

Conformational Analysis. IV. A Quantitative Method for the Determination of the Steric Environment of the Hydroxyl Group by Nuclear Magnetic Resonance^{1,2}

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A quantitative method for the determination of the steric environment of the hydroxyl proton is reported. The chemical shift of the hydroxyl proton in bicyclic alcohols has been examined as a function of concentration in carbon tetrachloride. It is shown that the limiting slope of the chemical shift-concentration relation is directly related to the steric environment of the hydroxyl proton. Additive, free-energy steric parameters for a methyl group substituted β to the hydroxyl group are given as a function of dihedral angle.

Introduction

The hydroxyl proton magnetic resonance has been examined quantitatively for only a few simple compounds. This widely occurring resonance has been ignored as a result of its concentration dependence. At concentrations normally employed in n.m.r., the hydroxyl signal is a time average of a weighed average of the various hydrogen-bonded species present in solution. In order to determine a theoretically significant chemical shift parameter, it is necessary to work under conditions such that the myriad hydrogen-bonded forms are eliminated. Chapman and King⁴ utilized dimethyl sulfoxide to stabilize the hydroxyl resonance signal. The multiplicity of the hydroxyl resonance can also be determined in this solvent. It should be possible to evaluate chemical shift parameters for the dimethyl sulfoxide complexed alcohol which should be directly related to its magnetic environment. However, it is clear that the chemical shift of the hydroxyl proton of complexed alcohols lies in a relatively narrow range.

An alternate approach to the determination of the chemical shift of the hydroxyl proton has been utilized in this laboratory. It has been shown in two papers that the chemical shift of the hydroxyl proton is linearly related to concentration in carbon tetrachloride in the 0.015 to 0.002 mole fraction range. By extrapolation to infinite dilution, the chemical shift of the monomeric hydroxyl proton can be determined. At infinite dilution, the chemical shift is solely a function of magnetic environment, and this resonance signal has been used as a conformational probe in the cyclohexane series.⁵ However, the resonances for a large number of

compounds investigated in this laboratory have been shown to be located in a relatively narrow, high-field region. Therefore, the usefulness of the dilution method as a structural determinant is as limited as the dimethyl sulfoxide method.

We now report an alternate approach which offers a sensitive quantitative method of evaluating the steric environment of the hydroxyl proton. The technique should be useful not only in the determination of steric effects but should also serve as a structural tool.

The method is derived from the early work of Becker, Liddel, and Shoolery⁶ who carried out a detailed study of the dilution shift of the hydroxyl proton of ethanol in carbon tetrachloride. With decreasing concentration, the hydroxyl resonance shifts to a higher field. In the region of 0.015 mole fraction alcohol, a reversal of curvature occurs, and the dilution curve linearly approaches a limiting value at infinite dilution. The inversion of curvature and subsequent linear relationship can be interpreted in terms of a transition from high-order polymeric hydrogen-bonded species to a monomer-dimer equilibrium.

Huggins, Pimentel, and Shoolery⁷ have shown that, if a system is governed by monomer-dimer equilibrium, the limiting slope of the dilution curve is related to the equilibrium constant for dimer formation by the following expression.

$$\left(\frac{\partial\delta}{\partial x}\right)_{x=0} = 2K\Delta_D$$

In the above expression $K = x_D/x_M^2$ where x_D and x_M are the mole fraction of dimer and monomer, respectively. The symbol Δ_D is equal to the difference between the chemical shifts of the dimer and the monomer, $\delta_D - \delta_M$. The equilibrium constant for the monomer-dimer equilibrium could be evaluated if the limiting slope and the chemical shifts of the dimer and monomer were available. The limiting slope and the chemical shift of the monomer are directly available from dilution studies. However, the chemical shift of the dimer is not directly observable. Estimates for the value Δ_D have been made in terms of Δ_P where Δ_P is the difference in the chemical shift of the polymer and the monomer. It has been suggested that a reasonable range for Δ_D is 0.5 to 0.25 Δ_P for open dimer structure and 0.5 to 1.0 Δ_P for cyclic dimer. It is evident that the equilibrium constant is not obtainable from n.m.r. studies alone but rather only in conjunction with other physical measurements. The relation of Huggins,

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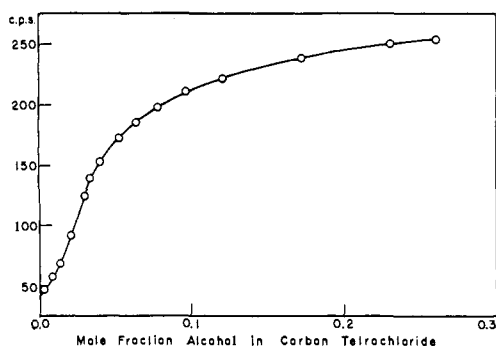


Figure 1. Chemical shift vs. concentration of dependence of cyclopentanol.

Pimentel, and Shooley is of little use with solid organic alcohols where even Δ_P is not available.

As a first approximation, the quantity $\delta_D - \delta_M$ can be assumed to be constant for a series of closely related alcohols. Alternatively, it might be considered to vary but in such a fashion as to not outweigh the changes in K . The assumed near constancy of the quantity $\delta_D - \delta_M$ is reasonable as all individual contributions to the shielding of the proton save the difference that results from the formation of a hydrogen bond should cancel. The effect of structural features on the chemical shift of the monomeric hydroxyl proton is of lower order magnitude than the shift caused by hydrogen bonding. Providing the structure of the alcohols do not change sufficiently such that the structure of the dimeric alcohol is affected, the quantity $\delta_D - \delta_M$ should be reasonably constant.

The above discussion is supported by our work in the cyclohexane series. The larger slope for *trans*-4-*t*-butylcyclohexanol as compared to *cis*-4-*t*-butylcyclohexanol indicates that the equilibrium constant for dimerization of the *trans* compound is more than that for the *cis* isomer. This observation is in agreement with the concept of a more open approach of reagents to the equatorial position relative to the axial position.⁸ Similarly, the slope of 1-ethynyl-*trans*-4-butylcyclohexanol is larger than that of 1-ethynyl-*cis*-4-butylcyclohexanol. The smaller values for the ethynyl compounds compared to the parent cyclohexanols can be viewed as a reflection of the decreased susceptibility of tertiary alcohols to hydrogen bonding.⁹

Bicyclic alcohols will be examined in this paper to test the constancy of $\delta_D - \delta_M$. These compounds offer the most direct approach as their geometry is rigidly defined. The number of degrees of freedom in the bicyclic skeleton is limited, and therefore the steric environment of the alcohol can be varied in a systematic fashion.

Results and Discussion

The chemical shift-concentration dependence of cyclopentanol was first examined as a model to determine the general shape of the dilution curve. Concentrations from 0.3 to 0.002 mole fraction alcohol in carbon tetrachloride were employed, and the results are presented in Figure 1. It is evident that at high con-

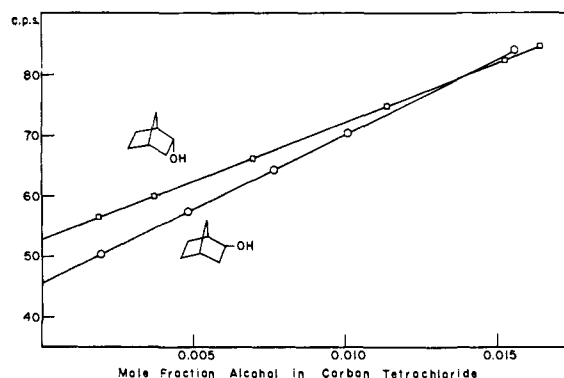


Figure 2. Low-dilution curves for bicyclic alcohols.

centration, the chemical shift of the hydroxyl proton is not extremely sensitive to concentration. However, a very rapid shift occurs in the 0.1 to 0.03 mole fraction range. Finally the limiting slope becomes linear in the 0.020 to 0.002 mole fraction range after an inversion of curvature. The general shape of the dilution curve is very similar to that observed for ethanol. The limiting slope of cyclopentanol is 2650 c.p.s./ N . All concentrations are expressed in terms of mole fractions, N , and the slopes of the dilution curves in c.p.s./ N .

In this study, 15 model bicyclic alcohols were investigated. The limiting slopes were determined in the 0.02 to 0.002 mole fraction range. All spectra were obtained at a probe temperature of 40°. For an enthalpy of dimerization of the order of 3000 cal., the value for the equilibrium constant for dimerization will vary by approximately 1% for a 1° change. Therefore, the reported slopes are only reported accurate to this value. Representative dilution curves for isonorborneol (9) and norborneol (1) are illustrated in Figure 2. The limiting slopes for all compounds investigated are given in Table I.

The limiting slopes of isonorborneol (9) and norborneol (1) are 2320 and 1860 c.p.s./ N , respectively. As indicated in the Introduction, if the value of $\delta_D - \delta_M$ is a constant for this pair of closely related alcohols, then the limiting slopes are directly proportional to the equilibrium constants for dimerization. Therefore, it can be concluded that the *endo* side of the bicyclo-[2.2.1]heptane system is more hindered than the *exo* side. This conclusion has long been accepted.¹⁰

Borneol (2) would be expected to behave similarly to norborneol (1) as the steric environments at the *endo* side of the bicyclic skeletons in each compound are independent of the methyl groups at the 7-position. The observed slope is 1480 c.p.s./ N , a value which is significantly smaller than that for norborneol (1). This difference is attributed to the presence of the methyl group at the 1-position. The limiting slope of 1-methylnorborneol (3) is 1460 c.p.s./ N . The identity of the slopes of 1-methylnorborneol (3) and borneol (2) suggests that the only steric factor operative relative to norborneol (1) is the methyl group at the 1-position. In confirmation of this conclusion, the limiting slope of aporborneol (4) is nearly identical with that of norborneol (1).

Isorborneol (10) would be expected to be hindered considerably by the methyl group in the 7-position and

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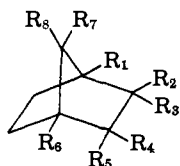


Table I. Limiting Slopes of Bicyclic Alcohols

No.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈	Limiting slope, c.p.s./N	Slope ratio ^a
1	H	H	OH	H	H	H	H	H	1860	1.00
2	CH ₃	H	OH	H	H	H	CH ₃	CH ₃	1480	1.26
3	CH ₃	H	OH	H	H	H	H	H	1460	1.27
4	H	H	OH	H	H	H	CH ₃	CH ₃	1850	1.00
5	H	H	OH	CH ₃	CH ₃	H	H	H	1050	1.77
6	CH ₃	H	OH	CH ₃	CH ₃	H	H	H	840	2.21
7	H	H	OH	CH ₃	H	H	H	H	1660	1.12
8	H	H	OH	H	CH ₃	H	H	H	1180	1.57
9	H	OH	H	H	H	H	H	H	2320	1.00
10	CH ₃	OH	H	H	H	H	CH ₃	CH ₃	700	3.31
11	CH ₃	OH	H	H	H	H	H	H	1560	1.49
12	H	OH	H	H	H	H	CH ₃	CH ₃	1050	2.21
13	CH ₃	OH	H	H	H	H	H	CH ₃	1540	1.50
14	CH ₃	OH	H	H	H	H	CH ₃	H	720	3.22
15	CH ₃	OH	H	H	H	CH ₃	CH ₃	CH ₃	720	3.22

^a Relative to the appropriate reference compound 1 or 9.

to some extent by the methyl group in the 1-position. The hindrance of the methyl group in the 1-position of isoborneol (10) would be expected to be larger than the hindrance of the methyl group in 1-methylnorborneol (3) due to the closer proximity of the methyl group. The relative importance of the methyl groups in the 1- and 7-positions is indicated from the slopes of 1-methylisoborneol (11) and apoisoborneol (12). The limiting slopes are 1560 and 1050 c.p.s./N, respectively. Clearly relative to isoborneol (10), the methyl groups at the 7-position are more effective at decreasing the equilibrium constant for dimerization than is the methyl group at the 1-position. It would be anticipated that only the methyl group in the 7-*syn* position relative to the hydroxyl would be sterically effective at preventing dimerization. The slopes of α -santenol (13) and β -santenol (14) are 1540 and 720 c.p.s., respectively.

At this point, it is convenient to define a quantitative structural parameter for the steric effect of the methyl group on the dimerization constant for an alcohol. If the term $\delta_D - \delta_M$ is a constant, then the slope of the dilution curve should be linearly related to the equilibrium constant for dimerization. Steric factors might be expressible in terms of an additive, free-energy increment. If indeed an additive free-energy term per structural unit is to be observed, the ratio of the equilibrium constants for pairs of structurally similar compounds which differ by one structural unit should be constant. The ratio of the slopes will be expressed such that the slope of the least hindered alcohol is divided by that of the more hindered alcohol. The ratio of the slopes of norborneol (1) to 1-methylnorborneol (3) is 1.27. This ratio is close to that of norborneol (1) to borneol (2) as the methyl groups in the 7-position do not contribute to the decrease in the dimerization constant for borneol (2). The slope ratio 1.27 is therefore a reflection of the decrease in the dimerization constant caused by the methyl group at the 1-position. If indeed the quantity is a constant, then the same ratio should be observed for other pairs of

structurally similar alcohols which differ only in the presence or absence of a methyl group at the 1-position. The slopes of camphenilol (5) and α -fenchol (6) are 1050 and 840 c.p.s./N, respectively. The slope ratio of 1.25 for these two compounds is within experimental error of that observed for the norborneol (1)–1-methylnorborneol (3) pair.

The additivity of the free-energy parameter can be tested by examining a series of compounds in which a combination of structural features are incorporated in the bicyclic skeleton. As an example, the slope ratio of isoborneol (9) to apoisoborneol (12) and 1-methylisoborneol (11) are 2.21 and 1.49, respectively. The product of these ratios is 3.29. The experimental observed ratio of isoborneol (9) to isoborneol (10) is 3.31. It therefore appears that the quantity $\delta_D - \delta_M$ is a constant within this series and is independent of added structural features. Furthermore the slope ratios can be used in predicting the slope of an unknown compound, if appropriate models are available. The slope of α -fenchol (6) should be equal to that of norborneol (1) divided by the slope ratios of 1-methylnorborneol (3), *exo*-3-methylnorborneol (7), and *endo*-3-methylnorborneol (8) all relative to norborneol (1). The slope ratios are 1.27, 1.12, and 1.57, respectively. The calculated slope of α -fenchol (6) is 835 c.p.s./N which is in close agreement with the observed slope of 840 c.p.s./N. It is obvious therefore that the slope of camphenilol (5) is equal to the slope of norborneol (1) divided by the slope ratios of 1.12 and 1.57 for the effect of the *exo*- and *endo*-3-methyl groups, respectively.

In the above discussion, the importance of the position of a given structural feature in space relative to the hydroxyl group is implied. The effect of a methyl group on an adjacent carbon would be expected to be a function of dihedral angle. Examination of the proper compounds yields slope ratios relative to a reference compound in which the interacting group is replaced by hydrogen. The logarithm of the slope ratio should be linear in free energy and therefore should be used in any attempt to correlate the effect of dihedral angle

on the dimerization constant. A cosine function would be expected to apply to this relationship. The maximum slope ratio would occur at 0° and the minimum at 180°. In Table II, the slope ratios and their

Table II

θ	S_θ	$\log S_\theta$
0	1.57	0.196
35	1.49	0.173
85	1.27	0.104
120	1.12	0.050
180	1.00	0.000

logarithms are given as a function of dihedral angle. The dihedral angles were estimated from Dreiding models. It is clear that the slope ratios decrease with increasing dihedral angle. Furthermore, the slope ratios appear to approach 1.0 as a limit at 180°. The method of defining the slope ratio, of course, cannot allow any ratios less than 1.0. Accordingly, an arbitrary value of 1.0 is assigned to the effect of the methyl group at 180°.

An equation which relates the logarithm of the slope ratio S for a given dihedral angle θ can be expressed in terms of $\cos \theta$ and S_0 . The quantity S_0 represents the effect of the substitute at a dihedral angle of 0°. A plot of $\log S_\theta$ vs. $\cos \theta$ is given in Figure 3.

$$\log S_\theta = \frac{\log S_0}{2}(1 + \cos \theta)$$

The internuclear carbon-oxygen distance between the methyl carbon and the hydroxyl oxygen increases with the increase in dihedral angle. While a correlation between the slope ratio and internuclear distance can be made for the methyl group at the β -carbon, this type of function is not general. The internuclear distances between a methyl group in the 1- and the 7-*syn* position relative to the *exo*-2-hydroxyl are nearly identical, but the effect on the slope ratios are not equal. The preferred conformational orientation of the hydroxyl group and the geometry of the dimer are not known at this time, and further discussion of these effects as a function of molecular geometry will be postponed until enthalpy and entropy contributions to the free energy of dimerization can be determined.

At the present time, it appears that the quantity $\delta_D - \delta_M$ is either constant or varying in an unbelievable fashion. Additive, free-energy relationships apparently are possible and dihedral angle effects can be correlated.

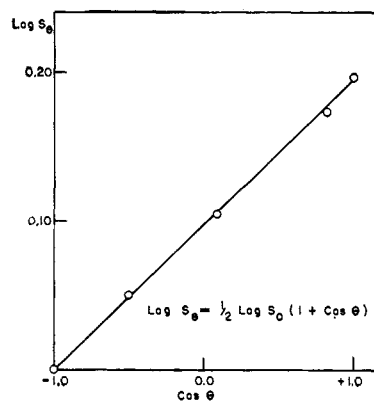


Figure 3. Linear, free-energy relationship between $\log S_\theta$ and $\cos \theta$.

The number of compounds having hydroxyl functions are numerous, and the technique outlined should be useful in structural determination and in the quantitative evaluation of steric effects.

Experimental

All of the compounds utilized in this study have previously been described in the literature.¹¹ Each compound was sublimed and collected by vapor phase chromatography where necessary to ensure purity.

The solutions were prepared gravimetrically, and the concentrations were known to at least 0.5% of the absolute value. Anhydrous carbon tetrachloride containing approximately 0.002 mole fraction tetramethylsilane as the internal standard was employed as the solvent. A minimum of four concentrations were employed to determine the slope of the chemical shift-concentration line. The assignment of the hydroxyl resonance was assigned on the basis of its shift with concentration relative to the other resonances which are concentration independent. In addition, since the probe temperature was maintained at 40°, a high-field shift of the hydroxyl proton was noted as the sample equilibrated to the temperature of the probe. Finally, the assignments were confirmed by adding deuterium oxide and shaking the sample to remove the hydroxyl resonance. All spectra were obtained on a Varian Associates A-60 instrument operated at a probe temperature of 40°. The n.m.r. tubes were 0.196 in. o.d. and 0.160 in. i.d. The signal to noise ratio at the lower concentrations was approximately 3.5.

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