhydrous magnesium sulfate and distilled. The yield of Threo-3,4-dimethyl-2-pentanol was 95% by vpc. The alcohol had a vpc retention time of 30 min. under the conditions: 20% Carbowax DMCS, Chromosorb W, 20 ft x 1/4 inch column, He pressure 20 psi, and column temperature 130°. The erythro alcohol, under identical conditions had a retention time of 27 min.

Nmr spectrum of a solution of the pure threo alcohol in pyridine showed the doublet of the diastereotopic methyl protons, $-CH(OH)-\underline{CH_3}$, centered at δ 1.25. The doublet of the erythro diastereomer, centered at δ 1.20 (Figure 11), was missing.

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