NONEQUIVALENT METHYLENES IN CERTAIN ETHER SYSTEMS

submitted by

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ACKNOWLEDGEMENT

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ABSTRACT

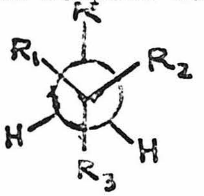
A series of ethers of the form $R_1R_2R_3CO\underset{\sim}{CH_2}R$ (where $R_1 \neq R_2 \neq R_3 \neq R_1$ and R can be the same as R_1 or different) were prepared. The ether methylenes (underlined) were analyzed by NMR spectroscopy and found to be magnetically non-equivalent (i.e. chemical shift between methylenes $\Delta\nu \neq 0$) in some cases. A semi-quantitative correlation between $\Delta\nu$ and the steric size of R_1, R_2, R_3, and R was observed suggesting restricted rotation around the C-O bond as the cause of the observed magnetically non-equivalent methylene protons.

NONEQUIVALENT METHYLENES IN CERTAIN ETHER SYSTEMS

It has been previously observed[1] that the methylene protons of systems of the type $R_1R_2R_3COCH_2R$ (where $R_1 \neq R_2 \neq R_3 \neq R_1$ and R can be the same as R_1 or different) may be magnetically nonequivalent and display AB rather than A_2 type spectra.[2]

Two plausible explanations exist for rationalizing this observed phenomenon:

1) The so called intrinsic asymmetry of the molecule with respect to the methylene group.[3]



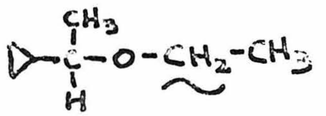
The methylene protons are magnetically nonequivalent even if rotation is absolutely "free." ($R_1 \neq R_2 \neq R_3 \neq R_1$)

2) Conformational Preference.

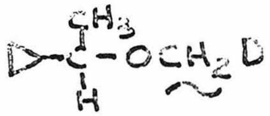
If one of the staggered conformations in the above diagram is preferred over the other two (restricted rotation), magnetic nonequivalence of the methylene protons results.

The first possibility seems unlikely due to some recent work[4] of Mr. G. M. Whitesides of Caltech. Whitesides synthesized and analyzed by NMR the following compounds.

I

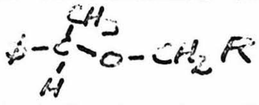


II



I had nonequivalent methylene protons (underlined); II did not, leading one to believe that intrinsic asymmetry of a molecule is not the reason for the observed nonequivalence of the methylene protons. On the other hand, if the conformational preference argument is correct, one should be able to find some dependence of the chemical shift difference between the methylene protons, $\Delta\nu$, on the steric bulk of R_1, R_2, R_3, and on R.

In an attempt to substantuate the conformational preference argument a series of ethers of the type $R_1R_2R_3COCH_2R$ were synthesized and their methylene proton resonances analyzed by NMR. For synthetic convenience the system phenylmethylcarbinyl methyleneR ether,

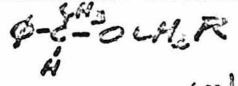


$\phi-\underset{H}{\overset{CH_3}{C}}-O-CH_2R$

, (R= methyl, ethyl, n-propyl, iso-propyl, ~~n-butyl~~, iso-butyl, n-octyl, and phenyl) was investigated first. The spectra of the above compounds were found to be extremely difficult to analyze even with the aid of high speed digital computers. Precise values for $\Delta\nu$ have so far been obtained for only two compounds (See Table I). However, from the general shape of the spectra for the remaining ethers of the series, a qualitative correlation between the steric size of R and $\Delta\nu$ of the methylenes seems to exist.

TABLE I

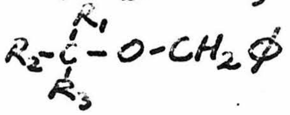
CHEMICAL SHIFT DIFFERENCES $\Delta\nu$ (in cycles per second at 60 Mc) BETWEEN ETHER METHYLENE PROTONS IN 10.0% MOLAR BENEZENE[5] SOLUTION FOR THE SYSTEM



$\phi-\underset{H}{\overset{CH_3}{C}}-O-CH_2R$

R	$\Delta\nu$
iso-propyl	4.0
phenyl	11.2
t-butyl[6]	6.9

A better correlation between $\Delta\nu$ and steric bulk was obtained when R_1, R_2, and R_3 were varied in the system $R_1R_2R_3$ benzyl ether



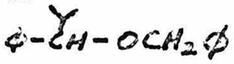
$R_2-\underset{R_3}{\overset{R_1}{C}}-O-CH_2\phi$

. The so called A values[7] were taken

as a measure of steric bulk. Results are shown in Table II.

TABLE II

CHEMICAL SHIFT DIFFERENCES $\Delta\nu$ (in cycles per second at 60 Mc) BETWEEN ETHER METHYLENE PROTONS IN 10.0% MOLAR BENEZENE[5] SOLUTION FOR THE SYSTEM  $R-\overset{CH_3}{\underset{H}{C}}-OCH_2\phi$

R	$\Delta\nu$	A^8 (kc/mole)
ethyl[6]	6.6	2.1
iso-propyl[6]	9.3	2.1-3.3
cyclohexyl[6]	10.2	——
phenyl	11.2	2.6
t-butyl[6]	15.5	5.4
	16.9	——
 10	20.2	——

As can be seen from Table II, there appears to be a direct correspondence between $\Delta\nu$ and the A value for a given substituient R implying a correspondence between $\Delta\nu$ and the steric bulk of R. A values could not be found for the three compounds noted. However, intuition suggests that $\Delta\nu$ is also related to steric bulk for them also.

The degree of correlation between $\Delta\nu$ and the steric size of R_1, R_2, R_3, and R strongly suggest that the conformational preference argument is the explanation to the magnetic nonequivalence of the methylene protons in the systems investigated. It is hoped that when $\Delta\nu$ data are obtained for the spectra of those ethers that have as yet defied analysis the evidence for the conformational preference argument will be even more compelling.

EXPERIMENTAL

The Varian A-60 analytical NMR spectrometer was used in taking NMR spectra.

Spectral samples were prepared 10.0% molar in benzene as follows:

> 1.00 ml of degassed benzene was pipetted into a 2 ml vial containing the proper amount of purified ether(weighed to four significant places) in order to make the resulting solution 10.0% molar in ether. NMR spectra of the prepared sample were taken as soon as possible to guard against possible evaporation.

Ethers were synthesized by two schemes; the classical Williamson method, and a modification of a method employed by Ingold[9] In the Williamson method ($RO^{\ominus}Na^{\oplus} + R''Br \longrightarrow ROR'' + NaBr$) the proper alcohol is made into its sodium salt and then reacted with the proper bromide to yield the desired ether. A typical synthesis follows:

> 2.8 gms. (0.115 mole) of NaH are placed in approximately 100 ml of anhydrous diethyl ether. A small fizzing results. 12.2 gms. (0.100 mole) of phenylmethylcarbinol are added all at once. An immediate reaction starts. The solution is magnetically stirred. In about one and one-half hours a loose paste solidifies. 17.1 gms. (0.100 mole) of benzyl bromide are then added dropwise (lachrymatory). No visible reaction occurs. The mixture is left to reflux overnight. The solution is then poured into water, washed three times with saturated sodium chloride solution, dried over sodium sulfate anhydrous and low boiling impurities removed by distillation. The pot residue is then vacuum distilled giving better than a 50% yield of phenylmethylcarbinyl benzyl ether b.p. 95°/1½mm.

phenylmethylcarbinyl benzyl ether	b.p. 95°/1½mm
phenylisopropylcarbinyl[10] benzyl ether	b.p. 124-130°/1½mm
menthyl benzyl ether	b.p. 90-92/<1mm

were prepared by this method.

The modification of a reaction first used by Ingold[9] was found to be much superior in every respect.($ROH + \phi-\underset{H}{\overset{CH_3}{C}}-Br \xrightarrow[40-70\ HRS]{100^\circ} \phi-\underset{H}{\overset{CH_3}{C}}-OR$). A typical synthesis follows:

To 52 gms.(0.4mole) of reagent 1-octanol placed in a 250 ml round bottomed flask are added 40.8 gms.(0.2 mole ± 20% impurity) of phenylmethylcarbinylbromide. Two layers form. The solution is magnetically stirred and heated at 100°C by a heating mantle for 45 hours. The resulting homogeneous yellow solution is washed twice with saturated sodium bicarbonate solution and then several times with water. After drying over calcium sulfate, the organic layer is vacuum distilled giving an almost quantitative yield of phenylmethylcarbinyl n-octyl ether b.p. 86-88/<4mm.

Phenylmethylcarbinyl bromide is easily prepared by bubbling HBr through styrene until saturation is achieved. The crude addition product is then used for the ether syntheses.

phenylmethylcarbinyl n-propyl ether	b.p. 90-92/30mm
phenylmethylcarbinyl n-butyl ether	b.p. 106-110/ 3mm
phenylmethylcarbinyl iso-butyl ether	b.p. 59-63/2-3mm
phenylmethylcarbinyl n octyl ether	b.p. 86-88/ 4mm
phenylmethylcarbinyl iso-amyl ether	b.p. 106-108/ 2mm

were prepared by this method.

Ethers were checked for purity by means of NMR spectra. Ethers were distilled until NMR spectra appeared to contain no starting materials or other impurities. The NMR can detect impurities present above 1% in concentration.

FOOTNOTES

1. J.D. Roberts, et al, *Proc. Nat. Acad. Sci.*, 47, 49-51 (1961).

2. Roberts, John D., *An Introduction to Spin Spin Splitting in High Resolution Nuclear Magnetic Resonance Spectra*, New York, W. A. Benjamin Inc., 1961, Chap.II.

3. H.S. Gutowsky, *J.Chem Phys*, 000, 000, (1962). Contract# 1834(13) NR 051-215.

4. G. M. Whitesides, F. Kaplan, K. Nagarajan, and J.D. Roberts, *Proc. Nat. Acad. Sci.*, 48, 1112-14 (1962)

5. Benzene was found to be a convenient solvent in which $\Delta\nu$ was accentuated as much as possible.

6. Grateful acknowledgement is made to Mr. G.M. Whitesides who synthesized and analyzed these compounds.

7. An A value represents the difference in free energy between an equatorial and axial conformation for a particular substituient attached to a cyclohexane ring. This difference in free energy is believed to be almost entirely due to the steric interaction of the substituient with the cyclohexane ring and thus A values give a relative measure of steric bulk. See for instance Hine, *Physical Organic Chemistry*, M^{c}Graw Hill Inc., N.Y.,1962, p.38; or Eliel, *The Stereochemistry of Carbon Compounds*, M^{c}Graw Hill Inc., N.Y.,1962, Chapter VIII.

8. A values taken from Eliel, *op cit.*, p. 236; and S. Winstein and N.J. Holness, *JACS*, *77*, 5574, (1955).

9. Ingold et al, *J Chem Soc* (London), 1937, 1201-8,(1937)

10. New Compound