

72-3943

AUERBACH, Robert Archer, 1945-
CONFORMATION AND REACTIVITY IN DIASTEREOMERIC
SYSTEMS.

The University of Nebraska, Ph.D., 1971
Chemistry, inorganic

University Microfilms, A XEROX Company, Ann Arbor, Michigan

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Conformation and Reactivity in Diastereomeric
Systems

by

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A DISSERTATION

Presented to the Faculty of
The Graduate College in the University of Nebraska
in Partial Fulfillment of Requirements
For the Degree of Doctor of Philosophy
Department of Chemistry

Under the Supervision of Professor Charles A. Kingsbury

Lincoln, Nebraska

August, 1971

TITLE

CONFORMATION AND REACTIVITY IN DIASTEREOMERIC SYSTEMS

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To My Parents

PREVIEW

ACKNOWLEDGEMENT

The author would like to thank Professor Charles A. Kingsbury for his guidance and patience during the course of this work.

RAA

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PREVIEW

Introduction

The application of nuclear magnetic resonance (nmr) spectrometry to the study of acyclic molecules has greatly facilitated the conformational analysis of such systems. Prior to about 1962, most nmr studies had been restricted to cyclic compounds, but since that time several investigations have determined relative configurations and/or conformational preferences of acyclic systems. The results have been based on both qualitative and quantitative analysis of the vicinal coupling constant, J , of the ethane-like backbone of the molecular system by application of the Karplus relationship.¹

The Karplus relationship (eq. 1, fig. 1) relates the magnitude of the vicinal coupling constant to the magnitude of the dihedral angle between the coupled protons.

$$\begin{aligned} J &= 8.5 \cos^2 \phi - 0.28 \text{ (Hz)} & 0 \leq \phi \leq 90 \\ J &= 9.5 \cos^2 \phi - 0.28 \text{ (Hz)} & 90 \leq \phi \leq 180 \end{aligned} \quad \text{eq. 1}$$

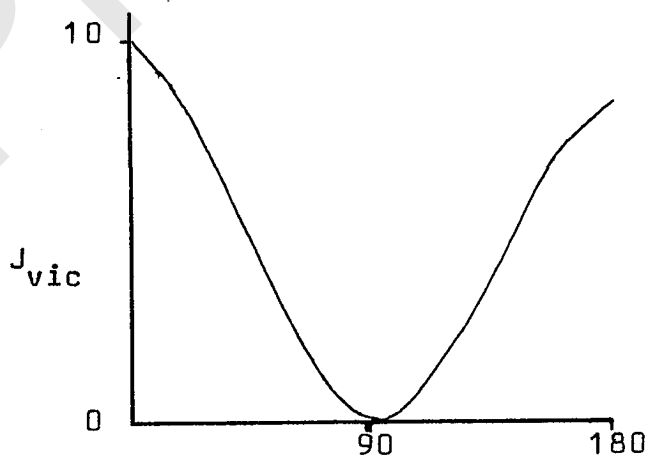


Fig.1

Dependence of $J_{vicinal}$ On Dihedral Angle

Detailed theoretical discussions of vicinal proton-proton coupling may be found in the recent papers and comprehensive reviews of Pople,² Bothner-By,³ and Barfield and Grant.⁴

In a cyclohexane system, trans diaxial protons exhibit a coupling constant of about 13 Hz, cis axial-equatorial protons a value of about 3.5 Hz, and trans diequatorial protons a value of about 3.0 Hz. A substituted ethane system having two vicinal protons similarly shows a large J value (10-12 Hz) if the protons are constricted to a trans relationship, and a small J value (2-3 Hz) for protons constricted to a gauche relationship.



In diastereomeric systems having a proton at each asymmetric center, the value of the coupling constant should be indicative of any preferred molecular conformation. Unfortunately, since the frequency of rotation about an sp^3 carbon atom is usually large in comparison to the nmr frequency separation between vicinal protons, the coupling constant is a weighted mean of values from many contributing conformations. Thus, a mixture of trans and gauche rotomers will result in intermediate values of J (5-7 Hz).

Furthermore, the substitution of an electronegative group at an asymmetric center results in a decrease of the

vicinal coupling constant.⁵⁻⁷ Bond angle deformations and consequent hybridization changes also affect the coupling constant to some extent.⁸ These effects, though usually small, render interpretation of small differences in coupling constant almost meaningless. Nevertheless, valuable information concerning preferred conformation may be inferred from the coupling constant data.

In one of the earliest investigations, Hyne⁹ determined the conformational preferences of the diastereomeric ephedrines by measuring the coupling constants of the vicinal protons.

Kingsbury and Thornton¹⁰ investigated the conformational preferences of a series of diastereomeric compounds possessing substituted phenylethyl skeletons. It was found that when the alkyl substituent at each asymmetric center was small, both trans and gauche rotomers were substantially populated. Bulkier alkyl groups, such as isopropyl, strongly preferred a trans orientation which allows a trans arrangement of protons in the erythro but gauche in the threo isomer (fig. II).

Truce and Klinger¹¹ have recently made configurational assignments to a series of hydroxy-sulfones on the basis of nmr spectral features. The diastereomeric isomers existed in predominant preferred conformations. The threo isomers showed a consistently large (9-10 Hz) J value. The erythro isomers, on the other hand, exhibited small (ca. 1-2 Hz) coupling constants.

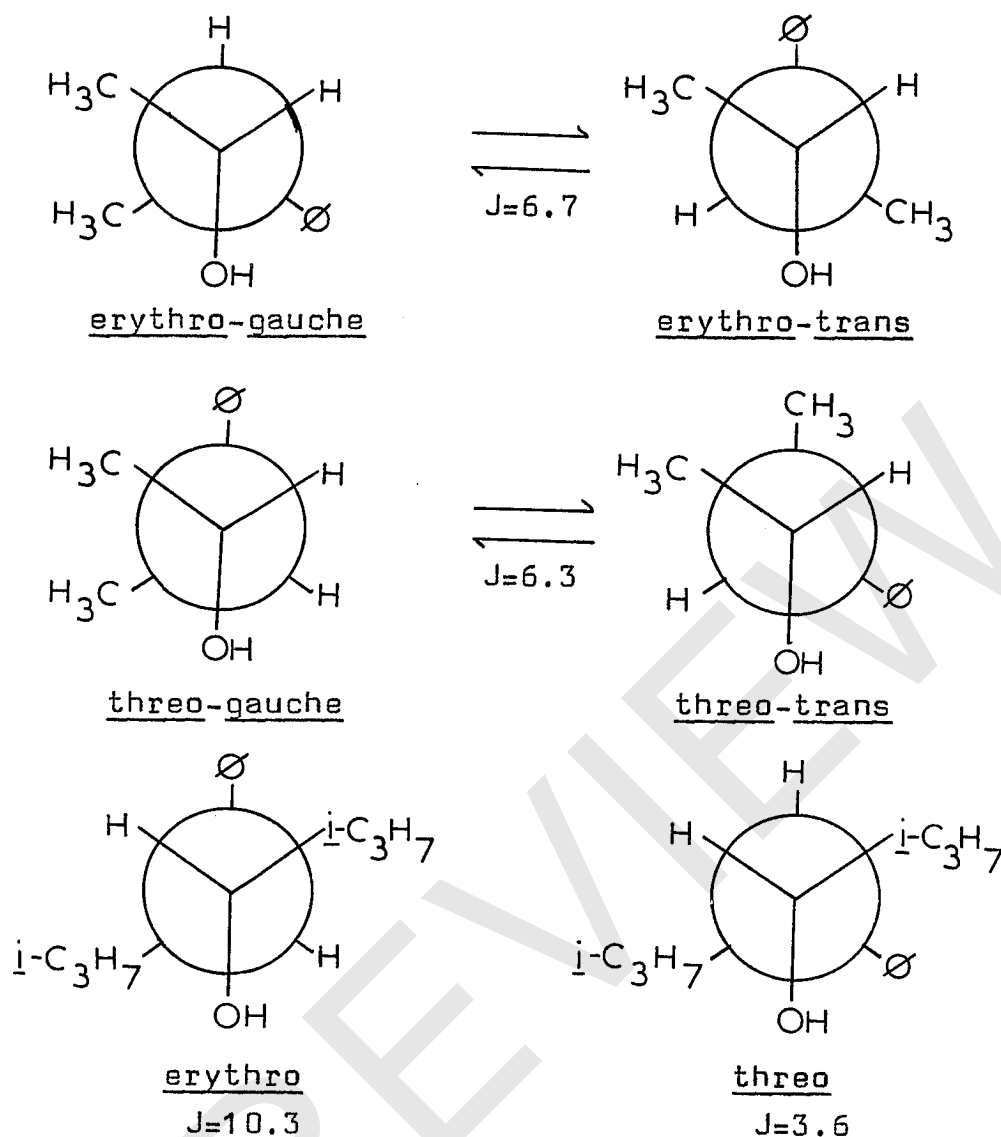


Fig. II

Conformations of Substituted Phenylethyl Systems

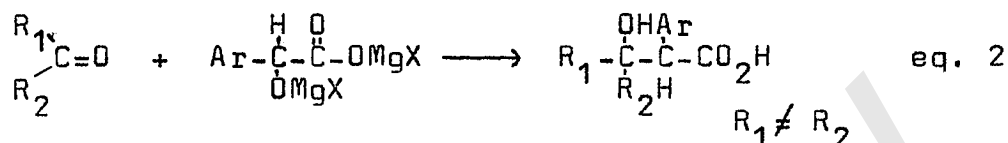
Other recent studies concerning the stereochemistry of diastereomeric systems involve 2,3-diphenylpropanoic acids,¹² 1,2-glycols,¹³ and 1,2-chlorhydrines.¹⁴

Obviously, nmr is an extremely powerful tool for studying molecular conformations and configurations. A more complete knowledge of the factors involved in determining conformational equilibria is requisite to a fuller understanding of the reactivity of organic compounds.

Part 1: The Ivanov Reaction and Internal Solvation
Effects on the Conformation of Acyclics

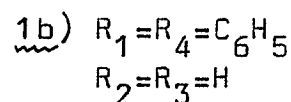
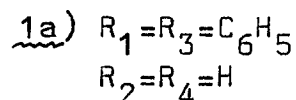
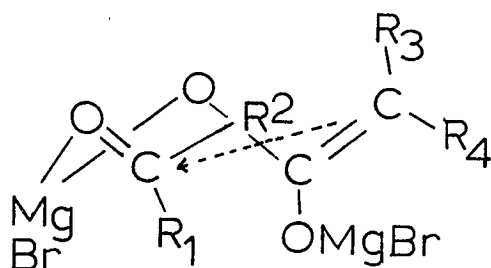
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Ivanov¹⁵ reported in 1932 that phenylacetic acid decomposes two moles of Grignard reagent to yield a magnesium enolate of the acid. Subsequent investigations¹⁶⁻²⁰ resulted in the isolation of only one diastereomer where two would have been expected (eq. 2).



In a limited attempt to elucidate the stereochemistry of the Ivanov reaction, Zimmerman and Traxler²¹ investigated the condensation of benzaldehyde and phenylacetic acid. The reaction had previously been reported to yield 2,3-diphenylpropanoic acid, mp 175°, in 60% yield.¹⁵

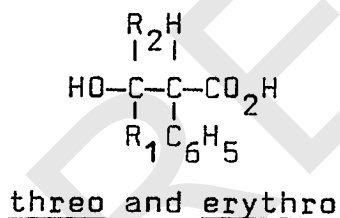
By utilization of careful column chromatography, Zimmerman and Traxler were able to isolate small quantities of a second isomer which had mp 142-143°. The ratio of major to minor product was determined to be ca. 3:1. The reaction appeared to be, therefore, quite stereoselective and this was rationalized according to the following argument. Zimmerman suggested that the reaction involves σ -bond formation by overlap of the Ivanov reagent p-orbital with the electron deficient p-orbital of benzaldehyde. An intramolecular coordination was suggested, as shown below.



Thus, transition state 1a, producing the predominant product, allows the lowest energy approach to bonding. Transition state 1b, on the other hand, presumably would result in serious non-bonded interactions and would be much less favorable to bonding.

This interpretation is open to criticism on several grounds, as will be pointed out, and in order to further investigate certain aspects of conformational equilibria phenomena, several isomeric pairs of 2-hydroxypropanoic acids were synthesized by the Ivanov condensation. The acids are listed in Table 1.

Table 1
Substituted 2-Phenyl-3-hydroxypropanoic Acids



- a) $\text{R}_1 = \text{H}, \text{R}_2 = \text{CH}_3$
- b) $\text{R}_1 = \text{H}, \text{R}_2 = \text{i-C}_3\text{H}_7$
- c) $\text{R}_1 = \text{H}, \text{R}_2 = \text{t-C}_4\text{H}_9$
- d) $\text{R}_1 = \text{H}, \text{R}_2 = \text{C}_6\text{H}_5$

The reaction of the Ivanov reagent derived from phenylacetic acid with the various aldehydes provided good yields of the corresponding hydroxy acids varying from 54% for $\text{R} = \text{t-C}_4\text{H}_9$ to 88% for $\text{R} = \text{C}_6\text{H}_5$. The hydroxy acids are listed in Table II with respective melting points, yields, and product ratios.

Table II
Diastereomeric Substituted Hydroxy Acids, I

R_2	<u>Yield Mixed Isomers, %</u>	<u>Mp, °C</u>	<u>Product Ratio^{a,b}</u>
1a CH_3 major	85	135-136	1.8:1
CH_3 minor		89-90	
1b $i\text{-C}_3\text{H}_7$ major	73	139-140	2.3:1
$i\text{-C}_3\text{H}_7$ minor		174-175	
1c $t\text{-C}_4\text{H}_9$ major	54	164-165	1.5:1
$t\text{-C}_4\text{H}_9$ minor		200-201	
1d C_6H_5 major	88	173-174	2.2:1

a. Reaction time of 5 hours.

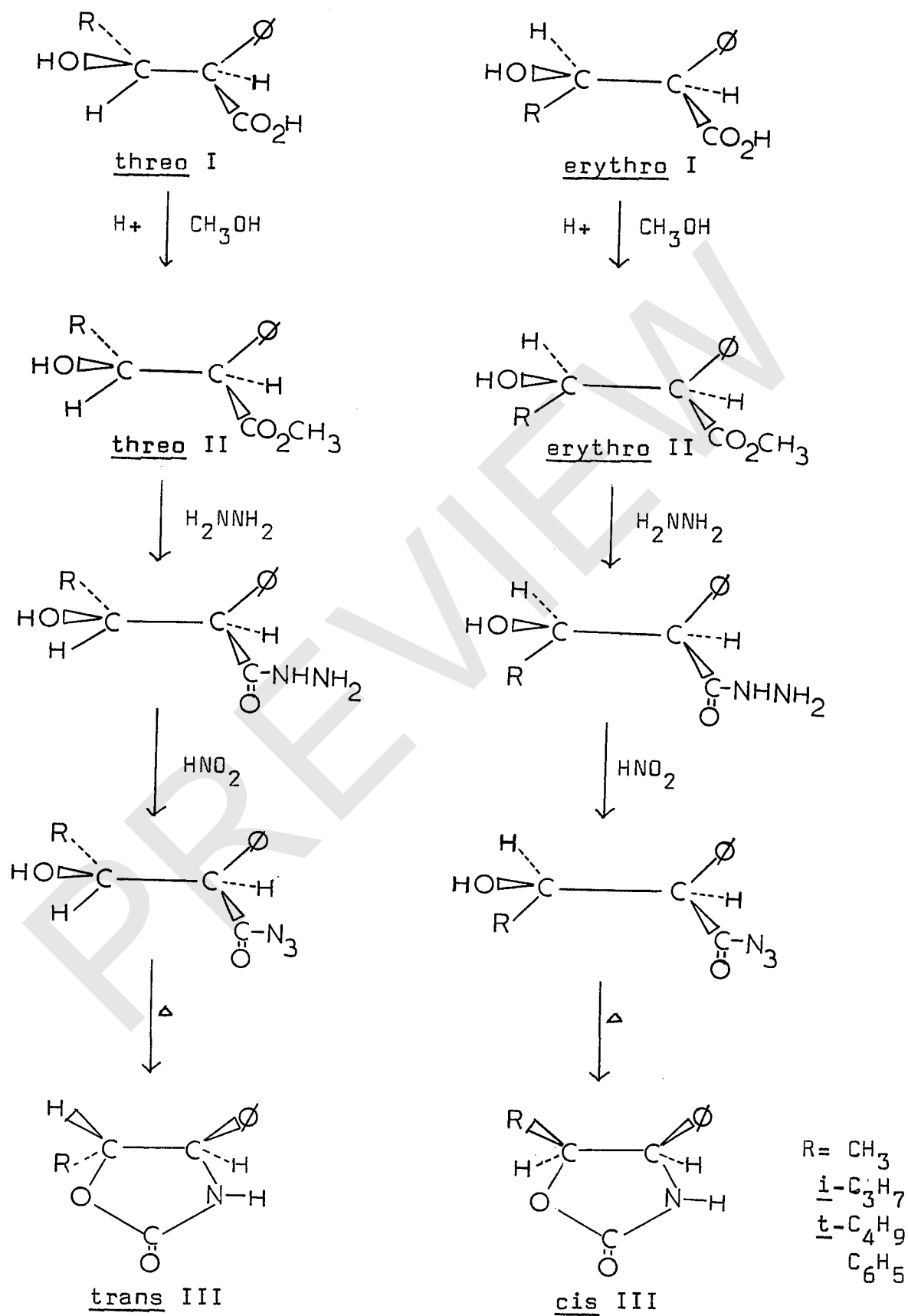
b. Determined by electronic integration.

Proof of Relative Configurations

The relative configurations of the isomeric hydroxy acids were proved by stereospecific conversion to the cis and trans oxazolidones III by way of the esters II, as shown in Scheme I. The Curtius degradation involved in the transformation is known to occur with complete retention of configuration,²² and since the conversion of the esters to the oxazolidones is stereospecific, the configurations of the isomeric acids I may be determined by extrapolation.

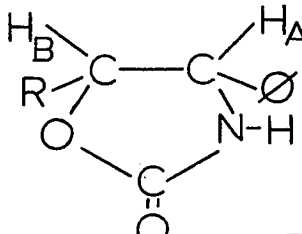
In five-membered heterocyclic rings, $J_{\text{cis}} > J_{\text{trans}}$.²³ The oxazolidones produced via degradation of the minor acid consistently exhibited the larger coupling constant

Scheme I



and were therefore assigned the cis configuration. The oxazolidones produced via degradation of the major acids exhibited the smaller coupling constant and were assigned the trans configuration. The coupling constant data for the oxazolidones are listed in Table III.

Table III
Vicinal Coupling Constants of Substituted
2-Oxazolidones, III^a

	<u>R</u>	<u>J_{AB}</u>
 <p style="text-align: center;">III</p>	<u>trans</u> CH ₃	6.2 ^b
	<u>cis</u> CH ₃	<u>ca.</u> 8.0 ^{b,c}
	<u>trans</u> <u>i</u> -C ₃ H ₇	5.8
	<u>cis</u> <u>i</u> -C ₃ H ₇	7.3
	<u>trans</u> <u>t</u> -C ₄ H ₉	5.2
	<u>cis</u> <u>t</u> -C ₄ H ₉	7.0
	<u>trans</u> C ₆ H ₅	7.4
	<u>cis</u> C ₆ H ₅	8.5

a. 15% w/v deuteriochloroform solution.

b. Pyridine solvent.

c. Determined from computer simulation of spectrum.

In this manner, it was determined that the major product of the Ivanov condensation in each case was the threo diastereomer and the minor product was the erythro diastereomer.

Futhermore, it was recently determined¹² that, for a series of analogous diastereomers, the methyl ester resonance of the erythro isomer appears at slightly higher field than the threo isomer, regardless of solvent used. This difference permits assignment of relative configurations with some degree of certainty and fully corroborates the degradative scheme previously described. The carbomethoxy resonances of the various methyl esters are listed in Table IV.

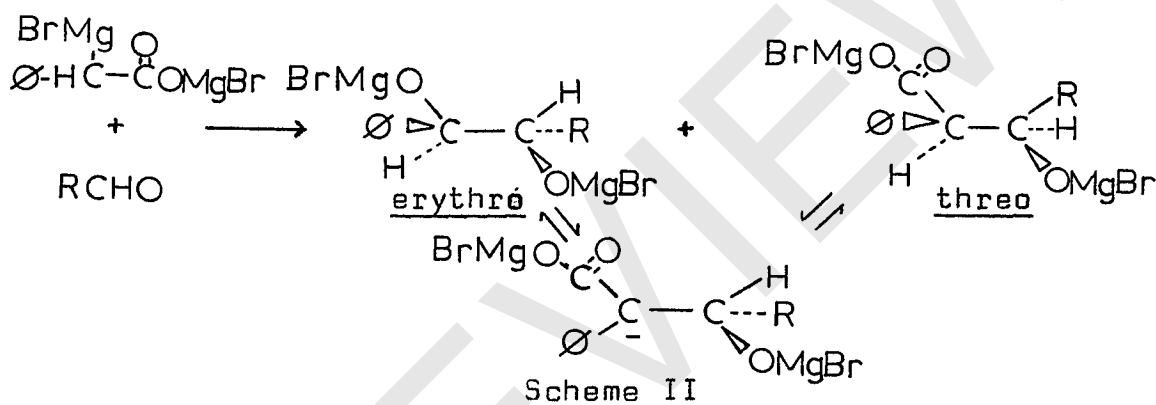
Table IV
Chemical Shifts of Methyl Ester Groups of the
Methyl Hydroxypropionates II^a

<u>R</u>	<u>ν_{CH_3} (Hz)</u>
IIa <u>threo</u> CH_3	219
<u>erythro</u> CH_3	216
IIb <u>threo</u> $i\text{-C}_3\text{H}_7$	220
<u>erythro</u> $i\text{-C}_3\text{H}_7$	218
IIc <u>threo</u> $t\text{-C}_4\text{H}_9$	219
<u>erythro</u> $t\text{-C}_4\text{H}_9$	214
IIId <u>threo</u> C_6H_5	220
<u>erythro</u> C_6H_5	208

a. 15% w/v deuteriochloroform solution

In the reaction of the Ivanov reagent with several aldehydes, it was found that the ratio of stereoisomers was somewhat dependent on the reaction time. Thus, reaction with p-tolualdehyde afforded products in the ratio of 1.1:1

after 30 minutes, 1.3:1 after 90 minutes, and 2.2:1 after 18 hours. Similarly, reaction with acetaldehyde resulted in a ratio of 1.6:1 after 30 minutes, and 2.1:1 after 7 hours. These results make the mechanistic rationale of Zimmerman previously mentioned somewhat suspect. Furthermore, Zimmerman's transition state suffers from the destabilizing effect of diaxial substituents in the pseudo-chair conformations envisioned. An alternative mechanism is outlined in Scheme II.



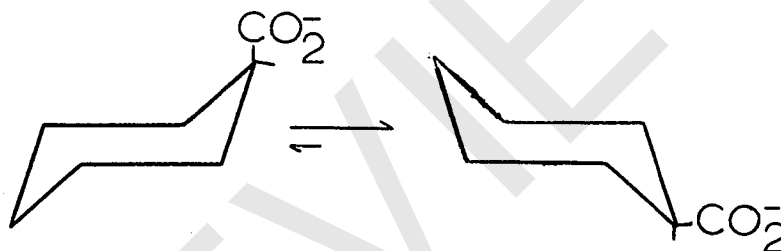
Thus, equilibration of the condensation products may occur through the anion resulting in the production of the major threo diastereomer as the more stable thermodynamic product. An attempt was made at base equilibration of the acids but merely resulted in decondensation.

Another mechanistic possibility is for equilibration to occur by means of reversible condensation-decondensation to the more stable product. This possibility is unlikely, however, since a crossover experiment with *p*-tolualdehyde in the reaction of the Ivanov reagent with benzaldehyde failed to give any detectable incorporation of tolualdehyde

in the products. It appears, therefore, that the most likely mode of equilibration is via the anion as shown in Scheme II.

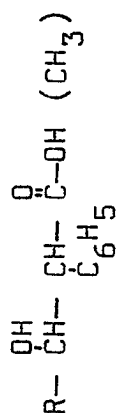
Conformational Equilibria of the Acids I

In cyclohexane carboxylic acids, the carboxylate anion exhibits a stronger preference for the equatorial position than does the free acid itself.²⁵ This behavior has been ascribed to the greater steric requirements of the highly solvated anion. Thus, the axial solvated anion experiences greater 1,3-nonbonded interaction than the effectively smaller free carboxyl group.



In the acyclic molecule malic acid, an increase in the population of conformers with trans carboxylates results as the solution pH increases. This behavior is undoubtedly partially attributable to increasing charge repulsion of carboxylates in the progression from singly ionized to doubly ionized species. Although charge repulsion and ionic size are of undoubted importance, an attractive interaction between hydroxyl and carboxylate may be at least partially operative in determining conformation. To investigate this possibility more fully, the hydroxy acids I and esters II were subjected to a systematic nmr study. The nmr data are listed in Table V.

Table V

NMR Parameters^a for Acids I and Esters (II)Chemical Shifts
(ppm) in 10%
PyridineJ_{AB} (Hz)

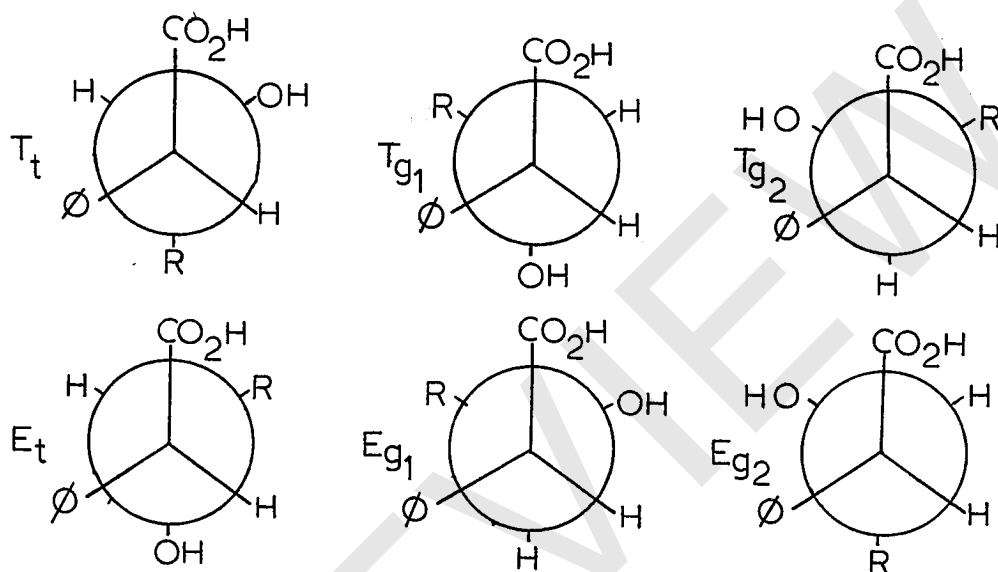
R	H _A	H _B	CDCl ₃ ^{f, j}	Pyridine	DMSO-d ₆	CH ₃ OD ^h	CH ₃ O ⁻ /CH ₃ OD ^k	D ₂ O/CO ₂ ⁼¹
a CH ₃ <u>threo</u>	4.92	4.05	9.4 (9.4)	9.4 (9.5)	9.8 (9.5)	9.9 (9.8)	8.3	9.8
<u>erythro</u>	4.90	4.06	7.0 (7.0)	7.9 (8.0)	8.1 (8.1)	8.2 (8.1)	5.9	8.5
b i-C ₃ H ₇ <u>threo</u>	4.68	4.27	9.7 ^c (9.6)	10.1 (10.1)	10.8 (10.8)	10.2 (10.4)	6.5	9.6
<u>erythro</u>	4.55	4.23	7.1 ^{c, d} (7.0)	8.0 (8.2)	8.7 (8.5)	8.0 (8.7)	5.7	9.3
c t-C ₄ H ₉ <u>threo</u> ⁹	4.33	4.22	b (4.6)	6.6	e (e)	e (e)	1.6	2.9
<u>erythro</u>	4.61	4.23	b (7.7)	7.0	8.2 (7.8)	8.4 (8.0)	5.1	9.4
d C ₆ H ₅ <u>threo</u>	5.85	4.51	b (9.3)	10.1 (9.9)	9.8 (10.0)	10.0 (10.0)	8.3	10.0
<u>erythro</u>	5.92	4.51	7.2 ^d (7.6)	8.5 (8.6)	9.6 (9.4)	9.5 (9.5)	5.8	9.0

a. Average of several runs; J_{AB} values taken from expanded spectra.b. Insoluble c. Isopropyl methine-HA coupling constant: 2.2 Hz (threo), 4.1 Hz (erythro).
d. Slightly heated for solubility. e. Superimposed resonances.

f. A trace of trifluoroacetic acid was added to promote rapid exchange of the hydroxyl proton.

g. Slightly impure with the erythro isomer. h. In some cases, CD₃OD was used.j. Concentration ca. 10% w/v. The J_{AB} values were invariant over a four-fold change in concentration. k. Apparent pH ca. 11. l. pH 8.5-9.0.

In all cases with the exception of **1c**, the threo isomers exhibit a larger vicinal coupling constant than the erythro isomers. The three possible staggered conformations of the various diastereomers are shown below. The dihedral angles of 60° are used for convenience only and are not meant to reflect actual conformational arrangements.



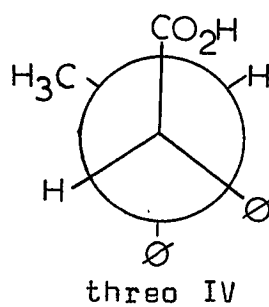
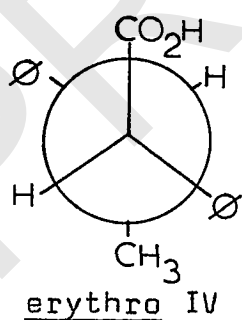
In moving from non-polar to polar solvents, a slight but consistent increase in J_{AB} is noted, indicative of a growing predominance of T_t (J_{AB} ca. 10-13 Hz) over T_{g1} and/or T_{g2} (J_{AB} ca. 1-3 Hz). In deuteriochloroform, intramolecular association is possible for both T_{g2} and T_t . The observed coupling constants for the threo isomers (ca. 9.5 Hz for **1a**, **b**, and **d** in CDCl_3) probably reflect a weighted mean of values for these conformations, with T_t the stronger contributor due to fewer unfavorable non-bonded interactions.

Infrared spectra of the threo methyl esters (which occupy the same conformations as the acids) exhibited relatively weak free hydroxyl absorptions at low concentrations, further indicating the comparative unimportance of conformer T_g . In strongly hydrogen-bonding solvents such as dimethylsulfoxide (DMSO) or pyridine, association with solvent becomes preferred^{24,26} and results in a concomitant decrease in intramolecular hydrogen bonding. Thus the conformation offering minimum steric hindrance to external solvation (T_t) becomes even more predominant and a further increase in J_{AB} is noted.

The data for the erythro isomers (J_{AB} ca. 7 Hz in $CDCl_3$) suggest that nearly identical populations of the conformer with trans protons (E_t) and the conformer(s) with gauche protons (E_{g1} and/or E_{g2}) exist. The infrared spectra of the erythro isomers (which again occupy similar conformations as the acids) usually exhibited much more intense free hydroxyl absorptions than the corresponding threo isomers. This observation is consistent with a substantial population of E_t which is unable to undergo intramolecular association. As noted for the threo isomers, but to a much greater degree, an increase in J_{AB} is noted upon moving from chloroform solvent to more powerfully hydrogen-bonding solvents. Thus an increase in population of E_t results with a concomitant decrease in population of E_{g1} and/or E_{g2} .

In basic aqueous media, the carboxylate anions appear to populate essentially the same conformers (T_t and E_t) as the free acids in other polar solvents. In methanol, however, the anions exhibit substantially reduced values for J_{AB} . Thus, intramolecular association between hydroxyl and carboxylate reappears and is apparently more intense than in the original chloroform solution of the free acid. That the intramolecular association or internal solvation of carboxylate by hydroxyl appears in methanol and not in water may be ascribed to the reduced solvating ability of the methanol.^{27,28}

A model system in which internal solvation is not possible, 2,3-diphenylbutanoic acid, IV, was studied. Both the erythro and threo isomers exhibited a large (11.2 ± 0.2 Hz) coupling constant which was completely insensitive to changes in solvent. Therefore, presence of the hydroxyl group is necessary for the solvent dependence of the other acids.



As reported for other cases,²⁶ the favored conformations seem to be those in which two sets of gauche interactions exist between large groups, each set being separated by protons.