

STRUCTURAL STUDIES OF ALDEHYDES
AND OXIME O-METHYL ETHERS
BY NUCLEAR MAGNETIC
RESONANCE SPECTROSCOPY

Thesis for the Degree of Ph. D.
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Nelson C. T. Hsi

1966



This is to certify that the

thesis entitled

STRUCTURAL STUDIES OF ALDEHYDES AND OXIME
O-METHYL ETHERS BY NUCLEAR MAGNETIC
RESONANCE SPECTROSCOPY

presented by

Nelson C. T. Hsi

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

A handwritten signature in cursive script that reads "G. S. Karabatsos".

Major professor

Date November 1, 1966

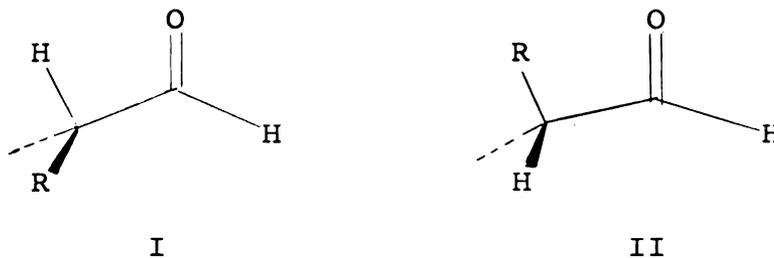
ABSTRACT

STRUCTURAL STUDIES OF ALDEHYDES AND OXIME
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RESONANCE SPECTROSCOPY

by Nelson C. T. Hsi

Nuclear magnetic resonance spectroscopy was applied to the study of semiquantitative conformational analysis in aliphatic aldehydes and oxime O-methyl ethers.

The time averaged spin-spin coupling constants between the aldehydic and α -protons of eighteen substituted acetaldehydes were studied as functions of temperature and solvent. Interpretation of the data in terms of rotamers I and II, whereby a single bond eclipses the carbonyl group, led to the



following conclusions. (1) Monosubstituted acetaldehydes: in the absence of solvent when R is methyl, ethyl, n-propyl, n-amyl, isopropyl or phenyl, II is favored over I by ΔH° of 800, 700, 600, 500, 400 and about 300 cal./mole, respectively. When R is t-butyl, II is less stable than I by an enthalpy of

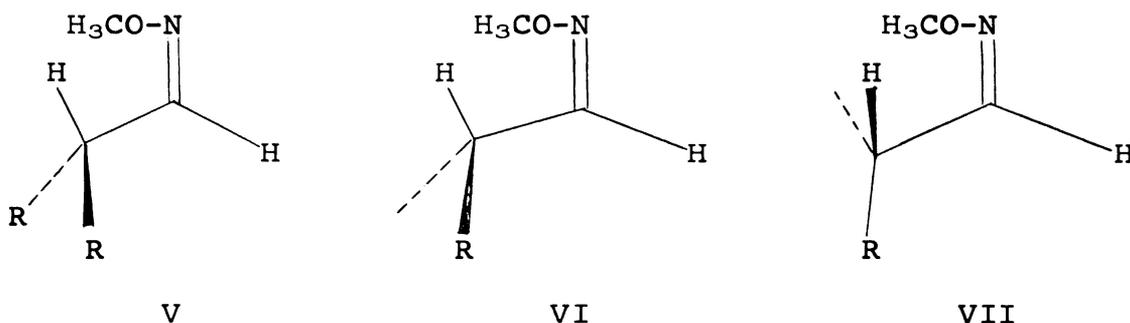
250 cal./mole. The ratio I/II increases with increase in solvent polarity, except for phenylacetaldehyde where it decreases. (2) Disubstituted acetaldehydes: in the absence of solvent when both substituents are methyls or only one of the substituents is methyl, the more stable rotamer, enthalpy-wise, has the methyl eclipsing the carbonyl (II); when neither substituent is methyl, I is the more stable rotamer. The ratio I/II increases with increase in solvent polarity. (3) Cycloalkanecarboxaldehydes: when the ring is cyclohexyl, II is more stable; when it is cyclopentyl, I is slightly more stable, when it is cyclobutyl, II is slightly more stable; and when it is cyclopropyl, I is much more favored. Again the ratio I/II increases with increase in solvent polarity.

Conformations and configurations were assigned to several aldehyde and ketone oxime O-methyl ethers from coupling constant and chemical shift studies. Interpretation of the data for the syn isomers (methoxy cis to the aldehydic proton) of the aldehyde derivatives in terms of rotamers III and IV led to the conclusion that for both mono- and



disubstituted acetaldehyde derivatives, III is energetically

avored. Interpretation of the data for the anti isomers led to the conclusion that, whereas V is the only significant rotamer for the disubstituted acetaldehyde derivatives, both VI and VII are equally important for the monosubstituted acetaldehyde derivatives.



Conformational analysis of the aldehyde derivatives by means of comparison of chemical shifts further substantiated the conclusions reached from the coupling constant studies. Conformations of the ketone derivatives were also assigned and discussed on a qualitative basis by comparing chemical shifts.

The effect of benzene on the chemical shifts of these derivatives was interpreted in terms of specific association between the solvent benzene and the solute. From the syn/anti isomer ratios, it was concluded that there is no meaningful correlation between group size and isomer stability.

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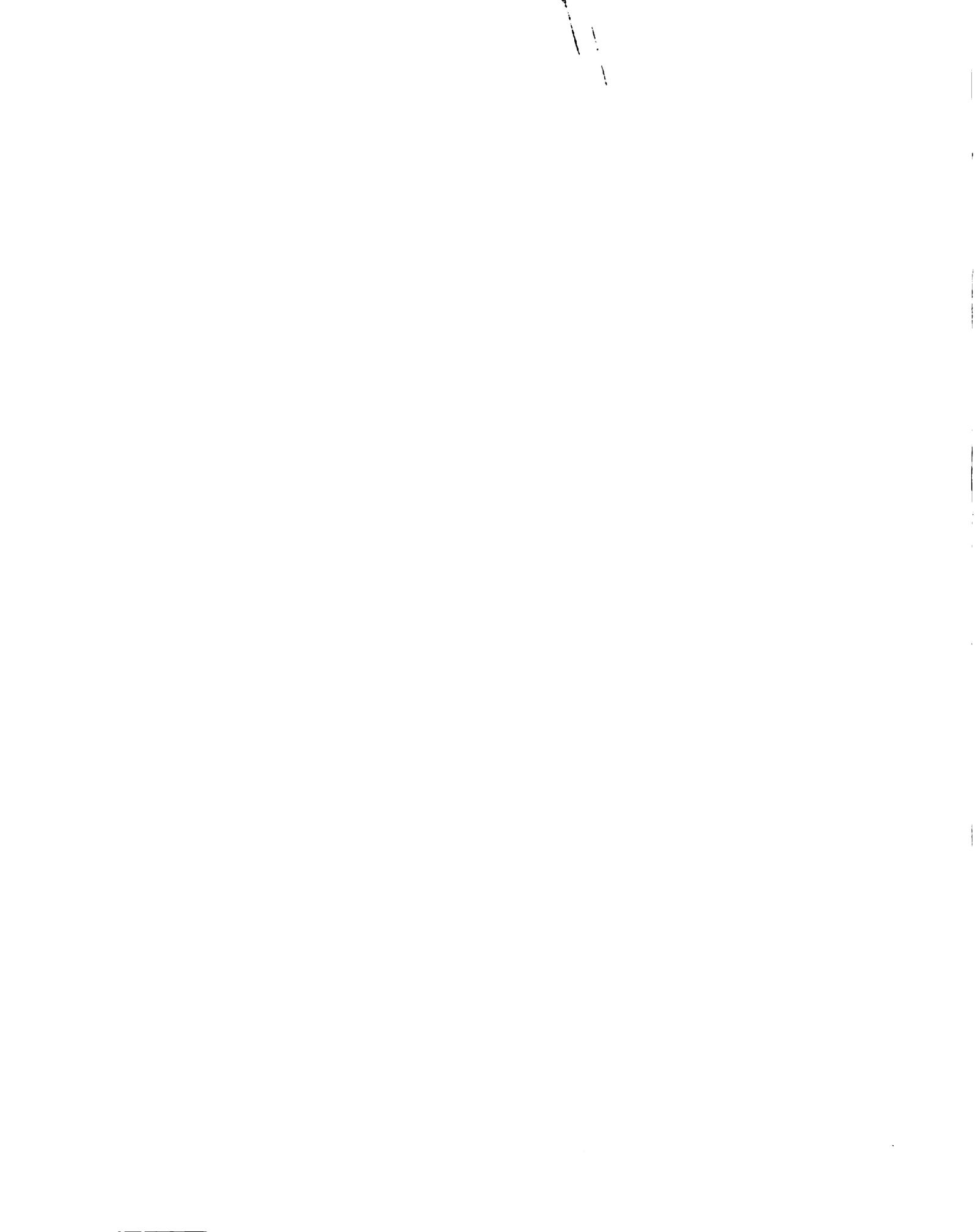
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To My Parents

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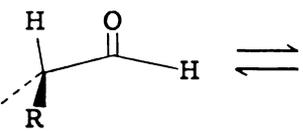
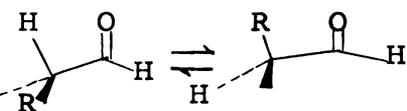
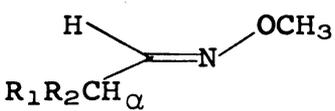
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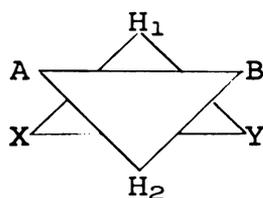
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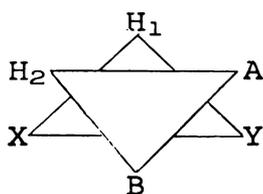
INTRODUCTION

Nuclear magnetic resonance spectroscopy has been successfully applied for the study of quantitative or semiquantitative conformational analysis in mobile systems under conformational equilibration (1,2,3,4,5,6). However, the success of this approach relies on the availability of conformational models from which the nuclear spin coupling and/or chemical shift parameters for the various possible rotamers are derived. In the absence of such models, the problem of conformational analysis is reduced to qualitative, or at best, semiquantitative level, for the necessary parameters must be estimated for the hypothetical conformational models from theoretical or empirical relationships or be obtained from "frozen out" rotamers at reduced temperatures.

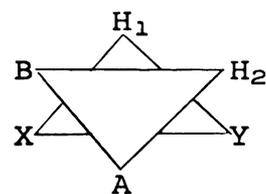
Conformational analysis of a compound can be successfully studied by employing either the time averaged coupling constants or the chemical shift parameters of appropriate nuclei. The work of Gutowsky and co-workers in substituted ethanes (6) amply illustrates such a case. The energetically favored forms, or rotamers, of substituted ethanes are the staggered configurations Ia, Ib and Ic. The experimentally observed



Ia



Ib



Ic

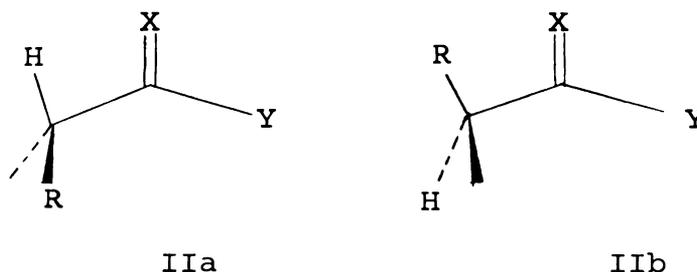
coupling constant, which is the time averaged coupling constant of Ia, Ib and Ic is given by equation (1), where J_t

$$J_{\text{obsd}} = X_{\text{Ia}} J_t + X_{\text{Ib}} J_g + X_{\text{Ic}} J_g \quad (1)$$

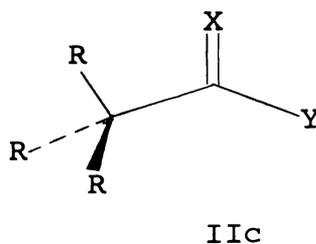
is the trans coupling (dihedral angle between H_1-C-C' and $C-C'-H_2$ planes is 180°), J_g the gauche coupling (dihedral angle is 60°) and the X's are the respective mole fractions. The factors governing the overall appearance of the n.m.r. spectra include the relative energies of the rotational isomers, the potential barriers to internal rotation about the C-C bond, and the chemical shifts and coupling constants characteristic of each rotamer. These quantities can be obtained most completely and directly for a compound if the potential barriers are high enough such that the n.m.r. spectrum at low temperatures is a superposition of spectra for the various rotamers. However, rotational averaging invariably occurs in most cases, which simplifies the spectrum but reduces its information content. Nonetheless, by careful estimation of J_t and J_g from theoretical and/or empirical relationships, the relative stabilities of the three rotamers have been calculated from the temperature dependence of the coupling constant.

Rotational isomerism about carbon-carbon single bond has been extensively studied for saturated hydrocarbons and substituted ethanes in the liquid phase. For example, ΔH° trans \rightarrow gauche is about +800 cal./mole for n-butane (7), +500

cal./mole for n-hexane (7), +730 cal./mole for 1,2-dibromoethane (8,9) and -900 cal./mole for 1,1,2,2-tetrabromoethane (10). There is, however, only very limited information on rotational isomerism involving a tetrahedral carbon bonded to a trigonal carbon. Therefore, the purpose of this research deals with investigations directed toward elucidation of the relative stabilities of rotamers IIa and IIb as functions of X, Y and R by n.m.r.



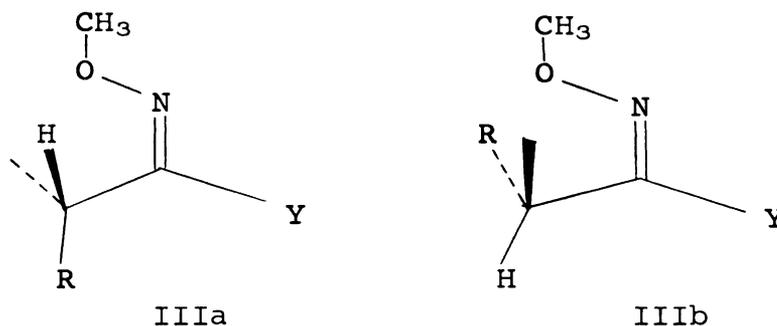
Several investigations have shown that the stable conformation of a tetrahedral carbon bonded to a trigonal carbon is IIc, whereby a single bond (C-R) eclipses the C=X



double bond. These include Raman and infrared studies on chloroacetone (11), haloacetyl halides (12,13) and N-methylchloroacetamide (14); microwave studies on acetaldehyde (15), propionaldehyde (16), acetyl chloride (17) and propene (18); electron diffraction studies on aliphatic ketones (19) and

aldehydes (20,21); and nuclear magnetic resonance studies on propionaldehyde (22) and olefins (23,24,25,26,27). Furthermore, the coupling constant of propionaldehyde has been found to be temperature dependent. On the basis of these evidences, rotational isomerism in aliphatic aldehydes ($X=O$) and oxime O-methyl ethers ($X=NOCH_3$) were studied, using the same general approach as in substituted ethanes.

The oxime O-methyl ethers represent an interesting case where both rotational and configurational isomerism can be studied simultaneously. They are suitable for the elucidation of the relative stabilities of IIa and IIb as functions of X, Y and R. Furthermore, because of configurational isomerism about the carbon-nitrogen double bond, they are also suitable models for studying the relative stabilities of IIa and IIb not only when the tetrahedral carbon is cis to the lone pair of electrons, but also when it is cis to the methoxy group. In the latter case, IIa and IIb may be sufficiently destabilized to make IIIa and IIIb competitive in stability with IIa and IIb. Cyclopropanecarboxaldehyde (21) and ethyl α, α -difluoro- and α, α -dichloroacetates (28) have been reported to have two-fold rather than three-fold barriers to rotation.



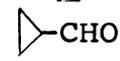
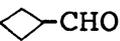
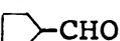
RESULTS

A. Aliphatic Aldehydes

Table I summarizes the coupling constants at various temperatures between the aldehydic proton and the α -protons of all the aliphatic aldehydes investigated. All coupling constant values were measured at 50 c.p.s. sweep width and were averages of several measurements with an accuracy of ± 0.03 c.p.s. To ensure internal consistency values were always checked against the coupling constant of acetaldehyde, 2.85, 2.88 and 2.90 c.p.s. at 36° , 0° and -30° , respectively (22,29).

The coupling constants of these aliphatic aldehydes except those of t-butylacetaldehyde, di-t-butylacetaldehyde and cyclopropanecarboxaldehyde are smaller than that of acetaldehyde. The coupling constants of monosubstituted acetaldehydes increase with increase in temperature, except that of t-butylacetaldehyde, which decreases with increase in temperature and that of phenylacetaldehyde which is temperature independent. The coupling constants of disubstituted acetaldehydes vary as follows: (1) when one of the substituents is methyl, the coupling constants increase with increase in temperature, and (2) when neither substituent is methyl, the coupling constants decrease with increase in temperature.

Table I. Spin-spin Coupling Constants^a of Aldehydes

Aldehyde	J_{CHCHO}			
	-30°	0°	36°	70°
CH_3CHO	2.90	2.88	2.85	
MeCH_2CHO	1.06	1.22	1.31	
EtCH_2CHO	1.42	1.53	1.69	1.80
$\underline{n}\text{-PrCH}_2\text{CHO}$	1.51	1.60	1.75	1.80
$\underline{n}\text{-AmCH}_2\text{CHO}$	1.48 ^b	1.56	1.73	1.78
$\underline{i}\text{-PrCH}_2\text{CHO}$	1.81	1.88	1.92	2.05
$\underline{t}\text{-BuCH}_2\text{CHO}$	2.95	2.94	2.92	2.84
$\text{C}_6\text{H}_5\text{CH}_2\text{CHO}$			2.18	2.20
				2.24 ^c
	2.40 ^b	2.40 ^b	2.40 ^b	2.43 ^b
$(\text{Me})_2\text{CHCHO}$	1.01	1.12	1.17	1.35 ^d
$(\text{Et})_2\text{CHCHO}$	2.52	2.35	2.36	2.25
$(\underline{t}\text{-Bu})_2\text{CHCHO}$	6.20 ^b		6.00 ^b	5.75 ^b
$\text{Me}(\text{Et})\text{CHCHO}$	1.56	1.60	1.67	1.70
$\text{Me}(\underline{n}\text{-Pr})\text{CHCHO}$	1.45	1.59	1.76	1.75
$\text{Me}(\text{C}_6\text{H}_5)\text{CHCHO}$	1.07	1.25	1.31	1.45
$\text{Et}(\underline{n}\text{-Bu})\text{CHCHO}$	2.70 ^b	2.55	2.52	2.35
 -CHO	6.14	5.95	5.75	5.35
 -CHO	1.72		1.82	
 -CHO	2.11	2.12	2.12	2.05
 -CHO	0.92	1.03	1.14	1.15

^aUnless otherwise denoted all coupling constants are those of neat solutions; values in c.p.s.

^bAbout 10% solution in carbon tetrachloride.

^cValue at 90° .

^dValue at 60° .

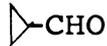
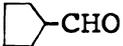
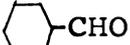
The coupling constants of cycloalkanecarboxaldehydes vary as follows: (1) those of cyclobutyl and cyclohexyl increase with increase in temperature, (2) that of cyclopropyl decreases appreciably with increase in temperature and (3) that of cyclopentyl is almost temperature independent.

Table II summarizes the effect of solvents on the coupling constants of several aldehydes. The coupling constants increase with increase in solvent polarity, except that of acetaldehyde, which shows only small variations and that of phenylacetaldehyde, which decreases with increase in solvent polarity.

The vicinal proton-proton coupling constant depends on several parameters and a qualitative estimate of the trends to be expected has been made by Karplus (30,31). According to the predications of valence bond calculations (30,32,33), the vicinal coupling constant depends on the dihedral angle ϕ , the hybridization, the HCC bond angles and the C-C bond length. It is certainly reasonable to assume that the changes of coupling constants observed for the aliphatic aldehydes result mainly, if not exclusively, from the changes of the dihedral angle.

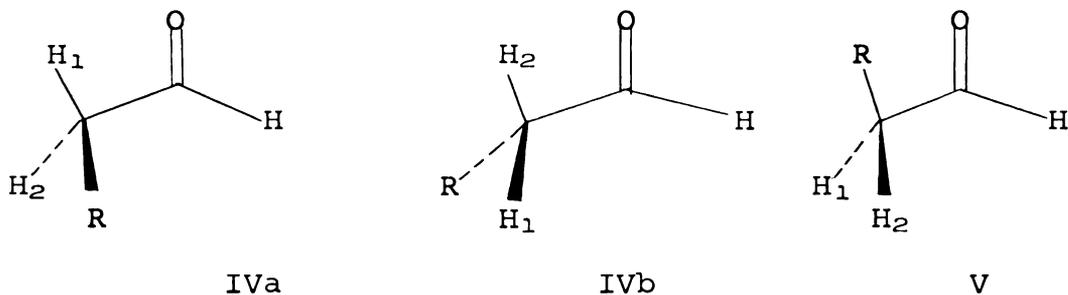
The temperature dependence of the coupling constant indicates that the relative stabilities of the various rotamers of a substituted acetaldehyde can be at least qualitatively assessed. Assuming $J_t > J_g$, where J_t is the trans coupling constant (dihedral angle of vicinal protons 180°) and J_g the

Table II. Solvent Effects on J_{CHCHO} of Aldehydes

Aldehyde	J_{HH} , c.p.s. ^a		
	Cyclohexane	Nitrobenzene	Acetonitrile
CH_3CHO	2.79	2.83	2.87
MeCH_2CHO	1.25	1.30	1.33
$\text{t-BuCH}_2\text{CHO}$	2.80	2.93	3.05
$(\text{Et})_2\text{CHCHO}$	2.25	2.40	2.55
$\text{Me}(\text{Et})\text{CHCHO}$	1.63	1.70	1.78
$\text{Et}(\text{n-Bu})\text{CHCHO}$	2.40	2.60	2.70
 -CHO	5.05	5.60	5.80
 -CHO	1.97	2.15	2.30
 -CHO	1.00	1.15	1.20
$\text{C}_6\text{H}_5\text{CH}_2\text{CHO}$	2.40	2.18	2.00

^aAll values are at 36°.

gauche coupling constant (dihedral angle 60°), the observed coupling constant which is an average of the contributions from all the rotamers should be independent of temperature if IVa, IVb and V are energetically equivalent. If V is



more stable than IVa, the coupling constant should increase with increase in temperature; and if less stable, it should decrease. Similarly, for disubstituted acetaldehydes and cycloalkanecarboxaldehydes, the observed coupling constant should be independent of temperature if VI, VIIa and VIIb (also, VIII, IXa and IXb) are energetically equivalent. If VIIa is more stable than VI (also IXa more stable than VIII), the coupling constant should increase with increase in temperature and if less stable, it should decrease.

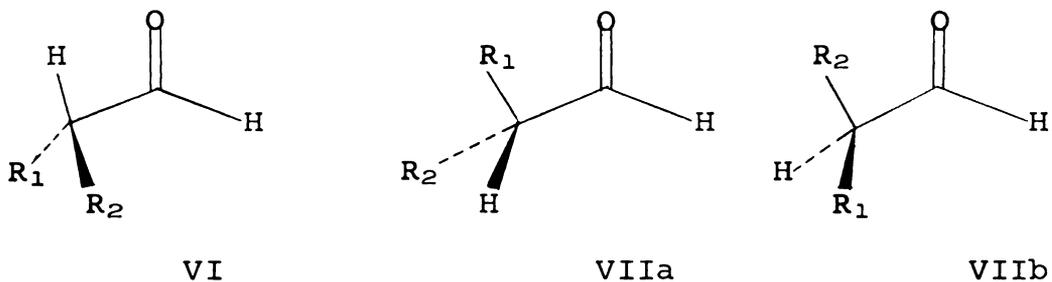


Table III. Relative Population of Aldehydic Rotamers^a

Aldehyde				
	-30°	0°	36°	70°
MeCH ₂ CHO	23	31	34	
EtCH ₂ CHO	37	40	45	48
<u>n</u> -PrCH ₂ CHO	39	42	46	48
<u>n</u> -AmCH ₂ CHO	39 ^c	41	46	47
<u>i</u> -PrCH ₂ CHO	48	50	51	55
<u>t</u> -BuCH ₂ CHO	80	79	79	77
C ₆ H ₅ CH ₂ CHO	65 ^c	65 ^c	64 ^c (58)	66 ^c (60)
(Me) ₂ CHCHO	19	20	21	23 ^d
(Et) ₂ CHCHO	40	37	37	36
(<u>t</u> -Bu) ₂ CHCHO	92 ^c		89 ^c	85 ^c
Me(Et)CHCHO	26	27	28	
Me(<u>n</u> -Pr)CHCHO	25	27	29	
Me(C ₆ H ₅)CHCHO	19	22	23	25
Et(<u>n</u> -Bu)CHCHO	42 ^c	40	40	37
-CHO	91	88	85	80
-CHO	28		30	
-CHO	34	34	34	33
-CHO	17	19	20	21

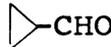
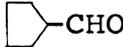
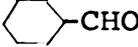
^aUnless otherwise indicated these values are those of neat solutions.

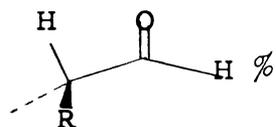
^bThe remaining per cent corresponds to the rotamer having the R group eclipsing the carbonyl

^cAbout 10% solution in carbon tetrachloride.

^dValue from 60°.

Table IV. Solvent Effect on the Relative Populations of Aldehydic Rotamers

Aldehyde	Cyclohexane	Acetonitrile
	36°	36°
MeCH ₂ CHO	33	35
<u>t</u> -BuCH ₂ CHO	78	83
(Et) ₂ CHCHO	36	40
Me(Et)CHCHO	27	29
Et(<u>n</u> -Bu)CHCHO	38	42
 -CHO	76	86
 -CHO	32	37
 -CHO	19	21
C ₆ H ₅ CH ₂ CHO	65	53



also of substituted acetaldehydes at very high temperatures (approaching free rotation) or at all temperatures if the various rotamers should happen to be energetically equivalent. Assuming t-butylacetaldehyde exists exclusively in IV, equation 5 expresses its coupling constant. Solution of equation 4 and equation 5 gives $J_t = 3.1$ and $J_g = 2.7$ c.p.s. If these values are correct, then the maximum value of the

$$J_{\text{obsd}} = 1/2 (J_t + J_g) \quad (5)$$

coupling constant for any substituted acetaldehyde would be equal to 3.1 c.p.s. It is obvious, therefore, that these values are incorrect, since the coupling constant for di-t-butylacetaldehyde is 6.2 c.p.s. Assuming di-t-butylacetaldehyde exists exclusively in VI, J_t should have a value of 6.2 c.p.s. and J_g a value of 1.2 c.p.s. These values represent the lower and upper limits respectively.

It is incorrect to assume that J_t and J_g are the same for acetaldehyde, monosubstituted acetaldehydes and disubstituted acetaldehydes, as substitution of an alkyl group for a proton decreases the coupling constant. For example, while the coupling constant of ethane (34) is 8.0 c.p.s., those of propane (35) and isobutane (36) are only 7.3 and 6.8 c.p.s. Considerations based on electronegativity have shown that the substitution of an alkyl group for a proton should decrease the coupling constant by 0.3 to 0.5 c.p.s. (37,38). It can be shown that in aliphatic aldehydes each

alkyl (also phenyl) substituent decreases the average coupling constant by about 0.4-0.5 c.p.s. For example, while the coupling constant of acetaldehyde (temperature independent) is 2.85 c.p.s., that of phenylacetaldehyde (monosubstituted and temperature independent) is only 2.40 c.p.s., and that of cyclopentanecarboxaldehyde (disubstituted and temperature independent) is about 2.1 c.p.s. When the coupling constants of various disubstituted acetaldehydes are plotted against temperature, as shown in Figure 1, the lines converge on extrapolation at high temperatures (approaching free rotation) around about 2.0 c.p.s. rather than 2.8 c.p.s. The difference of about 0.8 c.p.s. thus represents the combined effect of both alkyl substituents on the average coupling constant. In other words, each alkyl substituent decreases the average coupling constant by about 0.4 c.p.s.

A more rigorous and direct approach involves the simultaneous evaluation of J_t , J_g and ΔH° for each substituted acetaldehyde. For monosubstituted acetaldehydes, these quantities could be evaluated from eq. 7 and for disubstituted acetaldehydes from equation 9.

$$K_{eq.}(\text{monosubstituted}) = 2(1-x)/x \quad (6)$$

$$\Delta H^\circ = -RT \ln(J_t - J_g - 2 J_{obsd}) / (J_{obsd} - J_g) \quad (7)$$

$$K_{eq.}(\text{disubstituted}) = (1-y)/2y \quad (8)$$

$$\Delta H^\circ = -RT \ln 1/2(J_t - J_{obsd}) / (J_{obsd} - J_g) \quad (9)$$

This approach requires $\Delta S^\circ = 0$ for the equilibrium between the various rotamers. This assumption may be correct if the

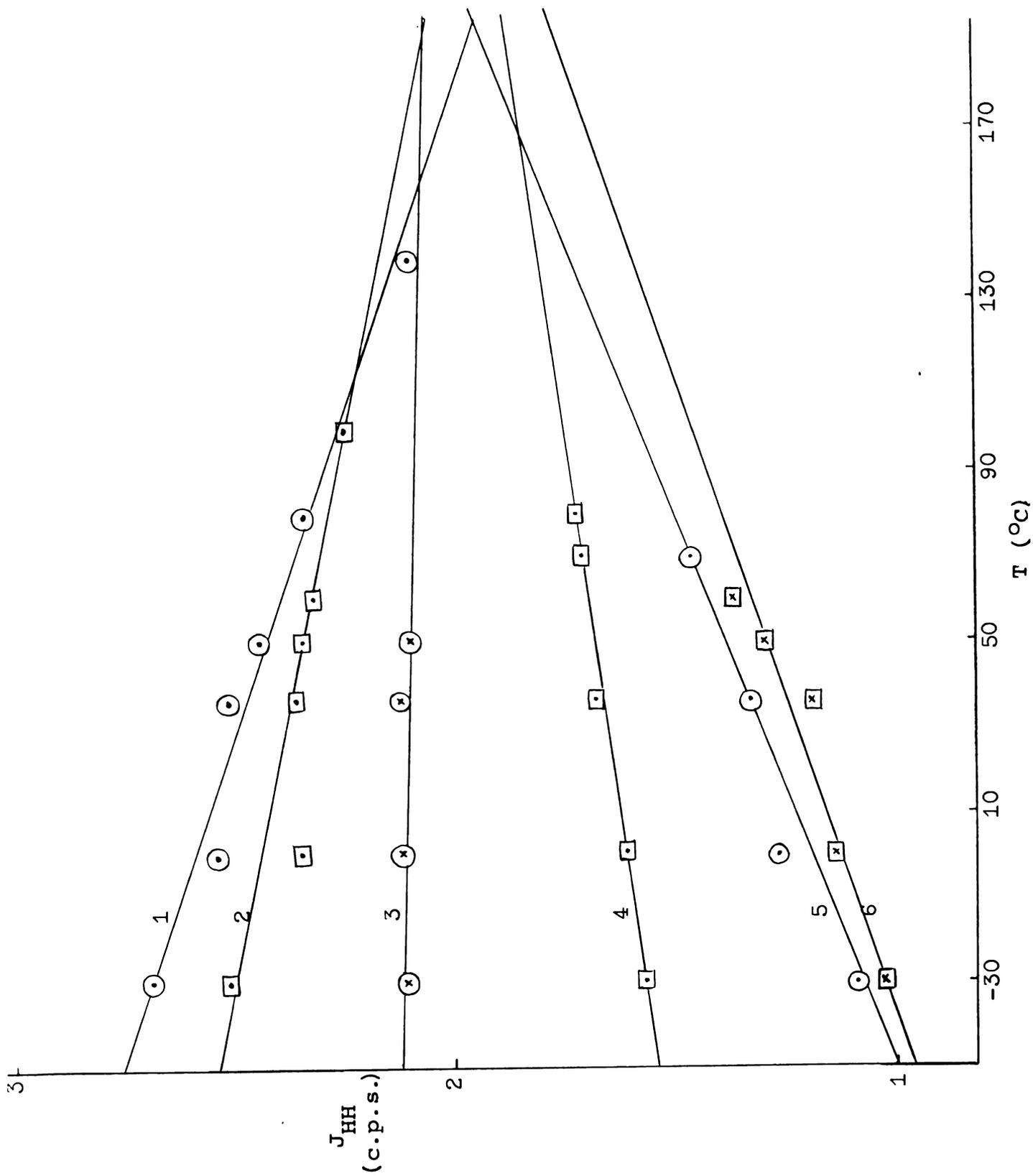


Figure 1. 1, $\text{Et}(\underline{n}\text{-Bu})\text{CHCHO}$; 2, $(\text{Et})_2\text{CHCHO}$; 3, $\text{C}_5\text{H}_9\text{CHO}$; 4, $\text{Me}(\text{Et})\text{CHCHO}$; 5, $\text{Me}(\text{C}_6\text{H}_5)\text{CHCHO}$; and 6, $(\text{Me})_2\text{CHCHO}$.

substituent is a relatively small group, such as a methyl; it could hardly be true when the substituent is a larger alkyl group, e.g., t-butyl group, as rotation of this group would be much more hindered in V than in IV.

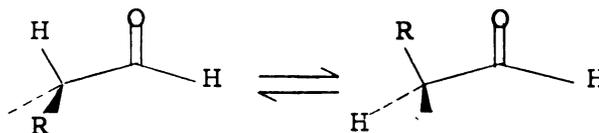
The difficulties involved with the exact solution of equations 7 and 9 for each substituted acetaldehyde have necessitated the use of a much simpler, though less rigorous, approach to this problem. If J_t and J_g for acetaldehyde could be ascertained, it is possible to use these values for all substituted acetaldehydes by correcting J_{obsd} for the effect of an alkyl substituent; namely, 0.4 c.p.s. The values that give the most consistent results are $J_t = 7.6$ and $J_g = 0.5$ c.p.s. (calculated from equation 4). A J_t of 7.6 c.p.s. for acetaldehyde is certainly reasonable. This value is chosen for the following reasons: (1) J_t should have a lower limit of 7.0 c.p.s. ($6.2 + 0.8$), as the highest coupling constant value for di-t-butylacetaldehyde is 6.2 c.p.s. and (2) a 7.7 c.p.s. coupling constant is observed with α, β -unsaturated aldehydes (39), which supposedly exist in the s-trans conformation. The data in Tables III and IV were calculated from equation 10 for monosubstituted acetaldehydes and equation 11 for disubstituted acetaldehydes using 0.4 c.p.s. as the correction factor for each alkyl or aryl substituent.

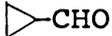
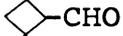
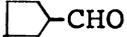
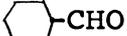
$$J_{obsd} + 0.4 = x (J_t + J_g)/2 + (1 - x)J_g \quad (10)$$

$$J_{obsd} + 0.8 = yJ_t + (1 - y)J_g \quad (11)$$

Table V summarizes the enthalpy differences, calculated from plots of $\log K$ vs $1/T$, between individual rotamers; e.g., V vs IVa, VI vs VIIa and VIII vs IXa. Table VI summarizes the effect of solvent on the free energy difference at 36° between such individual rotamers. For disubstituted acetaldehydes where $R_1 \neq R_2$, ΔH° and ΔG° values were calculated assuming VIIa and VIIb were equivalent. These values are therefore only meaningful for serving as a basis for comparison.

The accuracy of ΔH° and ΔG° values depends on the values chosen for J_t , J_g and the correction factor for substituent effect. To obtain an estimate on this accuracy, these values were calculated as functions of J_t , J_g and the substituent effect. The results were as follows: (1) with the substituent corrections set at 0.3 and 0.5 c.p.s., these values increased and decreased by about 5%, and (2) by changing J_t from 7.2 to 8.0 c.p.s., they varied by approximately 10%. Other factors that might affect the accuracy of these values are experimental errors, changes in the dielectric constants of liquids with temperature and contributions from excited states and torsional oscillations. Therefore an error of $\pm 30\%$ seems to be a reasonable upper estimate of the accuracy of these values.

Table V. ΔH° Values for

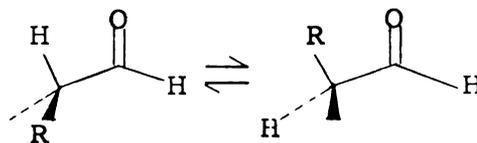
Aldehyde	ΔH° cal./mole ^a
MeCH ₂ CHO	-800
EtCH ₂ CHO	-700
<u>n</u> -PrCH ₂ CHO	-600
<u>n</u> -AmCH ₂ CHO	-500
<u>i</u> -PrCH ₂ CHO	-400
<u>t</u> -BuCH ₂ CHO	+250
C ₆ H ₅ CH ₂ CHO	-300 (0 ^b)
(Me) ₂ CHCHO	-500
(Et) ₂ CHCHO	+250
(<u>t</u> -Bu) ₂ CHCHO	+1100 ^b
Me(Et)CHCHO	-200 ^c
Me(<u>n</u> -Pr)CHCHO	-200 ^c
Me(C ₆ H ₅)CHCHO	-400 ^c
Et(<u>n</u> -Bu)CHCHO	+300 ^c
 -CHO	+1500
 -CHO	-150 ^d
 -CHO	~0
 -CHO	-400

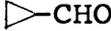
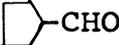
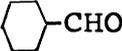
^aUnless otherwise stated these are values of neat solutions.

^bFrom about 10% solution in carbon tetrachloride.

^cThese values were calculated as if $R_1 = R_2$.

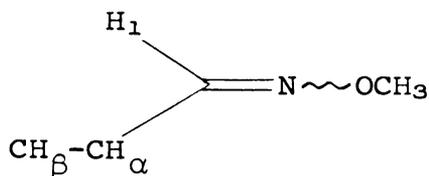
^dCalculated from only two temperatures.

Table VI. ΔG_{36}° as Function of Solvent

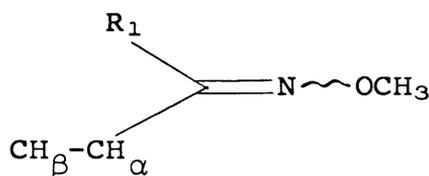
Aldehyde	ΔG_{36}° cal./mole	
	Cyclohexane	Acetonitrile
MeCH ₂ CHO	-880	-820
<u>t</u> -BuCH ₂ CHO	+330	+550
(Et) ₂ CHCHO	+70	+180
Me(Et)CHCHO	-180	-120
Et(<u>n</u> -Bu)CHCHO	+130	+230
 CHO	+1100	+1500
 CHO	-30	+90
 CHO	-480	-380
C ₆ H ₅ CH ₂ CHO	-50	-340

B. Oxime O-Methyl EthersI. Chemical Shifts

Table VII summarizes the chemical shifts of the oxime O-methyl ethers when in neat liquid, in benzene, or in carbon tetrachloride. The notation used to distinguish various protons is shown in Xa and Xb. Each proton is referred to as

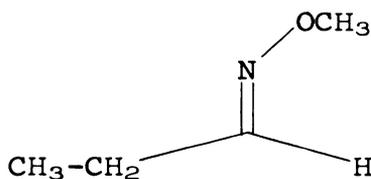


Xa

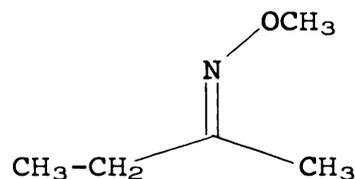


Xb

cis or trans with respect to the methoxy group. For simplicity, the following convention is used throughout the text: the syn isomer has the methoxy group cis to the smaller R group, e.g., the syn isomer of propionaldehyde oxime O-methyl ether has structure XI and that of 2-butanone oxime O-methyl ether



XI



XII

structure XII. Similarly the anti isomer has the methoxy group trans to the smaller R group.

Assignments of protons as cis or trans are based on the unequal isomer distribution for unsymmetrical oxime O-methyl ethers. Using the accepted concepts of steric effects, the more intense of the two signals was assigned to the syn isomer.

Table VII. Chemical Shifts (τ -Values) of Oxime O-Methyl Ethers

R_1	R_2	Solvent	H_α		$H_\alpha(CH_3)$		$H_\alpha(CH_2)$		$H_\alpha(CH)$		$H_\beta(CH_3)$		OCH_3	
			cis	trans	cis	trans	cis	trans	cis	trans	cis	trans	cis	trans
	CH ₃	Neat	2.70	3.35	8.27	8.27							6.20	6.27
	CH ₃	CCl ₄	2.77	3.45	8.25	8.21							6.23	6.32
	CH ₃	C ₆ H ₆	2.98	3.55	8.47	8.55							6.20	6.26
	CH ₂ C(CH) ₃	Neat	2.65	3.39			7.75	7.93					6.18	6.13
	CH ₂ C(CH ₃) ₃	CCl ₄	2.73	3.45			7.84	7.99					6.29	6.25
	CH ₂ C(CH ₃) ₃	C ₆ H ₆		3.33			7.77	8.04					6.16	6.13
	CH ₂ C ₆ H ₅	Neat	2.58	3.28			6.37	6.60					6.18	6.13
	CH ₂ C ₆ H ₅	CCl ₄	2.67	3.37			6.40	6.57					6.22	6.13
	CH ₂ C ₆ H ₅	C ₆ H ₆		3.33			6.42	6.72					6.18	6.12
	CH(CH ₃) ₂	Neat	2.77	3.61					6.92	7.57	8.99	8.93	6.20	6.14
	CH(CH ₃) ₂	CCl ₄	2.87	3.72					7.03	7.62	8.99	8.93	6.31	6.25
	CH(CH ₃) ₂	C ₆ H ₆		3.67					6.90	7.75	9.17	9.12	6.18	6.17
	CH(CH ₂ CH ₃) ₂	Neat	2.90	3.73					7.16	7.92			6.18	6.15
	CH(CH ₂ CH ₃) ₂	CCl ₄	2.98	3.80						7.90			6.30	6.26
	CH(CH ₂ CH ₃) ₂	C ₆ H ₆	2.85	3.73					6.97	8.03			6.18	6.18
	CH[C(CH ₃) ₃] ₂	Neat							8.10				6.20	
	CH[C(CH ₃) ₃] ₂	CCl ₄	2.83						8.15				6.25	
	CH[C(CH ₃) ₃] ₂	C ₆ H ₆	2.53						8.04				6.20	
		Neat	3.13	4.15									6.23	6.14
		CCl ₄	3.03	4.25									6.30	6.21

Continued

TABLE VII - Continued

R ₁ R ₂ C=NOCH ₃	Solvent	H ₁		H _α (CH ₃)		H _α (CH ₂)		H _α (CH)		H _β (CH ₃)		OCH ₃	
		cis	trans	cis	trans	cis	trans	cis	trans	cis	trans	cis	trans
	C ₆ H ₆	3.15	4.28									6.21	6.12
	Neat	2.75	3.53					6.85	7.40			6.23	6.18
	C ₆ H ₆	2.70	3.53					6.75	7.50			6.17	6.13
	Neat	2.82	3.65									6.22	6.18
	CCl ₄	2.88	3.73									6.32	6.27
	C ₆ H ₆		3.62									6.15	6.13
I ₃ CH ₃	Neat			8.22	8.20							6.25	6.25
I ₃ CH ₃	CCl ₄			8.25	8.21							6.29	6.29
I ₃ CH ₃	C ₆ H ₆			8.37	8.39							6.18	6.18
I ₃ CH ₂ CH ₃	Neat			8.24	8.22			7.83		9.00	8.96	6.21	6.22
I ₃ CH ₂ CH ₃	CCl ₄			8.27	8.23			7.88		8.98	8.94	6.28	6.30
I ₃ CH ₂ CH ₃	C ₆ H ₆			8.31	8.33			7.97		9.13	9.06	6.12	6.12
I ₃ CH ₂ C(CH ₃) ₃	Neat			8.18	8.16	7.75	7.93					6.17	6.25
I ₃ CH ₂ C(CH ₃) ₃	CCl ₄			8.23	8.18	7.82	7.98					6.27	6.33
I ₃ CH ₂ C(CH ₃) ₃	C ₆ H ₆			8.20	8.37	7.76	7.97					6.11	6.19
I ₃ CH ₂ C ₆ H ₅	Neat			8.32	8.33	6.33	6.57					6.12	6.13
I ₃ CH ₂ C ₆ H ₅	CCl ₄			8.33	8.30	6.39	6.61					6.17	6.17
I ₃ CH ₂ C ₆ H ₅	C ₆ H ₆			8.35	8.37	6.38	6.63					6.09	6.11
I ₃ CH(CH ₃) ₂	Neat			8.29	8.29			6.65	7.58	9.03	8.96	6.27	6.27

Continued

TABLE VII - Continued

R_1	R_2	Solvent	H_1		$\text{H}_\alpha(\text{CH}_3)$		$\text{H}_\alpha(\text{CH}_2)$		$\text{H}_\alpha(\text{CH})$		$\text{H}_\beta(\text{CH}_3)$		OCH_3	
			cis	trans	cis	trans	cis	trans	cis	trans	cis	trans	cis	trans
I_3	$\text{CH}(\text{CH}_3)_2$	CCl_4	8.30	8.29					6.68	7.58	9.02	8.94	6.28	6.30
I_3	$\text{CH}(\text{CH}_3)_2$	C_6H_6	8.33	8.38					6.54	7.62	9.14	9.04	6.18	6.18
I_3	C_6H_5	Neat	7.88										6.02	6.18
I_3	C_6H_5	CCl_4	7.84										6.05	6.23
I_3	C_6H_5	C_6H_6	7.92										6.04	6.18
I_2CH_3	CH_2CH_3	Neat			7.72	7.82			8.98	8.95	8.98	8.95	6.22	
I_2CH_3	CH_2CH_3	CCl_4			7.77	7.88			8.98	8.95	8.98	8.95	6.29	
I_2CH_3	CH_2CH_3	C_6H_6			7.73	7.93			9.06	8.99	9.06	8.99	6.13	
$\text{I}(\text{CH}_3)_2$	$\text{CH}(\text{CH}_3)_2$	Neat							6.95	7.51	8.92	8.89	6.23	23
$\text{I}(\text{CH}_3)_2$	$\text{CH}(\text{CH}_3)_2$	CCl_4							7.02	7.55	8.93	8.92	6.30	
$\text{I}(\text{CH}_3)_2$	$\text{CH}(\text{CH}_3)_2$	C_6H_6							6.87	7.56	8.92	8.89	6.18	
$\text{I}(\text{CH}_3)_2$	$\text{CH}_2\text{C}_6\text{H}_5$	Neat			6.30	6.54			6.73	7.58	9.11	8.98	6.15	6.13
$\text{I}(\text{CH}_3)_2$	$\text{CH}_2\text{C}_6\text{H}_5$	CCl_4			6.37	6.60				7.60	9.10	8.97	6.17	6.17
$\text{I}(\text{CH}_3)_2$	$\text{CH}_2\text{C}_6\text{H}_5$	C_6H_6			6.35	6.60			6.70	7.62	9.12	8.99	6.18	6.17
$\text{I}(\text{CH}_3)_2$	C_6H_5	Neat							6.47	7.22	8.89	8.83	6.08	6.24
$\text{I}(\text{CH}_3)_2$	C_6H_5	CCl_4							6.55	7.26	8.90	8.82	6.12	6.28
$\text{I}(\text{CH}_3)_2$	C_6H_5	C_6H_6							6.54	7.24	8.87	8.83	6.08	6.22

The assignments for symmetrical compounds were made to conform to those of the unsymmetrical ones. For more detailed discussion, refer to reference (40) and previous papers in that series.

The chemical shifts, calculated from first order spectral analysis, are accurate to ± 0.03 p.p.m., except those of ethyl, isopropyl, cyclopentyl and diethyl carbinyl groups, whose accuracy is less.

Table VIII summarizes the differences in chemical shifts of cis and trans protons, $\Delta\delta$, which are accurate to ± 0.001 p.p.m. A positive $\Delta\delta$ means the cis protons resonate at higher fields than the trans protons; a negative the reverse. The pertinent points are: (1) In neat liquid H_1 resonates at lower fields when cis than when trans to the methoxy, i.e., $\Delta\delta$ is negative (~ -0.08 p.p.m.); in benzene solution, $\Delta\delta$'s become more negative except that of acetaldoxime O-methyl ether. (2) In neat liquid, α -methyl protons resonate at slightly higher fields when cis than when trans, i.e., $\Delta\delta$ is positive, in benzene solution, the signals cross over, i.e., $\Delta\delta$ is negative. (3) In neat liquid, α -methylene and α -methine protons resonate at appreciably lower fields when cis than when trans, i.e., $\Delta\delta$ is negative. $\Delta\delta$ values for α -methine protons are comparable in magnitude to those of H_1 , whereas those for α -methylene protons are smaller. In benzene solution, $\Delta\delta$ values are about the same for α -methylene protons but become more negative for α -methine protons. (4) In neat

Table VIII. $\delta_{\text{cis}} - \delta_{\text{trans}}$ ($\Delta\delta$), in p.p.m., of Oxime O-Methyl Ethers ^a

R ₁	R ₂	$\frac{\Delta\delta(\text{H}_1)}{\text{C}_6\text{H}_6}$		$\frac{\Delta\delta(\alpha\text{-CH}_3)}{\text{C}_6\text{H}_6}$		$\frac{\Delta\delta(\alpha\text{-CH}_2)}{\text{C}_6\text{H}_6}$		$\frac{\Delta\delta(\alpha\text{-CH})}{\text{C}_6\text{H}_6}$		$\frac{\Delta\delta(\beta\text{-CH}_3)}{\text{C}_6\text{H}_6}$		$\frac{\Delta\delta(\text{OCH}_3)}{\text{C}_6\text{H}_6}$	
		Neat	C ₆ H ₆	Neat	C ₆ H ₆	Neat	C ₆ H ₆	Neat	C ₆ H ₆	Neat	C ₆ H ₆	Neat	C ₆ H ₆
H	CH ₃	-0.65	-0.57	+0.01	-0.08							0.00	-0.06
H	CH ₂ CH ₃	-0.83										+0.06	
H	CH ₂ CH ₂ CH ₃	-0.78										+0.08	+0.04
H	(CH ₂) ₅ CH ₃	-0.78	-0.82									+0.07	+0.05
H	CH ₂ CH(CH ₃) ₂	-0.74	-0.80			-0.25						+0.06	+0.04
H	CH ₂ C(CH ₃) ₃	-0.74				-0.18	-0.27					+0.05	+0.03
H	CH ₂ C ₆ H ₅	-0.70				-0.23	-0.30					+0.05	+0.06
H	CH(CH ₃) ₂	-0.84						-0.65	-0.85	+0.06	+0.05	+0.06	+0.01
H	CH(CH ₃)CH ₂ CH ₃	-0.85	-0.93					-0.72	-0.89	+0.08	+0.08	+0.05	0.00
H	CH(CH ₃)CH(CH ₃)CH ₂ CH ₃	-0.84						-0.75	-0.90			+0.02	0.00
H	CH(CH ₂ CH ₃) ₂	-0.83	-0.88					-0.76	-1.06			+0.03	0.00
H	CH(CH ₂ CH ₃)(CH ₂) ₃ CH ₃	-0.81						-0.83	-1.14			+0.03	0.00
H		-1.02	-1.13									+0.09	+0.09
H		-0.78	-0.85					-0.55	-0.75			+0.05	+0.04
H		-0.83										+0.04	+0.02
CH ₃	CH ₃			+0.02	-0.02								
CH ₃	CH ₂ CH ₃			+0.02	-0.02			-0.24		+0.04	+0.07	-0.01	0.00
CH ₃	CH ₂ CH ₂ CH ₃			+0.01	-0.02							-0.02	-0.02

Continued

Table VIII - Continued

R ₁ R ₂ C=NOCH ₃	R ₂	$\Delta\delta(H_1)$		$\Delta\delta(\alpha\text{-CH}_3)$		$\Delta\delta(\alpha\text{-CH}_2)$		$\Delta\delta(\alpha\text{-CH})$		$\Delta\delta(\beta\text{-CH}_3)$		$\Delta\delta(\text{OCH}_3)$	
		Neat	C ₆ H ₆	Neat	C ₆ H ₆	Neat	C ₆ H ₆	Neat	C ₆ H ₆	Neat	C ₆ H ₆	Neat	C ₆ H ₆
CH ₃	CH ₂ CH(CH ₃) ₂			+0.02	-0.09							-0.05	-0.05
CH ₃	CH ₂ C(CH ₃) ₃			+0.02	-0.17	-0.18	-0.21			-0.01 ^c	-0.02 ^c	-0.08	-0.08
CH ₃	CH ₂ C ₆ H ₅			-0.01	-0.02	-0.24	-0.25					-0.01	-0.02
CH ₃	CH(CH ₃) ₂			0.00	-0.05			-0.93	-1.08	+0.07	+0.10	0.00	0.00
CH ₃	C ₆ H ₅											-0.16	-0.14
CH ₂ CH ₃	CH ₂ CH ₃					-0.10	-0.20			+0.03	+0.05		
CH ₂ CH ₃	C ₆ H ₅											-0.18	-0.14
CH ₂ CH ₂ CH ₃	C ₆ H ₅											-0.17	-0.13
CH(CH ₃) ₂	CH(CH ₃) ₂							-0.56	-0.69	+0.03	+0.05		
CH(CH ₃) ₂	CH ₂ C ₆ H ₅					-0.24	-0.24	-0.85	-0.92	+0.13	+0.13	+0.02	+0.01
CH(CH ₃) ₂	C ₆ H ₅							-0.75	-0.70	+0.06	-0.04	-0.16	-0.14

^aNegative values mean that the cis to the methoxy proton resonates at a lower magnetic field than the trans; positive the reverse.

^bCis values for the methoxy group are those of the isomer having OCH₃ cis to R₁.

^c γ -Methyl.

liquid and in benzene solution, β -methyl protons resonate at higher fields when cis than when trans, i.e., $\Delta\delta$ is positive.

Table IX summarizes the $\Delta\nu$ values ($\Delta\nu = \nu$ in benzene - ν in carbon tetrachloride). A positive $\Delta\nu$ means that the proton resonates at a higher field in benzene than in carbon tetrachloride; a negative, the reverse. The most striking feature of the data is the lower field absorption of so many protons in benzene, which generally causes upfield shifts, than in carbon tetrachloride. The pertinent points for subsequent discussions are: (1) benzene shifts both cis and trans H_1 downfield, except those of acetaldehyde and cyclopropanecarboxaldehyde derivatives; cis protons are shifted more than trans. (2) Benzene shifts both cis and trans α -methyl protons upfield, except the cis protons of the methyl t-butyl ketone derivative. (3) Benzene shifts cis α -methylene and α -methine protons downfield, whereas it shifts the trans protons upfield, with the exception of the trans α -methine proton of the di-t-butyl-acetaldehyde derivative. (4) Benzene shifts both cis and trans β -methyl protons upfield, except the cis protons of the ethyl group of the ethyl t-butyl ketone derivative. (5) Benzene shifts methoxy protons downfield.

The half widths, 0.6-0.9 c.p.s., of cis- H_1 differ noticeably from those of trans- H_1 , 1.2-1.7 c.p.s., in the temperature range -30° to 90° . Similar broadening observed in formaldoxime O-methyl ether was attributed to incomplete quadrupole washout of J_{HCN} (41).

Table IX. ν in benzene $-\nu$ in carbon tetrachloride $(\Delta\nu)^a$, in c.p.s., of Oxime O-Methyl Ethers

R ₁	R ₂	$\Delta\nu(H_1)$		$\Delta\nu(\alpha-CH_3)$		$\Delta\nu(\alpha-CH_2)$		$\Delta\nu(\alpha-CH)$		$\Delta\nu(\beta-CH_3)$		$\Delta\nu(OCH_3)$	
		cis	trans	cis	trans	cis	trans	cis	trans	cis	trans	cis	trans
H	CH ₃	+12.6	+6.0	+13.2	+20.4							-1.8	-3.6
H	CH ₂ CH ₃		-1.8										
H	CH ₂ CH ₂ CH ₃		-3.0			+8.4 ^b						-7.8	-6.6
H	(CH ₂) ₅ CH ₃	-5.4	-1.8			+12.6 ^b						-9.0	-7.8
H	CH ₂ CH(CH ₃) ₂	-4.8	-1.2			+6.6 ^b						-8.4	-7.2
H	CH ₂ C(CH ₃) ₃	-7.2	-7.2			-4.2	+3.0					-7.8	-7.2
H	CH ₂ C ₆ H ₅	-2.4	-2.4			-1.2	+9.0					-2.4	-0.6
H	CH(CH ₃) ₂	-3.0	-3.0										
H	CH(CH ₃)CH ₂ CH ₃	-7.2	-1.2									-13.8	+7.8
H	CH(CH ₃)CH(CH ₃)CH ₂ CH ₃	-6.0	-6.0									+10.8	+11.4
H	CH(CH ₂ CH ₃) ₂	-7.8	-4.2									-9.0 ^b	+1.2 ^b
H	CH(CH ₂ CH ₃)(CH ₂) ₃ CH ₃	-4.8	-4.8									-11.4 ^b	+7.8
H	CH[C(CH ₃) ₃] ₂	-18.0	-18.0									-13.2 ^b	+5.4 ^b
H		+7.2	+1.8									-6.6	-6.6
H		-6.6	-6.6									-5.4	-5.4
CH ₃	CH ₃			+7.2	+10.8							-10.2	-8.4

Continued

Table IX - Continued

R ₁	R ₂	Δv(H ₁)		Δv(α-CH ₃)		Δv(α-CH ₂)		Δv(α-CH)		Δv(β-CH ₃)		Δv(OCH ₃)	
		cis	trans	cis	trans	cis	trans	cis	trans	cis	trans	cis	trans
CH ₃	CH ₂ CH ₃	+2.4	+6.0		+5.4					+9.0	+7.2	-9.6	-10.2
CH ₃	CH ₂ C(CH ₃) ₃	+1.8	+11.4	-3.6	-0.6							-9.6	-8.4
CH ₃	CH ₂ C ₆ H ₅	+1.2	+4.2	-0.6	+1.2							-4.8	-3.6
CH ₃	CH(CH ₃) ₂	+1.8	+5.4			-8.4	+2.4	+7.2	+6.0	+1.2		-6.0	-7.2
CH ₃	C(CH ₃) ₃	-0.6										-6.6	
CH ₃	C ₆ H ₅	+4.8										-0.6	-3.0
CH ₂ CH ₂	CH ₂ CH ₃			-2.4	+3.0			+4.8	+2.4			-9.6	
CH ₂ CH ₃	C(CH ₃) ₃			-0.6				-3.0				-1.2	
CH(CH ₃) ₂	CH(CH ₃) ₂					-9.0	+0.6					-7.2	
CH(CH ₃) ₂	CH ₂ C ₆ H ₅			-1.2	0.0	+1.2	+1.2	+1.2	+1.2	+1.2		-0.6	
CH(CH ₃) ₂	C ₆ H ₅					-0.6	-1.2	+13.2	+10.2			-2.4	-3.6

^aPositive values mean that resonance in benzene is at higher field; negative the reverse.

^b_v in benzene -^vneat.

II. Syn-anti Isomers

Table X summarizes syn and anti percentages (accurate to $\pm 5\%$) and the free energy differences between these isomers at 40° . Assuming the stabilities of these geometric isomers are mainly controlled by the steric factors of the sub-stituents, it seemed desirable to establish a relative scale of "effective" group size that could be applied to configurational isomerism about carbon-nitrogen double bonds. Unfortunately, the data failed to give any meaningful correlation between group size and isomer stability. For example, from the syn/anti ratio for acetaldoxime O-methyl ether methyl would have to be effectively smaller than hydrogen. From the aldehyde series ethyl would be smaller than any other alkyl group except methyl, benzyl, and cyclopropyl, yet from the ketone series it would have to be larger than all other n-alkyl groups including neopentyl. Similarly, from the methyl ketone series, phenyl would be larger than isopropyl, yet from direct competition between the two groups, the reverse would have to be true.

Table XI summarizes the ultraviolet spectra data of several oxime O-methyl ethers. Alkyl phenyl oxime O-methyl ethers were chosen, since the derivatives of the aliphatic carbonyl compounds show no strong absorption above $220 \text{ m}\mu$. The results show that as the alkyl group was varied from methyl to ethyl to isopropyl, and the percentage of the cis-phenyl isomer increased from 2% to 16% to 61%, both λ_{max} and ϵ decreased.

Table X. Syn and anti Percentages and ΔG_{40}° Values for syn \rightarrow anti of Oxime O-Methyl Ethers^a

$R_1R_2C=NOCH_3$		Percent	Percent	ΔG_{40}°
R_1	R_2	<u>syn</u> ^b	<u>anti</u>	(Kcal/mole)
H	CH ₃	48	52	-0.06
H	CH ₂ CH ₃	54	46	+0.10
H	CH ₂ CH ₂ CH ₃	61	39	0.28
H	(CH ₂) ₅ CH ₃	58	42	0.20
H	CH ₂ CH(CH ₃) ₂	58	42	0.20
H	CH ₂ C(CH ₃) ₃	64	36	0.36
H	CH ₂ C ₆ H ₅	51	49	0.02
H	CH(CH ₃) ₂	76	24	0.71
H	CH(CH ₃)CH ₂ CH ₃	71	29	0.55
H	CH(CH ₃)CH(CH ₃)CH ₂ CH ₃	69	31	0.48
H	CH(CH ₂ CH ₃) ₂	71	29	0.55
H	CH(CH ₂ CH ₃)(CH ₂) ₃ CH ₃	65	35	0.38
H	CH[C(CH ₃) ₃] ₂	100	0	
H		54	46	0.10
H		68	32	0.46
H		74	26	0.65
CH ₃	CH ₂ CH ₃	81	19	0.90
CH ₃	CH ₂ CH ₂ CH ₃	72	28	0.58
CH ₃	CH ₂ CH(CH ₃) ₂	74	26	0.64
CH ₃	CH ₂ C(CH ₃) ₃	76	24	0.71
CH ₃	CH ₂ C ₆ H ₅	71	29	0.56
CH ₃	CH(CH ₃) ₂	86	14	1.1
CH ₃	C(CH ₃) ₃	100	0	
CH ₂ CH ₃	CH(CH ₃) ₂	63	37	0.33
CH ₂ CH ₃	C(CH ₃) ₃	100	0	
CH ₃	C ₆ H ₅	98	2	2.4

Continued

Table X - Continued

$R_1R_2C=NOCH_3$		Percent <u>syn</u> ^b	Percent <u>anti</u>	ΔG_{40}° (Kcal/mole)
R_1	R_2			
CH ₂ CH ₃	C ₆ H ₅	84	16	1.0
CH ₂ CH ₂ CH ₃	C ₆ H ₅	80	20	0.85
CH(CH ₃) ₂	C ₆ H ₅	39	61	-0.28
CH ₂ C ₆ H ₅	CH(CH ₃) ₂	60	40	0.25

^aData from neat liquids.

^bSyn is the isomer having the methoxy group cis to R₁.

Table XI. Ultraviolet Spectra of Some Oxime O-Methyl Ethers in Cyclohexane

$R_1R_2C=NOCH_3$		$\lambda_{max}, m\mu$	$\epsilon \times 10^5$
R_1	R_2		
H	C_6H_5	263	13.8
CH_3	C_6H_5	252	10.8
CH_2CH_3	C_6H_5	248 ^a	8.5
$CH_2CH_2CH_3$	C_6H_5	248 ^a	7.7
$CH(CH_3)_2$	C_6H_5	236 ^b	5.0

^aWeak shoulder at about 262 $m\mu$.

^bWeak shoulder at about 247 $m\mu$.

III. Spin-spin Coupling Constants

Table XII summarizes the coupling constants between proton H_1 and the α -protons for the syn isomer of the oxime O-methyl ethers at various temperatures. All values were averages of several measurements with an accuracy of ± 0.03 c.p.s. To ensure internal consistency, values were always checked with the coupling constant of acetaldehyde. All coupling constants decreased with increase in temperature, except that of acetaldoxime O-methyl ether which remained constant. The coupling constant of cyclopropanecarboxaldehyde oxime O-methyl ether experienced the largest decrease, about 15% in the range -30° to 90° .

Table XIII summarizes the effect of solvent on the coupling constants for the syn isomers. Increase in solvent polarity increased the coupling constants, except that of the phenylacetaldehyde derivative, which decreased with increase in solvent polarity and that of the acetaldehyde derivative, which showed only small variations.

Table XIV summarizes the coupling constants between proton H_1 and the α -protons for the anti isomers of the oxime O-methyl ethers at various temperatures. Table XV summarizes the effect of solvent on the coupling constants of these isomers. Several features of the data are worth noting and comparing with those of the data for the syn isomers.

(1) There is an abrupt increase in the coupling constant in changing from the monosubstituted acetaldehyde derivatives

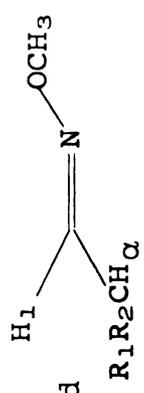
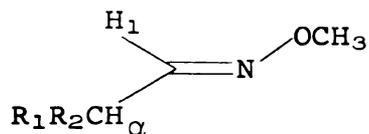


Table XII. Spin-spin Coupling Constants of Neat Liquid

		 $J_{H_1H_\alpha}$ (c.p.s.)					
R ₁	R ₂	-30°	0°	40°	50°	70°	90°
H	H	5.90	5.90	5.87			
H	CH ₃	5.92	5.87	5.80	5.75		
H	CH ₂ CH ₃	6.05	6.02	5.90	5.80		
H	(CH ₂) ₄ CH ₃	6.10	6.00	5.95	5.90	5.86	5.82
H	CH(CH ₃) ₂	6.40	6.38	6.30	6.20	6.20	6.20
H	C(CH ₃) ₃	6.85	6.85	6.83	6.80	6.60	6.50
H	C ₆ H ₅	6.60		6.55	6.55	6.50	6.40
CH ₃	CH ₃	6.18	6.05	6.00	5.90	5.80	
CH ₃	CH ₂ CH ₃	7.10	6.90	6.55	6.45	6.45	6.30
CH ₃	CH(CH ₃)CH ₂ CH ₃	7.25	7.20	6.95	6.80	6.80	6.75
CH ₂ CH ₃	CH ₂ CH ₃	7.95	7.75	7.35	7.20	7.15	7.00
CH ₂ CH ₃	(CH ₂) ₃ CH ₃	8.10	7.90	7.65	7.40	7.30	7.20
C(CH ₃) ₃	C(CH ₃) ₃	10.40 ^a	10.35	10.25	10.15	10.05	10.00
		8.70	8.50	7.85	7.70	7.55	7.40
		8.15 ^a	7.75 ^a	7.60 ^a	7.45 ^a	7.20 ^a	
		7.30	7.00	6.55	6.45	6.35	6.20
		6.15	6.05	5.75	5.65	5.60	5.55

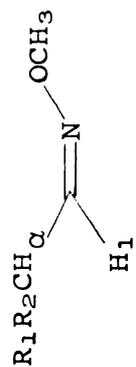
^aFrom a 10% carbon tetrachloride solution.

Table XIII. Effect of Solvent Polarity on $J_{H_1H_\alpha}$ of

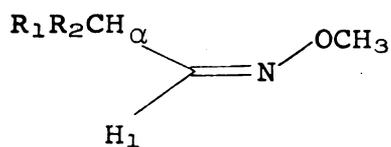
		$J_{H_1H_\alpha}$ (c.p.s.)	
R ₁	R ₂	Cyclohexane ^a	Acetonitrile ^a
H	H	5.88	5.90
H	CH ₃	5.70	5.90
H	CH ₂ CH ₃	5.95	6.15
H	(CH ₂) ₄ CH ₃	6.00	6.15
H	CH(CH ₃) ₂	6.30	6.50
H	C(CH ₃) ₃	6.90	6.90
H	C ₆ H ₅	6.65	6.55
CH ₃	CH ₃	5.80	6.05
CH ₃	CH ₂ CH ₃	6.60	6.95
CH ₃	CH(CH ₃)CH ₂ CH ₃	7.00	7.35
CH ₂ CH ₃	CH ₂ CH ₃	7.35	7.80
CH ₂ CH ₃	(CH ₂) ₃ CH ₃	7.65	8.05
C(CH ₃) ₃	C(CH ₃) ₃	10.35	10.45
		7.50	8.30
		6.50	7.05
		5.80	6.15

^a10% solutions at 40°.

Table XIV. Spin-spin Coupling Constants of Neat Liquid



R_1	R_2	-30°	0°	40°	50°	70°	90°
		$\text{J}_{\text{H}_1\text{H}_\alpha}$ (c.p.s.)					
H	H	5.62	5.50	5.57			
H	CH ₃	5.35	5.48	5.55	5.45		
H	CH ₂ CH ₃	5.40	5.45	5.50	5.45	5.45	
H	(CH ₂) ₄ CH ₃	5.40	5.45	5.50	5.40	5.55	5.50
H	CH(CH ₃) ₂	5.42	5.50	5.60	5.55	5.50	5.60
H	C(CH ₃) ₃	5.88	5.91	5.96	5.90	5.95	5.95
H	C ₆ H ₅	5.30	5.40	5.50	5.50	5.40	5.45
CH ₃	CH ₃	7.30	7.35	7.35	7.20	7.15	
CH ₃	CH ₂ CH ₃	7.75	7.78	7.65	7.60	7.50	7.45
CH ₃	CH(CH ₃)CH ₂ CH ₃	8.05	8.10	8.00	7.90	7.90	7.85
CH ₂ CH ₃	CH ₂ CH ₃	8.35	8.25	8.15	8.00	8.00	7.85
CH ₂ CH ₃	(CH ₂) ₃ CH ₃	8.35	8.35	8.25	8.15	8.10	8.05
		9.10	9.10	9.00	8.75	8.70	8.55
		7.20	7.05	7.00	6.85	6.80	6.75
		7.30	7.23	7.20	7.10	7.05	7.00

Table XV. Effect of Solvent Polarity on $J_{H_1H_\alpha}$ of

$ \begin{array}{c} R_1R_2CH_\alpha \\ \diagdown \\ \text{C}=\text{N}-OCH_3 \\ \diagup \\ H_1 \end{array} $		$J_{H_1H_\alpha}$ (c.p.s.)	
R_1	R_2	Cyclohexane (40°) ^a	Acetonitrile (40°) ^a
H	H	5.70	5.60
H	CH ₃	5.50	5.50
H	CH ₂ CH ₃	5.60	5.50
H	(CH ₂) ₄ CH ₃	5.60	5.60
H	CH(CH ₃) ₂	5.65	5.55
H	C(CH ₃) ₃	6.10	6.00
H	C ₆ H ₅	5.50	5.70
CH ₃	CH ₃	7.30	7.40
CH ₃	CH ₂ CH ₃	7.70	7.80
CH ₃	CH(CH ₃)CH ₂ CH ₃	8.10	8.25
CH ₂ CH ₃	CH ₂ CH ₃	8.30	8.40
CH ₂ CH ₃	(CH ₂) ₃ CH ₃	8.20	8.40
		8.80	9.25
		7.00	7.30
		7.20	7.40

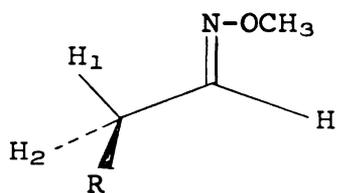
^a10% solutions.

to the disubstituted acetaldehyde derivatives. (2) Whereas the coupling constant of the disubstituted acetaldehyde derivatives decreased with increase in temperature, those of the monosubstituted acetaldehyde derivatives behaved irregularly. (3) The coupling constants of the disubstituted acetaldehyde derivatives increased with increase in solvent polarity. The coupling constants of the monosubstituted acetaldehyde derivatives, however, decreased slightly or remained unchanged, except that of the phenylacetaldehyde derivative, which increased with increase in solvent polarity. The fact that the coupling constants for the anti isomers of the disubstituted acetaldehyde derivatives behaved similarly to those of the syn isomers, whereas those of monosubstituted acetaldehyde derivatives did not, is important in subsequent discussions of the conformations of the syn and anti isomers.

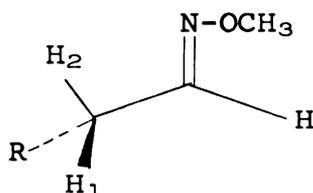
On the basis of the same considerations applied to the aldehydes, the relative stabilities of the various rotamers for the syn isomer of a substituted acetaldehyde derivative can be qualitatively assessed from the temperature dependence of the coupling constant. Equation 12 expresses the per cent

$$J_{\text{obsd}} = p(J_t + J_g)/2 + (1 - p)J_g \quad (12)$$

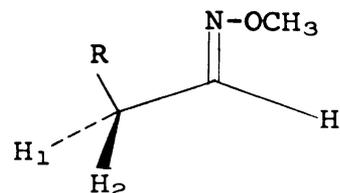
populations of the various rotamers for the syn isomer of the monosubstituted acetaldehyde derivatives, where p is the per cent population of XIII and $(1-p)$ that of XIV. Similarly, equation 13 expresses the per cent populations of the



XIIIa



XIIIb

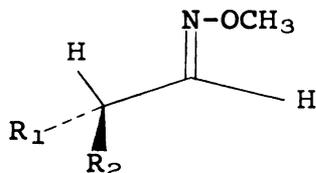


XIV

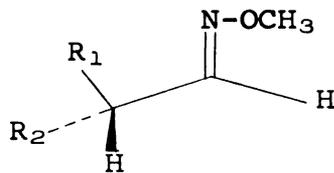
disubstituted acetaldehyde derivatives, where q is the per cent

$$J_{\text{obsd}} = qJ_t + (1-q)J_g \quad (13)$$

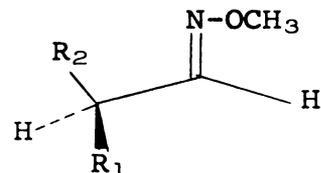
population of XV and $(1-q)$ that of XVI.



XV



XVIa



XVIb

Applying the same type of arguments used for the aldehydes, these values are calculated by evaluating J_t and J_g for acetaldoxime O-methyl ether. This could be done as follows. Assuming di-t-butylacetaldehyde oxime O-methyl ether exists exclusively in XV, then its J_{obsd} is J_t . J_g could then be calculated from equation 14 which expresses the coupling constant of acetaldoxime O-methyl ether. These values can be checked by assuming t-butylacetaldehyde oxime O-methyl

$$J_{\text{obsd}} = 1/3 (J_t + 2J_g) \quad (14)$$

ether also exists exclusively in XIII. From equation 15

$$J_{\text{obsd}} = 1/2 (J_t + J_g) \quad (15)$$

which expresses its coupling constant and equation 13, J_t and J_g can be calculated. However, this evaluation involves the incorrect assumption that J_t and J_g are the same for acetaldehyde, monosubstituted acetaldehyde and disubstituted acetaldehyde derivatives. The error thus introduced could be reduced by applying a correction factor for each alkyl or aryl substituent, just as in the case of the aldehydes. Using a correction factor of 0.4 c.p.s. for each substituent, the values $J_t = 11.3$ and $J_g = 3.2$ c.p.s. were obtained from both t-butyl and di-t-butyl acetaldehyde oxime O-methyl ethers. The small variation of the coupling constants of these two compounds at low temperatures and the insensitivity of the coupling constants to solvent polarity supports the assumption that they exist mainly in XIII and XV (hydrogen eclipsing the carbonyl).

Table XVI summarizes per cent populations of the various rotamers for the syn isomer of substituted acetaldehyde derivatives. These values were calculated from equation 16 for monosubstituted acetaldehyde derivatives and equation 17 for disubstituted acetaldehyde derivatives.

$$J_{\text{obsd}} + 0.4 = p(J_t + J_g)/2 + (1-p)J_g \quad (16)$$

$$J_{\text{obsd}} + 0.8 = qJ_t + (1-q)J_g \quad (17)$$

Table XVII summarizes the enthalpy differences that were calculated from plots of $\log K$ vs $1/T$. These values are probably accurate to $\pm 30\%$. In addition to errors of about 5-10%

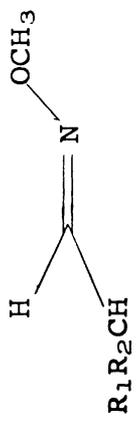
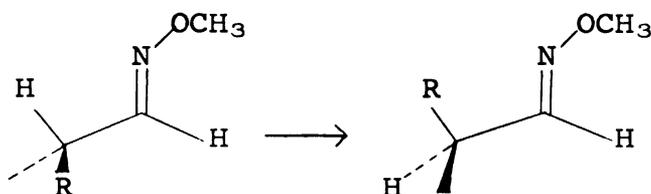


Table XVI. Rotamer Population of

R_1R_2CH		R_1R_2CH		R_1R_2CH		R_1R_2CH		R_1R_2CH	
R_1	R_2	-30°	0°	40°	50°	70°	90°	N-OCH ₃ %	
H	CH ₃	77	76	74	73				
H	CH ₂ CH ₃	80	79	76	74				
H	(CH ₂) ₄ CH ₃	81	79	78	76	75	74		
H	CH(CH ₃) ₂	89	88	86	84	84	84		
H	C(CH ₃) ₃	100	100		99	94	91		
H	C ₆ H ₅	88		85	85	83	79		
CH ₃	CH ₃	47	45	44	43	42			
CH ₃	CH ₂ CH ₃	58	55	51	50	50	48		
CH ₃	CH(CH ₃)CH ₂ CH ₃	60	59	56	54	54	53		
CH ₂ CH ₃	CH ₂ CH ₃	68	66	61	59	58	57		
CH ₂ CH ₃	(CH ₂) ₃ CH ₃	71	68	65	62	60	59		
C(CH ₃) ₃	C(CH ₃) ₃	99	98	97	96	95	94		
		78	76	68	66	64	62		
		71 ^a	66 ^a	64 ^a	63 ^a	59 ^a			
		61	57	51	50	49	47		
		46	45	42	40	39	39		

^aIn 10% solution in carbon tetrachloride.

Table XVII. ΔH° for

$RCH_2CH=NOCH_3$	ΔH° (cal/mole)
R	
CH ₃	+380
CH ₂ CH ₃	+570
(CH ₂) ₄ CH ₃	+590 (~500 ^a)
CH(CH ₃) ₂	+650
C(CH ₃) ₃	+4,500
C ₆ H ₅	+1,200
$R_1R_2CHCH=NOCH_3$	
R ₁ R ₂	
CH ₃ CH ₃	+300
CH ₂ CH ₃ CH ₂ CH ₃	+700
C(CH ₃) ₃ C(CH ₃) ₃	+4,400
	+1,200 (~800 ^a)
	+780
	+450

^aFrom 5% solution in carbon tetrachloride.

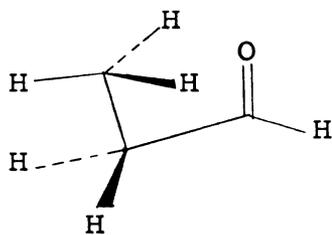
that are introduced by experimental uncertainties in J_{obsd} and temperature control, appreciable and presently undeterminable errors may be introduced by disregarding the contributions to J_{obsd} from torsional oscillations and excited vibrational states and by using only one set of J_t and J_g for all monosubstituted and disubstituted acetaldehyde derivatives.

DISCUSSION

A. Aliphatic Aldehydes

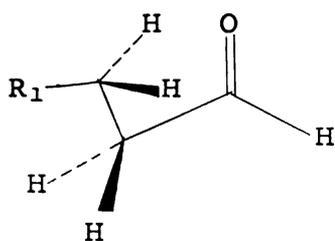
I. Monosubstituted Acetaldehydes

When R is methyl, ethyl, n-propyl, n-amyl or isopropyl, V (alkyl eclipsing the carbonyl) is more stable than IVa or IVb (hydrogen eclipsing the carbonyl). When R is t-butyl, V is less stable than IVa or IVb. The 800 cal./mole enthalpy difference between IVa and V when R is methyl is comparable to the 900 cal./mole difference obtained by microwave (16) and 1000 cal./mole difference obtained by nuclear magnetic resonance spectroscopy (22). Wilson and Butcher (16) proposed XVII as the structure for the most stable rotamer for

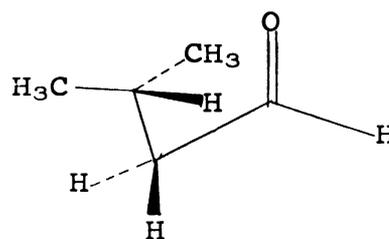


XVII

propionaldehyde. Therefore it is quite reasonable to assign structure XVIII when R is ethyl, n-propyl and n-amyl and structure XIX when R is isopropyl as the most stable rotamer for the monosubstituted acetaldehydes.

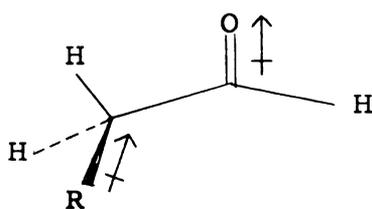


XVIII

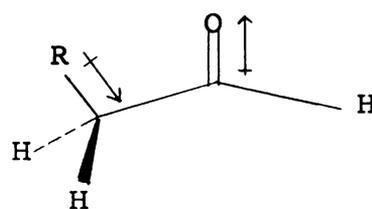


XIX

The relative populations of IV and V are solvent dependent. For all monosubstituted acetaldehydes except when R is phenyl, the population of V (alkyl eclipsing the carbonyl) decreases as the solvent polarity increases; e.g., when R is *t*-butyl the population of V is 23% in cyclohexane and 17% in acetonitrile. This means the free energy difference ΔG° IV \rightarrow V becomes more positive in going from cyclohexane to acetonitrile. Such changes with solvent polarity are certainly reasonable, in view of the expected higher dipole moment of IV over V, as shown in XX and XXI. However, it is pertinent



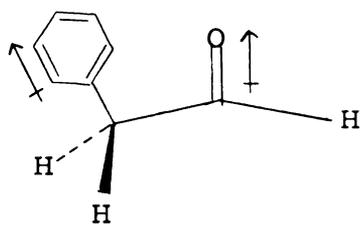
XX



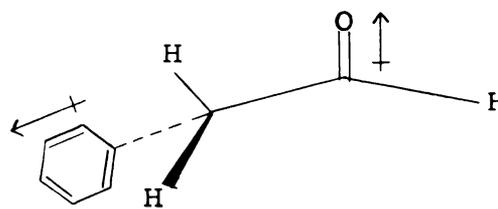
XXI

to point out that the increase in J_{obsd} cannot be due solely to changes in the relative populations of IV and V, since the coupling constant of acetaldehyde also increases (by only about 2 to 3%) in going from cyclohexane to acetonitrile.

Phenylacetaldehyde represents an interesting case. In non-polar solvents, such as carbon tetrachloride, IVa and V are energetically equivalent. In polar solvents, V becomes more stable than IVa; e.g., V is more stable than IVa by about 300 cal./mole in acetonitrile. This is in sharp contrast to the other monosubstituted acetaldehydes, and can be readily explained on the reasonable assumption that V has a higher dipole moment than IV (sp^2 carbon more electronegative than sp^3 carbon), as shown in XXII and XXIII. The greater



XXII



XXIII

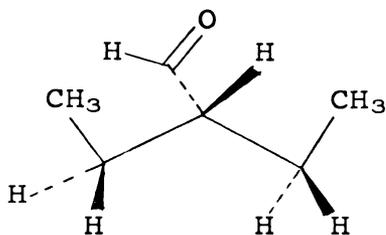
effect of solvent polarity on the ratio IV/V when R is phenyl than alkyl agrees well with the fact that the phenyl group contributes more to the dipole moment of the individual rotamers than the alkyl group.

II. Disubstituted Acetaldehydes

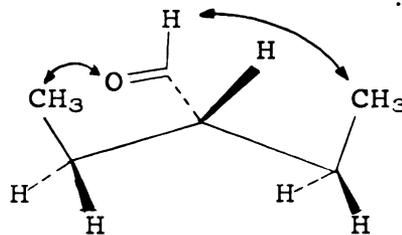
When $R_1=R_2$, the data afford the following conclusions:

(1) If the alkyl groups are methyl, VIIa (alkyl eclipsing the carbonyl) is more stable than VI (hydrogen eclipsing the carbonyl) by 500 cal./mole and (2) if the alkyl groups are ethyl or t-butyl, VI is more stable than VIIa by 250 cal./mole and 1100 cal./mole, respectively.

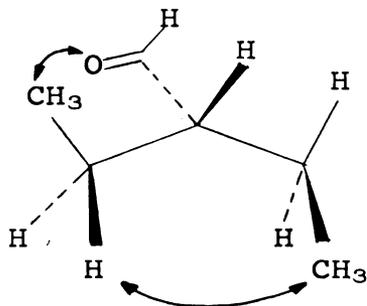
The apparent inconsistency of VI (hydrogen eclipsing) being the more stable rotamer of diethylacetaldehyde and V (ethyl eclipsing) of ethylacetaldehyde needs some explanation. In order to understand this difference, it is necessary to examine in detail the conformation of each rotamer. The most stable conformation of the ethyl group when the hydrogen eclipses the carbonyl is XXIV, whereby the alkyl chain is all trans and completely staggered. If the alkyl chain were to be kept all trans staggered in VII, a 1,3-eclipsing methyl-



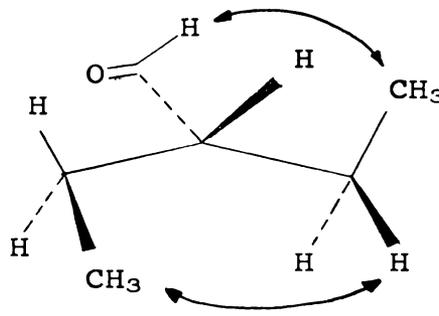
XXIV



XXV



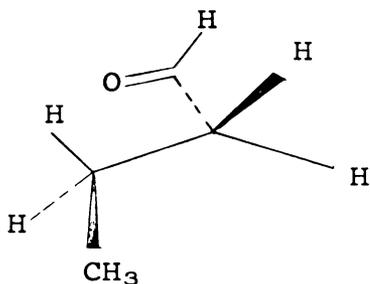
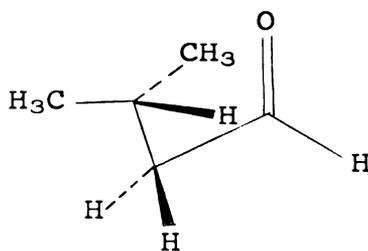
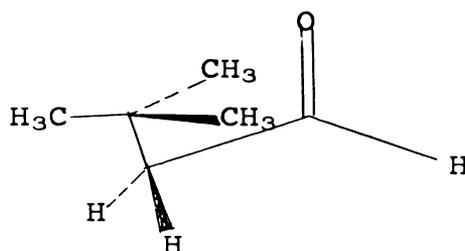
XXVI



XXVII

proton interaction and a less severe methyl-carbonyl interaction (XXV) would result. Rotation of one of the ethyl groups to avoid these interactions leads to conformations XXVI and XXVII, which suffer similar interactions. Consequently, VI becomes more stable than VII. In ethylacetaldehyde, however,

the conformation having the ethyl group eclipsing the carbonyl does not suffer from such interactions, as shown in **XXVIII**.

**XXVIII****XXIX****XXX**

Of the two interactions shown in **XXV**, the 1,3-eclipsing methyl-proton interaction is probably the more severe one and hence the one responsible for **VI** being more stable than **VII**. That the methyl-carbonyl interaction cannot be too significant is attested by the fact that when **R** is isopropyl, **V** is more stable than **IV**, even though in **V**, as shown in **XXIX**, such an interaction does exist. Apparently two such interactions, as in t-butylacetaldehyde (**XXX**), are sufficient to reverse the relative stability of the rotamers.

When $R_1 \neq R_2$, the data afford the following conclusions. If R_1 =methyl and R_2 =alkyl, **VIIa** (methyl eclipsing) is the more stable rotamer. **VI** (hydrogen eclipsing) and **VIIb** (alkyl

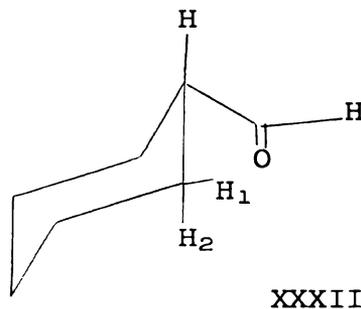
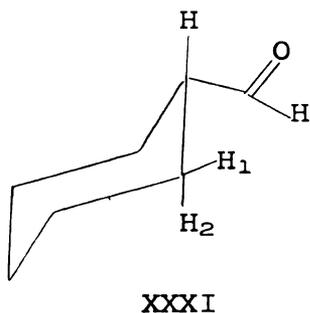
eclipsing) are practically energetically equivalent. The latter conclusion is drawn from the observation that ΔH° for these compounds, if R_1 is treated as equivalent to R_2 , is about half that of dimethylacetaldehyde. If neither R_1 or R_2 are methyl, then the most stable rotamer is VI, apparently for the same reasons given for diethylacetaldehyde.

The solvent effects for disubstituted acetaldehydes parallel that of monosubstituted acetaldehydes and are in accord with the proposed conformations. Since VI has a higher dipole moment than VII, the ratio VI/VII increases with increase in solvent polarity.

III. Cycloalkanecarboxaldehydes

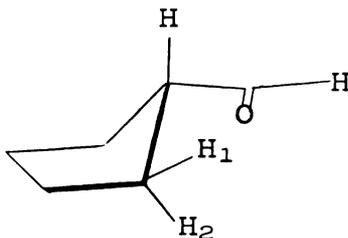
The relative stabilities of VIII and IX depend very much on the ring size. When $n=3$ (cyclohexyl), IX is more stable. When $n=2$ (cyclopentyl), IX is slightly less stable. When $n=1$ (cyclobutyl), IX is slightly more stable. When $n=0$ (cyclopropyl), IX is much less stable than VIII.

(a) Cyclohexanecarboxaldehyde. The fact that IX (alkyl eclipsing the carbonyl) is more stable than VIII by about 400 cal./mole is as expected. In either conformation XXXI or XXXII, the alkyl chain is all gauche and staggered, and the



1,3-eclipsing methyl-proton and the methyl-carbonyl interactions shown in XXV are absent in these conformations. Furthermore, since in conformation XXXII the carbonyl bisects the H_1CH_2 angle, it is not at all surprising that cyclohexanecarboxaldehyde shows exactly the same behavior as dimethylacetaldehyde.

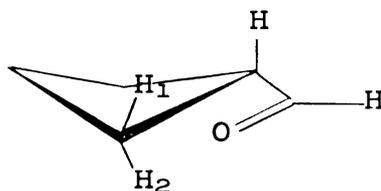
(b) Cyclopentanecarboxaldehyde. The fact that IXa (alkyl eclipsing) is very slightly less stable than VIII was not anticipated. However, this interesting observation can be readily explained if one compares XXXIII with XXII. The cyclopentyl ring is certainly less puckered than the cyclohexyl. Using the envelope form (42) for cyclopentanecarboxaldehyde, it can be seen that in conformation XXXIII (alkyl eclipsing the carbonyl), the carbonyl is closer to H_2 than H_1 .



XXXIII

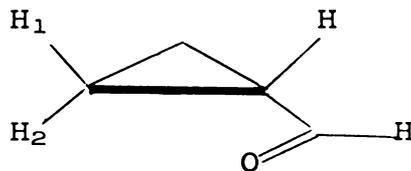
The ideal situation where the carbonyl bisects the H_1CH_2 angle, such as in the case in cyclohexanecarboxaldehyde (XXXII) no longer exists. Apparently the proximity between the carbonyl and H_2 is sufficient to destabilize IXa to the extent that it becomes slightly less stable than VIII.

(c) Cyclobutanecarboxaldehyde. It is certainly reasonable to assume that cyclobutanecarboxaldehyde is also puckered. There is ample evidence in the literature (43) that has established the puckering of the cyclobutyl ring. The same argument used for cyclopentanecarboxaldehyde can be applied to cyclobutanecarboxaldehyde, XXXIV.



XXXIV

(d) Cyclopropanecarboxaldehyde. The complete reversal in cyclopropanecarboxaldehyde, *i.e.*, VIII (hydrogen eclipsing) being more stable than IXa (alkyl eclipsing) by about 1.5 kcal./mole, can be explained by extending the arguments used for cyclopentane- and cyclobutanecarboxaldehyde. It can be seen that in IX the carbonyl eclipses H₂ (XXXV). This

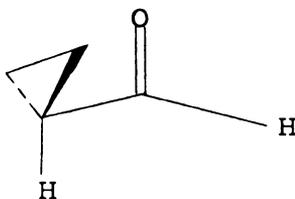


XXXV

interaction apparently destabilizes IX to such an extent that VIII becomes energetically favored. In addition, whatever factors force α, β -unsaturated aldehydes to assume the s-trans conformation (39) may be responsible for the greater stability

of VIII over IXa. It is pertinent to point out that in calculating ΔH° , J_t and J_g for cyclopropanecarboxaldehyde were assumed to be the same as those of other substituted acetaldehydes. This assumption is probably incorrect, because of the changes in angles and in carbon hybridization in the cyclopropane ring. If J_t is larger than the value that was used, then a more reasonable value for ΔH° may be 1 kcal./mole rather than 1.5 kcal./mole.

Bartell (20,21) has suggested that in the gas phase cyclopropanecarboxaldehyde exists 50% in VIII (hydrogen eclipsing the carbonyl) and 50% in XXXVI (carbonyl bisecting the cyclopropane ring) rather than VIII and IX. The present data do



XXXVI

not permit one to make an unequivocal choice between the two possibilities. However, on the basis of the following arguments, VIII and IX rather than VIII and XXXVI seem more reasonable in the liquid phase.

Assuming VIII and XXXVI as the only rotamers, the observed coupling constant is expressed by equation 18, where y is the fractional population of VIII, $(1-y)$ that of XXXVI and J_c is the cis coupling constant (dihedral angle 0).

$$J_{\text{obsd}} = yJ_t + (1-y)J_c \quad (18)$$

The strong dependence of J on temperature clearly indicates that VIII and ~~XXXVI~~ are not energetically equivalent. On the basis of Karplus's calculations on the relative magnitude of J_t and J_c , it can be concluded that VIII is more stable than ~~XXXVI~~. The difference of the coupling constants at two different temperatures can be expressed by equation 19, where p and q are the population of VIII at T_1 and T_2 , respectively.

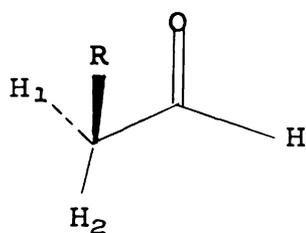
$$J_{\text{obsd}}(T_1) - J_{\text{obsd}}(T_2) = (p-q)(J_t - J_c) \quad (19)$$

To account for the large variation of the coupling constant with temperature, it can be seen from equation 19 that Bartell's interpretation requires either p to be much larger than q or J_c to be much smaller than J_t . Neither possibility is very likely to be true.

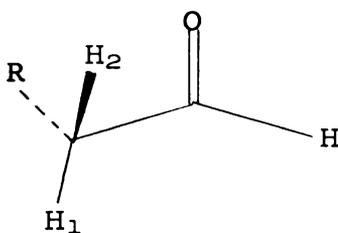
The variation of the coupling with solvent polarity is again in agreement with the higher dipole moment of VIII over IX.

IV. Consideration of Other Conformations

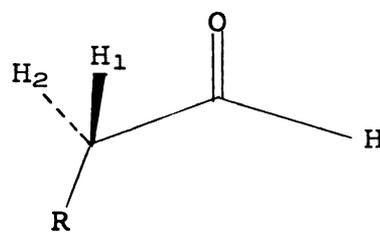
The preceding discussion has shown that the data can be well interpreted in terms of eclipsed conformations. It is, however, pertinent and necessary to consider the bisecting conformations, ~~XXXVII~~ and ~~XXXVIII~~ for monosubstituted acetaldehydes and ~~XXXIX~~ and XL for disubstituted acetaldehydes. Equations 2, 3 and 4 become 20, 21, 22 respectively, where J_c is the cis coupling and J_{120} is the coupling constant



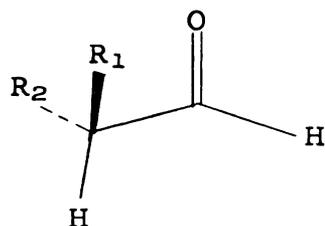
XXXVIIa



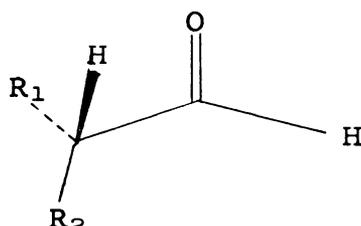
XXXVIIb



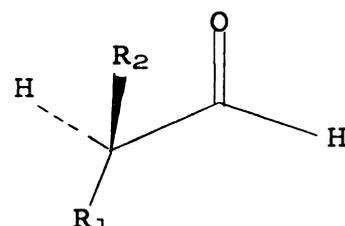
XXXVIII



XXXIX



XLa



XLb

when the dihedral angle is 120° . Since J_c should be comparable

$$J_{\text{obsd}} (\text{monosubstituted}) = x(J_c + J_{120})/2 + (1-x)J_{120} \quad (20)$$

$$J_{\text{obsd}} (\text{disubstituted}) = yJ_c + (1-y)J_{120} \quad (21)$$

$$J_{\text{obsd}} = 1/3 (J_c + 2J_{120}) \quad (22)$$

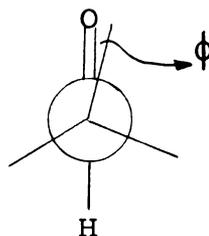
in magnitude to J_t and J_{120} comparable to J_g , the data on the temperature studies could also be interpreted in terms of bisecting conformations. However, these conformations can be excluded on the basis of the following arguments.

(1) As discussed previously, microwave and electron diffraction studies have established that in the gas phase the minimum energy conformations are eclipsing rather than bisecting. There is no reason to expect the reverse to occur in solution.

(2) Since ~~XXXVII~~ and ~~XXXIX~~ should have higher coupling constants than ~~XXXVIII~~ and ~~XL~~, one is forced to conclude that increase in the size of R shifts the equilibrium in favor of ~~XXXVII~~ and ~~XXXIX~~ (in general J_{obsd} increases as R increases in size). In terms of steric factors such a conclusion is highly improbable.

(3) Since ~~XXXVIII~~ and ~~XL~~ should have higher dipole moments than ~~XXXVII~~ and ~~XXXIX~~, the observed coupling constants should decrease with increase in solvent polarity. Experimentally, however, the observed coupling constants increase with increase in solvent polarity.

Although the data have been successfully interpreted in terms of eclipsing conformations, i.e., with the assumption that the dihedral angle ϕ is zero (XLI), it is necessary to



XLI

emphasize that small variations in ϕ would not in any respect alter the interpretation of the results. In fact the results should not be viewed as proof that the dihedral angle is zero.

The causes responsible for the greater stability of V (alkyl eclipsing the carbonyl) over IV (hydrogen eclipsing the carbonyl), even when R is isopropyl, are not well understood.

The possibility of hydrogen bonding in V is a plausible explanation. However, it cannot be the sole factor responsible for V being more stable, as attested by the phenyl-acetaldehyde case. An alternate and more attractive explanation involves the more favorable dipole-dipole and dipole-induced dipole interactions in V over IV, resulting from two interacting groups whose distance is in the attractive portion of the van der Waals curve.

B. Oxime O-Methyl Ethers

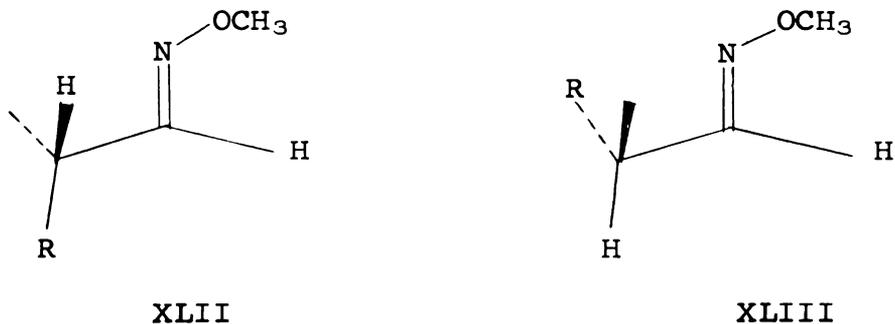
I. Conformations of the Syn Isomers

The data on the coupling constants are in good accord with eclipsed conformations. In fact, the behavior of the syn isomers of the oxime O-methyl ethers parallels closely that of the aldehydes. For example, for monosubstituted acetaldehyde derivatives ΔH° becomes more positive in changing R from methyl to t-butyl, e.g., R = methyl, $\Delta H^\circ = +380$ cal./mole; R = t-butyl, $\Delta H^\circ = +4500$ cal./mole. For disubstituted acetaldehyde derivatives, ΔH° becomes more positive as the alkyl substituents get larger. For cycloalkanecarboxaldehyde derivatives, ΔH° of the cyclopropyl is more positive than that of cyclopentyl, which in turn is more positive than that of the cyclohexyl. ΔH° of the diethylacetaldehyde derivative is more positive than that of the monoethyl; that of the cyclohexyl is similar to that of the dimethyl rather than that of the diethyl.

The interpretation of these results is the same as that used to interpret those of the aldehydes.

The effect of solvent polarity on rotamer population further supports the proposed conformations. Because of the higher dipole moment of XIII over XIV and XV over XVI, the ratio XIII/XIV and XV/XVI should increase with increase of solvent polarity. J_{obsd} does indeed increase as the solvent is changed from cyclohexane to acetonitrile. As expected, phenylacetaldehyde oxime O-methyl ether behaves exactly the opposite.

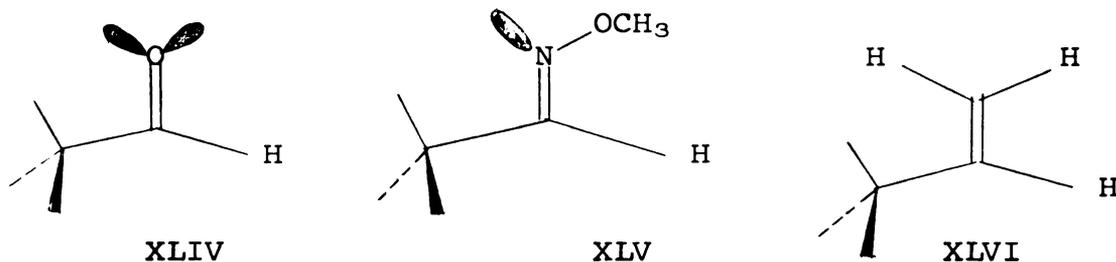
The arguments previously applied to aldehydes against bisecting conformations (XLII and XLIII) can also be applied here. The most important evidence against XLII and XLIII is



the increase of J_{obsd} with increase of solvent polarity. Since XLII should have a higher dipole moment than XLIII, increase of solvent polarity should decrease J_{obsd} (assuming $J_c > J_{120}$).

It is necessary to point out that there is one significant difference between the syn isomers of the oxime O-methyl ethers and the aldehydes; namely, the rotamer populations of

the oxime O-methyl ethers parallel closely those of olefins (26) rather than those of aldehydes, although from structural considerations (XLIV-XLV-XLVI), the reverse might have been expected. Whereas the alkyl-carbonyl eclipsing conformation



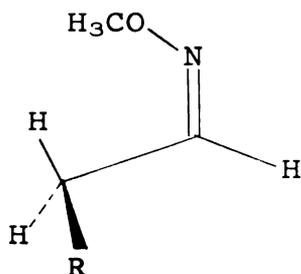
is more stable for the aldehydes, the reverse is true for olefins and oxime O-methyl ethers. Although the causes responsible for this difference are not clear, the availability of electrons for possible dipole-dipole (or dipole-induced dipole) interactions might be the controlling factor.

II. Conformations of the Anti Isomers

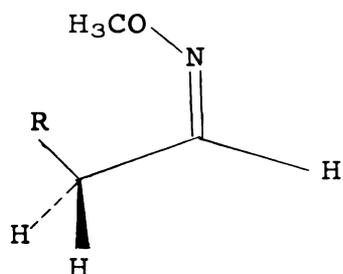
Since a quantitative interpretation of the spin-spin coupling constants of the anti isomers is not possible, several qualitative interpretations will be presented.

(a) Monosubstituted acetaldehyde derivatives. The data on the coupling constants contain two noticeable features: (1) J_{obsd} varies irregularly with temperature and the variation is small. (2) J_{obsd} decreases or remains constant as the solvent polarity increases. A reasonable interpretation in terms of conformations will have to accommodate both of these features.

If XLVII and XLVIII (eclipsing conformations) are the only rotamers of the anti isomers, the coupling constants should increase with increase of solvent polarity when R is alkyl and decrease when R is phenyl. The observed trend is

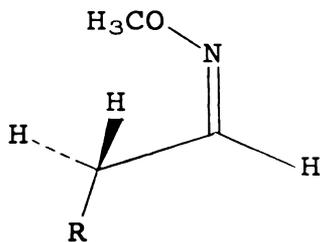


XLVII

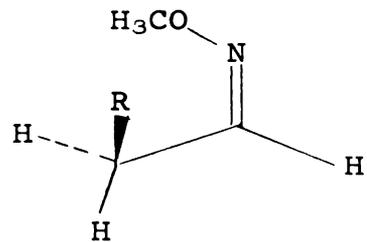


XLVIII

quite the opposite. Furthermore, judging from the small variation of the coupling constants with temperature, XLVII and XLVIII will have to be almost energetically equivalent, i.e., ΔH° between them is zero, except when R is t-butyl. Such an interpretation is obviously unreasonable. One is therefore forced to consider XLIX and L (bisecting conformations).



XLIX



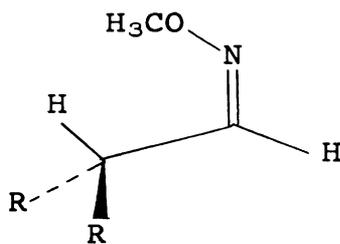
L

Since XLIX should have a higher dipole moment than L, the coupling constant should decrease as the solvent polarity increases, except that of the phenylacetaldehyde derivative.

The data agree reasonably well with this interpretation, although the variation of J_{obsd} with solvent polarity is too small. However, judging from the temperature dependence of J_{obsd} , ΔH° between XLIX and L should be almost zero, except when R is t-butyl. Again this interpretation seems unreasonable.

The data are best interpreted in terms of XLVII and XLIX as the important rotamers. Since XLIX should have a slightly higher dipole moment than XLVII, increase of solvent polarity should decrease J_{obsd} only slightly. The fact that XLVII and XLIX are almost energetically equivalent except when R is t-butyl is also understandable.

(b) Disubstituted acetaldehyde derivatives. The data are in good accord with eclipsed conformations. Since the coupling constants parallel closely those of the syn isomers and aldehydes, a priori considerations lead to the conclusion that, regardless of the size of R, the most stable rotamer should be LI.

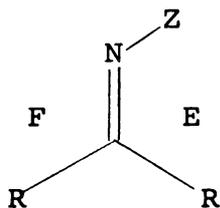


LI

III. Chemical Shifts

Elucidation of conformations by means of chemical shifts can be quite useful. Accurate knowledge of the anisotropy of

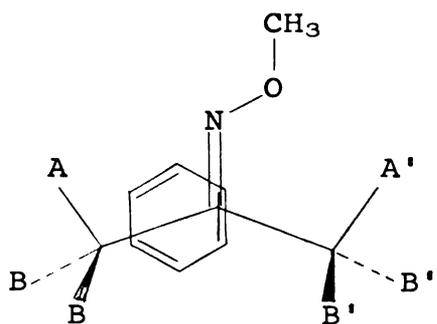
the N-OCH₃ group would simplify the problem and permit the assignment of reliable conformations. In the absence of such information, however, the simplest solution is intelligent guessing of the anisotropic effect of N-OCH₃ by comparing it with other groups. As in so many other compounds of the general structure LII, the region in the C=NZ plane (E and F)



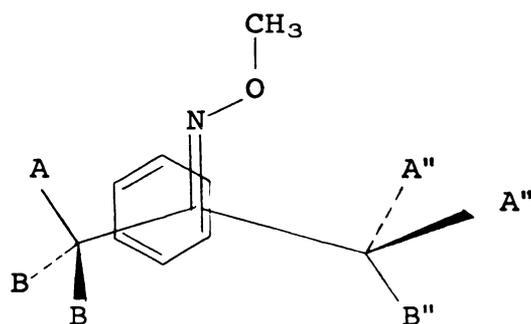
LII

is probably deshielded with respect to the region above and below the plane. In addition, region E is deshielded with respect to F, e.g., cis-H₁ resonates at lower fields than trans-H₁ for compounds of structure LII. Thus, subsequent discussion will be based on the assumption that this is also true for the N-OCH₃ group.

(a) Solvent effects. The striking feature of the chemical shifts is the effect of benzene on them; namely, whereas some resonances are shifted upfield, several others are shifted downfield (Table IX). A reasonable interpretation of this effect requires stereospecific association between the benzene and the oxime O-methyl ether. The data are adequately interpretable in terms of LIII and LIV, whereby the benzene



LIII



LIV

is attracted by the positive charge on the sp^2 -hybridized carbon and is closer to the group that is trans to the methoxy. The s-trans conformation of the $C=NOCH_3$ fragment is chosen in accordance with formaldoxime (44) and with p-p lone pair electron repulsions (45). Models LIII and LIV require that the methoxy be deshielded in benzene, as is indeed the case. Positions A and A', and to a lesser extent B'', would be deshielded, whereas B, B' and A'' would be shielded.

(b) Conformations

1) Syn-isomers of substituted acetaldehyde derivatives.

From coupling constant studies it has been concluded that XIII (hydrogen eclipsing $C=N$) is the more stable rotamer for both mono- and disubstituted acetaldehyde derivatives. As the alkyl substituent increases in size, both α -methylene and α -methine protons should spend progressively more time in region F (LII). Consequently one would expect progressive shifting of the chemical shifts to lower fields, i.e., the α -methylene protons of the t-butylacetaldehyde derive should resonate at lower fields than those of all other monosubstituted

acetaldehyde derivatives and the α -methine proton of the di-t-butylacetaldehyde derivative at lower fields than those of any other disubstituted derivatives. The data do not agree with this deduction. This failure could be the result of several factors; such as, differences in the inductive effects of the alkyl groups, change of the α -carbon hybridization, and availability of α -proton(s) for hyperconjugation.

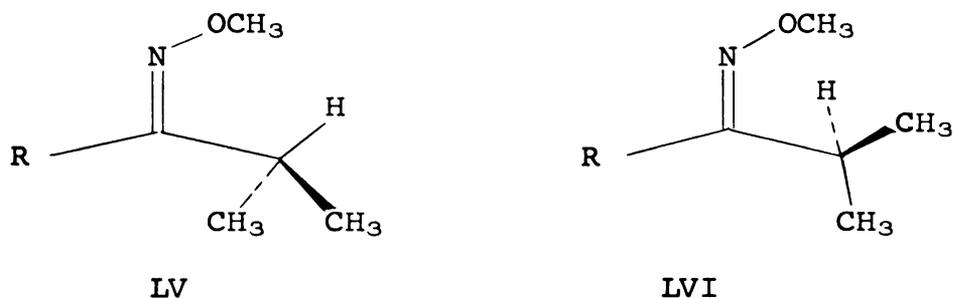
The only trans α -methine proton that is shifted downfield by benzene, as compared to the neat sample, is that of the di-t-butylacetaldehyde derivative. This finding implies that the α -methine proton lies mainly in region A, as shown in LIII, and further supports the conclusion that this compound exists solely in conformation XIII (hydrogen eclipsing).

2) Anti-isomers of monosubstituted acetaldehyde derivatives. The small shift of cis- α -methylene protons in benzene solution as compared to the neat liquid is consistent with the conclusion drawn from coupling constant studies that XLVII and XLIX are significantly populated. However, it is pertinent to point out that the results of the chemical shifts alone do not permit one to draw any definite conclusions.

3) Anti-isomers of disubstituted acetaldehyde derivatives. The observation that both cis and trans α -methyl protons resonate at about the same field in the neat liquid, whereas cis- α -methine protons resonate at appreciably lower fields than trans clearly indicates that the α -methine proton spends most of its time in E (E is deshielded with respect to F) as

shown in LII. This agrees well with the conclusion drawn from coupling constant studies that LI is the most stable rotamer of the anti isomers of disubstituted acetaldehyde derivatives.

4) Cis groups of ketone derivatives. Of the cis groups of ketone oxime O-methyl ethers, the data afford reasonably accurate conformational assignments only for the isopropyl group. Of the two conformations LV and LVI, only LV is



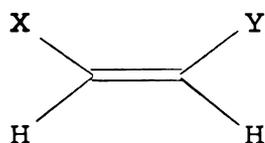
consistent with the results. It explains the fact that α -methine protons, in contrast to α -methyl and α -methylene protons, resonate at appreciably lower fields when cis than when trans to the oxygen, e.g., for the di-isopropyl ketone derivative, $\Delta\delta = -0.56$ p.p.m. (neat).

IV. Syn-Anti Isomers

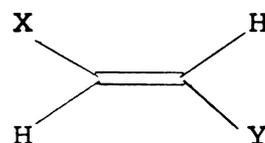
One interesting feature of the results of syn and anti isomer percentages (Table X) is the greater stability of LVII (anti isomer) over LVIII (syn isomer). This represents yet



another case demonstrating the importance of attractive forces between two groups, when at least one group has available polarizable electrons. The greater stability of LIX over LX when $X = Y = \text{Cl}$ (46), Br (47), F (48); $X = \text{CH}_3$, $Y = \text{Cl}$ (49), Br (50), CN (51) has been established.

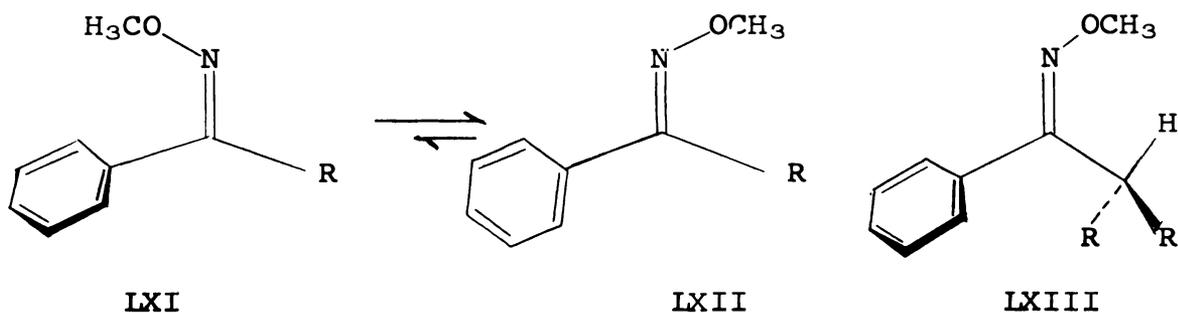


LIX



LX

The large dependence of the ratio LXI/LXII on R is best interpreted in terms of methoxy-phenyl interactions in LXI, which force the phenyl out of conjugation with the $\text{C}=\text{N}$, and in terms of phenyl-R interactions in LXII. When R is methyl,



LXI

LXII

LXIII

ethyl or n-propyl, LXII is much more favored. However, when R is isopropyl, the phenyl-R interactions become severe enough to force the phenyl ring out of conjugation (LXIII) with $\text{C}=\text{N}$, and causes the equilibrium to be shifted in favor of LXI. The ultraviolet spectral data amply justify this explanation.

EXPERIMENTAL

A. Reagents and Compounds

Except for t-butylacetaldehyde, di-t-butylacetaldehyde, cyclopropane-, cyclobutane- and cyclopentanecarboxaldehyde, all aldehydes used were freshly distilled samples of commercially available materials. Cyclopentyl bromide, cyclopentanecarboxylic acid and t-butyl acetic acid were obtained from Aldrich Chemical Company, Inc. Cyclopentyl nitrile was obtained from Columbia Organic Chemical Company, Inc., and methoxylamine hydrochloride from Eastern Organic Chemicals.

B. Solvents

Benzene, carbon tetrachloride, acetonitrile and cyclohexane were purified from commercially available material by standard methods (52). Benzene- d_6 was purchased from Merck, Sharp and Dohme of Canada, Limited.

C. Synthesis

I. Cyclopropanecarboxaldehyde

Cyclopropanecarboxaldehyde was prepared according to the procedure of Brown and Garg (53). In a 1-*l.*, three-necked, round-bottomed flask equipped with a condenser, a dropping funnel and a stirrer, was placed 11.4 g (0.3 mole) of lithium

aluminum hydride in 300 ml of ether. A nitrogen atmosphere was maintained throughout the reaction. To this stirred solution, 39.65 g (0.45 mole) of ethyl acetate was added over a period of 75 min, the temperature being maintained at 3-7°. The reaction mixture was stirred for an additional 30 min. To this solution was added in 5 min 20.1 g (0.3 mole) of cyclopropyl nitrile. The reaction mixture was stirred for 1 hr at 0°, and then decomposed with 300 ml of 5N sulfuric acid. The ether layer was separated and the aqueous layer extracted three times with 50-ml portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution and water and then dried over anhydrous magnesium sulfate. Cyclopropanecarboxaldehyde, b.p. 99-104°, lit. (54) 97-100°, was obtained in a yield of 4.2 g (20.0%).

II. Cyclopentanecarboxylic Acid

In a 1-l., three-necked, round-bottomed flask, equipped with a stirrer, a condenser with a drying tube and a dropping funnel, was placed 12.15 g (0.5 mole) of activated magnesium turnings in 200 ml of ether. A solution of 74.45 g (0.5 mole) of cyclopentylbromide in 300 ml of ether was placed in the funnel. About 25 ml of the halide solution was added. Once the reaction started, stirring was commenced and the rest of the halide solution was added over a period of 1 hr to the vigorously refluxing mixture. After completion of the addition, refluxing was maintained by external heating for 30 min. The reaction mixture was then cooled and the solution of the alkyl

magnesium bromide was poured slowly onto about 50 g of dry ice with stirring. When the dry ice had evaporated, 400 ml of 20% hydrochloric acid and enough ice to keep the mixture cold were added with stirring. After all the solid had dissolved, the ether layer was separated, washed with three portions of water and dried over anhydrous magnesium sulfate. The ether was stripped and the residual liquid distilled under reduced pressure to yield 25.4 g (45.0%) of cyclopentanecarboxylic acid, b.p. 88° (4.0 mm), lit. (55) 118° (23 mm).

III. N,N-Dimethyl Cyclopentanecarboxamide

In a 150 ml, two-necked, round-bottomed flask, equipped with a condenser and a drying tube, a magnetic stirring bar and a dropping funnel, was placed 33.0 g (0.276 mole) of freshly distilled thionyl chloride. To this solution was added 21.0 g (0.184 mole) of cyclopentanecarboxylic acid over a period of 1 hr with stirring. The reaction mixture was heated by a steam bath for 2 hr and was then allowed to cool. The excess thionyl chloride was removed by distillation. The residual liquid was quickly transferred to another dropping funnel.

In a 1-ℓ., three-necked flask, equipped with a condenser, a stirrer and a dropping funnel was placed 100 ml (0.553 mole) of 25% aqueous dimethylamine solution. The solution was cooled in an ice-salt mixture. To this solution the crude acid chloride was added dropwise over a period of 3 hrs. After completion of addition, the reaction mixture was stirred at

room temperature for 1 hr. The aqueous solution was saturated with sodium chloride and then extracted three times with 100-ml portions of ether. The ether layer was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The ether was distilled off and the residual brownish liquid was distilled under reduced pressure to give 19.5 g (75.0%) of N,N-dimethylcyclopentanecarboxamide, b.p. $92-3^{\circ}$ (3.0 mm).

IV. Cyclopentanecarboxaldehyde

The procedure of Brown and Tsukamoto (56) was followed. In a 500 ml, three-necked flask, equipped with a condenser and a drying tube, a stirrer and a dropping funnel, was placed 4.85 g (0.128 mole) of lithium aluminum hydride in 160 ml of ether (1.25 M solution). The flask was cooled by an ice bath. To the stirred solution of the hydride was added over a period of 1 hr 16.9 g (0.192 mole) of ethyl acetate. The reaction mixture was stirred for 30 min at 0° . To the stirred slurry of the hydride reagent thus prepared, cooled with an ice bath, was added 18.0 g (0.128 mole) of N,N-dimethylcyclopentanecarboxamide as rapidly as possible while avoiding too vigorous refluxing of the ether. The reaction mixture was stirred for 1 hr at the same temperature and then decomposed with 5N sulfuric acid. The ether layer was separated and the aqueous layer was extracted twice with 100-ml portions of ether. The combined ether solution was washed with water, shaken with solid sodium bicarbonate, washed again with water and dried

over anhydrous magnesium sulfate. After evaporation of the ether, the residual liquid distilled at 134-138^o, lit. (57) 135^o, yield 9.0 g (72%).

V. N,N-Dimethyl Cyclobutanecarboxamide

N,N-Dimethyl cyclobutanecarboxamide was prepared by the same procedure used for the preparation of N,N-dimethyl cyclopentanecarboxamide. It was obtained in 60% yield, b.p. 77-78^o (4 mm), lit. (58) 106^o (20 mm).

VI. Cyclobutanecarboxaldehyde

Cyclobutanecarboxaldehyde was prepared from N,N-dimethylcyclobutanecarboxamide according to the procedure of Brown and Tsukamoto (56). It was obtained in 40% yield, b.p. 115-117^o, lit. (59) 113-115^o.

VII. N,N-Dimethyl-3,3-dimethyl-butyramide

N,N-Dimethyl-3,3-dimethyl-butyramide was prepared from t-butyl acetic acid by the same procedure used for the preparation of N,N-dimethylcyclopentanecarboxamide. It was obtained in 72% yield, b.p. 74-75^o (6-7 mm).

VIII. t-Butylacetaldehyde

t-Butylacetaldehyde was prepared from the corresponding N,N-dimethyl amide according to the procedure of Brown and Tsukamoto (56). It was obtained in 60% yield, b.p. 107-108^o, lit. (60), 102-104^o.

IX. Oxime O-Methyl Ethers

To an aqueous solution of 0.1 mole aldehyde or ketone, 0.11 mole methoxylamine hydrochloride and 0.11 mole sodium acetate trihydrate was added 95% ethanol until the solution was clear (except for water soluble compounds such as acetaldehyde). After 20 hrs reflux the solution was extracted three times with 50-ml portions of ether. The ether layer was washed three times with 5% sodium bicarbonate solution, once with water and dried over anhydrous magnesium sulfate. After removal of the ether by slow distillation, the residual liquid was distilled through a fractionating column to give the oxime O-methyl ether in about 50-70% yield. All oxime ethers were clear, sweet smelling liquids.

D. N.M.R. and U.V. Spectra

All n.m.r. spectra were taken at 60 Mc on a Model A-60 Spectrometer (Varian Associates, Palo Alto, Calif.). Undegassed samples were used with tetramethylsilane (TMS) as the internal reference standard ($\tau = 10.00$). Chemical shifts were measured with sweep widths of 1000, 500 and 250 c.p.s. Spin-spin coupling constants were measured with sweep width of 50 c.p.s.

Ultraviolet spectra were taken with a Cary 14 recording spectrometer.

Table XVIII. Boiling Points of Oxime O-Methyl Ethers

$R_1R_2C=NOCH_3$		B.P. ($^{\circ}C$)
R_1	R_2	
H	CH ₃	47
H	CH ₂ CH ₃	73-75
H	CH ₂ CH ₂ CH ₃	83-86
H	CH ₂ CH(CH ₃) ₂	114-115
H	CH ₂ C(CH ₃) ₃	115-117
H	CH ₂ C ₆ H ₅	77(5-6 mm)
H	CH(CH ₃) ₂	87-90
H	CH(CH ₃)CH ₂ CH ₃	110-113
H	CH(CH ₃)CH(CH ₃)CH ₂ CH ₃	141-143
H	CH(CH ₂ CH ₃) ₂	128
H	CH(CH ₂ CH ₃)(CH ₂) ₃ CH ₃	109 (60 mm)
H	CH[C(CH ₃) ₃] ₂	88-90 (35 mm)
H		110
H		59 (5 mm)
H		78 (19-20 mm)
CH ₃	CH ₃	72-73
CH ₃	CH ₂ CH ₃	92-93
CH ₃	CH ₂ CH(CH ₃) ₂	126-128
CH ₃	CH ₂ C(CH ₃) ₃	64-65 (35 mm)
CH ₃	CH ₂ C ₆ H ₅	88-89 (3-4 mm)
CH ₃	CH(CH ₃) ₂	109-110
CH ₃	C(CH ₃) ₃	79-80 (134 mm)
CH ₂ CH ₃	CH ₂ CH ₃	114-116
CH ₂ CH ₃	CH(CH ₃) ₂	128-129
CH ₂ CH ₃	C(CH ₃) ₃	127-129
CH(CH ₃) ₂	CH(CH ₃) ₂	125-126
CH ₃	C ₆ H ₅	97-99 (14-15 mm)
CH ₂ CH ₃	C ₆ H ₅	74-80 (2-4 mm)
CH ₂ CH ₂ CH ₃	C ₇ H ₅	88-90 (2-3 mm)
CH(CH ₃) ₂	C ₆ H ₅	46-48 (0.5 mm)

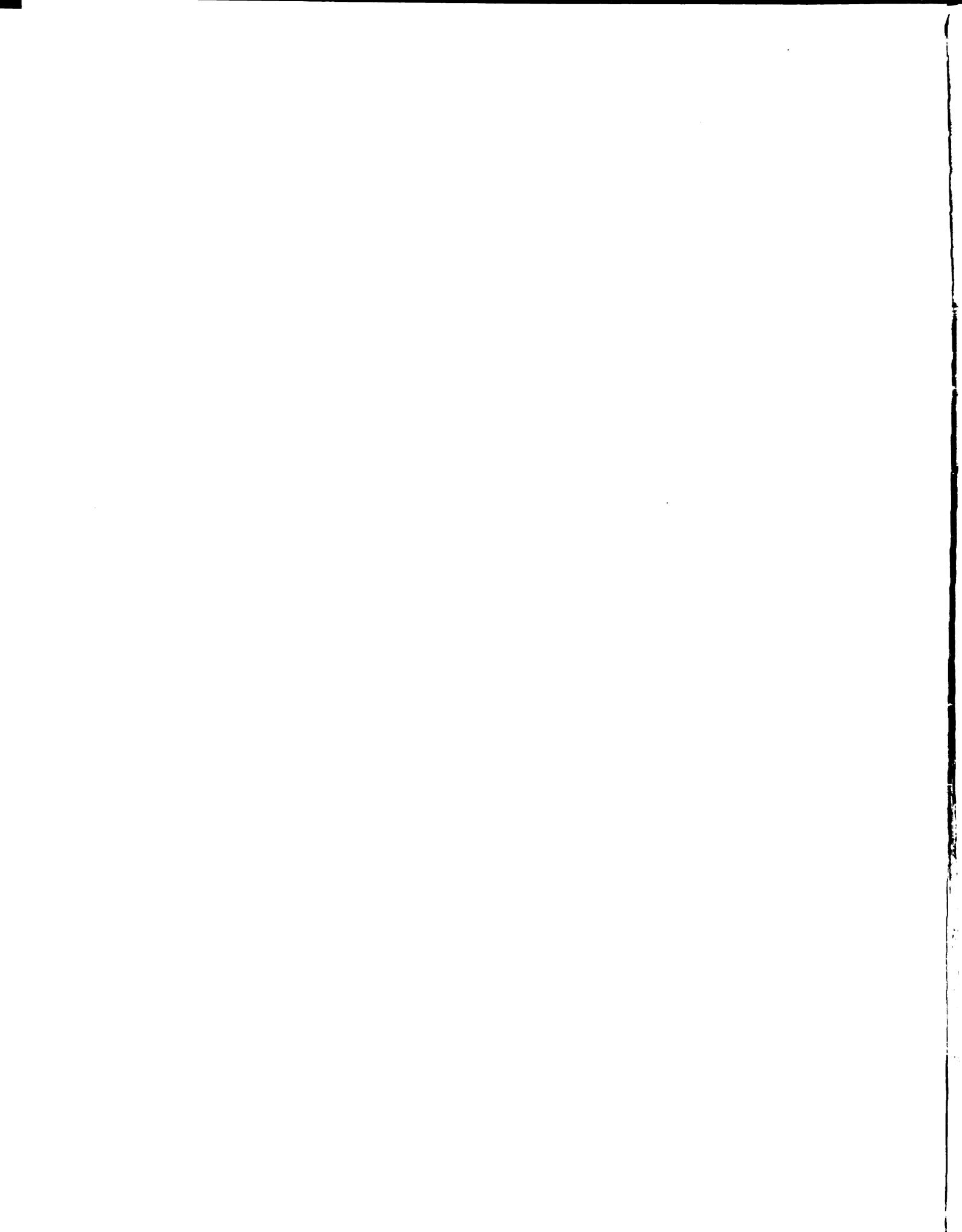
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