

[Reprinted from the Journal of the American Chemical Society, 86, 2623 (1964).]

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Nonequivalence Due to Molecular
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By George M. Whitesides, David Holtz, and John D. Roberts

[CONTRIBUTION NO. 3072 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY,
PASADENA, CALIF.]

Nuclear Magnetic Resonance Spectroscopy. The Effect of Structure on Magnetic Nonequivalence Due to Molecular Asymmetry¹

BY GEORGE M. WHITESIDES, DAVID HOLTZ, AND JOHN D. ROBERTS

RECEIVED FEBRUARY 20, 1964

The difference in chemical shift between the methylene protons of a number of compounds related structurally to 1-phenylethyl benzyl ether has been measured. Correlations between structural features of these compounds and the magnitude of the magnetic nonequivalence induced by the center of molecular asymmetry provide a basis for qualitative identification of the most important factors contributing to the chemical-shift difference. Although it is clear that no single factor completely determines the magnitude of the methylene proton nonequivalence in these ethers, it is suggested that the proximity of the asymmetric center to the benzyl group results in a preferred conformation of the phenyl ring with respect to the methylene protons, and that the principal contribution to the nonequivalence originates in the magnetic anisotropy of the phenyl group.

Introduction

The protons of a methylene group or isopropyl group removed by one or more bonds from a center of molecular asymmetry may be magnetically nonequivalent and display AB-type nuclear magnetic resonance spectra.² The origin of this magnetic nonequivalence has been a subject of several investigations.²⁻⁴ Although the existence of preferred conformations of the methylene group or the isopropyl group with respect to the asymmetric center⁵ has generally been considered necessary for magnetic nonequivalence, several workers have pointed out that such preferred conformations are not a theoretical prerequisite for observable asymmetry.⁶ The problem of the possible importance of small contributions to magnetic nonequivalence arising from an

"intrinsic" asymmetry, independent of rotational conformer populations, has not yet been completely resolved; however, no convincing experiment has so far been reported which has demonstrated significant contributions from intrinsic asymmetry to an observed chemical shift. However, it should be emphasized that in discussing the relative importance of conformational preference and intrinsic asymmetry, the question at issue is not whether the former or the latter is *alone* responsible for magnetic nonequivalence, but rather how much, if any, of an observed nonequivalence should be ascribed to intrinsic asymmetry. There seems little doubt that conformational preference with respect to the asymmetric center must in general be responsible for the major contributions to the magnetic nonequivalence.

The work reported in this paper is concerned with an empirical study of the effect of structure on the magnitude of the magnetic nonequivalence of methylene and isopropyl groups close to the center of molecular asymmetry in relatively simple model compounds. As such, its immediate purpose was to determine those types of structural features which could be associated with large values of magnetic nonequivalence. However, attempts to reconcile the results obtained with an explanation of the manner in which the asymmetric

(1) Supported in part by the Office of Naval Research and the Undergraduate Research Participation Program of the National Science Foundation.

(2) For a compilation of references to pertinent examples, see E. I. Snyder, *J. Am. Chem. Soc.*, **85**, 2624 (1963).

(3) G. M. Whitesides, F. Kaplan, K. Nagarajan, and J. D. Roberts, *Proc. Natl. Acad. Sci. U. S. A.*, **48**, 1113 (1962), and references therein.

(4) H. S. Gutowsky, *J. Chem. Phys.*, **37**, 2196 (1962); H. S. Gutowsky, G. G. Belford, and P. E. McMahon, *ibid.*, **36**, 3353 (1962).

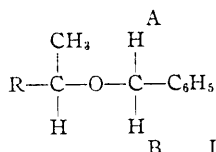
(5) It should be noted that the discussion in this paper is equally applicable to methylene groups adjacent to a dissymmetric center: see, for example, W. L. Meyer and R. B. Meyer, *J. Am. Chem. Soc.*, **85**, 2170 (1963).

(6) J. S. Waugh and F. A. Cotton, *J. Phys. Chem.*, **65**, 562 (1961); J. A. Pople, *Mol. Phys.*, **1**, 3 (1958).

center exerts its influence on surrounding nuclei suggest that the study of AB-type methylene groups may provide a sensitive method of examining problems of conformation and solvation in solution.

Results

The Effect of the Structure of the Asymmetric Center on the Magnetic Nonequivalence of an Adjacent Methylene Group.—The experimental approach to this part of the problem was chosen to be as simple as possible, the idea being to vary one structural feature of the asymmetric center and to determine the effect of the charge on the chemical-shift difference between the protons of an adjacent methylene group. The compounds chosen were benzyl ethers of structure I.



These compounds have the advantage that analysis of the AB-type methylene proton spectra to obtain the desired spectral parameters is extremely simple. They suffer from two disadvantages: first, unresolved coupling between the benzyl methylene protons and the adjacent ring protons results in a line width of approximately 0.5 c.p.s. for the components of the AB spectrum. Consequently, the separation of the two central components of the AB quartet becomes uncertain for values of the difference in chemical shift, $\nu_A - \nu_B$, less than approximately 3 c.p.s., due to overlap. Second, introduction of an ether oxygen atom between the asymmetric center and the methylene group results in a considerable increase in the number of possible conformations of these two centers relative to one another, and consequently complicates attempts to discuss details of their interaction.

The groups selected as R of I were alkyl groups of varying size (ethyl, isopropyl, cyclohexyl, and *t*-butyl) and two unsaturated groups (phenyl and carbethoxy). The results of analysis of the methylene proton spectra of these compounds in benzene, acetone, and carbon tetrachloride solutions are summarized in Table I. The chemical-shift differences were obtained for approximately 10% solutions; tetramethylsilane was used as an internal standard. The chemical-shift difference between the methylene protons depends to a small extent on the concentration of the benzyl ether and on the concentration of tetramethylsilane; however, the errors introduced by not extrapolating the differences in chemical shift to infinite dilution of both solute and tetramethylsilane are not large enough to influence significantly the relative magnitudes of the values reported in Table I.

The most important feature of these numbers is the correlation between the magnitude of the chemical shift between the methylene protons and the size of R, when R is an alkyl group. As a measure of size, we use here the *A*-values determined by Winstein and Holness.⁷ The *A*-values probably do not describe the size of each group in more than a qualitative manner because of the major differences between a cyclohexane ring and compounds of structure I. They do however lend support to the intuitive ordering of the size of the alkyl

(7) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

groups in Table I as *t*-butyl \gg cyclohexyl $>$ isopropyl $>$ ethyl. The magnitude of the observed magnetic nonequivalences follows the same order.

The two unsaturated groups in Table I, phenyl and carbethoxy, clearly do not fit the same pattern as do the alkyl substituents. The *A*-value of a phenyl group suggests that it is slightly larger than an isopropyl group; the magnitude of the magnetic nonequivalence for 1-phenylethyl benzyl ether in carbon tetrachloride and benzene solutions (10.2 and 10.9 c.p.s., respectively) is correspondingly larger than the values for benzyl isopropylmethylcarbinyl ether in the same solvents (8.8 and 9.3 c.p.s.). In contrast, however, the value of the magnetic nonequivalence for the phenyl-substituted compound is much smaller (2.5 c.p.s.) in acetone solution than that of its alkyl-substituted counterpart (8.4 c.p.s.).

The degree of magnetic nonequivalence for carbethoxymethylcarbinyl benzyl ether is also greater than would be expected if the bulk of the substituent R were the only factor important in determining the relative magnitudes of the chemical-shift differences reported in Table I. Carbethoxy has an *A*-value of approximately

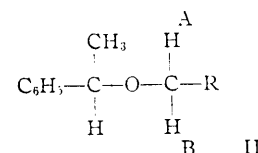
TABLE I
MAGNETIC NONEQUIVALENCE OF THE BENZYLIC PROTONS OF
BENZYL METHYLALKYL CARBINYL ETHERS OF STRUCTURE I

R	$\nu_A - \nu_B$, c.p.s., and solvent ^a			<i>A</i>
	Carbon tetrachloride	Benzene	Acetone	
Ethyl	5.8	6.6	5.8	1.86 ^b
Isopropyl	8.8	9.3	8.6	2.1 ^c
Cyclohexyl	9.7	10.2	9.6	...
Phenyl	10.2	10.9	2.5	3.0 ^d
<i>t</i> -Butyl	14.8	15.7	14.7	>5.4 ^e
Carbethoxy	16.5	20.7	11.8	1.1 ^f

^a Solutions were 10 \pm 2% by volume in solute; the experimental error in the chemical shift values are no greater than ± 0.5 c.p.s. ^b N. L. Allinger and S. Hu, *J. Am. Chem. Soc.*, **84**, 370 (1962). ^c N. Allinger and S. Hu, *J. Org. Chem.*, **27**, 3417 (1962). ^d F. W. Garbisch, Jr., and D. B. Patterson, *J. Am. Chem. Soc.*, **85**, 3228 (1963). ^e S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955). ^f E. L. Eliel and M. Granni, *Tetrahedron Letters*, 97 (1962).

1.1, smaller even than methyl; yet the values of the magnetic nonequivalence in benzene and carbon tetrachloride solutions are larger for this compound than for *t*-butylmethylcarbinyl benzyl ether in the same solvents.

The chemical shifts between the methylene protons of four ethers of structure II are summarized in Table



II. The results indicate that the dependence of the magnetic nonequivalence on the structure of the substituent directly bonded to the methylene group does not follow the pattern suggested by Table I. In carbon tetrachloride and acetone solution, $\nu_A - \nu_B$ is close to zero for the three alkyl groups examined. In benzene solution, the magnitude of the chemical shift between the methylene protons does increase with increasing bulk of the substituent R. However, in contrast to the data given in Table I, the value of $\nu_A - \nu_B$ when R is phenyl

TABLE II
MAGNETIC NONEQUIVALENCE OF THE METHYLENE PROTONS
OF ETHERS OF STRUCTURE II

R	$\nu_A - \nu_B$, c.p.s., and solvent ^a		
	Carbon tetrachloride	Benzene	Acetone
Methyl	<i>b</i>	~3	- <i>b</i>
Isopropyl	<0.2	4.1	1.4
<i>t</i> -Butyl	<0.2	6.9	<0.2
Phenyl	10.2	10.9	2.5

^a Solutions were 10 ± 2% by volume in solute. ^b These spectra were not explicitly analyzed; however, an upper limit of approximately 2 c.p.s. can be placed on $\nu_A - \nu_B$ by inspection.

is appreciably larger than that when R is *t*-butyl in all three solvents.

The Effect of the Proximity to Asymmetric Center on the Magnitude of Magnetic Nonequivalence.—The influence of proximity to the asymmetric center on the magnitude of the nonequivalence has been investigated for a series of compounds containing an increasing number of bonds between a common asymmetric center and an isopropyl group (Table III). An isopropyl group was used instead of a methylene group for two reasons: first, the methyl resonances were not complicated by overlap with the resonance of other groups in the molecule, as would have been the resonance of a methylene group. Second, as was mentioned previously, the methylene proton resonances of the benzyl methylene groups examined in this study were appreciably broadened by unresolved coupling to the phenyl ring protons. Consequently, the rather small chemical-shift differences expected for compounds containing several bonds between a methylene group and the asymmetric center would not have been detected.

TABLE III
DEPENDENCE OF ISOPROPYL GROUP NONEQUIVALENCE ON
PROXIMITY TO THE ASYMMETRIC CENTER

Compound	$\nu_A - \nu_B$, c.p.s., and solvent ^a			
	Acetone	Ben- zene	tetra- chloride	Pyri- dine
C ₆ H ₅ CH(CH ₃)CH(CH ₃) ₂	11.7	8.0	10.9	8.9
C ₆ H ₅ CH(CH ₃)OCH(CH ₃) ₂	5.8	0.8	4.0	3.0
C ₆ H ₅ CH(CH ₃)OCH ₂ CH(CH ₃) ₂	0.0	0.5	0.3	0.0
C ₆ H ₅ CH(CH ₃)OCH ₂ CH ₂ CH(CH ₃) ₂	2.2	1.8	2.5	1.8
C ₆ H ₅ CH(CH ₃)OCH ₂ CH ₂ OCH(CH ₃) ₂	0.0	0.8	0.0	0.0
C ₆ H ₅ CH(CH ₃)OCH ₂ CH ₂ OCH ₂ CH(CH ₃) ₂	0.0	0.0	0.0	0.0

^a Solutions were 10 ± 2% by volume in solute.

The chemical shift between the methyl groups of the isopropyl group of each compound is reported in several solvents. It is interesting that significant effects of asymmetry have been detected for protons which are as many as seven bonds away from an asymmetric center in open-chain compounds.

It should be noted that the nonequivalence does not decrease monotonically as the number of bonds separating the asymmetric center from the isopropyl group increases, but rather decreases, increases, and then falls to zero; in each of the four solvents examined, the isopropyl nonequivalence *increased* on changing the separation between the asymmetric center and the isopropyl group from three to four bonds.

Discussion

Before going into detail about the factors responsible for the difference in the magnitude of the shielding at the benzylic methylene protons of compounds of type I, we shall first consider whether the magnetic nonequiv-

alence arises from local or remote shielding of the protons. The observed chemical shielding σ of each methylene proton can conveniently be divided into two parts

$$\sigma = \sigma_e + \sigma_d$$

where σ_e is the shielding due to the electrons in the carbon-hydrogen bond and σ_d is the shielding due to parts of the molecule distant from the methylene carbon-hydrogen bonds.⁸ The apparent electronegativity of the carbon bonding orbital directed toward each hydrogen is most important in determining σ_e ; factors contributing to σ_d include the magnetic anisotropies of nearby groups, van der Waals and reaction-field effects, as well as shielding originating in solvent molecules.

It would seem unlikely that the local chemical shielding term σ_e contributes in an important way to the chemical shift between the methylene protons of the ethers being examined, because the two methylene carbon-hydrogen bonds should have very similar bond characters. We have not examined specifically the bonding in these ethers; however, in four similar compounds there is evidence that the carbon-hydrogen bonds to the magnetically nonequivalent groups are in fact very similar. Diethyl sulfoxide, diethyl sulfite, isopropyl methyl sulfoxide and isopropylmethylcarbinol have equal ¹³C-H coupling constants between the methylene carbon atom and the two methylene protons (in the first two compounds) and between the methyl carbon atoms and the methyl protons (in the last two); the magnitudes of the magnetic nonequivalence in these compounds are comparable to those observed in the ethers being discussed. If the differences in the shielding at the nonequivalent protons of these compounds were due to a difference in the orbital electronegativity of the carbon bonding orbitals directed toward them (in other words, to a difference in the s-character of these orbitals) one would expect this difference to be reflected in the ¹³C-H coupling constants between these protons and their directly-bonded carbon atoms.⁹ The observation of identical ¹³C-H coupling constants between corresponding nonequivalent protons thus suggests that σ_e is not a major contributor to the difference in chemical shift between the methylene hydrogens.

A priori, several different factors might appear capable of making significant contributions to the difference in σ_d for the magnetically nonequivalent benzyl methylene protons. The most important of these factors are the magnetic anisotropies of the σ -bonds in the molecule; the magnetic anisotropy associated with unsaturated groups, both in the ether molecule and in solvent molecules; the reaction field induced in the medium by the solute; van der Waals interactions between solute and solvent; and hydrogen bonding or specific complex formation between solute and solvent.

The simplest of the ethers to discuss in terms of these interactions are those having only alkyl groups in the asymmetric center. The data in Table IV provide the best available evidence that the solvent does not

(8) P. T. Narasimhan and M. T. Rogers, *J. Chem. Phys.*, **31**, 1302 (1959).

(9) N. Müller, *ibid.*, **36**, 359 (1962); C. Juan and H. S. Gutowsky, *ibid.*, **37**, 2198 (1962); J. N. Shoolery, *ibid.*, **31**, 1427 (1959); N. A. Matwiyoff and R. S. Drago, *ibid.*, **38**, 2582 (1963).

play an important role in determining the magnitude of the nonequivalence.¹⁰ The variation in the chemical-shift values for each compound in this table is less than 1.5 c.p.s. for a variety of solvents. Particularly noteworthy in the solvents listed in Table IV are acetic acid, benzene, and dimethyl sulfoxide.

TABLE IV
SOLVENT DEPENDENCE OF THE MAGNETIC NONEQUIVALENCE OF THE METHYLENE PROTONS FOR ALKYL METHYL CARBINYL BENZYL ETHERS OF STRUCTURE I^a

Solvent	R = ethyl	R = isopropyl	R = <i>t</i> -butyl
Carbon tetrachloride	5.8 c.p.s.	8.8 c.p.s.	14.8 c.p.s.
Benzene	6.6	9.3	15.7
Cyclohexane	5.7	8.6	..
Acetone	5.7	8.6	14.7
Dimethyl sulfoxide	4.9	8.2	15.1
Acetic acid	5.4	8.0	..
<i>t</i> -Butyl alcohol	14.9

^a Solutions were 10 ± 2% by volume in solute. The experimental error in $\nu_A - \nu_B$ is approximately 0.5 c.p.s.

The observation that chemical shifts in acetic acid are no larger than those in carbon tetrachloride or cyclohexane suggests strongly that specific interactions involving the ether oxygen atom are of minor importance. The unexceptional value of the nonequivalence in benzene solutions indicates that magnetic anisotropy originating in the solvent molecule is not a major contributor to the magnetic nonequivalence.¹¹ The values of the nonequivalence in dimethyl sulfoxide and in cyclohexane solutions indicate that the chemical shift is insensitive to the dielectric constant of the solvent. Thus, at the simplest level of discussion, it seems justified to neglect the effect of solvent on the degree of nonequivalence of the methylene protons, and consequently to discard reaction-field effects and specific solvent-solute interactions as responsible for the nonequivalence.

If the solvent is unimportant in determining the chemical shift between the methylene protons, the origin of the magnetic nonequivalence is most probably intramolecular. The two most reasonable sources of the difference in shielding at the methylene protons are electrons circulating in the σ -bonds of the molecule and electronic circulations associated with the unsaturated centers. In order to discuss the magnitudes of these effects, it would be helpful to know the details of the stereochemistry about an ether oxygen atom. In particular, an estimate of the "size" of the nonbonding electrons on the oxygen atom would be useful. The C-O-C bond angle has been determined for diethyl ether from electron-diffraction data, and found to be $108 \pm 3^\circ$ ¹²; this angle suggests that the hybridization at the ether oxygen atom is close to tetrahedral. X-Ray crystallographic or electron-diffraction data pertaining to the configuration around

(10) The subject of the solvent dependence of the magnetic nonequivalence in these compounds will be treated in detail in a following paper. In brief, however, the spectra of ethers containing unsaturated groups on both sides of the ether oxygen link are very dependent on solvent dielectric constant; the spectra of those containing only one unsaturated group are not.

(11) It should be pointed out here that the value of the nonequivalence for a benzene solution of the compounds in Table IV and most other compounds examined is always 0.5-5 c.p.s. larger than for solutions in other solvents. In the present examples, this effect is clearly minor; it does however indicate that the magnetic anisotropy of the solvent can be a significant contributor to the methylene nonequivalence.

(12) "Interatomic Distances," Special Publication No. 11, The Chemical Society, London, 1958.

an ether oxygen unfortunately are not available. However, some structure work has dealt with the related problem of configuration around the ether oxygens of esters.

Kashima has carried out an electron-diffraction study of chloromethyl chloroformate and has found that the chlorine atom of the chloromethyl group is *trans* to the carbonyl carbon atom across the oxygen-carbon single bond.¹³ The same stereochemical result has been reported for the configuration about the ether oxygen atom in diethyl terephthalate¹⁴ and in potassium ethyl sulfate.¹⁵ To the extent that the stereochemistry about the ether oxygen atom of these compounds can be considered a model for the stereochemistry about the ether oxygen atom of a benzyl ether in solution, these data suggest that a lone pair of electrons on oxygen is smaller than an alkyl substituent attached to oxygen.

These structure determinations and examination of molecular models suggest that an ether of the type under discussion should exist predominantly in a conformation represented schematically by IIIa provided that R₁ is larger than methyl, and provided that steric interactions completely determine the relative energies of the conformations.¹⁶ Conformations of type IIIb should probably also be appreciably populated.



In conformation IIIa, one proton is close to a carbon-carbon bond and one is close to a carbon-hydrogen bond. The magnetic anisotropy of carbon-carbon and carbon-hydrogen σ -bonds has been the subject of extensive (if inconclusive) theoretical¹⁷ and experimental¹⁸ study. Although approximate calculations based on the equations derived by McConnell¹⁹ using "experimental" values¹³ of $\Delta\chi$ indicate that σ -bond anisotropy might be a significant factor in certain cases,²⁰ there is convincing evidence that it is not important in the compounds studied here. If the magnetic anisotropy of the σ -bonds were to determine the magnitude of $\nu_A - \nu_B$, replacing either of the phenyl groups of 1-phenylethyl benzyl ether with an isopropyl group should make relatively little change in the chemical-shift difference because any shielding of the methylene protons arising from σ -bond anisotropy will depend primarily on the conformation of the molecule in the region of the methylene group. A

(13) M. Kashima, *Bull. Chem. Soc. Japan*, **25**, 79 (1952).

(14) M. Bailey, *Acta Cryst.*, **2**, 120 (1949).

(15) J. A. Jarvis, *ibid.*, **6**, 327 (1953).

(16) For a general discussion of the difficult problem of determining conformational energies in simple substituted hydrocarbons, see S. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, Inc., New York, N. Y., 1954.

(17) For references to work in this area, see *Discussions Faraday Soc.*, **34**, 64 (1963); R. F. Zürcher, *J. Chem. Phys.*, **37**, 2421 (1962).

(18) A. G. Moritz and N. Sheppard, *Mol. Phys.*, **5**, 361 (1963); G. S. Reddy and J. H. Goldstein, *J. Chem. Phys.*, **38**, 2736 (1963), and references therein.

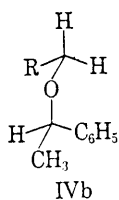
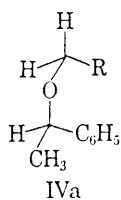
(19) H. McConnell, *ibid.*, **27**, 226 (1957).

(20) For a possible example, see T. J. Flautt and W. F. Erman, *J. Am. Chem. Soc.*, **85**, 3212 (1963).

phenyl group and an isopropyl group are sufficiently similar in size that their interchange should not result in major changes in the population of the conformations open to the molecule. Consequently, replacing a phenyl group with an isopropyl group should have little effect on the magnitude of the nonequivalence. The data of Table I indicate that interchanging phenyl and isopropyl at the asymmetric center does in fact have but little effect on the methylene proton nonequivalence in a low dielectric constant solvent.¹⁰ However, when the phenyl group bonded to the methylene group is replaced by an isopropyl group, the magnetic nonequivalence of the methylene protons is reduced drastically (Table II). This observation suggests that the chemical shift between the methylene hydrogens cannot be due primarily to the magnetic anisotropy associated with the σ -bonds in the molecule.

Johnson and Bovey²¹ have calculated the shielding of a proton in the vicinity of a phenyl ring by considering the precession of the π -electrons in two circular regions above and below the plane of the ring under the influence of the component of the static magnetic field perpendicular to the ring. Measurements taken from Dreiding models indicate that the average distance of the methylene protons of 1-phenylethyl benzyl ether from the center of the closer phenyl ring is approximately 3.5 Å.; when one methylene proton is in the plane of the ring, the second is approximately 0.9 Å. above it. With these distances, it is possible to estimate²¹ that the maximum chemical shift between the two methylene protons due to the ring current of the phenyl group bonded to the methylene group will be approximately 9 c.p.s. and will occur when one proton lies in the same plane as the benzene ring.

The chemical shift due to the ring current of a benzene ring attached to the center of asymmetry will of course depend upon the conformation. In conformation IIIa, the distance between the methylene protons and the center of the ring is approximately 5.2 Å. and the maximum value for the difference in chemical shift due to this ring will be less than 1 c.p.s. (The maximum difference again occurs when one proton is close to the plane of the ring and the second is relatively far from this plane.) The effect of ring current in the phenyl group attached to the asymmetric center on the chemical shift between the methylene protons will thus be small in conformation IIIa (R_1 = phenyl). In conformations of type IVa, the difference in chemical shift due to the phenyl ring can be estimated to be approximately 3 c.p.s., using appropriate distances on a



Dreiding model and the approach of Johnson and Bovey.²¹ In contrast, the phenyl ring in conformation IVb is estimated to produce a chemical-shift difference between the methylene protons of approximately 30 c.p.s. Physically the difference between IVb and the

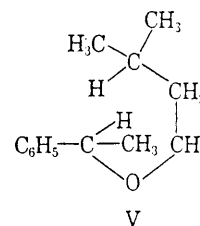
other less effective conformations is that the phenyl ring in this conformation lies very close to one of the methylene protons.

Although there is no indication that conformation IVb is populated to a significant extent for 1-phenylethyl benzyl ether, the anomalously large values of $\nu_A - \nu_B$ for carbethoxyethylcarbonyl benzyl ether can be rationalized on the basis of a conformation of this type. From both steric and electrostatic considerations, the most favored conformation for this latter compound should be one in which the carbethoxy group is *gauche* to the lone pairs on the ether oxygen atom as in IVb. In this conformation the carbonyl group should deshield the nearer proton strongly.

The foregoing discussion suggests that the factor responsible for the major part of the methylene proton nonequivalence in the benzyl ethers studies is a preferred conformation of the methylene group with respect to the plane of the nearer phenyl ring, such that one methylene proton lies in the plane of the ring and the second is situated appreciably out of this plane. The ring current of a phenyl ring located on the asymmetric center contributes little to this chemical shift.

Models of these ethers suggest that the phenyl group in conformation IIIa should be able to rotate freely around the $\text{CH}_2\text{-C}_6\text{H}_5$ bond. The conformations which seem most likely to induce a conformational preference of the phenyl group with respect to the asymmetric center are those in which the benzylic phenyl ring is close to the asymmetric center—in other words, conformations of type IIIb.

It is interesting to speculate briefly on the factors responsible for the progression of values reported in Table III. Clearly, the explanation proposed for the benzylic methylene proton nonequivalence cannot explain nonequivalence in isopropyl groups. However, the observation that the chemical shift between the methyl groups is unexpectedly large when these methyls are five bonds removed from the center of asymmetry is in accord with the Newman "rule of six,"²² and suggests that conformational preference of the isopropyl group with respect to the asymmetric center may again be important. In this case, coiled conformations of the type V may be populated to a significant extent. The observation that the chemical shift between the methyl groups is approximately the same for pyridine solutions as for solutions in carbon



tetrachloride or acetone for these compounds suggests that hydrogen bonding involving the ether oxygen is again unimportant. It seems possible that the phenyl group attached to the asymmetric center might shield the two isopropyl methyl groups in a conformation of type V to a significantly different extent. We have not examined compounds containing only saturated groups at the asymmetric center to test this possibility.

(21) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958), and references therein.

(22) M. S. Newman in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 4.

Experimental

All spectra were taken at 60 Mc.p.s. on a Varian A-60 spectrometer using samples $10 \pm 2\%$ by volume in solute.

Benzyl isobutyl ether was prepared by refluxing 14.8 g. (0.2 mole) of isobutyl alcohol and 18.9 g. (0.15 mole) of benzyl chloride with an excess of potassium hydroxide pellets for 24 hr. The organic layer was separated, washed twice with 500-ml. portions of water, and dried over calcium sulfate. Distillation through a 30-cm. wire-spiral packed column yielded approximately 10 g. of product, b.p. 75–80° (3 mm.). The product was identified by its n.m.r. spectrum. This ether (and the other ethers described in this section) were easily identified by comparison of their n.m.r. spectra with those of the starting materials.

Benzyl Isopropylmethylcarbinyl Ether.—Commercial silver oxide, (18.9 g., 0.15 mole) and a Teflon-covered stirring bar were placed in a 100-ml. round-bottomed flask equipped with a reflux condenser. To the flask was added 18.9 g. (0.15 mole) of benzyl bromide and 12.0 g. (0.14 mole) of 3-methyl-2-butanol, and the resulting slurry heated under reflux with stirring for 24 hr. The mixture was cooled and the inorganic solids were removed by filtration. The organic layer was washed once with acidic 5% aqueous ferrous sulfate solution to destroy peroxides, once with water, and then dried over calcium sulfate. Distillation through a 30-cm. Holzman²³ column yielded approximately 10 g. of product, b.p. 85–87° (6 mm.). The product was identified by its n.m.r. spectrum.

Benzyl *t*-Butylmethylcarbinyl Ether.—In a 500-ml. round-bottomed flask equipped with a reflux condenser and a Teflon-covered stirring bar were mixed 12 g. (0.11 mole) of 3,3-dimethyl-2-butanol, 2.6 g. of sodium hydride (as a 50% dispersion in mineral oil), and 250 ml. of anhydrous ether. The slurry was refluxed with stirring for 8 hr. to form the sodium alkoxide. Benzyl bromide (18.8 g., 0.11 mole) was then added and refluxing continued for 12 hr. The reaction mixture was cautiously washed with two 100-ml. portions of water, dried over calcium sulfate, and distilled under reduced pressure to yield approximately 7 g. of product. The purest fraction had b.p. 90–92° (7 mm.), and was characterized by its n.m.r. spectrum. The analytical samples of this (and following) ethers were obtained by preparative vapor-phase chromatography.

Anal. Calcd. for $C_{15}H_{20}O$: C, 80.20; H, 10.48. Found: C, 80.21; H, 9.92.

Cyclohexylmethylcarbinol was prepared by addition of 80 g. of acetaldehyde to the Grignard reagent from 30 g. of magnesium turnings, 150 g. of cyclohexyl bromide, and 500 ml. of ether, in the usual apparatus. Hydrolysis of the reaction mixture with saturated aqueous ammonium chloride solution, followed by removal of water with calcium sulfate and distillation, yielded a considerable quantity of colorless liquid, b.p. 65–70° (9 mm.). The infrared spectrum of this material showed very strong absorption at 1700 cm^{-1} and weak hydroxyl absorption.

Addition of several small pieces of sodium to the material at room temperature resulted in an exothermic polymerization of the bulk of the liquid. After 12 hr., the polymer was removed by filtration, the filtrate being essentially pure cyclohexylmethylcarbinol, characterized by its strong infrared absorption at 3350 cm^{-1} , by its n.m.r. spectrum, and by its b.p. 77–83° (11 mm.), lit.²⁴ b.p. 87° (11 mm.). The infrared carbonyl absorption of the distilled product was almost unnoticeable.

Benzyl Cyclohexylmethylcarbinyl Ether.—Silver oxide (16 g., 0.07 mole), benzyl bromide (10 g., 0.057 mole), and cyclohexylmethylcarbinol (8 g., 0.057 mole) were heated together with stirring for 48 hr. at approximately 150°. At the end of this time, the slurry was cooled, taken up in five times its volume of ether, filtered, and distilled, yielding approximately 2 g. of product, b.p. 126–133° (4 mm.), contaminated with approximately 20% of benzyl alcohol. The product was characterized by its n.m.r. spectrum.

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.88; H, 9.64.

1-Phenylethyl Benzyl Ether.—Benzyl alcohol and 1-phenylethyl bromide (mole ratio 1:1) were heated on a steam bath for 6 hr. The solution was cooled, the inorganic salts were removed by filtration, and the organic filtrate was washed with water and dried over excess powdered calcium chloride. The organic layer was

then distilled to yield 45% of the desired ether, b.p. 123–124° (0.3 mm.). The infrared spectrum showed a strong band at 1100 cm^{-1} and no absorption in the 3500 cm^{-1} region. The n.m.r. spectrum of the compound was consistent with the assigned structure. The high boiling point of this material prevented its purification by preparative v.p.c.; the analytical sample used was therefore obtained by ordinary distillation.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.78; H, 7.64.

Carbethoxymethylcarbinyl Benzyl Ether.—Sodium benzyolate was prepared by the reaction of 22 g. (0.2 mole) of benzyl alcohol with 5.6 g. (0.22 mole) of sodium hydride (50% suspension in mineral oil) in 300 ml. of ether in a 1-l., three-necked, round-bottomed flask equipped with reflux condenser, mechanical stirrer, dropping funnel, and heating mantle. When formation of the alkoxide was complete (as judged by cessation of evolution of hydrogen), 36.2 g. of ethyl α -bromopropionate was added. The mixture was stirred overnight, then filtered to remove inorganic salts. The ether was removed on a rotary evaporator and the residue distilled to yield approximately 5 g. of product, b.p. 88–92° (2 mm.). The n.m.r. spectrum of the compound was consistent with the assigned structure.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.06; H, 7.74.

1-Phenylethyl ether was prepared by refluxing a mixture of 20 ml. of 1-phenylethyl bromide and 60 ml. of isopropyl alcohol for 48 hr. The resulting turbid solution was cooled, neutralized with sodium carbonate, washed with two 500-ml. portions of water, and dried over calcium sulfate. Distillation at reduced pressure yielded approximately 25 ml. of product, b.p. 94–97° (35 mm.), whose n.m.r. spectrum was consistent with the assigned structure.

Anal. Calcd. for $C_{11}H_{12}O$: C, 80.40; H, 9.83. Found: C, 80.03; H, 9.97.

1-Phenylethyl 2-methylpropyl ether was prepared by an identical procedure, starting with 93 ml. of 2-methyl-1-propanol and 45 g. of 1-phenylethyl bromide. The product had b.p. 58–63° (3 mm.). Its n.m.r. spectrum was consistent with the assigned structure.

Anal. Calcd. for $C_{12}H_{16}O$: C, 80.85; H, 10.18. Found: C, 80.45; H, 9.87.

1-Phenylethyl 3-methylbutyl ether was also prepared using this procedure, starting with 36.6 ml. of 3-methyl-1-butanol and 41 g. of 1-phenylethyl bromide. The product had b.p. 106–108° (2 mm.).

Anal. Calcd. for $C_{13}H_{18}O$: C, 81.20; H, 10.48. Found: C, 80.62; H, 9.97.

2-Isopropoxyethanol was prepared by refluxing 200 ml. of ethylene glycol and 100 ml. of isopropyl bromide over 60 g. of sodium carbonate for 48 hr. The mixture was cooled, and the inorganic salts were removed by filtration. Distillation through a 30-cm. Holzman column gave 45 ml. of product, b.p. 128–138° (wet), lit.²⁵ b.p. 144°. The product was not purified further, but was used directly in the following step.

1-Isopropoxy-2-(1-phenylethoxy)ethane.—In a 100-ml. round-bottomed flask fitted with a heating mantle were placed a Teflon-covered stirring bar, 5 ml. of 1-phenylethyl bromide, and 10 ml. of 2-isopropoxyethanol, and the slurry was heated to approximately 150°. Silver oxide (5 g.) was added. After an induction period of approximately 30 min., a vigorous exothermic reaction occurred. When this had subsided, 7 g. more of silver oxide and 15 ml. more of 1-phenylethyl bromide were added in portions. Finally, the slurry was allowed to stir at 150° overnight. The mixture was then cooled, taken up in 25 ml. of ether, filtered, washed once with 20 ml. of 10% aqueous acidic ferrous sulfate solution, once with water, and dried over calcium sulfate. The ether was removed on a rotary evaporator and the residue fractionated through a 10-cm. Vigreux column at reduced pressure. The yield of product, b.p. 95–105° (1 mm.), was 10 ml.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.77; H, 9.73.

2-Isobutoxyethanol was prepared from 130 ml. of ethylene glycol, 80 ml. of isobutyl bromide, and 50 g. of sodium carbonate as described previously for 2-isopropoxyethanol. The yield of product, b.p. 138–145° (wet), lit.²⁵ b.p. 154°, was 17 ml.

1-Isobutoxy-2-(1-phenylethoxy)ethane was prepared from 17 ml. of crude 2-isobutoxyethanol, 12 g. of silver oxide, and 20

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ml. of 1-phenylethyl bromide as described above for 1-isopropoxy-2-(1-phenylethoxy)ethane. The product was obtained in approximately 10 ml. yield and had b.p. 100–108° (1 mm.).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.01; H, 9.81.

1-Phenylethyl neopentyl ether was prepared in approximately 30% yield by mixing 8.8 g. (0.1 mole) of neopentyl alcohol, 20 g. (0.1 mole) of 1-phenylethyl bromide, and 13 g. (0.1 mole) of silver oxide. After the initial exothermic reaction had subsided, 3 g. more of silver oxide and 5 ml. more of 1-phenylethyl bromide were added and the reaction mixture was heated on the steam bath for 24 hr. The mixture was cooled and the product isolated as described for 1-isopropoxy-2-(1-phenylethoxy)ethane. The crude ether had b.p. 86–91° (16 mm.) and was contaminated with appreciable quantities of 1-phenylethyl bromide. Purification was effected by dissolving the mixture of halide and ether in di-

ethyl ether, and allowing the solution to stand over sodium for 24 hr. The solution was decanted from the unreacted sodium and redistilled. The n.m.r. spectrum of this material was consistent with the assigned structure.

1-Phenylethyl ethyl ether was prepared in these laboratories by Dr. F. Kaplan.

2-Methyl-2-phenylbutane was prepared in poor yield by reaction of approximately 0.2 mole of isopropylmagnesium bromide with an equivalent amount of 1-phenylethyl bromide in ether. The reaction mixture was hydrolyzed with saturated aqueous ammonium chloride solution, and the ether layer from the hydrolysis was dried and distilled in the usual manner to yield approximately 2 ml. of the desired hydrocarbon, b.p. 85–105° (18 mm.). The principal product of this reaction is 2,3-diphenylbutane, apparently arising from a metal-halogen exchange reaction between isopropyl Grignard reagent and 1-phenylethyl bromide.