A STUDY OF FACTORS AFFECTING ASYMMETRIC INDUCTION IN ADDITIONS TO 3-PHENYL-2-BUTANONE

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3-Phenyl-2-butanone

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F. J. Kienbeth

Major professor

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ABSTRACT

A STUDY
OF FACTORS AFFECTING ASYMMETRIC INDUCTION
IN ADDITIONS TO
3-PHENYL-2-BUTANONE

By

Stamatios G. Mylonakis

The model for additions to carbonyl directly bonded to asymmetric centers proposed by Karabatsos[1] predicts not only the major diastereomer but also the diastereomeric product ratio as well. These predictions are based on differences of the interactions of the carbonyl group with the large and medium groups on the asymmetric center.

To examine the applicability of the model under a variety of conditions the following effects were investigated: The effect of nucleophile/ketone molar ratio, the effect of concentration and of temperature and the effects of solvent and nature of nucleophile. For this purpose a variety of asymmetric inductions to 3-phenyl-2-butanone were carried out: additions of methylmagnesium bromide, methylmagnesium iodide, methyllithium, dimethylmagnesium and lithium aluminum hydride in ether, and methylmagnesium chloride, methylmagnesium bromide, dimethylmagnesium and lithium aluminum hydride in tetrahydrofuran at concentrations ranging from 1.0 to 0.05 M and temperatures from 66° to -69°. The ratio of the diastereomeric alcohols resulting from the above reactions was determined by v.p.c. or by n.m.r.

Differences in the free energy of the diasteriomeric transition states for these reactions were calculated in accord with the Curtin-Hammett principle[2],

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

From plots of ln(A/B) vs. 1/T $\Delta\Delta H^{\ddagger}_{AB}$ and $\Delta\Delta S^{\ddagger}_{AB}$ were also calculated for the above systems.

The following observations were made: 1) $\Delta\Delta G^{\ddagger}_{AB}$ values are temperature independent for most of the reactions studied; thus $\Delta\Delta H^{\ddagger}_{AB}$ controls the value of $\Delta\Delta G^{\ddagger}_{AB}$. 2) The product stereospecificity depends on concentration, usually increasing with dilution. 3) The stereospecificity depends also on nucleophile/ketone ratio. 4) Stereospecificity is the same in ether and tetrahydrofuran solutions. 5) The stereospecificity of alkylmagnesium halides increases as the halogen of Grignard reagents is varied from iodine to chlorine. 6) Lithium aluminum hydride is less stereospecific than Grignard reagents, dimethylmagnesium and methyllithium.

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[1]G. J. Karabatsos, J. Amer. Chem. Soc., 89, 1367 (1967).

[2]D. Y. Curtin, Record Chem. Progr., 15, 111 (1954). See also E. L. Eliel, "Stereochemistry of carbone compounds", McGraw-Hill Book Co., Inc., New York, 1962, pp. 151-156.

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A THESIS

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To Pam

When you set out for Ithaka
ask that your way be long,
full of adventure, full of instruction
. . . . . .
so that when you reach the island you are old,
rich with all you have gained on the way,
not expecting Ithaka to give you wealth.
Ithaka gave you the splended journey.
Without her you would not have set out.
She hasn't anything else to give you.

And if you find her poor, Ithaka has not deceived you.
So wise have you become, of such experience,
that already you will have understood what these Ithakas mean.

From "Ithaka" by C. P. Cavafy

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The author wishes to express his gratitude for the helpful guidance, advice, and encouragement given him by his advisor, Professor G. J. Karabatsos.

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INTRODUCTION

When an asymmetric center is produced in a reaction for which $\Delta G^\circ = 0$ and $\Delta\Delta G^\ddagger = 0$, where ΔG° and $\Delta G^\ddagger$ represent the free energies of ground and transition states, respectively, the two transition states leading to the two enantiomeric products are said to be enantiomeric.[1] The two reactions proceed at exactly the same rate and the two enantiomerically related products are produced in exactly equal amounts. Grignard reagents, for example, have an equal probability of approaching from either side of the propionaldehyde molecule, thus producing equal amounts of (+)- and (-)- butanol-2.[2]

In reactions where $\Delta\Delta G^\ddagger \neq 0$, whether $\Delta G^\circ = 0$ or $\Delta G^\circ \neq 0$, two or more stereoisomers are produced, and the reactions are called stereoselective.[1] The degree of stereoselectivity depends on the magnitude of $\Delta\Delta G^\ddagger$; the greater $\Delta\Delta G^\ddagger$, the greater the stereoselectivity.

A stereoselective reaction in which new dissymmetric groupings (e.g. asymmetric carbons) are produced in unequal amounts is termed asymmetric synthesis or asymmetric induction. Four types of asymmetric induction have been recognized the energy diagrams for which are given in Figure I. Examples for each type have been presented by Mislow.[1]

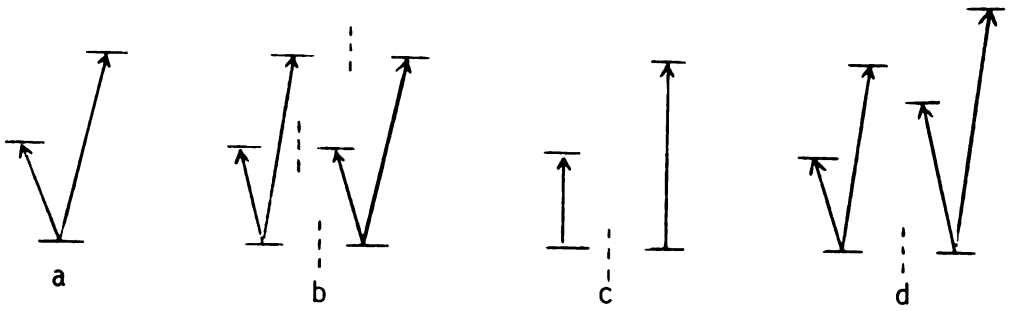
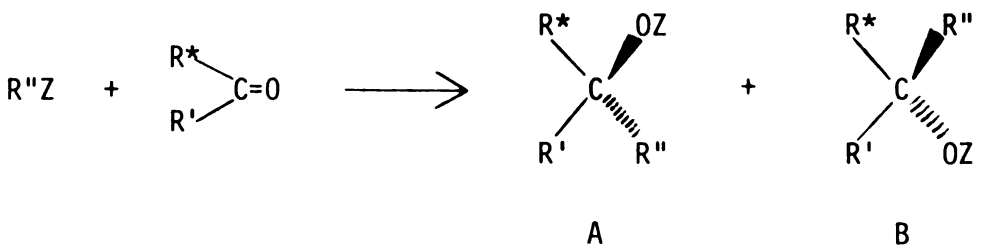
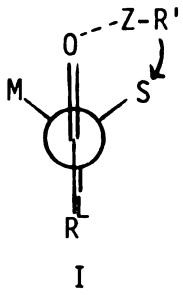


FIGURE 1 Types of energy relationships in asymmetric induction. Mirror-image relationships are indicated by vertical dashed lines.

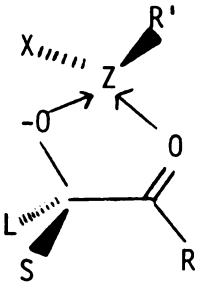
Asymmetric induction is observed in a variety of chemical and biological reactions.[3] The additions of achiral reagents to aldehydes or ketones with a chiral center adjacent to the carbonyl group have been the most widely studied. The starting material in this case is dissymmetric existing in two enantiomers ($\Delta G° = 0$). Each enantiomer is capable of leading to two diastereomerically related transition states. The energy diagram for the above type of asymmetric induction is given in Figure I-b. This type of asymmetric induction is termed "1,2-asymmetric induction" and is shown by the following equation.



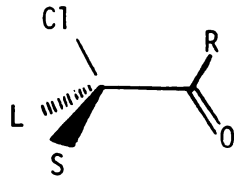
Cram and his co-workers[4,5] have used the following empirical model (I) for the prediction of the major diastereomer resulting from additions to carbonyls:



I



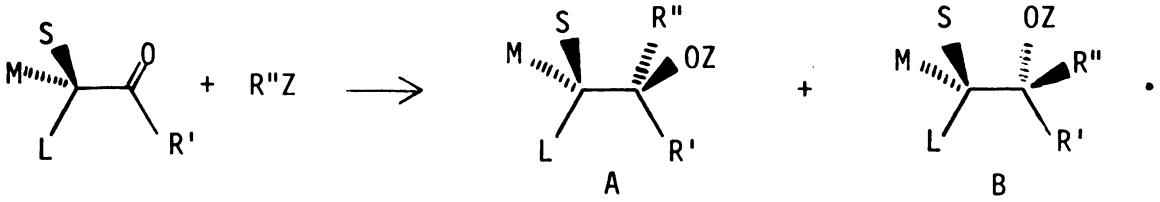
I'



I"

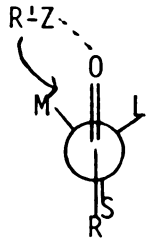
I-Open-chain model; I'-Rigid model; I"-Dipolar model. L, M, and S stand for largest, medium sized, and smallest substituent, respectively.

In Cram's open chain model (I) the carbonyl compound is fixed in the ground state in one conformation, in which the carbonyl group is flanked by the two least hindered bulky groups (S and M) and that diastereomer will predominate which would be formed by approach of the entering group from the less hindered side of the double bond. The relative amounts of A and B, that is, in the reaction below, will depend on the relative interactions of R"Z with S and M



A second model, rigid model (I'), has been used to explain asymmetric induction in carbonyl compounds with one of the groups of the asymmetric carbon capable of complexing with organometallic reagents.[6] A third model, dipolar model (I"), has been used to account for reductions of α-chlorocarbonyl compounds.[7]

Although Cram's model has been successful, in general, in predicting the preponderant diastereomeric product, it is important to note that the same success would have resulted if model (II) had been chosen and the reagent assummed to approach from the side of M rather than the side of L.

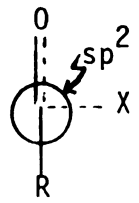


II

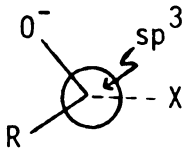
Several aspects associated with the success and failure of the above Cram's model (I) have been discussed by Karabatsos[8] and have led him to propose a new model.[8]

Grignard[9] and hydride[10] reductions of carbonyl groups have Ea and $\Delta S^{\ddagger}$ values between 8 and 15 kcal/mole and -20 to -40 eu, respectively. Rotational barriers about the relevant sp^2-sp^3 carbon-carbon bonds should be much lower. According to the Curtin-Hammett[11] principle then, the diastereomeric product ratio depends solely on the free-energy difference, $\Delta G_A^{\ddagger}$-$\Delta G_B^{\ddagger}$, between the two diastereomeric transition states. Karabatsos' model, therefore, is based on the fact that "successful prediction of product stereospecificity requires knowledge of the structures of the pertinent diastereomeric transition states". The energies, on the other hand, of the diastereomeric transition states will depend mainly on three factors: the substrate, the reagent and the solvent.

With respect to reaction coordinate, two extreme situations are possible: reactant-like transition states (III) and product-like transition states (IV).



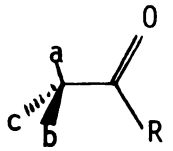
III



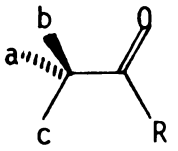
IV

The rapidity, exothermicity and product stereospecificity of the additions to carbonyl compounds led Karabatsos to the first assumption on which the proposed model was based: "little bond breaking and making has occurred at the transition state. 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 bonds". That is reactant-like transition state (III).

According to the first assumption, one should look for the most stable conformation in the ground state. Evidence from n.m.r. and microwave spectroscopy indicate that the eclipsed carbonyl ground state (V) is generally more stable then the alternate staggered carbonyl conformation (VI).[12]

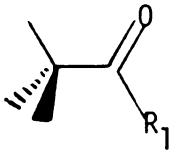


V

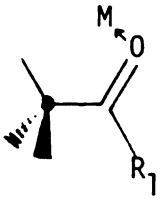


VI

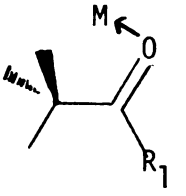
Since the carbonyl group is expected to be complexed with the metal rather than free the question arises whether conformation VII will still be the most stable:



VII

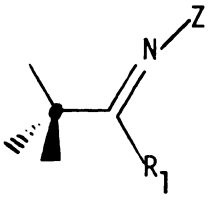


VIII



IX

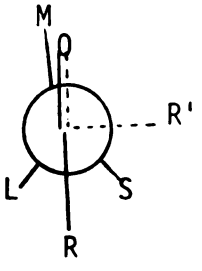
In somewhat analogous systems, (Z = alkyl, OR, NR_2), the stable conformation is X[13] when R_1 is methyl or hydrogen. When R_1 becomes isopropyl or t-butyl



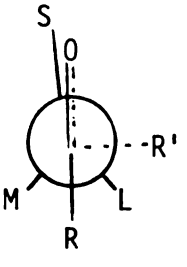
X

then conformations of the types of VIII and IX become more important.[13]

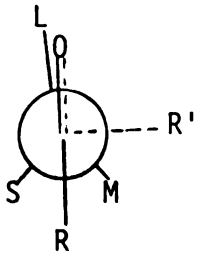
On the basis of the first assumption, the relative energies of the following transition states XI - XI" and XII - XII", leading respectively to the two diastereomers A and B, have to be considered:



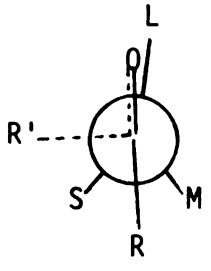
XI



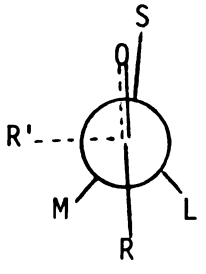
XI'



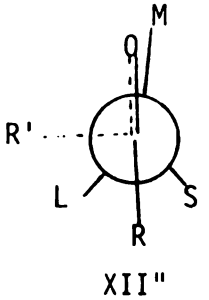
XI"



XII



XII'



XII"

Of these, transition state XI is more important than XI' because R ↔ S and R' ↔ S should be favored over R ↔ M and R' ↔ L, respectively. The M ↔ O interaction in XI is also favored over S ↔ O in XI'. For example, when S is hydrogen and M is methyl, the M ↔ O is favored by 800 cal/mole.[12] XI is also favored over XI" because of the interactions involving R' and the fact that M ↔ O is favored over L ↔ O by 600 cal/mole[12] when M is methyl and L is phenyl. From similar arguments XII should be the most stable of the three transition states XII, XII' and XII" leading to the diastereomer B. Based on the above, the second assumption was formulated by Karabatsos[8] as follows: "The diastereomeric transition states that control product stereospecificity have the smallest group, S, closest to the incoming bulky group R' (XI and XII).

The importance of the relative stabilities of the transition states XI and XII is recognized by the fact that the ratio of the two diastereomers, A/B, is given by the equation below, according to the Curtin-Hammett principle:[11]

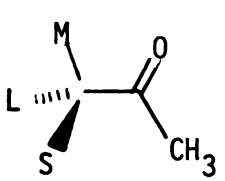
$$\Delta\Delta G^{\ddagger} = - RT\ln(A/B)$$

Evaluation of the relative stabilities of XI and XII must be primarily based upon the following interactions: R' ↔ M, R ↔ L, and M ↔ O in XI and correspondingly R' ↔ L, R ↔ M, and L ↔ O in XII. Of these, the first favors XI and the second XII. To the first, therefore, approximation, the two are considered to cancel each other. The important interactions that determine the relative energies of the two diastereomeric transition states are then the M ↔O <u>vs</u>. L ↔ O which are evaluable.[12] This is especially true when R and R' become the same.

It was pointed out[8] that discrepancies between predicted and experimental ratios ought to be expected in cases where extensive bond breaking and making has occurred in the transition state, since the experimental ratio, A/B, in such cases would be influenced by the relative stabilities of A and B. It was also pointed out that the model will apply in the cases where $\Delta\Delta H^{\ddagger}_{AB}$ controls $\Delta\Delta G^{\ddagger}_{AB}$. Contributions from $\Delta\Delta S^{\ddagger}_{AB}$ to $\Delta\Delta G^{\ddagger}_{AB}$ will limit the usefulness of the model, as it does not make allowance for such contributions.

Values for $\Delta\Delta G^{\ddagger}_{AB}$ calculated from Karabatsos' semiempirical model were found in fairly close agreement with the experimental values available in the literature.[8] A more extensive investigation of the validity of the model in a variety of substrates, reagents, solvents and at different temperatures also complemented the model.[13]

However, it was recently found that the concentration of nucleophile and ketone have a profound effect on the diastereomeric ratio A/B.[15] For comparison, then, of the $\Delta\Delta G^{\ddagger}_{AB}$ values asymmetric inductions have to be carried out at concentrations accurately measured. A thorough investigation to examine all factors determining the applicability and limitations of Karabatsos' model and of the $\Delta\Delta G^{\ddagger}_{AB}$ values calculated from it, is, therefore, still necessary. Valuable information, on the other hand, can be obtained by studying some of the above mentioned factors in systems represented by

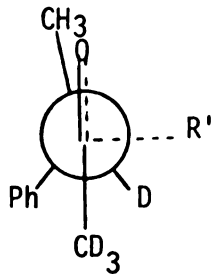


where S and M is hydrogen and methyl, respectively, and L phenyl, methoxy, or t-butyl group. In addition, the diastereomeric product ratio, A/B, in these systems can be analyzed from their n.m.r. spectra by integration of the magnetically nonequivalent diastereotopic groups.

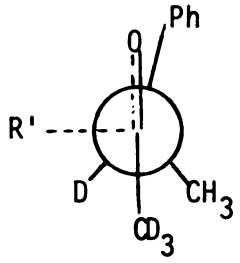
In this work the addition reactions to 3-phenyl-2-butanone were studied and the results can be compared with similar studies on 3-methoxy-2-butanone[15] and 3,4,4-trimethylpentanone[16] currently carried out in this laboratory. The effect of varying the nucleophile was studied with reactions involving the additions to the ketone of methylmagnesium halides, methyllithium, dimethylmagnesium and reductions with lithium aluminum hydride. The above reactions were carried out at four different temperatures ranging from 66° to -69° in order to calculate activation parameters and estimate the $\Delta\Delta S^{\ddagger}_{AB}$ contribution to the value of $\Delta\Delta G^{\ddagger}_{AB}$. The effect of concentration of nucleophile and ketone and the ratio of the nucleophile to ketone were also studied for a number of the above reactions with concentrations ranging from 1.0 M to 0.005 M and ratios from 1.3/1 to 13/1. Finally, a number of the above reactions were carried out in both ether and tetrahydrofuran in order to gain some information of the solvent effect on the asymmetric induction.

RESULTS AND DISCUSSIONS

The results of the additions of methylmagnesium halides, methyllithium, dimethylmagnesium, and lithium aluminum hydride to 3-phenyl-2-butanone[17] are summarized in Tables I-IV together with results for similar reactions from the literature. In all these systems the difference in free energy of the two diastereomeric transition states, XIII and XIV,



XIII



XIV

has been calculated in accord with the Curtin-Hammett principle:[11]

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

Similar studies on 3-methoxy-2-butanone[15,17] and 3,4,4-trimethylpentanone[16,17] are included in Tables V-VIII and IX for comparison.

A. Errors Involved in the Calculation of $\Delta\Delta G^{\ddagger}_{AB}$ Values

The errors involved in the calculation of $\Delta\Delta G^{\ddagger}_{AB}$ values are introduced mainly from the error in the calculation of the percentage of each diastereomer. From reproducibility alone this error was estimated to be no greater than ±1% for ratios of less than 90/10. That is, a diastereomeric

TABLE I. The Effect of Nucleophile/Ketone Ratio in the Asymmetric Induction of 3-Phenyl-2-butanone-1,1,3-$\underline{d}_4$.[a]

Nucleophile	Solvent	N/K[d]	A/B[b]	$\Delta\Delta G^{\ddagger}_{AB}$[c]
CH_3MgBr	Ether	1.3 : 1	92 : 8	-1.5 ± 0.1
		2.6 : 1	89 : 11	-1.3 ± 0.1
		5.2 : 1	88 : 12	-1.2 ± 0.1
		13.0 : 1	86 : 14	-1.1 ± 0.1
CH_3Li	Ether	1.3 : 1	93 : 7	-1.6 ± 0.2
		2.6 : 1	94 : 6	-1.7 ± 0.2
		3.9 : 1	94 : 6	-1.7 ± 0.2
		6.5 : 1	93 : 7	-1.6 ± 0.2

[a]All reactions on this table were carried out at 35° and 0.05 M concentration of the nucleophile.

[b]The ratio of diastereomeric 2-methyl-3-phenyl-2-butanols-1,1,1,3-$\underline{d}_4$ was determined by integration of the areas of the major (τ 8.70) and minor (τ 8.77) diastereotopic absorptions in 10% solutions in pyridine.

[c]Expressed in kcal/mole.

[d]Ratio of nucleophile/ketone.

TABLE II. The Effect of Concentration on the Asymmetric Induction of 3-Phenyl-2-butanone-1,1,1,3-$\underline{d}_4$.[a]

Nucleophile	Solvent	Concentration[b]	A/B[c]	$\Delta\Delta G^{\ddagger}_{AB}$[d]
CH_3MgCl	THF	1.0	90 : 10	-1.5 ± 0.1
		0.5	93 : 7	-1.7 ± 0.2
		0.05	98 : 2	-1.9 ± 0.4
CH_3MgBr	Ether	1.0	87 : 13	-1.1 ± 0.1
		0.5	84 : 16	-1.0 ± 0.1
		0.14	92 : 8	-1.5 ± 0.1
		0.05	92 : 8	-1.5 ± 0.1
CH_3MgBr	THF	1.0	91 : 9	-1.5 ± 0.1
		0.5	89 : 11	-1.4 ± 0.1
		0.05	90 : 10	-1.5 ± 0.1
CH_3MgI	Ether	1.0	78 : 22	-0.8 ± 0.1
		0.5	83 : 17	-1.0 ± 0.1
		0.05	83 : 17	-1.0 ± 0.1
		0.005	86 : 14	-1.1 ± 0.1
CH_3Li	Ether	1.0	91 : 8	-1.5 ± 0.1
		0.5	83 : 17	-1.0 ± 0.1
		0.05	93 : 7	-1.6 ± 0.2
$LiAlH_4$	Ether	1.0	68 : 32[e]	-0.5 ± 0.1
		0.5	73 : 37[e]	-0.6 ± 0.1
		0.05	75 : 25[e]	-0.7 ± 0.1

TABLE II. (Continued)

Nucleophile	Solvent	Concentration[b]	A/B[c]	$\Delta\Delta G^{\ddagger}_{AB}$[d]
$LiAlH_4$	THF	1.0	69 : 31[e]	-0.5 ± 0.1
		0.5	72 : 28[e]	-0.6 ± 0.1
		0.05	74 : 26[e]	-0.6 ± 0.1

[a]Reactions carried out at 34° and 1.3:1 nucleophile/ketone ratio.

[b]Nucleophile concentration expressed in mole/l.

[c]The ratio of diastereomeric 2-methyl-3-phenyl-2-butanols-1,1,1,3-d_4 was determined by integration of the areas of the major (τ 8.70) and minor (τ 8.77) diastereotopic absorptions in 10% solution in pyridine.

[d]Expressed in kcal/mole.

[e]The ratio of diastereomeric 3-phenyl-2-butanols was determined by v.p.c.

TABLE III. The Effect of Temperature on the Asymmetric Induction of 3-Phenyl-2-butanone-1,1,1,3-$\underline{d}_4$.[a]

Nucleophile	Solvent	Concentration[b]	Temperature	A/B[c]	$\Delta\Delta G^{\ddagger}_{AB}$[d]	Ref.
CH_3MgCl	THF	0.05	66°	93 : 7	-1.7 ± 0.2	
			2°	96 : 4	-1.7 ± 0.3	
			-22°	98 : 2	-1.9 ± 0.4	
			-69°	98 : 2	-1.6 ± 0.4	
			-66°	83 : 17	-1.0 ± 0.1	18
			3°	87 : 13	-1.0 ± 0.1	18
CH_3MgBr	Ether	0.5	34°	84 : 16	-1.0 ± 0.1	
			2°	87 : 13	-1.0 ± 0.1	
			-10°	91 : 9	-1.2 ± 0.1	
			-22°	90 : 10	-1.1 ± 0.1	
		0.14	34°	92 : 8	-1.5 ± 0.1	
			2°	92 : 8	-1.3 ± 0.1	
			-21°	93 : 6	-1.3 ± 0.2	
			-69°	97 : 3	-1.5 ± 0.4	
		0.05	34°	92 : 8	-1.5 ± 0.1	
			2°	94 : 6	-1.5 ± 0.2	
			-22°	95 : 5	-1.5 ± 0.2	
			-69°	97 : 3	-1.5 ± 0.4	
			35°	79 : 21	-0.8 ± 0.1	18
			35°	81 : 19	-0.9 ± 0.1	18
			3°	83 : 17	-0.9 ± 0.1	18
CH_3MgBr	THF	0.05	66°	90 : 10	-1.5 ± 0.1	
			2°	92 : 8	-1.6 ± 0.1	
			-22°	96 : 4	-1.6 ± 0.3	
			-69°	97 : 3	-1.4 ± 0.4	

TABLE III. (Continued)

Nucleophile	Solvent	Concentration[b]	Temperature	A/B[c]	$\Delta\Delta G^{\ddagger}_{AB}$[d]	Ref.
CH_3MgI	Ether	0.05	34°	83 : 17	-1.0 ± 0.1	
			2°	81 : 19	-0.8 ± 0.1	
			-21°	91 : 9	-1.1 ± 0.1	
			-69°	97 : 3	-1.4 ± 0.1	
			25°	75 : 25	-0.6 ± 0.1	18
			-55°	82 : 18	-0.6 ± 0.1	18
$(CH_3)_2Mg$	Ether	0.005	34°	87 : 13	-1.2 ± 0.1	
			2°	90 : 10	-1.2 ± 0.1	
			-25°	93 : 7	-1.3 ± 0.1	
$(CH_3)_2Mg$	THF	0.005	34°	88 : 12	-1.2 ± 0.1	
			2°	89 : 11	-1.1 ± 0.1	
			-21°	94 : 6	-1.1 ± 0.1	
CH_3Li	Ether	0.05	34°	93 : 7	-1.6 ± 0.2	
			2°	94 : 6	-1.5 ± 0.2	
			-22°	92 : 8	-1.2 ± 0.1	
			-69°	92 : 8	-1.0 ± 0.1	
			35°	83 : 17	-1.0 ± 0.1	18
			-56°	92 : 8	-1.0 ± 0.1	18
$LiAlH_4$	Ether	0.05	34°	75 : 25[e]	-0.7 ± 0.1	
			2°	80 : 20[e]	-0.8 ± 0.1	
			-22°	83 : 17[e]	-0.8 ± 0.1	
			-69°	89 : 11[e]	-0.8 ± 0.1	

TABLE III. (Continued)

Nucleophile	Solvent	Concentration	Temperature	A/B	$\Delta\Delta G^{\ddagger}_{AB}$	Ref.
$LiAlH_4$	Ether	0.05	35°	72.5 : 27.5	-0.6	21
			35°	2.8 : 1	-0.6	19
			25°	2.5 : 1	-0.6	5
			0°	77.5 : 22.5	-0.7	21
			-70°	85 : 15	-0.7	21
$LiAlH_4$	THF	0.05	34°	74 : 26[e]	-0.6 ± 0.1	
			2°	79 : 21[e]	-0.7 ± 0.1	
			-22°	84 : 16[e]	-0.8 ± 0.1	
			-69°	88 : 12[e]	-0.8 ± 0.1	

[a]Reactions carried out at 1.3:1 nucleophile/ketone ratio.

[b]Nucleophile concentration, expressed in mole/l.

[c]The ratio of diastereomeric 2-methyl-3-phenyl-2-butanols-1,1,1,3-$\underline{d}_4$ was determined by integration of the major (τ 8.70) and minor (τ 8.77) diastereotopic absorptions in 10% solution in pyridine.

[d]Expressed in kcal/mole.

[e]The ratio of diastereomeric 3-phenyl-2-butanols was determined by v.p.c.

TABLE IV. Activation Parameters of the Reactions in Table III.

Nucleophile	Solvent	Concentration[a]	$\Delta\Delta G^{\ddagger}_{AB}$[b]	$\Delta\Delta H^{\ddagger}_{AB}$[c]	$\Delta\Delta S^{\ddagger}_{AB}$[d]
CH_3MgCl	THF	0.05	-1.7 ± 0.2[f]	-1540 ± 40	+1.3 ± 0.2
CH_3MgBr	Ether	0.5	-1.0 ± 0.1[e]	-1290 ± 70	-0.7 ± 0.3
		0.14	-1.5 ± 0.2[e]	-1520 ± 50	-0.5 ± 0.4
		0.05	-1.5 ± 0.2[e]	-1200 ± 50	+1.2 ± 0.5
CH_3MgBr	THF	0.05	-1.5 ± 0.1[f]	-1530 ± 40	-0.4 ± 0.2
CH_3MgI	Ether	0.05	-1.0 ± 0.1[e]	-2640 ± 50	-5.8 ± 0.5
$(CH_3)_2Mg$	Ether	0.005	-1.2 ± 0.1[e]	-1660 ± 50	-1.6 ± 0.5
$(CH_3)_2Mg$	THF	0.005	-1.2 ± 0.1[f]	-1660 ± 50	-0.9 ± 0.5
CH_3Li	Ether	0.05	-1.6 ± 0.3[e]	- 330 ± 50	+4.2 ± 0.5
$LiAlH_4$	Ether	0.05	-0.7 ± 0.1[e]	-1200 ± 50	-1.8 ± 0.5
$LiAlH_4$	THF	0.05	-0.6 ± 0.1[f]	-1500 ± 50	-2.3 ± 0.5

[a]Nucleophile concentration, expressed in mole/l.

[b]Expressed in kcal/mole.

[c]Expressed in cal/mole.

[d]Expressed in e.u. cal/mole degree).

[e]At 34°; [f]at 66°.

TABLE V. The Effect of Nucleophile/Ketone Ratio in the Asymmetric Induction of 3-Methoxy-2-butanone-1,1,1,3-$\underline{d}_4$ and 3,4,4-Trimethylpentanone-1,1,1-$\underline{d}_3$.[a]

Substrate	Nuceeophile	Solvent	N/K[b]	A/B	$\Delta\Delta G^{\ddagger}_{AB}$[c]	Ref.
CH_3O O CH_3CDCCD_3	CH_3Li	Ether	1.3 : 1	70 : 30	-520	15
			5.2 : 1	71 : 29	-530	15
CH_3 CH_3 O CH_3C——CH—CCD_3 CH_3			1.3 : 1	4.1	-860	16
			2.6 : 1	3.9	-840	16
			5.2 : 1	4.7	-940	16

[a]All reactions in this Table were carried out at 35° and 0.05 M concentration of the nucleophile.

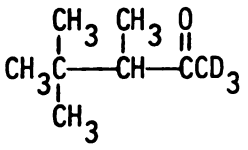
[b]Ratio of nucleophile/ketone.

[c]Expressed in cal/mole.

TABLE VI. The Effect of Concentration on the Asymmetric Induction of 3-Methoxy-2-butanone-1,1,1,3-$\underline{d}_4$ and 3,4,4-Trimethylpentanone-1,1,1-$\underline{d}_3$.[a]

Substrate	Nucleophile	Solvent	Concentration	A/B	$\Delta\Delta G^{\ddagger}_{AB}$	Ref.
$CH_3O\ O$ CH_3CDCCD_3	CH_3MgCl	THF	1.0	98 : 2	-2.4	15
			0.5	98 : 2	-2.4	15
			0.05	98 : 2	-2.4	15
	CH_3MgBr	Ether	1.0	88 : 12	-1.2	15
			0.4	89 : 11	-1.3	15
			0.1	94 : 6	-1.7	15
	CH_3MgBr	THF	1.0	98 : 2	-2.3	15
			0.5	98 : 2	-2.4	15
			0.05	98 : 1	-2.7	15
	CH_3MgI	Ether	0.5	91 : 9	-1.4	15
			0.05	91 : 9	-1.4	15
			0.005	93 : 7	-1.6	15
	CH_3Li	Ether	1.0	77 : 23	-0.7	15
			0.5	76 : 24	-0.7	15
			0.05	70 : 30	-0.5	15
$CH_3\ CH_3\ O$ $CH_3C—CH—CCD_3$ CH_3	CH_3MgCl	THF	1.0	3.0	-0.7	16
			0.5	2.8	-0.6	16
			0.05	3.4	-0.8	16

TABLE VI. (Continued)

Substrate	Nucleophile	Solvent	Concentration[b]	A/B	$\Delta\Delta G^{\ddagger}_{AB}$[c]	Ref.
	CH_3MgBr	Ether	0.6	3.8	-0.8	16
			0.1	3.6	-0.8	16
			0.05	2.9	-0.7	16
	CH_3MgBr	THF	1.0			
			0.05	5.6	-1.1	16
				3.8	-0.8	16
	CH_3MgI	Ether	1.0	3.7	-0.8	16
			0.5	3.6	-0.8	16
			0.005	3.2	-0.7	16
	CH_3Li	Ether	1.0	3.2	-0.7	16
			0.5	3.2	-0.7	16
			0.05	4.1	-0.9	16

[a]All reactions were carried out at 34° and 1.3:1 nucleophile/ketone ratio.

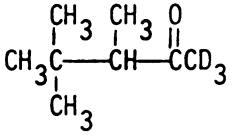
[b]Nucleophile concentration, expressed in mole/l.

[c]Expressed in kcal/mole.

TABLE VII. The Effect of Temperature on the Asymmetric Induction of 3-Methoxy-2-butanone-1,1,1,3-$\underline{d}_4$ and 3,4,4-Trimethylpentanone-1,1,1-$\underline{d}_3$.[a]

Substrate	Nucleophile	Solvent	Concentration[b]	Temperature	A/B	$\Delta\Delta G^{+}_{AB}$[c]	Ref.
$CH_3O\ O$ CH_3CDCCD_3	CH_3MgCl	THF	0.05	66°	97 : 3	-2.4	15
				2°	98 : 2	-2.2	15
				-22°	98 : 2	-2.0	15
				-69°	99 : 1	-1.7	15
	CH_3MgBr	Ether	0.5	34°	89 : 11	-1.3	15
				2°	96 : 4	-1.7	15
				-10°	96 : 4	-1.7	15
				-22°	97 : 3	-1.7	15
			0.1	34°	94 : 6	-1.7	15
				2°	95 : 5	-1.6	15
				-22°	96 : 4	-1.6	15
				-46°	96 : 4	-1.5	15
	CH_3MgBr	THF	0.05	66°	98 : 2	-2.7	15
				2°	99 : 1	-2.4	15
				-22°	99 : 1	-2.2	15
				-69°	99 : 1	-2.0	15
	CH_3MgI	Ether	0.05	34°	91 : 9	-1.4	15
				2°	91 : 9	-1.2	15
				-22°	92 : 8	-1.3	15
				-69°	94 : 6	-1.1	15

TABLE VII. (Continued)

Substrate	Nucleophile	Solvent	Concentration[b]	Temperature	A/B	$\Delta\Delta G^{\ddagger}_{AB}$[c]	Ref.
	CH_3Li	*Ether*	0.05	34°	70 : 30	-0.5	15
				2°	70 : 30	-0.4	15
				-22°	69 : 31	-0.4	15
				-69°	69 : 31	-0.3	15
	CH_3MgCl	THF	0.05	66°	2.8	-0.7	16
				35°	3.4	-0.8	16
				15°	2.0	-0.4	16
				2°	2.5	-0.5	16
				-15°	0.8	0.1	16
				-24	0.5	0.3	16
	CH_3MgBr	Ether	0.6	34°	3.8	-0.8	16
			0.5	13°	3.2	-0.7	16
				-22°	3.2	-0.6	16
				-46°	4.5	-0.7	16
			0.1	34°	3.6	-0.8	16
				2°	3.6	-0.7	16
				-46°	4.0	-0.6	16
			0.05	34°	2.9	-0.7	16
				15°	3.2	-0.7	16
				- 2°	3.6	-0.7	16
	CH_3MgBr	THF	0.05	66°	4.1	-0.9	16
				35°	3.7	-0.8	16

[a] All reactions were carried out at 1.3:1 nucleophile/ketone ratio.

[b] Nucleophile concentration, expressed in mole/l.

[c] Expressed in kcal/mole.

TABLE VIII. Solvent Dependence of the Relative Rotamer Populations[a] of Substituted Phenylacetaldehydes[25]

Solvent	$PhCH_2CHO$ %XVI	p-CH_3PhCH_2CHO %XVI	p-CH_3OPhCH_2CHO %XVI	p-$ClPhCH_2CHO$ %XVI		$2,6\text{-}Cl_2PhCH_2CHO$ %XVI	
				A[b]	B[c]	A[d]	B[c]
cyclohexane	32	28		34	39	38	68
trans-decalin	32	28		34	40	37	67
$(CH_3CH_2)_2O$	33	28	31	36	41	40	69
THF	36		33	39	45	42	72
CH_2Br_2	37	34	37	39	44	39	69
$(CH_3)_2CO$						46	77
$(CH_3)_2NCHO$	43	38	41	45	51	50	80
C_6H_5CN	41	38	39	44	50	44	74

[a]All values calculated for 5% solutions at 38°. [b]J_{obsd} = 2.20 Hz. [c]J_{obsd} = 2.40 Hz. [d]J_{obsd} = 1.35 Hz.

TABLE IX. Activation Parameters of the Reactions in Table VII

Substrate	Nucleophile	Solvent	Concentration[a]	$\Delta\Delta G^{\ddagger}_{AB}$[b]	$\Delta\Delta H^{\ddagger}_{AB}$[c]	$\Delta\Delta S^{\ddagger}_{AB}$[d]	Ref.
$CH_3\underset{\displaystyle CH_3}{\overset{\displaystyle O}{|}}C\overset{\displaystyle O}{\overset{\|}{C}}CD_3$	CH_3MgCl	THF	0.05	-2.4 ± 0.1[f]	- 690	- 8.9	15
	CH_3MgBr	Ether	0.5	-1.3 ± 0.1[e]	-1090	- 7.6	15
			0.1	-1.7 ± 0.1[e]	-1090	- 9.0	15
	CH_3MgBr	THF	0.05	-2.7 ± 0.1[f]	- 910	-10.3	15
	CH_3MgI	Ether	0.05	-1.4 ± 0.1[e]	- 560	- 6.4	15
	CH_3Li	Ether	0.05	-0.5 ± 0.1[e]	+ 820	+ 1.0	15
$CH_3\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{|}}C-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{|}}CH-\overset{\displaystyle O}{\overset{\|}{C}}CD_3$	CH_3MgBr	Ether	0.5	-0.7 ± 0.1[g]	-740 ± 200	-0.4	16
			0.1	-0.8 ± 0.1[e]	-500 ± 200	-0.7	16
			0.05	-0.7 ± 0.1[e]	-790 ± 450	-0.4	16

[a]Nucleophile concentration expressed in mole/l.

[b]Expressed in kcal/mole.

[c]Expressed in cal/mole.

[d]Expressed in e.u. (cal/mole degree)

[e]At 34°. [f]At 66°. [g]At 13°.

product ratio of 80/20 cannot be considered more accurate than 79/21 or 81/19. When the stereoselectivity was higher than 90% the error was estimated to be of the order of ±3%. This was due to the decrease in the signal to noise ratio in the n.m.r. for the minor diastereomeric product. The temperature variation of ±2° contributes approximately one percent to the error in $\Delta\Delta G^{\ddagger}_{AB}$. Considering that the errors in the diastereomeric product ratios contribute errors of about twenty-five percent of the $\Delta\Delta G^{\ddagger}_{AB}$ values, the error due to the temperature variation can be regarded as insignificant.

Previous investigators have not considered the dependence of product stereospecificity upon concentration, or nucleophile to ketone ratio, and only recently[18,19,20] the temperature factor has been taken into account. The accuracy, therefore, of the diastereomeric product ratios reported previously is questionable.

Whereas the absolute configurations of the products obtained from additions of lithium aluminum hydride to 3-phenyl-2-butanone have been determined[19] and found to be as predicted by the Karabatsos' model, those of the products from methyl Grignard additions to the above ketone have not. On the basis of the similarity between these and systems of proven stereochemistry[5,19,21,22] the major diastereomer of these additions is presumed to be the one predicted by the Karabatsos' model.

B. Calculations of Activation Parameters.

By the Curtin-Hammett principle[11]

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

and the thermodynamic relationship

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

we obtain

$$\ln(A/B) = -\frac{\Delta\Delta H^{\ddagger}_{AB}}{RT} + \frac{\Delta\Delta S^{\ddagger}_{AB}}{R} \qquad (1)$$

where (A/B) is the diastereomeric product ratio, T is the absolute temperature, R is the ideal gas constant and $\Delta\Delta G^{\ddagger}_{AB}$, $\Delta\Delta H^{\ddagger}_{AB}$ and $\Delta\Delta S^{\ddagger}_{AB}$ are the differences, respectively, of the free energy, enthalpy and entropy of activation of the two diastereomeric transition states. Measurements of (A/B) at two or more temperatures can be used to evaluate $\Delta\Delta H^{\ddagger}_{AB}$ and $\Delta\Delta S^{\ddagger}_{AB}$ provided the activation parameters are independent of temperature. In this work (A/B) was measured for at least four temperatures. $\Delta\Delta H^{\ddagger}_{AB}$ was calculated from the slope of plots of ln(A/B) *vs.* 1/T and $\Delta\Delta S^{\ddagger}_{AB}$ from the relationship (1) above.

C. Errors Involved in Calculations of $\Delta\Delta H^{\ddagger}_{AB}$ and $\Delta\Delta S^{\ddagger}_{AB}$.

The error in $\Delta\Delta H^{\ddagger}_{AB}$ can be obtained by reference to equation 1. $\Delta\Delta H^{\ddagger}_{AB}$ is computed in principle[14] from two values of product ratio, (A/B) and (A/B)', measured at two temperatures, T and T', from which

$$\Delta\Delta H^{\ddagger}_{AB} = R\frac{T'T}{T'-T}\ln\frac{(A/B)'}{(A/B)} .$$

Errors in the temperature term are negligible relative to the error contributed by ln(A/B)'/(A/B). The maximum possible error (δ) in $\Delta\Delta H^{\ddagger}_{AB}$ is then given[14] by:

$$\delta = R\frac{T'T}{T'-T}\ln\frac{(1+\alpha)}{(1-\alpha)}$$

where α is the maximum possible fractional error in A/B; or, for $\alpha << 1$, by:

$$\delta = 2R\frac{T'T}{T'-T}\alpha .$$

Reproducibility considerations suggest a value of less then 3 percent for α.

From equation (1) above the maximum possible error (σ) in $\Delta\Delta S^{\ddagger}_{AB}$ is given[14] by:

$$\sigma = \delta(1/T) + R\ln(1+\alpha)$$

or, for $\alpha << 1$, by:

$$\sigma = \delta[\frac{1}{T} + \frac{T'-T}{2T'T}] .$$

D. Effect of Concentration

Substrate concentration is not expected to affect the relative stabilities of the two diastereomeric transition states XIII and XIV. Reagent concentration on the other hand might do so, especially if the overall structure of the reagent, i.e., state of aggregation and extent of solvation, is concentration dependent.

The composition of Grignard reagents has been pictured as an equilibrium involving RMgX, R_2Mg, and MgX_2 species.[23] It has been found that the equilibrium constant for this equilibrium changes depending on

$$2RMgX \underset{}{\overset{K}{\rightleftharpoons}} R_2Mg + MgX_2 \qquad (2)$$

the nature of the organic group, the halide, the solvent, the temperature and the concentration of the solution.[24] With respect to concentration it has been found that with increasing concentrations Schlenk's equilibrium (2) shifts toward higher concentrations of R_2Mg. This is primarily due to the insolubility of MgX_2.

From the results presented in Table II for asymmetric inductions on 3-phenyl-2-butanone with methyl Grignard reagents and lithium aluminum hydride it can be seen that the concentration has a profound affect on the product stereospecificity for most of the reactions studied. The diastereomeric ratio, A/B, increases with dilution in the cases of methylmagnesium bromide in ether, methylmagnesium iodide in ether, methylmagnesium chloride in tetrahydrofuran and lithium aluminum hydride in both ether and tetrahydrofuran. For the above reactions changes 1.0 to 0.05 M (or to 0.005 M for the case of methylmagnesium iodide) alter $\Delta\Delta G^{\ddagger}_{AB}$ by about 0.4 kcal./mole.

No effect was observed in the reactions of methyllithium in ether and methylmagnesium bromide in tetrahydrofuran in the concentration range of 1.0 to 0.05 M. Differences in the activation parameters for the reaction of 3-phenyl-2-butanone with methylmagnesium bromide in ether are summarized in Table IV. It is interesting to note that the differences in $\Delta\Delta G^{\ddagger}_{AB}$ values, as expected, are controlled by $\Delta\Delta S^{\ddagger}_{AB}$ rather than by $\Delta\Delta H^{\ddagger}_{AB}$. In the concentration range of 1.0 to 0.05 M, $\Delta\Delta S^{\ddagger}_{AB}$ varies from -0.7 to +1.2 e.u.

For comparison purposes, analogous studies on the effect of concentration on the asymmetric induction of 3-methoxy-2-butanone[15] and 3,4,4-trimethylpentanone[16] are included in Table VI. The results are similar to those obtained in this study. There is only one case, that of methylmagnesium bromide additions to 3,4,4-trimethylpentanone in terahydrofuran, in which decreased dilution results in decreased, rather than increased, stereospecificity.

We conclude that in most of the reactions studied decreases in reagent concentration increase product stereospecificity. The quantitative aspects of the Karabatsos's model are, therefore, somewhat tarnished by these results.

E. Effect of Nucleophile to Ketone Ratio

The results of the nucleophile to ketone ratios on additions to 3-phenyl-2-butanone are presented in Table I. In the case of methyllithium as nucleophile and for ratios ranging from 1.3/1 to 6.5/1 no effect was observed on the product stereospecificity. In the case of methylmagnesium bromide, however, $\Delta\Delta G^{\ddagger}_{AB}$ changed from -1.5 to 1.1 kcal/mole for ratios ranging from 1.3/1 to 13/1.

Similar studies with methyllithium additions to 3-methoxy-2-butanone[15,17] and 3,4,4-trimethylpentanone[16,71] are presented in Table V. Variations in the nucleophile to ketone ratio from 1.3/1 to 5.2/1 did not affect product stereospecificity in either of the above systems.

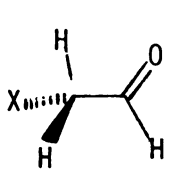
As in the case of substrate and reagent concentration, variations in the ratio of nucleophile to ketone are not expected to effect the relative stabilities of the two diastereomeric transition states XIII and XIV, if the nature of the reactant remains the same throughout the reaction. Changes in the relative stabilities of the two diastereomeric transition states could arise either from changes in the differential solvation of these states, or from changes in the nature of the reagent, e.g., replacement of a halogen or hydride ligand by an alkoxide ligand. It is evident from the results that such changes, if present, do not perceptibly affect most $\Delta\Delta G^{\ddagger}_{AB}$ values.

F. Solvent Effects.

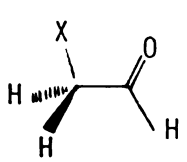
Studies of solvent effects on the relative stabilities of the two diastereomeric transition states are expected to provide more cogent information of the validity of the model as representative of the two transition states than studies of either concentration or nucleophile to ketone ratio. One expects the relative stabilities of transition states XIII and XIV to depend on the polarity of the solvent. For example, in more polar solvents the more polar transition states XIV is expected to be stabilized more than in non-polar solvents. Thus, the diastereomeric product ratio A/B ought to decrease with increasing solvent polarity.

It was soon realized, however, that our studies of solvent effects were to be limited to only two solvents, diethyl ether and tetrahydrofuran. This limitation was imposed by the fact that these are the only two solvents in which the solibility and composition of the Grignard reagents are known from previous studies.[23,24] Furthermore, the only three direct comparisons possible were those of methylmagnesium bromide, dimethylmagnesium and lithium aluminum hydride in ether and tetrahydrofuran. Methylmagnesium iodide is unstable in tetrahydrofuran,[24] methylmagnesium chloride disproportionates in ether solutions at room temperature depositing magnesium chloride,[24] and methyllithium reacts with tetrahydrofuran and is only slightly soluble in pentane. As a matter of fact, most of the reactions reported in the literature[18,20] involving additions of methyllithium in pentane are heterogeneous and the reported effects can be attributed to concentration rather than solvent.

From the results presented in Table III we conclude that in changing the solvent from ether to tetrahydrofuran the extent of asymmetric induction remained unchanged with any of the three nucleophiles for which direct comparison was possible. This fact can be attributed to the small difference in polarity between the two solvents (ether and tetrahydrofuran) which does not appreciably change the population of the two diastereomeric transition states XIII and XIV. Nuclear magnetic resonance spectroscopy studies[25] for the solvent dependence of the rotamer population XV and XVI, which are presented in Table VIII, are consonant



XV



XVI

with our observations. For example, when X is phenyl, the percent population of XVI in ether and tetrahydrofuran was found to be the same within experimental error. Even in systems expected to be more sensitive to solvent polarity, e.g. when X is p-methoxyphenyl or p-chlorophenyl, the percent population of XVI remained the same.

To further check the validity of the model, solvent studies must be performed on systems where the two diastereomeric transition states differ widely in polarity.

G. Entropy Effect

Entropy studies on asymmetric inductions are necessary in order to determine the applicability of the Karabatsos' model. The model is only applicable in cases where $\Delta\Delta H^{\ddagger}_{AB}$ controls $\Delta\Delta G^{\ddagger}_{AB}$. In cases where an appreciable contribtuion by $\Delta\Delta S^{\ddagger}_{AB}$ is made to $\Delta\Delta G^{\ddagger}_{AB}$, the model is inapplicable. Of twenty reactions studied, Karabatsos and Althius[18] found only one whose $\Delta\Delta G^{\ddagger}_{AB}$ varied significantly with temperature. This led them to conclude that, for the systems studied by them, $\Delta\Delta G^{\ddagger}_{AB}$ was controlled solely by $\Delta\Delta H^{\ddagger}_{AB}$.

The results of the temperature studies on the asymmetric induction of 3-phenyl-2-butanone with methylmagnesium bromide, methylmagnesium iodide, methyllithium, dimethylmagnesium and lithium aluminum hydride in ether, and methylmagnesium chloride, methylmagnesium bromide, dimethylmagnesium and lithium aluminum hydride in tetrahydrofuran are presented in Table III. Of the forty-one reactions studied only those of methylmagnesium iodide and methyllithium in ether gave $\Delta\Delta G^{\ddagger}_{AB}$ values whose temperature dependence is outside experimental error. For the above two systems $\Delta\Delta G^{\ddagger}_{AB}$ changed 0.4 and 0.6 kcal/mole, respectively, over a 104° change in temperature.

The value of $\Delta\Delta H^{\ddagger}_{AB}$ for asymmetric inductions on 3-phenyl-2-butanone has been calculated from Karabatsos' model[12a] to be of the order of -600 cal/mole. $\Delta\Delta H^{\ddagger}_{AB}$ and $\Delta\Delta S^{\ddagger}_{AB}$ values calculated from experimental results obtained at four temperatures are presented in Table IV. Although our $\Delta\Delta H^{\ddagger}_{AB}$ values and those obtained by Karabatsos and Althius[18] are in good agreement, they are nevertheless considerably larger (-1400 cal/mole) than those predicted by the model (-600 cal/mole).

For comparison purposes similar temperature studies with 3-methoxy-2-butanone[15] and 3,4,4-trimethylpentanone are presented in Tables VII and IX. The reactions of 3,4,4-trimethylpentanone gave $\Delta\Delta H^{\ddagger}_{AB}$ values that are independent of temperature, except the one involving the addition of methylmagnesium chloride in tetrahydrofuran where $\Delta\Delta G^{\ddagger}_{AB}$ changed by 1.0 kcal/mole over a 90° temperature range. This reaction is a clear case where product stereospecificity is controlled by $\Delta\Delta S^{\ddagger}_{AB}$, not $\Delta\Delta H^{\ddagger}_{AB}$. The values of $\Delta\Delta G^{\ddagger}_{AB}$ for asymmetric inductions with 3-methoxy-2-butanone are all temperature dependent, as predicted by the model on the basis of significant differences in the structure of the two diastereomeric transition states.

In conclusion, when the Karabatsos' model is applicable, $\Delta\Delta G^{\ddagger}_{AB}$ is independent of temperature and controlled by $\Delta\Delta H^{\ddagger}_{AB}$. When $\Delta\Delta S^{\ddagger}_{AB}$ contributes significantly to $\Delta\Delta G^{\ddagger}_{AB}$ the model is inapplicable. Fortunately, in most of the reactions studied so far $\Delta\Delta G^{\ddagger}_{AB}$ is independent of temperature and the model is still useful.

H. Conclusions.

This study of product stereospecificities obtained from additions to the carbonyl group of 3-phenyl-2-butanone revealed that these stereospecificities depend on the concentrations of nucleophile and ketone, on their molar ratios and on the nature of the nucleophile. Decreasing nucleophile concentrations result in increasing product stereospecificities. Grignard reagents, dimethylmagnesium and methyllithium are more stereoselective than lithium aluminum hydride. The stereoselectivity of methylmagnesium halides increases as the halide of the Grignard reagent is varied from iodide to chloride. For the two solvents studied, ether and tetrahydrofuran, no significant effect on product stereospecificity was observed. Except for the cases of methyllithium and methylmagnesium bromide in ether, $\Delta\Delta H^{\ddagger}_{AB}$ controls $\Delta\Delta G^{\ddagger}_{AB}$.

The values of $\Delta\Delta H^{\ddagger}_{AB}$ calculated from the experimental results are in good agreement with those previously obtained by Karabatsos and Althius.[18] In both cases, however, higher $\Delta\Delta H^{\ddagger}_{AB}$ values (-1400 cal/mole) than those predicted by the model (-600 cal/mole) were found. It should be emphasized that in the semiempirical model proposed by Karabatsos only two of the interactions (M $\leftrightarrow$ O *vs.* L $\leftrightarrow$ O) involved in the transition state were taken into account in calculating $\Delta\Delta H^{\ddagger}_{AB}$. It is thus concluded that the neglected other interactions that are present in the two diastereomeric transition states are often at least as significant as the one upon which the model is based.

EXPERIMENTAL SECTION

A. General Method for Asymmetric Induction

Apparatus: The apparatus used for the asymmetric induction studies was a three-necked round bottomed flask equipped with magnetic stirrer, thermometer, condenser and a septum. The system was filled with nitrogen and closed by placing a balloon on the other end of the condenser.

General procedure: The required amount of solvent was distilled over lithium aluminum hydride into the reaction apparatus, under nitrogen. The apparatus was then filled with nitrogen and closed. The required amount of the reagent was introduced into the apparatus through the septum by means of a syringe. The solution was brought to the required temperature and the corresponding amount of stock solution of ketone, described below, was added by means of a syringe through the septum. The rate of the addition was such as to prevent changes of the temperature of the reaction mixture (10 to 30 min.). The reaction mixture was allowed to react at constant temperature for 5 to 7 hours. The reaction was quenched with an equimolar to the grignard amount of 10% aqueous solution of ammonium chloride. The alcohol was extracted with ether, the ether layer was washed with distilled water and dried over anhydrous sodium sulfate for a few hours, and then filtered. After distillation of the ether under nitrogen, the remaining alcohols were purified by v.p.c. The diastereomeric product ratio (A/B) was determined by n.m.r. or by v.p.c.

Temperature control: The temperature at reflux was controlled with an ordinary oil bath. A Dewar vessel with the following mixtures was used for temperature control at lower temperatures: ice-water, carbon tetrachloride-dry ice, hexanol-dry ice and isopropyl alcohol-dry ice for 2°, -21°, -46° and -69°, respectively. The estimated maximum error introduced on the temperature control by this method was ±3°.

Reagents: Approximately 3 M solutions in ether of methylmagnesium bromide, methylmagnesium chloride, methylmagnesium iodide, phenylmagnesium bromide and methyl lithium, as well as a 3 M solution in tetrahydrofuran of methylmagnesium chloride, were obtained from Alpha Inorganic Inc. A 3 M solution of methylmagnesium bromide in tetrahydrofuran was prepared from the 3 M grignard solution in ether by evaporating the ether and adding anhydrous tetrahydrofuran under a nitrogen atmosphere. Solutions of lithium aluminum hydride in ether and in tetrahydrofuran (3-4 M) were obtained from Foot Mineral Co. Dimethylmagnesium was prepared by introducing under nitrogen 27.2 ml. of dioxane to 50.0 ml. of approximately 3 M solution of methylmagnesium bromide in ether. The mixture was centrifuged at 50 r.p.m. for about 12 hours, the solution was removed with a syringe and titrated.

Solvents: All solvents used for asymmetric induction were directly distilled into the reaction apparatus from mixtures of solvent and lithium aluminum hydride.

Stock solution of ketones: A weighted amount of ketone in a 50-ml volumetric flask was diluted with anhydrous solvent to the 50 mark. The empty space above the solution was filled with nitrogen and the flask was closed with a septum. The required amounts of ketone solutions for asymmetric induction studies were withdrawn through the septum with a syringe.

B. Preparation of 3-Phenyl-2-butanone

3-Phenyl-2-butanone was prepared by the alkylation of phenyl acetone by a procedure similar to the one employed by Suter and Weston.[26] To a solution of 18.4 g (0.8 mole) of sodium in 600 ml. of isopropyl alcohol, which was prepared by heating the solution at 78° for about 3 hours, was added slowly 107 g (0.8 mole) of phenyl-2-propanone (Eastman Organic Chemicals). The solution was cooled with ice-water. While stirring with a mechanical stirrer, 115 g (0.88 mole) of methyl iodide (MC/B) was added quickly. The fraction distilling at 90° and 20 mm. Hg was collected. It had the following properties: n_D^{25} 1.5066; n.m.r. spectrum, one doublet at τ 8.72, a singlet at τ 8.13, a quartet at τ 6.34 and a singlet at τ 2.82 with integrated areas of 3.0:3.0:1.0:5.0, respectively. Yield: 58.6 g.

C. Preparation of 3-Phenyl-2-butanone-1,1,1,3-d_4.

The alpha protons of 3-phenyl-2-butanone were exchanged in the presence of deuterium oxide as follows: 100 ml. deuterium oxide of approximately 90 percent isotopic purity was mixed with 160 g of 3-phenyl-2-butanone prepared as above. The mixture was maintained at pH of 9-10 with anhydrous potassium carbonate and was refluxed for about 12 hours. The organic layer was separated and mixed with 100 ml. of fresh deuterium oxide of 99.5 percent isotopic purity. The exchange was repeated once more with 100 ml. deuterium oxide of minimum isotopic purity of 99.7 percent (Merck Sharp & Dohme Lmtd.). The organic Layer was separated and the aqueous layer was extracted with ether. The ether solutions were mixed with the ketone, dried over magnesium sulfate, filtered and distilled under vacuum. The fraction distilling at 90° and 20 mm. Hg was collected, having the following properties: n_D^{25} 1.5053; n.m.r. spectrum, two singlets at τ2.96 and 8.72 with an integrated area ratio of 5.0:3.0. Yield 152 g.

D. Methyl Grignard Additions to 3-Phenyl-2-butanone-1,1,1,3-$\underline{d}_4$.

Approximately 3 M stock solutions of the ketone in ether and tetrahydrofuran were prepared, as described in the general method, to be used for addition reactions. The required amount of solvent (ether or tetrahydrofuran) was distilled over lithium aluminum hydride into the reaction apparatus, and kept under nitrogen. The required amount of 3 M solution of the reagent was introduced through the septum by means of a syringe and the solution maintained at the desired temperature. The required amount of stock solution of ketone was also introduced through the septum by means of a syringe, and at such a rate as to prevent changes in the temperature of the reaction mixture. The mixture was stirred for an additional 5 to 7 hours at the desired temperature, after which an equimolar to the Grignard solution of 10 percent ammonium chloride was added. After extracting the alcohol with ether, the ether solution was washed twice with distilled water and dried over anhydrous sodium sulfate. Upon removal of the solvent under nitrogen, 2-methyl-3-phenyl-2-butanol-1,1,1,3-$\underline{d}_4$ was recovered and purified by vapor phase chromatography by using a 15% FFAP 60-80 DMCS, Chromosorb W, 6 ft. column.

N.m.r. spectra of 10 percent solutions of the purified alcohol in pyridine were taken with a Varian 100 MHz n.m.r. spectrometer. The diastereomeric ratios were determined by integration of the areas of the major (τ 8.70) and minor (τ 8.76) absorptions by the cutting and weighing technique.

E. Lithium Aluminum Hydride Additions to 3-phenyl-2-butanone

A procedure similar to the one described for the methyl Grignard additions was followed. An approximately 4.4 M solution of litiuum aluminum hydride in ether or tetrahydrofurane was diluted with the required amount of solvent freshly distilled over lithium aluminum hydride. The required amount of ketone solution was introduced slowly in order to prevent changes in the temperature. The mixture was stirred for an additional three hours at the desired temperature maintained constant by means of a bath with the proper coolant as described under the general procedure. The reaction was quenched with 3 ml. of methanol followed by 10 ml. of distilled water. The diastereomeric alcohols were extracted with ether, washed with distilled water and dried over sodium sulfate. Removal of the solvent under nitrogen gave 3-phenyl-2-butanol whose diastereomeric ratio was determined by vapor phase chromatography, by using a 15% FFAP 60/80 DMCS, Chromosorb W, 6 ft. column.

F. Nuclear Magnetic Resonance Spectroscopy Studies of 2-Methyl-3-phenyl-2-butanol and 2-Methyl-3-phenyl-2-butanol-1,1,1,3-$\underline{d}_4$.

Nuclear Magnetic Resoancne spectroscopy studies of 2-methyl-3-phenyl-2-butanol had been previously performed by Karabatsos and Althius.[18] The n.m.r. spectrum of the "neat" compound consisted of a singlet at τ 2.82, a quartet centered at τ 7.27, a singlet at τ 7.35, a doublet centered at τ 8.68 and a singlet at τ 8.88 (ratio 5.0:1.0:1.0:3.0:6.0). The six proton singlet assigned to the two diastereotopic methyl groups was resolved into two equal intensity singlets at τ 8.67 and τ 8.73 in a 10% solution in pyridine (see Figure 2 A).

In the n.m.r. spectrum of 2-methyl-3-phenyl-2-butanol-1,1,1,3-$\underline{d}_4$ (Figure 2, B) the absorptions for the two diastereotopic 2-methyl groups appear at τ 8.70 and 8.76. Those of the other two diastereotopic methyl groups appear as a broad singlet at τ 8.57.

G. Nuclear Magnetic Resonance Spectroscopy Studies of 3-Phenyl-2-butanol.

The n.m.r. spectrum of 3-phenyl-2-butanol, resulting from additions of lithium aluminum hydride to 3-phenyl-2-butanone, in 10% solution of carbon tetrachloride (see Figure 2) consisted of a doubled centered at τ 8.92, a doublet centered at τ 8.79, a singlet at τ 7.67, a quartet at τ 7.39, a quartet at τ 6.29 and a singlet at τ 2.80 (ratio 3.0:3.0:1.0:1.0:1.0:5.0, respectively). The two doublets assigned to the four diastereotopic methyl groups were further resolved to four doublets with the addition to the carbon tetrachloride solution of 25 mg. of $Eu(Fod)_3$.

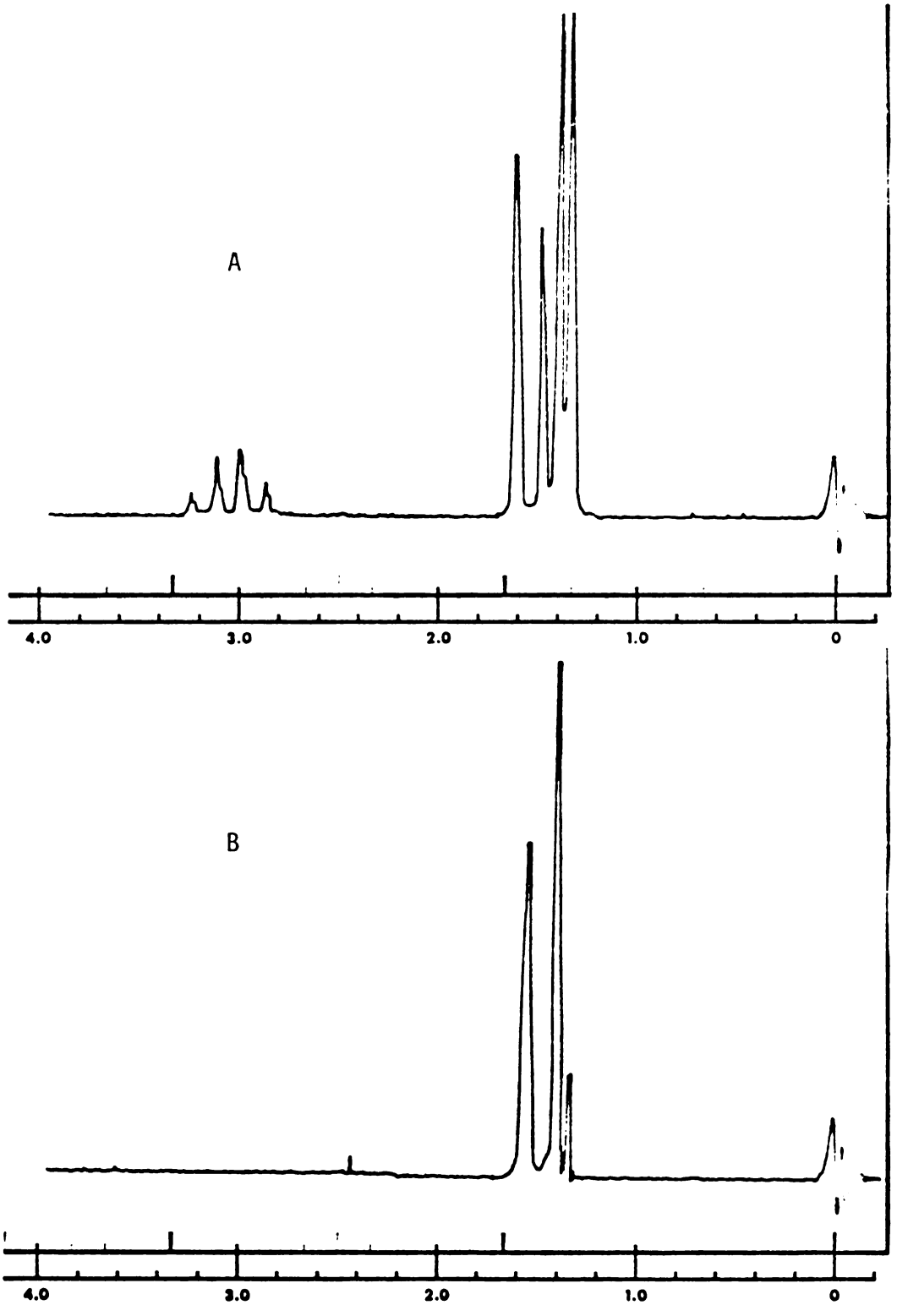


FIGURE 2. N.m.r. spectra of 10% solutions of (A) 2-methyl-3-phenyl-2-butanol and (B) 2-methyl-3-phenyl-2-butanol-1,1,1,3-$\underline{d}_4$ in pyridine.

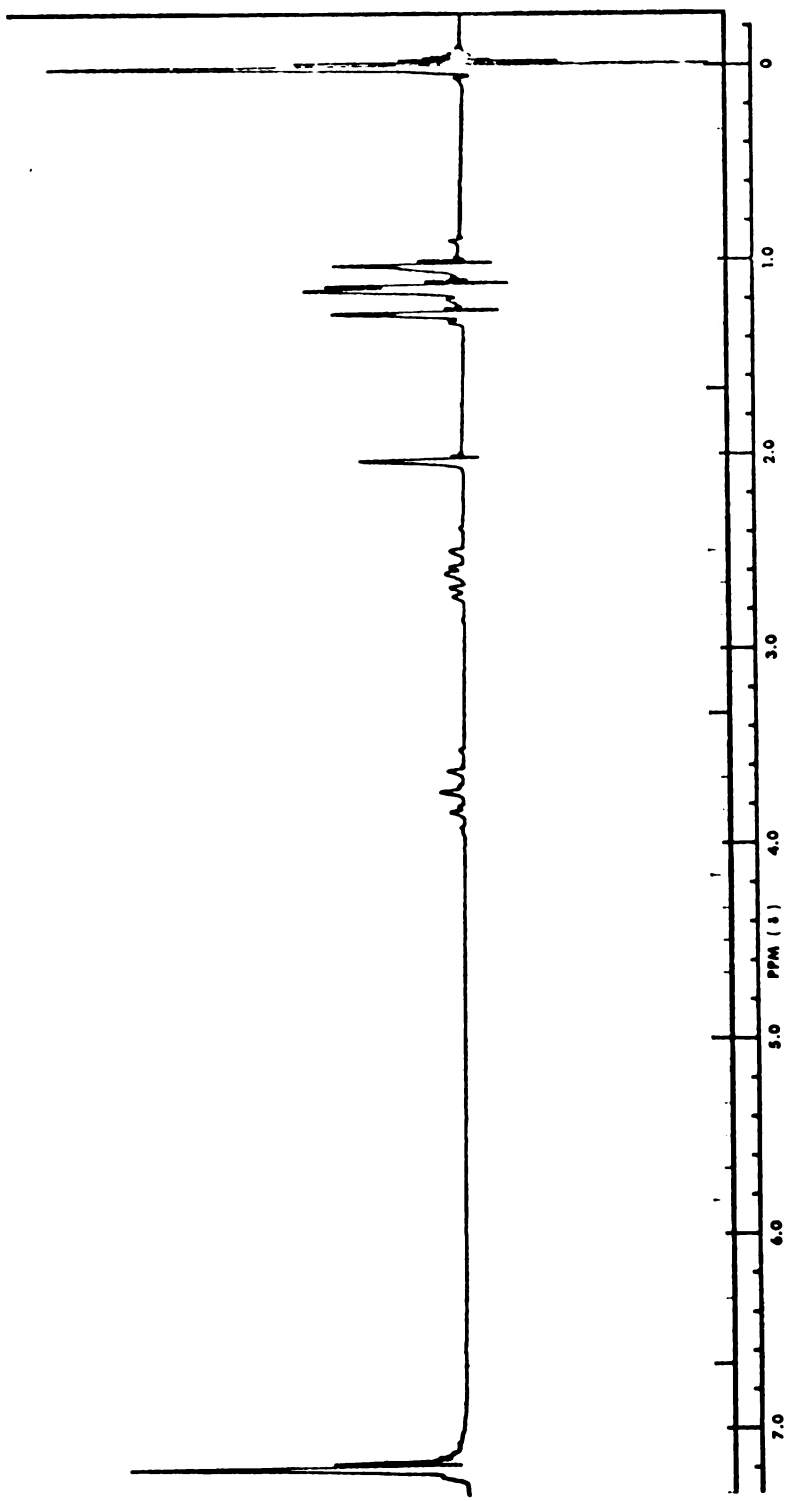


FIGURE 3. N.m.r. spectrum of 10% solution of 3-phenyl-2-butanol in carbon tetrachloride.

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