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Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Chemical and Carbon-13 Proton Couplings in Some Esters and Ethers.¹

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Carbon-13 chemical shifts and three- (or more) bond ¹³C–proton couplings have been obtained for a variety of alkyl ethers and esters. The results have been interpreted on the basis of preferred rotational conformations.

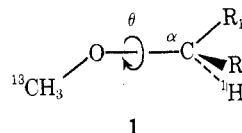
The current availability of commercial spectrometers has made the measurement of carbon chemical shifts relatively routine. Thus, in unpublished work, we have compiled from the literature carbon chemical-shift data for nearly 2000 compounds on molecular fragments, and the current explosion of published ¹³C data appears to make the task of continually updating this compilation quite impossible.

Despite the interest in carbon-13 nuclear magnetic resonance (¹³C NMR) spectroscopy, the complete assignment of resonances remains one of the most difficult problems faced by the users of this method, and the application of carbon chemical-shift information to problems of structure elucidation and conformational analysis has, as a result, been relatively limited.

The measurement of relaxation times (*T*₁) for carbon nuclei is now becoming quite common, even for rather large molecules.² The unique information regarding molecular motions which can be derived from such measurements promises to give increasing importance to *T*₁ measurements in the future. Other techniques, notably the measurement of nuclear Overhauser enhancements,³ will doubtless also provide much valuable information to organic chemists who seek to understand the structure and conformations of molecules.

In the present paper, we report some preliminary results regarding the measurement of geminal and vicinal carbon–proton couplings, and the application of such coupling data to problems in acyclic conformational analysis. A review⁴ of the literature shows that a surprising number of measurements of these coupling constants have been made. Although their counterparts in proton–proton coupling commonly provide extensive and useful information about structure and conformation, few systematic investigations of vicinal and geminal carbon–proton couplings in other than aromatic systems⁵ have appeared.⁶ Frequently, these couplings are described as "long-range", thereby implying that they are small. In fact, their magnitudes are commonly comparable to those of the analogous proton–proton couplings and are easily measured with modern ¹³C NMR spectrometers. In view of this, we have begun an extensive investigation of the measurement of carbon–proton couplings and report here some aspects of vicinal carbon–proton coupling, leaving the geminal cases for a later, more general, discussion. Our primary interest was the investigation of the earlier report⁷ of a dihedral dependence of this coupling. More recently, the dihedral dependence of vicinal

carbon–proton coupling has been verified in other laboratories, and the variation has been described as being similar in form to that of the analogous proton–proton coupling.⁸ Our approach has been to study systems in which geminal coupling would be absent, thus facilitating the measurement of vicinal coupling. We therefore initiated our study with a survey of *O*-methyl ethers. Examination of 1 suggests that the dihedral angle θ should be, to at least



some extent, dependent on the character and bulk of R₁ and R₂. By studying the vicinal coupling between the *O*-methyl carbon and the α proton as a function of R₁ and R₂, we sought to understand its dependence upon dihedral and substituent effects. During the course of this work it became clear that it was frequently possible to measure the vicinal coupling between the α carbon and the *O*-methyl protons, even though this situation was complicated by the presence of geminal and, in some cases, other vicinal couplings. This finding allowed the extension of this research to include a number of related compounds, including a selection of esters and cyclic ethers.

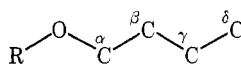
The measurement of splittings in proton-coupled spectra are rather more difficult than taking carbon spectra with full proton decoupling. For this reason, we have made some attempts to correlate carbon chemical-shift changes with conformational effects which influence the couplings. An earlier effort to correlate carbon chemical shifts of *O*-methyl ethers with conformation has been described for somewhat more complicated systems.⁹

Experimental Section

Carbon chemical shifts were measured in 1,4-dioxane or cyclohexane solutions under conditions of full proton decoupling with a digital frequency-sweep spectrometer described previously.¹⁰ Chemical shifts were subsequently referred to external carbon disulfide on the basis of the chemical shifts of 1,4-dioxane and cyclohexane relative to that reference (126.2 and 166.2 ppm, respectively). They can be reasonably accurately converted to the Me₄Si scale by subtracting them from 192.8 ppm.

Proton-coupled carbon-13 spectra were measured with the same spectrometer, using neat solutions and internal proton lock. Several experiments using varied internal lock power had no effect on the spacings in the obtained spectra.

Table I
Carbon Chemical Shifts^a of Selected Ethers and Esters



Registry no.		α	β	γ	δ	R
A. <i>O</i> -Methyl Ethers						
115-10-6	Methyl ^b	133.5				O-CH 133.5
540-67-0	Ethyl ^b	125.5	178.5			135.6
557-17-5	<i>n</i> -Propyl	126.5	171.2	184.1		136.5
628-28-4	<i>n</i> -Butyl	120.9	161.3	173.8	179.5	135.4
25154-53-4	1,2-Dimethoxyethane	121.5				135.4
625-44-5	Isobutyl	114.3	165.5	175.0		136.0
1118-00-9	Neopentyl	110.4	162.0	167.4		135.3
598-53-8	Isopropyl ^b	120.6	171.8			138.3
6795-87-5	<i>sec</i> -Butyl	115.8	165.1 (CH ₂) 175.9 (CH ₃)	184.9		137.7
1634-04-4	<i>tert</i> -Butyl ^b	121.1	166.3			144.6
B. Formates						
107-31-3	Methyl	143.7				CHO 31.9
109-94-4	Ethyl	134.0	79.8			32.4
110-74-7	<i>n</i> -Propyl	128.5	171.5	183.7		32.5
592-84-7	<i>n</i> -Butyl	130.3	162.7	174.4	180.2	32.7
542-55-2	Isobutyl	124.0	165.6	174.8		32.6
23361-67-3	Neopentyl	120.7	162.1	167.1		32.8
104-62-1	2-Phenylethyl ^c	129.2	158.5			32.3
625-55-8	Isopropyl	172.1	126.5			33.1
589-40-2	<i>sec</i> -Butyl	174.3	121.8	164.6	184.3	32.9
762-75-4	<i>tert</i> -Butyl	165.4	112.9			33.3
C. Acetates						
79-20-9	Methyl	142.9				C=O 22.9 CH ₃ 174.1
141-78-6	Ethyl	133.7	179.7			23.6 173.5
109-60-4	<i>n</i> -Propyl	128.2	171.2	183.5		23.8 173.2
123-86-4	<i>n</i> -Butyl	129.7	162.4	174.2	180.1	23.7 173.4
108-21-4	Isopropyl	172.0	126.5			24.3 173.0
540-88-5	<i>tert</i> -Butyl	165.6	114.3			24.4 171.7

^a All chemical shifts measured in parts per million relative to external carbon disulfide. ^b Data from ref 13. ^c Shifts of aromatic carbons: C-1, 55.5; C-2, 3, 5, 6, 64.3, 64.7; C-4, 66.6 ppm.

Table II
Carbon Chemical Shifts^a of Cyclic Ethers

Compd	C-2	C-3	C-4	C-5	Registry no.
Tetrahydrofuran	125.7	167.7			109-99-9
1,3-Dioxolane	98.5		129.0		505-22-6
1,4-Dioxane	126.2				123-91-1
1,3,5-Trioxane	93.1				111-88-3

^a Chemical shifts measured in parts per million relative to external carbon disulfide.

Proton NMR spectra were measured with a Varian A-56/60A spectrometer. Computer programs, used to enhance resolution in NMR spectra, were adapted from programs described elsewhere.¹¹

All compounds were of either commercial origin or were prepared by standard procedures and were distilled before use. Methyl ethers were prepared from the corresponding alcohol using dimethyl sulfate and sodium hydride. Formates were generally prepared from the alcohol and formic acid. Tertiary esters were prepared by the method of Stevens and Van Es.¹²

Results

Carbon chemical-shift data used in subsequent discussion are presented in Tables I and II. All chemical shifts are considered accurate to at least ± 0.1 ppm. Data for some of the more common methyl ethers were taken from the lit-

Table III
Vicinal Carbon-Proton Coupling Constants of Some Methyl Ethers

Compd	³ J _{C_γOCC_αH} ^b	³ J _{C_αOCC_γH} ^c
Dimethyl ether ^d	+5.7	+5.7
Methyl <i>n</i> -propyl ether	5.2	3.2
Methyl <i>n</i> -butyl ether	5.25	3.1
Methyl isobutyl ether	5.2	3.05
Methyl neopentyl ether	5.3	2.65
Methyl isopropyl ether	5.0	3.85
Methyl <i>sec</i> -butyl ether	4.8	4.2
Methyl <i>tert</i> -butyl ether	4.0	
1,2-Dimethoxyethane	5.15	1.85
Diethyl ether ^e		3.1

^a All coupling constants given in hertz. ^b ± 0.1 Hz. ^c ± 0.05 Hz. ^d Reference 30. ^e Registry no., 60-29-7.

erature.¹³ Because these published shifts were measured relative to internal carbon disulfide, we have adjusted these data by +0.7 ppm, an increment which has been found to bring data measured in these two ways into accord.

Carbon-proton spin-spin coupling constants are reported in Tables III-V. The convention used in the present paper to designate specific coupling constants is defined in

Table IV
Vicinal Carbon-Proton Coupling Constants^a
in Simple Esters

Ester	³ J _{C_yOC_xH}	³ J _{C_xOC_yH}
Methyl formate	4.27	4.00
Ethyl formate	4.14	3.32
<i>n</i> -Propyl formate		3.15
<i>n</i> -Butyl formate		3.15
Isobutyl formate		3.10
Neopentyl formate	4.20	2.80
Isopropyl formate	4.25	3.22
<i>sec</i> -Butyl formate		3.45
<i>tert</i> -Butyl formate	0.99	
Methyl acetate ^b		3.83, 3.95 ^c
Ethyl acetate		3.20, 3.25 ^c
Benzyl acetate ^d		3.40 ^c
Neopentyl acetate ^e		2.70 ^c
Isopropyl acetate		3.00, 2.90 ^c
2,2,4,4-Tetramethyl-3-pentyl acetate ^f		4.60 ^c

^a All coupling constants are in hertz. Experimental uncertainty is approximately ±0.05 Hz. ^b The geminal coupling between the carbonyl carbon and the protons of the adjacent methyl group was approximately 6.9 Hz throughout the acetates. ^c Data taken from ref 35. ^d Registry no., 140-11-4. ^e Registry no., 926-41-0. ^f Registry no., 13432-79-6.

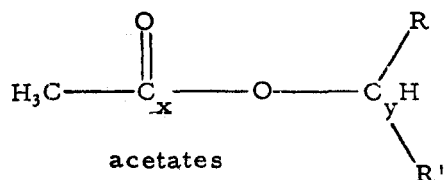
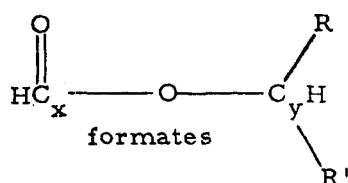
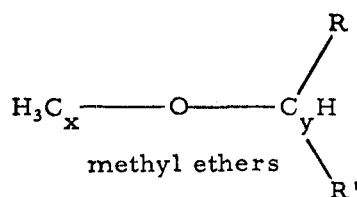


Figure 1. Labeling convention used in this paper in describing carbon-proton coupling. Thus, $J_{C_xOC_yH}$ will represent the coupling constant for the spin-spin interaction between C_x and the proton(s) attached to C_y .

Figure 1. Most of the data in Tables III-V were derived from simple first-order analyses of the proton-coupled ¹³C NMR spectra. Because the spectrometer sweep and recorder were digitized,⁹ side-band calibration was not necessary. The data reported for 1,4-dioxane and for carbons 4 and 5 of 1,3-dioxolane (Table V) were derived from computer analysis using LAOCOON III,¹⁴ and, in some of these cases, it is possible to specify the sign of the coupling constants.

Four- and five-bond proton-proton coupling constants measured in this study are compared with published data in Table VI. It is seen that our values, obtained by resolution-enhancing line-shape and LAOCOON analyses, are in

Table V
Carbon-Proton Coupling Constants
in Simple Cyclic Ethers

Compd	Type of coupling	Coupled nuclei		<i>J</i> , Hz
		¹³ C	¹ H	
1,3-Dioxolane	Geminal	4	5	+2.29
	Vicinal	4	2	+3.55
1,4-Dioxane	Vicinal	2	4,5	3.25
	Geminal	2	3	2.16
1,3,5-Trioxane	Vicinal	2	6	4.23
	Vicinal	2	4,6	5.65

Table VI
Long-Range Proton-Proton Coupling
in Simple Formates^a

Formate	Present study		Literature ^b	
	⁴ J _{HH}	⁵ J _{HH}	⁴ J _{HH}	⁵ J _{HH}
Methyl	0.86		-0.82	
Ethyl	0.83	0.60	-0.83	0.63
<i>n</i> -Propyl	0.86	0.57	-0.82	0.54
<i>n</i> -Butyl	0.85	0.52	-0.86	0.54
2-Phenylethyl	0.83	0.51		
Isobutyl	0.89	0.42	-0.87	0.42
Neopentyl	0.84			
Isopropyl	1.02	0.51	-1.00	0.52
<i>sec</i> -Butyl	1.01	0.53 (CH ₃)	-0.91	0.52 (CH ₃)
		0.43 (CH ₂)		0.48 (CH ₂)
<i>tert</i> -Butyl		0.38	0.40 ^c	

^a All coupling constants are reported in hertz. Experimental error is approximately ±0.03 Hz. ^b Unless indicated otherwise, all data are taken from ref 14. ^c Reference 15.

excellent agreement with the previously reported values.^{15,16} The only ether which showed a measurable four-bond proton-proton coupling was 1,3-dioxolane, for which $J_{H_2H_4}$ was found to be 0.22 ± 0.04 Hz. For the acetates, we were only able to measure the five-bond coupling between the protons of the acetyl methyl and those on the α carbon for the methyl ($J = 0.26 \pm 0.03$ Hz) and the ethyl ($J = 0.20 \pm 0.03$ Hz) esters. This is again in accord with previously reported data.¹⁷

Discussion

The Ethers. The conformational behavior of acyclic ethers is generally assumed to be similar to that of the analogous alkanes.¹⁸ Certainly the conformations of dimethyl ether¹⁹ and propane²⁰ are qualitatively similar, as demonstrated by microwave spectroscopy. In the case of ethyl methyl ether, there exist two conformations, *gauche* and *trans*, the latter being more stable by approximately 1.35 kcal/mol.^{18,21} Similarly, methyl isopropyl ether shows evidence of two rotamers in the liquid form, one of which, presumably that with two *gauche* interactions, is only slightly populated.¹⁸ In the present study, then, we shall assume that the general, qualitative conformational characteristics of the acyclic ethers will parallel those of the acyclic alkanes.²²

We will use here a convenient convention for describing carbon chemical-shift changes in biological molecules.²³ In the past,²⁴ it has become common to relate the chemical shift of a particular carbon, °C, to the number of substituents introduced at the α , β , γ , and δ positions (cf. Figure 2). Unfortunately, in both biological and organic chemistry, Greek letters are used to specify positions relative to functional groups and the dual usage of these symbols frequently becomes rather confusing. We therefore replace the

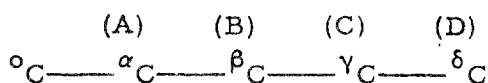


Figure 2. Definition of the conventions used in discussing carbon chemical-shift changes. The original²⁴ convention related the chemical shift of $^{\circ}\text{C}$ to the number of $^{\alpha}\text{C}$, $^{\beta}\text{C}$, $^{\gamma}\text{C}$. . . carbons, i.e., the number of carbons in those positions relative to $^{\circ}\text{C}$. We replace the Greek letters with **A**, **B**, **C**, etc., as shown in parentheses, in referring to particular carbons.

Greek letters with the boldface capital letters **A**, **B**, **C** . . . (Figure 2).

This convention allows us to discuss conveniently the **B** effect shown by the α -carbon resonance (Table VII). The data in Table VII were obtained by comparing the spectra of the ethers with those of the analogous, unsubstituted alcohols.²⁵ The changes in chemical shift at the α carbon would therefore be attributed to the **B** effect. It appears to be amply demonstrated that the **B** effect is broadly independent of the **A** substituent past which it must be transmitted.^{13,24-26} In the acyclic alkanes, the **B** effect is greatest (ca. -9.0 to -9.5 ppm) when $^{\circ}\text{C}$ is primary or secondary, somewhat reduced when $^{\circ}\text{C}$ is tertiary (-6.6 ppm), and severely attenuated when $^{\circ}\text{C}$ is quaternary (-2.3 ppm).²⁷ Reference to Table VII shows that the same characteristics are evident at the α carbon. Thus, when the α carbon is secondary, the **B** effect is approximately -10 ppm, while in cases where α/C is tertiary and quaternary, the **B** effects are ca. -9 and -4 ppm, respectively.

Continued comparisons show other interesting parallels between the chemical shifts of ethers and alkanes. Thus, the chemical-shift changes observed at the β carbon (Table VII) can be attributed to the **C** effect of the *O*-methyl group. This effect is known to be generally shielding in character,²⁴⁻²⁷ and this accords with the data in Table VII. Moreover, this effect is seen to be attenuated in those cases where the β carbon is more heavily substituted, as is the case for the isobutyl and neopentyl ethers. This is again as observed in the alkanes.²⁷ In the latter group of compounds, however, the **C** effect becomes deshielding when $^{\circ}\text{C}$ is quaternary. For methyl neopentyl ether it is evident that the same situation does not obtain for the ethers. In addition, the **C** effects observed at this position for some of the ethers appear to be somewhat larger than observed for the alkanes. These differences may be due in part to the presence of carbon-oxygen bonds in the ethers. These bonds are shorter than the analogous carbon-carbon bonds,^{18,19} a fact which could emphasize the steric effects to which the **C** effect is generally attributed.²⁸ Additionally, the presence of the carbon-oxygen bond dipole could lead to electric-field²⁹ or other effects.

Some insight into the origin of these **C** effects in the ethers can be drawn from comparisons of the *O*-methyl resonances of these ethers to that of dimethyl ether (Table VII, first column). The β carbons of these ethers are in the **C** position relative to the *O*-methyl group. Thus, in dimethyl ether, the *O*-methyl carbon has no **C** substituent, while the ethers of primary, secondary, and tertiary alcohols have one, two, and three **C** carbons, respectively. The data in Table VII shows that for all cases except that of methyl *tert*-butyl ether, which will be discussed separately, there is an average **C** effect of approximately $+2.5$ ppm for each **C** carbon. This value is very close to those observed for the alkanes.^{24,27} Here again, we have the shorter intermediary carbon-oxygen bonds between $^{\circ}\text{C}$ and $^{\circ}\text{C}$, yet the steric effect is not enhanced. The most probable explanation for this phenomenon lies in the greater energy difference between the trans and gauche rotational conformations of the ethers²¹ than in the alkanes.²² Thus, in the

Table VII
Chemical-Shift Changes Associated with Methylation for $\text{CH}_3\text{-O-C}_\alpha\text{-C}_\beta\text{-C}_\gamma\text{-C}_\delta$ ^a

Methyl ether	OCH_3 ^b	α	β	γ	δ
Methyl	0	-10.7			
Ethyl	+2.1	-10.7	+2.9		
<i>n</i> -Propyl	+3.0	-3.1	+3.8	+0.9	
<i>n</i> -Butyl	+2.8	-10.1	+3.8	+0.5	+0.8
Isobutyl	+2.5	-10.0	+3.1	+0.7	
Neopentyl	+1.8	-10.2	+1.4	+0.5	
Isopropyl	+4.8	-9.2	+3.7		
<i>sec</i> -Butyl	+5.2	-8.7	+3.9 (CH_2)	+1.6	
			+5.3 (CH_3)		
<i>tert</i> -Butyl	+11.1	-3.7	+4.4		

^a Chemical shifts in parts per million measured relative to the analogous carbon of the alcohol.²⁵ ^b This column represents the chemical shift of the *O*-methyl carbon relative to that of dimethyl ether.

ethers, the gauche form, the only conformation in which steric effects can become important, is less populated, and the expected enhancement of the steric effect due to the shorter carbon-oxygen bonds would be in part nullified.

Methyl *tert*-butyl ether is especially relevant to this explanation. In this molecule, the conformation is constrained to that shown in Figure 3d, in which the *O*-methyl carbon is forced into a gauche relationship to two methyls of the *tert*-butyl group. Here, the **C** effect observed at the *O*-methyl carbon is much larger than observed at carbon 4 of the analogous case of 2,2-dimethylbutane.²⁴ Thus, when gauche interactions are enforced, the shorter carbon-oxygen bond lengths appear to lead to intensified steric²⁸ effects.

Additional information regarding the populations of the various conformational states of these ethers is available from analysis of the vicinal coupling between the *O*-methyl carbon and the α proton ($J_{\text{C}_\alpha\text{OC}_\gamma\text{H}}$ in Table III). In the case of dimethyl ether, for which the conformation shown in Figure 3a has been determined,¹⁹ the vicinal carbon-proton coupling has been measured to be $+5.7$ Hz.³⁰ One can suppose that this observed coupling is the average of one trans (J_t) and two gauche (J_g) couplings.³¹

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

Assuming that J_g is approximately 2.7 Hz (vide infra), the trans coupling comes out as approximately 11.8 Hz.

For the methyl ethers of primary alcohols, we shall assume^{18,21} that the conformational equilibria are as represented in Figure 3b, with the trans form being favored by 1-1.5 kcal/mol.²¹ The population of the gauche form should then be only about 10% of that of the trans. Using $J_t \approx 11.8$ Hz and $J_g \approx 2.7$ Hz, one can estimate that the vicinal couplings should be about 3.4 Hz. This is in reasonable agreement with the observed values in Table III. These data also show that as R (Figure 3b) becomes bulkier, the observed coupling is reduced, reaching a minimum of 2.65 Hz when R is *tert*-butyl. It is from this datum that we approximate J_g on the assumption that the gauche rotamer of methyl neopentyl ether will be negligibly populated.

The $J_{\text{C}_\alpha\text{OC}_\gamma\text{H}}$ couplings in the methyl ethers of isopropyl and *sec*-butyl alcohols are significantly higher than the foregoing cases. For methyl isopropyl ether, one of the expected conformations, g_2 of Figure 3c, has been shown to be only very slightly populated.¹⁸ If g and g' , the conformations involving only one gauche interaction, were the only contributing forms, the observed coupling should be equivalent to J_g , or ca. 2.65 Hz. Unless there is a substituent effect operating here (vide infra), the substantially larger

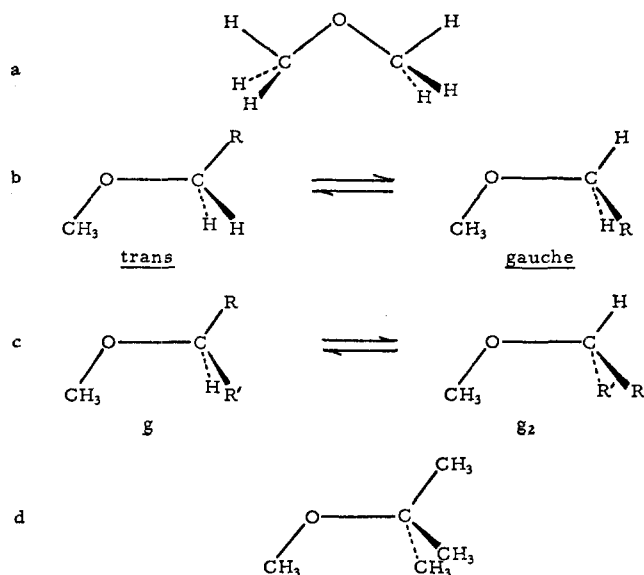


Figure 3. Some possible conformations of methyl ethers.

coupling observed may indicate a distortion of the conformation away from the perfectly staggered form to a situation wherein the α proton approaches the eclipsed disposition relative to the C-methyl carbon.

For 1,2-dimethoxyethane, $J_{C\alpha OC\beta H}$ is significantly smaller (1.85 Hz) than the analogous coupling in the methyl ethers of primary alcohols. This is rather surprising in that one might have expected the dihedral angles around the oxygen-methylene carbon bonds to be rather similar in these compounds. It is possible that this difference in coupling is due to a substituent effect, though in view of other results this appears unlikely. Thus, for example, the coupling between the α carbon and the O-methyl protons ($J_{C\beta OC\alpha H}$) in 1,2-dimethoxyethane is very similar to those of the methyl ethers of primary alcohols. In view of these results, it may be significant that the most stable conformation about the carbon-carbon bond of 1,2-dimethoxyethane is that in which the ether oxygens are gauche to one another.³² It is possible that this phenomenon could lead to dipole-dipole interactions or other effects which would distort the dihedral angles of the adjoining carbon-oxygen bonds slightly from the staggered conformation.

The above analysis is based upon the assumption that dihedral angles are the only important effect determining the magnitude of vicinal carbon-proton coupling. Some of the $J_{C\beta OC\alpha H}$ data (Table III), however, suggest that there may also be an important substituent effect. Thus, the coupling between the α carbon and the O-methyl protons is significantly larger for dimethyl ether than for all other cases. Also, there appear to be small differences in this coupling between the methyl ethers of primary ($J_{C\beta OC\alpha H} \approx 5.2-5.3$ Hz) and secondary ($J_{C\beta OC\alpha H} \leq 5$ Hz) alcohols. There is a further reduction in this coupling when the α carbon is quaternary, as in methyl *tert*-butyl ether. There are other indications, however, that this substituent effect may be negligible in those cases in which the extent of substitution on the coupled carbon is the same. Thus, the vicinal coupling in diethyl ether is not significantly different from the $J_{C\beta OC\alpha H}$ values observed in methyl ethers of primary alcohols. At present, we believe that the greatest changes in the coupling constants in Table III are due to the effects of dihedral angles.

At this time, there are too few data for the cyclic ethers to allow extended discussion. There are, nevertheless, some interesting results tabulated in Table V. Thus, the values for the vicinal coupling between carbons 4 and 5 of 1,3-

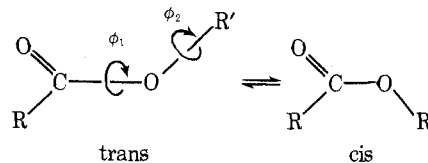
Table VIII
¹³C Chemical-Shift Changes on Ester Formation^a

Ester	α	β	γ	δ
Methyl formate	-0.5			
Ethyl formate	-2.2	+4.2		
<i>n</i> -Propyl formate	-1.1	+4.1	+0.5	
<i>n</i> -Butyl formate	-1.5	+4.5	+0.3	+0.6
Isobutyl formate	-0.3	+3.2	+0.5	
Neopentyl formate				
Isopropyl formate	-3.3	+4.0		
<i>sec</i> -Butyl formate	-2.7	+3.7		
<i>tert</i> -Butyl formate	-11.9	+3.5		
Methyl acetate	-1.3			
Ethyl acetate	-2.5	+4.1		
<i>n</i> -Propyl acetate	-1.4	+3.8	+0.3	
<i>n</i> -Butyl acetate	-2.1	+4.2	+0.1	+0.5
Isobutyl acetate				
Neopentyl acetate				
Isopropyl acetate	-3.3	+3.9		
<i>sec</i> -Butyl acetate				
<i>tert</i> -Butyl acetate	-10.5	+3.7		

^a The data tabulated represent the chemical shifts of the indicated carbons of the esters relative to the analogous carbon in the alcohol. All shifts are in parts per million.

dioxolane and the protons on carbon 2 is positive, like the corresponding coupling in dimethyl ether.³⁰ It has been our presumption throughout the above discussion that all other vicinal coupling constants in this series are positive. Second, there are notable differences in some of the vicinal coupling constants which do not seem attributable to the effects of dihedral angles. Most probably the small differences between the vicinal couplings in 1,4-dioxane and 1,3,5-trioxane are due to the substitution effect of oxygen. If the substituent effect on vicinal carbon-proton coupling is dependent upon the electronegativity of the substituent, as in the analogous proton-proton coupling,³³ these results again suggest that carbon substitution is associated with rather small effects.

The Esters. The conformational behavior of esters must be rather different from that of the alkanes because the resonance effect allows only two stable planar conformations about the acyl-oxygen bond, with ϕ_1 equal to 0° or 180°. The enforced planarity doubtless influences the rotational equilibria around the alkyl-oxygen bond which involves ϕ_2 . Thus, we expect, and observe, rather different effects in the spectra of these compounds from those of the ethers (see Table VIII).



The carbon chemical shifts of esters show that the α -carbon resonance of a primary alcohol undergoes a small (generally ≤ 2 ppm) deshielding effect on formylation or acetylation. For secondary alcohols, this deshielding effect is slightly larger, averaging about -3 ppm. For the *tert*-butyl esters, however, this effect becomes much larger, and acetylation leads to shifts of at least -10 ppm at the α carbon. Thus, while the effect of acetylation at this position resembles that of methylation (Table VII) in that this nucleus is deshielded, the dependences of the magnitude of the effect upon substitution at the α carbon in the two types of compound are quite different.

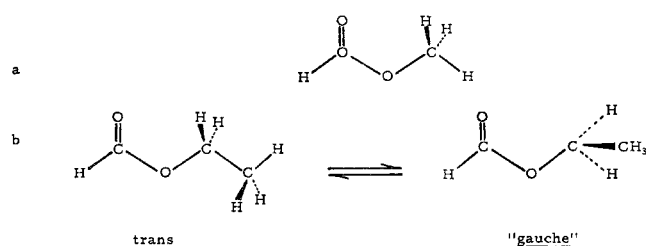


Figure 4. Conformations of methyl and ethyl formate, as deduced from microwave spectroscopy.^{33,34}

Some aid to understanding these changes is available from the carbon-proton coupling data of Table IV. In the formates, the ${}^3J_{C_yOC_xH}$ coupling constant should be expected to reflect the dihedral angle about the acyl-oxygen bond. For methyl³⁴ and ethyl³⁵ formate, the cis conformation was found to be undetectable by microwave spectroscopy, and the trans form seems generally preferred energetically. Certainly, in most of the cases studied to date (Table IV), the ${}^3J_{C_yOC_xH}$ couplings appear to be independent of substitution at the α carbon. This suggests not only that the simple esters exist preferentially in the trans conformation but that there is only a small substituent effect. However, for *tert*-butyl formate, ${}^3J_{C_yOC_xH}$ is rather different from the other examples. This suggests that the cis conformation makes a much more important contribution to the conformational population than with the other examples.

This conclusion also accounts for the acylation shift changes discussed above. For amides and peptides, it has been found that carbon nuclei which are proximal to the carbonyl oxygen are subject to strong shielding effects.²³ In the amides, this effect had been previously recognized and attributed to an electric-field effect.²⁹ Such a mechanism might also be expected to operate in the esters, and in the trans conformation would be expected to counteract the deshielding **B** effect arising from the acyl group. If, however, the *tert*-butyl group forced the molecule into the cis rotational conformation, the α carbon would be much more remote from the carbonyl oxygen and should be much less affected by its electric field, and the **B** effect would become dominant.

At present, there seems to be no recognizable pattern in the effects of acylation on the β - and γ -carbon resonances. The constancy of the acylation shifts at the β carbon suggests that these changes are not dependent to any large degree on proximity effects.

We have already suggested that the properties of the acyl group may well be expected to have an effect on the conformation around the alkyl-oxygen bond. There is evidence derived from microwave spectroscopy that this is indeed true. Thus, although the conformation of methyl formate³⁴ was found to be perfectly staggered, one of the major contributors to the conformational equilibrium of ethyl formate³⁵ is not. (Cf. Figure 4.) In the "gauche" conformer of Figure 4b, the dihedral angle between the acyl oxygen and α -C- β CH₃ bond is approximately 85°, not 120° as would be the case in the perfectly staggered form. Furthermore, the energy difference between these two conformers is less than 200 cal/mol, with the trans form being favored. The conformational situation of the esters is therefore rather different from that of the ethers.

In view of this, it is rather surprising that the ${}^3J_{C_xOC_yH}$ values in Table IV are so similar to the analogous couplings observed for the ethers (Table III). For derivatives of primary alcohols, these vicinal couplings in the two classes of compound are very similar. As observed for the analogous chemical-shift differences, these couplings seem broadly

independent of whether the acyl group is acetate or formate. On the basis of these couplings one might easily be tempted to conclude that the conformations of the esters and ethers are very similar. However, for the methyl esters, ${}^3J_{C_xOC_yH}$ values are quite different from those of dimethyl ether.

Earlier workers³⁶ have used ¹³C isotopic enrichment and proton nuclear magnetic resonance spectroscopy to analyze the conformation around the acyl-oxygen bond of acetates. By studying the variation of ${}^3J_{C_xOC_yH}$ with temperature, these investigators were able to make rough estimates of the values J_t and J_g . Unfortunately, these estimates were based on the assumption of perfectly staggered conformations which, in view of the more recent microwave study of ethyl formate,³⁵ may not be valid. From the fact that no temperature dependence for ${}^3J_{C_xOC_yH}$ would be detected for di-*tert*-butylcarbinyl acetate (2,2,4,4-tetramethyl-3-pentyl acetate), it was concluded³⁶ that this molecule was conformationally rigid and that the observed coupling constant (4.6 Hz) approximated that of cis coupling between vicinally disposed carbon and hydrogen.

At present, we do not feel that sufficient data exist to allow detailed analyses of these couplings in the esters. However, some interesting conclusions emerge from the data in Table IV. First, by comparing the $J_{C_xOC_yH}$ couplings in the formate and acetate esters of methyl, ethyl, neopentyl, and isopropyl alcohols, it can be concluded that the effect of carbon substitution on C_x is very small. The greatest difference is observed for the isopropyl cases, and in view of the other examples, it seems likely that this particular difference may reflect changes in the alkyl-oxygen dihedral angle.

Second, in the esters of primary alcohols, there is a trend for the magnitude of the ${}^3J_{C_xOC_yH}$ values to decrease as the bulk of the R group attached to the α carbon is increased. If we assume that the coupling in the "gauche" type of conformation (Figure 4b) is larger than that of the trans, this trend signals an increase in the energy difference between these two conformations, as was concluded for the ethers.

Third, there seems to be a tendency for the coupling in the formates of secondary alcohols to be slightly larger than for primary alcohols. Again, isopropyl acetate forms the only exception to this generalization. The striking difference between the ${}^3J_{C_xOC_yH}$ values of the formate esters of isopropyl and *sec*-butyl alcohols again suggests that the assumption of perfectly staggered conformations is likely to be an oversimplification. Because the same difference is observed for the *O*-methyl ethers of these alcohols, this caveat may apply to the ethers as well.

Finally, we shall consider the long-range proton-proton coupling constants presented in Table VI. The theoretical aspects of such couplings has been reviewed.³⁷ It is apparent that the trends observed in the vicinal ${}^3J_{C_xOC_yH}$ values are not reproduced in the ${}^4J_{HH}$ values of Table VI. Indeed, ${}^4J_{HH}$ appears to be insensitive to any but substituent effects, which may or may not be related to the influence of dihedral angles. The theoretical interpretation of ${}^4J_{HH}$ appears to be complicated and is influenced by many factors.³⁷ At present, these data appear to add little to our analysis of the conformations of these systems.

The ${}^5J_{HH}$ data in Table VI, however, can be interpreted in terms of our previous conclusions based on carbon chemical shifts and vicinal carbon-proton coupling. The theoretical model for this coupling suggests that five-bond proton-proton coupling to the formyl proton should be independent of the dihedral angle about the alkyl-oxygen bond.³⁷ Instead, this coupling should depend on the dihedral angles about the acyl-oxygen and the α -C- β C bonds, being at a maximum when the bonds transmitting the coupling are

trans.³⁷ This situation is most likely for ethyl formate (cf. the trans conformer, Figure 4b) and, indeed, the largest $^5J_{\text{HH}}$ is observed for this compound. As substituents are added to the β carbon, the optimum conformation around the $\text{C}_\alpha\text{-C}_\beta$ bond becomes less likely, as it requires gauche interactions between the γ carbon(s) and the ester oxygen. This is as observed in Table VI. For isobutyl formate, where the optimum conformation requires two gauche interactions, $^5J_{\text{HH}}$ becomes particularly reduced. A similar effect is observed for *tert*-butyl formate, in which we have deduced a cis acyl-oxygen bond. Unfortunately, these speculations involve presumptions of perfectly staggered forms and are based on a theoretical model³⁷ derived for hydrocarbons.

Conclusion

It seems clear that measurement of vicinal carbon-proton couplings can be useful in the analysis of conformations. Furthermore, these couplings seems to be related to much more easily measured carbon chemical-shift changes.

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Benzoin Oximes in Sulfuric Acid. Cyclization and Fragmentation

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The kinetics of the reaction of benzoin, α -methylbenzoin, and α -phenylbenzoin oximes with sulfuric acid in acetic acid, resulting in concurrent cyclization to the corresponding 1-hydroxyindoles and fragmentation to benzonitrile and benzaldehyde, acetophenone, or benzophenone respectively, have been investigated at several temperatures in 60–100% sulfuric acid. Cyclization predominates at higher acidities. Mechanisms involving initial protonation on both oxime and carbinol followed by either direct fragmentation or dehydration and cyclization are proposed based on rate vs. acidity data, oxime basicity and the effects of perdeuteration and substitution of the benzoin oximes.

While benzoin oxime cyclizes to 1-hydroxy-2-phenylindole in concentrated sulfuric acid,² fragmentation to benzaldehyde and benzonitrile has been observed under other acidic conditions.³ We have explored the concurrent cyclization and fragmentation reactions of benzoin oxime over a range of acidities produced from appropriate mixtures of sulfuric acid and acetic acid. As mechanistic interpretations frequently can be made from the relationship between reaction rate and solvent acidity,⁴ we initially determined the H_0 values of anhydrous sulfuric acid in acetic acid for the concentration range used in this investigation (50–95%) at the temperatures used for the kinetic determinations. In addition to the detailed investigation of the reactions of benzoin oxime we obtained limited kinetic data

for ring perdeuterated benzoin oxime, for α -methyl and α -phenyl benzoin oximes, and for benzoin oxime methylated on the α -hydroxyl position. All the oximes used in this investigation had the anti (or α) geometry.

The results of the H_0 determinations in the range 50–95% sulfuric acid are in Table I. The indicators used, with sulfuric acid concentration range and appropriate pK values at 30, 50, and 70°, obtained by interpolation from the data of Tickle, Briggs, and Wilson,⁵ are as follows: 2,6-dinitroaniline, 50–60%, -5.35 , -5.28 , -5.21 ; 2-bromo-4,6-dinitroaniline, 55–70%, -6.43 , -6.26 , -6.10 ; 2,4,6-trinitro-*m*-toluidine, 70–85%, -8.03 , -7.80 , -7.68 ; picramide, 85–95%, -9.82 , -9.62 , -9.42 . Figure 1 shows the relationship H_0 vs. % H_2SO_4 w/w for solutions in water,⁶ acetic acid,⁷