To the Graduate Council:

I am submitting herewith a thesis written by Duane Allen Hall entitled "NMR Studies of Hydrogen Bonding Systems and Resultant Conformational Attitudes." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

Newell S. Bowman, Major Professor

We have read this thesis and recommend its acceptance:

George W Kabalka

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Accepted for the Council:

L Evans Pack

Vice Chancellor
Graduate Studies and Research

# NMR STUDIES OF HYDROGEN BONDING SYSTEMS AND RESULTANT CONFORMATIONAL ATTITUDES

A Thesis

Presented for the

Master of Science

Degree

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Duane Allen Hall

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# ABSTRACT

NMR studies of selected alcohols were undertaken in an attempt to explain the anomalous results obtained in earlier works on the compounds 2-butanol and ethyl α-hydroxybutyrate. Arising from this study was a further understanding of the relative importance of gauche alkyl-alkyl and alkyl-hydroxyl steric interactions.

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# CHAPTER I

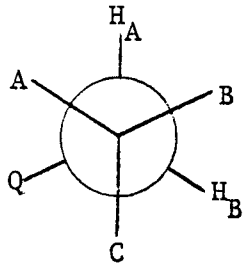
# INTRODUCTION

## A. Geminal Nonequivalence

The phenonemon of geminal nonequivalence has been studied extensively since 1957. The teams of Nair and Roberts,[1] and Drysdale and Phillips[2] appear to have been the first workers to observe acyclic geminal nonequivalence. In the same year, Nair and Roberts suggested that geminal nonequivalence could be rationalized in terms of conformational preference. They also proposed that, in principle, it might be possible to estimate the population of different conformers, despite rapid interconversion.

In 1961, Waugh and Cotton[3] pointed out that geminal nonequivalence would still persist in the absence of a conformational preference. One year later, H. S. Gutowsky[4] considered this aspect more fully, terming it the "asymmetry effect." Gutowsky stated that the asymmetry effect makes nuclei nonequivalent even though conformational populations are equal, but population differences do not lead to nonequivalence unless there is a high degree of molecular asymmetry. This concept was readily illustrated by Whitesides.[5] If one examines the spectrum of the methylene protons of a $CH_2$-Q group in an asymmetric environment and realizes that three distinct conformers exist, the methylene protons, $H_A$ and $H_B$, will be seen as an AB-type nuclear magnetic resonance spectrum.

If Q = H, the three conformers (I-III) and their populations are identical, and the three conformers cannot be differentiated. Since $\nu_A = \nu_B$, the protons, including Q = H, are magnetically equivalent.

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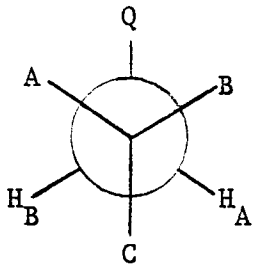


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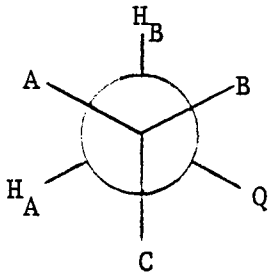



III

Unfortunately, this fact reveals nothing concerning the relative values of the proton shifts due to the intrinsic asymmetry of the three non-equivalent sites.

If Q ≠ H, the increased molecular asymmetry due to Q converts the system from a single conformer to three. Generally, the presence of Q causes the energies and populations of these three conformers to differ. This leads to a net chemical shift difference between the $H_A$ and $H_B$ protons given by Equation 1,[6]

$$\Delta \delta_H \equiv \delta H_A - \delta H_B = \sum_n X_n (\delta_n^A - \delta_n^B) \qquad (1)$$

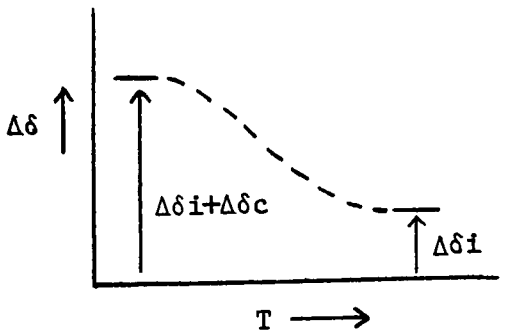
where $X_n$ is the mole fraction of conformer n, and $\delta_n^i$ is the resonance frequency, or chemical shift, of the $i^{th}$ nucleus in conformer n.

Thus Gutowsky[4] has shown that the observed nonequivalence ($\Delta\delta_{obsd}$) can therefore be partitioned into an intrinsic term ($\Delta\delta i$) and a second term ($\Delta\delta c$) which depends on the relative conformer populations as shown in Equation 2.

$$\Delta\delta_{obsd} = \Delta\delta c + \Delta\delta i \qquad (2)$$

Much work has been undertaken in an attempt to evaluate the relative importance of these two components in particular cases.

One suggested approach[7,8] to this problem has been to record the effect of increasing the temperature on $\Delta\delta$ and then extrapolate the curve to a limit.




This limiting value of the nonequivalence has been equated with the intrinsic term ($\Delta\delta i$). However this procedure is unreliable as it assumes that all three conformers will be equally populated at high temperatures.[a]

The only reliable method of estimating the intrinsic term is to use the procedure of Raban.[9] In evaluating the geminal fluorine nonequivalence in $BrCF_2CFBrCl$ and $BrCF_2CHBrCl$, the NMR spectrum of these compounds had been investigated[10] at low temperature where rotation around the C-C bond had become slow on the NMR time scale, enabling

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[a]Even an entropy difference as small as 1 e.u. is sufficient to cause a deviation of $X_n$ from one-third and thus possibly masking the intrinsic term.

the spectrum of each individual conformer to be observed. Thus the chemical shifts of the fluorine nuclei in each conformer could be obtained, and by integration, the relative conformer populations determined. These $\delta_n$ and $X_n$ terms can then be substituted into Equation 5 to give $\Delta\delta$, or, alternately, $\Delta\delta i$ may be estimated by setting all the $X_n$ terms equal to one-third.

$$\delta(H_A)_{obsd} = \delta(H_A)_I X_I + \delta(H_A)_{II} X_{II} + \delta(H_A)_{III} X_{III} \quad (3)$$

$$\delta(H_B)_{obsd} = \delta(H_B)_I X_I + \delta(H_B)_{II} X_{II} + \delta(H_B)_{III} X_{III} \quad (4)$$

$$\Delta\delta_{obsd} = X_I [\delta(H_A)_I - \delta(H_B)_I] + X_{II} [\delta(H_A)_{II} - \delta(H_B)_{II}] + X_{III} [\delta(H_A)_{III} - \delta(H_B)_{III}] \quad (5)$$

Since conformational preference is often more significant in determining $\Delta\delta$ values[9,11,12], many early researchers neglected the intrinsic asymmetry concept, or experimentally attempted to prove conformational preference was the only factor to consider in determining $\Delta\delta_{obsd}$.[6] Subsequent studies have shown this approach to be invalid.

## B. Solvent Effects

It has been known for many years that the position of resonance lines, in relation to a reference such as TMS, are often a function of concentration and the nature of solvents.[13-15] In some systems solvent shifts as much as a few ppm are known to exist. This type of shift is illustrated by the hydroxyl proton in alcohols and phenols.

In those compounds where shifts are relatively small, in the range of 0.01-0.1 ppm the origin and interpretation of the shifts presents

serious difficulties. There are two main problems associated with the analysis of solvent shifts. First, the small magnitude of the observed shifts requires accurate calibration procedures. The second problem is the uncertainty in identifying resonance lines since they may be shifted unequally in magnitude or even in different directions.[13]

H. H. Fowler,[16] using the compound ethyl α-hydroxybutyrate, demonstrated that by varying the solvent ($CCl_4$) concentration, the nonequivalent methylene protons were observed to exhibit unequal shifts in resonance line positions. A similar effect was observed by Jackman and Bowman[13] in their system, 2-butanol.

The same two systems, ethyl α-hydroxybutyrate and 2-butanol, were also examined for possible changes in vicinal couplings of the geminal protons. Significant changes in these coupling values would definitely indicate changes in conformer populations. Upon sample dilution, the vicinal couplings ($J_{AX}$ and $J_{BX}$) in 2-butanol were noted to change by approximately 1.0 Hz, indicating some changes in conformer populations. A similar phenomenon was not observed in ethyl α-hydroxybutyrate, thus indicating no changes in conformer populations.

In 1963, Snyder[17] and co-workers were able to show an inverse correlation between the extent of nonequivalence in certain compounds, containing methylene protons or methyl groups, and the dielectric constant of the solvent. Originally, it was proposed that this effect was due to changes in conformer populations, thus reducing dipole-dipole repulsions in solvents of high dielectric constant.[18] Since similar effects have been observed in rigid systems, it was concluded that solvent dependence of nonequivalence does not accurately reflect changes in conformer poulations.

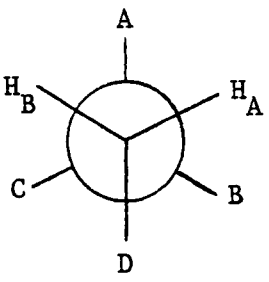
In addition to investigating solvent effects on resonance line positions, it is important to examine this effect on spin-spin coupling values.

It has been shown[17] that vicinal coupling constants are sensitive to solvent changes. Snyder[14] has demonstrated the direct relationship of vicinal couplings with the dihedral angle between coupled protons. It has been noted for many systems[13,14.16,19] that the solvent dependence of the vicinal couplings is small, on the order of 0.5 Hz or less.

## C. NMR Investigations

### 1. Asymmetry Effect

As presented earlier, geminal protons may be magnetically nonequivalent due to $\Delta\delta c$ and $\Delta\delta i$, as given in Equation 2. Magnetic nonequivalence arising from conformational preference has already been considered. However, nonequivalence produced by the asymmetry effect is somewhat more complex in understanding. By examining the three conformers of the compound P(A)(B)(C)-M($H_A$)($H_B$)(D), the asymmetry effect may be illustrated.

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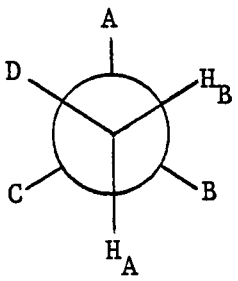


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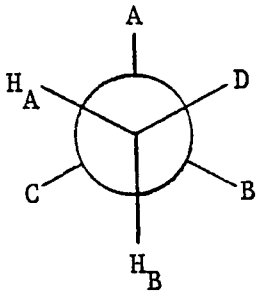



VI

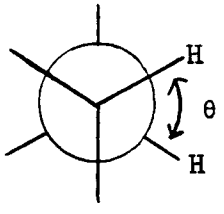
The differing environments of the geminal protons ($H_A$ and $H_B$) in each conformer is produced by a different set of non-bonding interactions. Thus $H_A$ in (IV) between group A and group B, is not in the same environment as $H_B$ in (V), also between group A and group B, because in (IV) group B is adjacent to $H_A$ and group D, whereas in (V) group B is next to $H_A$ and $H_B$. A similar argument can be made for any two of the three conformations. Since $H_A$ and $H_B$ are never in the same environment, they will have different average chemical shifts regardless of conformer populations, resulting in an AB type spectrum.

2. Vicinal Coupling Constants

One of the most useful theoretical contributions to the interpretation of conformational analysis in acylic saturated systems is the Karplus relation[20] for vicinal coupling constants as shown in Equation 6.[b]

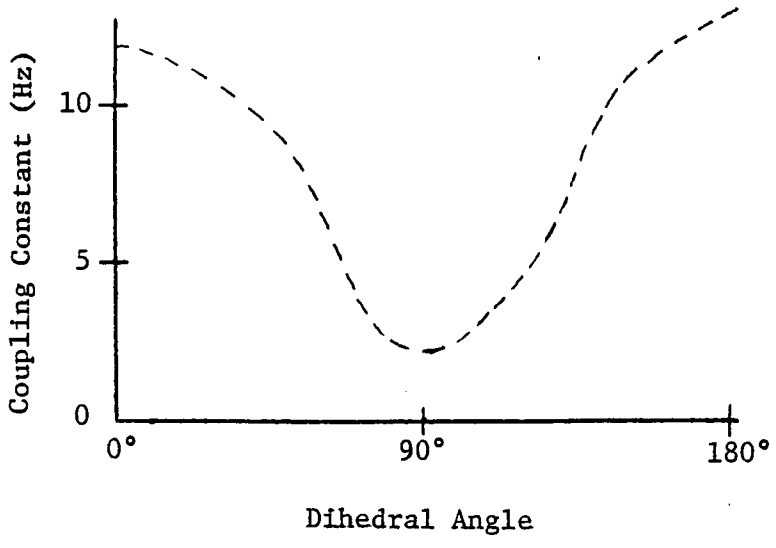
$$J = A + B \cos \theta + C \cos 2\theta \qquad (6)$$

The most interesting factor revealed by the Karplus relation is the critical dependence of the coupling value on the dihedral angle $\theta$,




[b]Many sets of values for A, B, and C are found in the literature, but it must be realized that the Karplus relation contains inherent limitations due to the necessary approximations made in the quantum mechanical treatment. Thus quantitative applications to a few degrees are not justified.

By using modified values chosen by Bothner-By,[21] the following plot is obtained.




Thus a direct relationship exists between the dihedral angle and the vicinal coupling constant. As exhibited above, an anti coupling constant, $J_{anti}$ ($\theta = 180°$), will necessarily be larger than a gauche coupling constant, $J_{gauche}$ ($\theta = 60°$).

## D. Discussion of Problem

In the study of 2-butanol[13] by Jackman and Bowman, it was observed that of the two magnetically nonequivalent protons, the chemical shift of only one was appreciably affected by a change in concentration. This phenomenon was attributed to the shielding effect of the diamagnetic anisotropy of the $C_1 - C_2$ bond. In work by H. H. Fowler,[16] it was shown using the compound ethyl α-hydroxybutyrate, that the phenomenon of only one proton changing in chemical shift value, was

not due to changes in conformational populations. This was shown through invariance of the vicinal coupling constants, $J_{AX}$ and $J_{BX}$. It was proposed to investigate this anomaly via a series of hydroxy compounds which would exhibit geminal magnetic nonequivalence. Our intention was to examine the significance of the shielding effect due to the anisotropy of gauche or anti C-C bonds. Since it was proposed by Jackman[22] using cyclohexyl systems that shielding or deshielding was a function of conformational position, it was deemed necessary to study individual conformers in an attempt to propose probable populations. Magnitudes and changes of coupling constants could then be used to determine whether or not there was a preference for a single conformer of the chosen molecules.

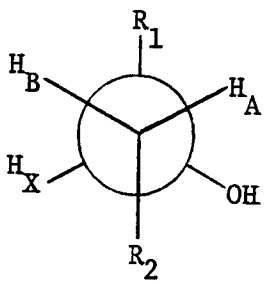
# CHAPTER II

# EXPERIMENTAL

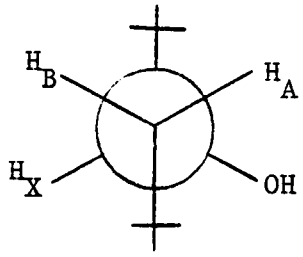
## A. Compounds for Analysis

### 1. Selection of Model Compounds

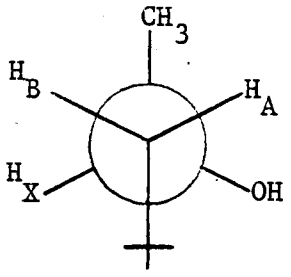
Four compounds were selected for analysis. All compounds may be represented by the general conformer



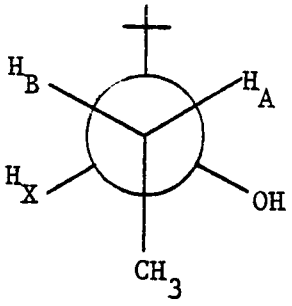

where $R_1$ and $R_2$ were varied as hydrogen, methyl, and tert-butyl groups. The selected compounds have been listed below. All compounds used in this research were obtained from Aldrich except 2,2,5,5-tetramethyl-3-hexanol. This compound was obtained from Chemsampco. Purity for all samples was in excess of 98 mole %. After initial examination of spectra, no further purification was deemed necessary.



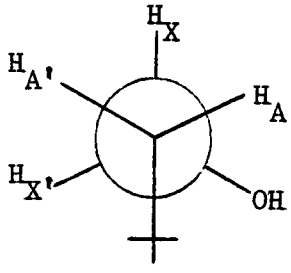

2,2,5,5 Tetramethyl-3-Hexanol




4,4 Dimethyl-2-Pentanol




2,2 Dimethyl-3-Pentanol




3,3 Dimethyl-1-Butanol

## B. Preparation of Spectral Samples

### 1. Preparation Procedure for HA-100 Samples

Two samples differing only in concentration, were prepared for each compound. The compounds of interest, carbon tetrachloride, and tetramethylsilane were added to a tared NMR tube and weighed consecutively, the weight of each component thus being found by difference. Additions were carried out using a capillary pipet.

2. Preparation Procedure for C-13 Samples

Spectral samples were prepared in a manner analogous to the procedure given for HA-100 samples. The solvent and reference for all samples was carbon tetrachloride.

## C. Instrumentation

1. Nuclear Magnetic Resonance

Spectra were run on a Varian HA 100 spectrometer using sweep widths of 100-Hz. The sweep was calibrated against a frequency counter every 2.0 Hz, a calibration curve constructed, and observed peak positions determined and corrected to the nearest 0.1 Hz. A check was made on line positions of the spectra by "ticking" two frequencies instead of the usual one in order to assist in obtaining values to the nearest 0.1 Hz. The validity of the calibration curve was monitored by frequent "ticking" at 20 Hz and 80 Hz, of a 100 Hz sweep width, obtaining a difference with the frequency counter, and comparing this difference with that obtained from the calibration curve.

2. Computer Analysis

Spectra are analyzed using an IBM 360 computer using a modification of the program of Ferguson and Marquardt.[c] The computer analysis of a spectrum includes three stages. The first stage NMRIT(0) involves input of an estimated set of chemical shifts and coupling constants which gives a computed spectrum obtained from a generated set of energy

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[c]See R. C. Ferguson and D. W. Marquardt, J. Chem. Phys., 41, 2087 (1964).

levels. The indices identifying the upper and lower energy levels participating in the transition are given for each spectral line. This procedure is repeated until a computed spectrum corresponding closely to the observed spectrum is obtained, and the assignment of energy levels associated with each observed transition may be made from the observed line positions. In the second stage, the line positions of the generated spectra are corrected to give agreement with those of the observed spectrum. These corrected lines are then used as new input data to give an improved set of energy levels involved in the transition. If the set of energy levels is overdetermined, the program employs a least squares fit in calculating these levels. The final stage of this program involves the iterative feature of [NMRIT] which is used to adjust the parameters of chemical shifts and coupling constants to obtain an optimum match between the experimental energy levels from [NMREN] and the calculated energy levels from [NMRIT]. Upon convergence a new set of coupling constants and chemical shifts is obtained, and a new set of lines generated which should then agree with those observed in the experimental spectrum.

# CHAPTER III

## RESULTS

### A. Spectral Data

The initial step in the analysis was the selection of appropriate model compounds. Concentrations were then selected to exhibit maximum variations in observable chemical shifts while at the same time maintaining an acceptable signal/noise ratio.

Thus two spectra were obtained for each compound as noted in Table I.

TABLE I

SAMPLE CONCENTRATIONS

| Sample | Concentrated Value[a] | Dilute Value[a] |
|---|---|---|
| 2,2-Dimethyl-3-Pentanol | 73.4 | 5.89 |
| 2,2,5,5-Tetramethyl-3-Hexanol | 61.0[b] | 5.75 |
| 3,3-Dimethyl-1-Butanol | 74.3 | 5.20 |
| 4,4-Dimethyl-2-Pentanol | 74.0 | 5.59 |

[a] Dilution of each compound was carried out by the addition of only $CCl_4$ and T.M.S. All values reported in mole %.

[b] Concentration was lowered in order to obtain a lock on T.M.S. The skipping of lock signal was due to the two tert-butyl groups signals in close proximity to the lock signal, T.M.S.

1. FTNMR

It is known that the chemical shift of hydroxyl protons may continue to vary at concentrations less than 5 mole %. It was deemed useful to investigate the AB region of a model compound at low concentrations to ascertain if a similar phenomenon occurs at the nonequivalent methylene hydrogens ($H_A$ and $H_B$). This procedure was performed by the preparation of two sample concentrations of 2,2-dimethyl-3-pentanol. This compound was selected due to the invariance of the vicinal coupling constants, $J_{AX}$ and $J_{BX}$, indicating no conformational changes over the concentration range studied. Since the hydroxyl group may still experience breaking of hydrogen bonds at even lower concentrations, the effective group size of the hydroxyl changes, thus steric interactions between groups should be different. Therefore it was still possible that conformer populations might be altered. A 5.6 mole % sample was the usual concentration for an HA-100 run, while the 0.88 mole % sample was for the dilute analysis. After comparison of spectra, it was observed that spectral parameters associated with A and B were essentially unaltered.

2. General Spectra Analysis

Basically, two types of spectra were observed, the ABX and AA'XX'. In two of the cases the ABX spectrum was complicated by the introduction of a methyl group leading to additional splitting, either in the AB region or in the X region, giving an actual $ABC_3X$. These spectra were observed for 2,2-dimethyl-3-pentanol and 4,4-dimethyl-2-pentanol. The third ABX spectrum was uncomplicated by additional groups, and was observed in the compound 2,2,5,5-tetramethyl-3-hexanol.

The fourth compound, 3,3-dimethyl-1-butanol, was an AA'XX' for which $|\nu_A-\nu_X| >> J_{AX}$.

3. Analysis of AB, X, AA' and XX' Regions of Model Compounds Using 100 Hz Sweep Width Spectra

Using the HA-100 and 100 Hz sweep widths, it is possible to assign transitions to the nearest 0.1 Hz.

Preliminary runs were made on all spectra using a T-60 spectrometer in order to ascertain if broadening in the hydroxyl-proton region was present. A similar broadening also occurs on protons alpha to the hydroxyl carbon. Transitions cannot be accurately determined if a broadening of line positions occur.

To eliminate this broadening effect, the introduction of acids such as HCl to the sample, is sufficient. The HCl catalyzes the exchange of the hydroxyl proton to a rate such that the lifetime of a proton on any molecule is much less than the lifetime required for NMR to observe a single state. Sharp transitions are then observed enabling more accurate determination of line positions.

At this juncture some general comments concerning interpretation of spectra might be useful.

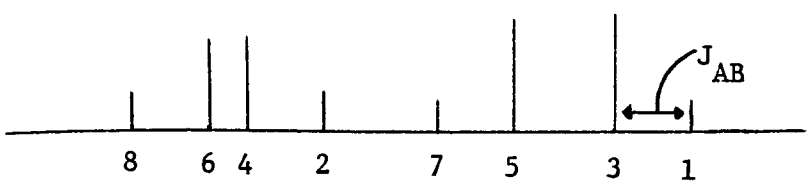
The methine proton "$H_X$" and the methylene protons "$H_X$ and $H_X'$ " of 3,3-dimethyl-1-butanol appear in the region 3.00 to 4.00 ppm. The $H_X$ proton of the ABX spectrum is recognized as a quartet if $\nu_A-\nu_B >> 0$. As $\nu_A-\nu_B$ approaches zero, two additional combination lines begin to appear and increase in intensity. The combination transitions involve change in spin of nuclei.

Since the lines are symmetrically arranged about $\nu_X$, determination of the chemical shift of $H_X$ is straightforward.

The XX' methylene protons of 3,3-dimethyl-1-butanol are characterized by a more complicated spectrum. The XX' half-spectrum is composed of two AB subspectra and two additional lines of high intensity. It should be noted that the AA' half-spectrum is identical to the XX' half-spectrum. Further analysis of the AA'XX' spectra will not be discussed here.[c]

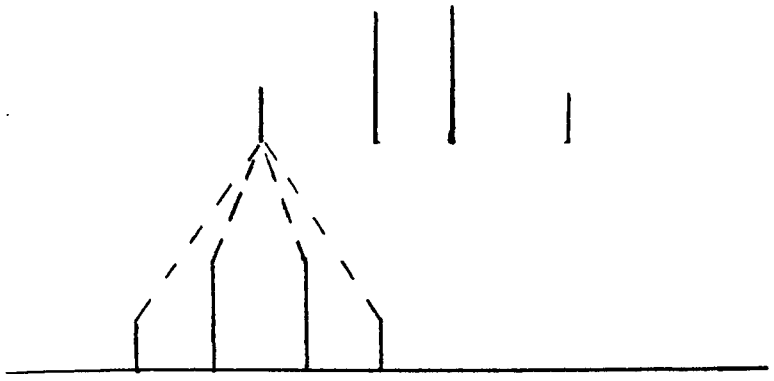
The AB region of each ABX spectrum is observed at approximately 1.00 to 2.00 ppm. Concentration variation has no significant effect on proton $H_B$ ($\nu_{conc.} - \nu_{dil.} \simeq 1.0$Hz). Conversely, proton $H_A$ is observed to change appreciably ($\nu_{conc.} - \nu_{dil.} \simeq 4$-10Hz).

Below it is observed that the AB region may be divided into two AB-type quartets. The differences in frequency between lines 1 and 3, lines 2 and 4, lines 5 and 7 and lines 6 and 8 are equal to $J_{AB}$.



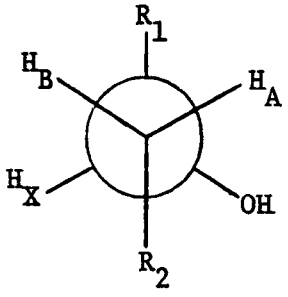

[c]For an in-depth discussion of this type spectrum, See E. Becker, "High Resolution NMR," Academic Press, New York (1972), p 166.

As stated previously, introduction of adjacent methyl groups can cause additional splitting as observed in the compound 2,2-dimethyl-3-pentanol as shown on page 20. Each of the original eight lines of the AB-type quartets are now split into an additional 1:3:3:1 quartet by the placement of a methyl group alpha to the methylene hydrogen as illustrated in the following.



This, as can undoubtedly be seen, causes the first-order analysis to be complicated. In all, a total of thirty-two transitions are now observed.

For the sake of clarity a Newman projection of the general type



was chosen for the purpose of describing gauche and anti interactions in relation to observed chemical shift values for all compounds. Thus proton $H_A$ is always designated as that gauche to the hydroxyl group, while proton $H_B$ is always gauche to proton $H_X$ in the given conformation. The coupling constant, $J_{AX}$ (anti interaction), will thus be greater than $J_{BX}$ (gauche interaction). It should be noted that $J_{AX}$ and $J_{BX}$, three bond coupling constants, are assigned positive values. On the other hand $J_{AB}$, a two bond coupling constant is assigned a negative value.

4. Computer Analysis: A Typical Problem - the 2,2-Dimethyl-3-Butanol Case

The procedure outlined for this molecule may readily be extended to the remaining cases.

Since the compound 2,2-dimethyl-3-butanol is an $ABC_3X$ spectrum, the following information must be approximated by analysis of the 100 Hz sweep width spectra (see Figures 1 and 2): $\nu_A$, $\nu_B$, $\nu_C$, $\nu_X$, $J_{AB}$, $J_{AX}$, $J_{BX}$, $J_{AC}$ and $J_{BC}$. The chemical shifts $\nu_X$ and $\nu_C$ may be obtained directly from the spectra. These approximate chemical shift values are 300.1 Hz and 101.2 Hz, respectively. Unfortunately, it is not possible to obtain directly the chemical shifts for $\nu_A$ and $\nu_B$. It is possible though, by hand calculation to make rough estimates for $\nu_A$ and $\nu_B$. The task is complicated since it is necessary to assign appropriate transitions in the AB region, where each transition is split into a quartet. This splitting, which is produced by the proximity of the methyl group alpha to the methylene carbon, has a value approximating the couplings $J_{AC}$ in the A region and $J_{BC}$ in the

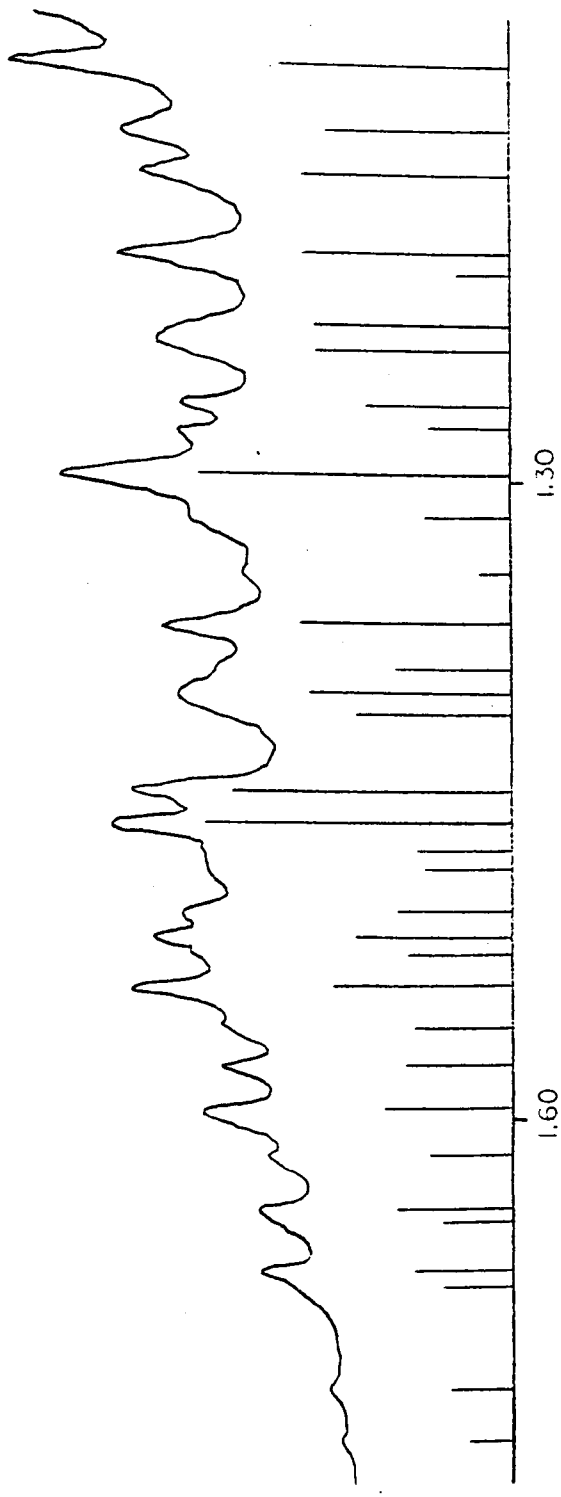



Figure 1. AB-Region of 2,2 Dimethyl-3-Pentanol

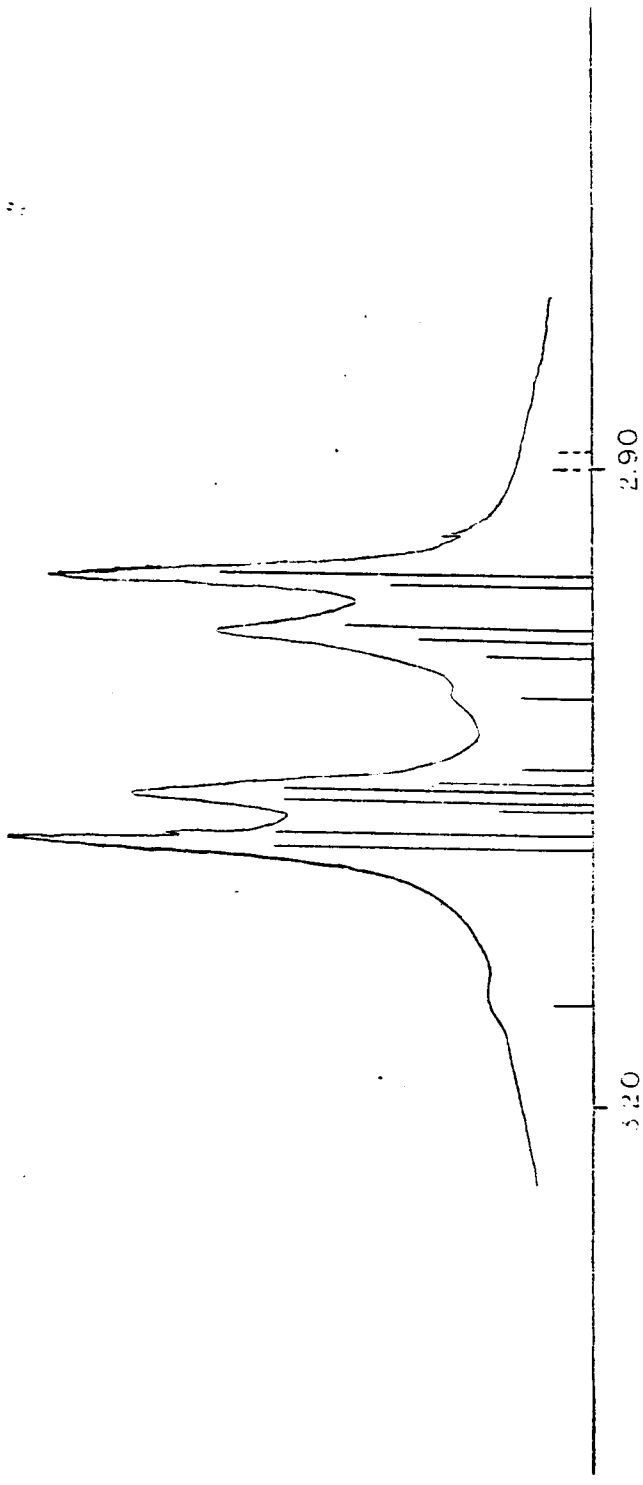



Figure 2. X-Region of 2,2-Dimethyl-3-Pentanol

B region. This coupling can be estimated ∿7.6 Hz from the C (methyl) region of the spectrum and values for $J_{AC}$ and $J_{BC}$ are thus approximated. It is now possible to make rough assignments of line positions of the uncomplicated AB subspectrum and arrive by hand calculation at approximate values for $\nu_A$ (123 Hz) and $\nu_B$ (152 Hz).[d] Finally, in the determination of $J_{AX}$ and $J_{BX}$, it is necessary to examine the X region of the compound. Since only four lines are observed, $J_{AX}$ and $J_{BX}$ are readily approximated. The separation between the outer lines in the X region is equal to the sum of $J_{AX}$ and $J_{BX}$. Also, the separation of the two inner lines is associated with the difference in the coupling constants $J_{AX}$ and $J_{BX}$. The values 10.0 Hz and 2.2 Hz, respectively, are obtained. The first stage of the computer program, NMRIT(0) may now be run since all nine spectral parameters have been estimated.

The computer output of these input data indicates the existence of 48 possible energy levels, which give rise to the observed transitions. The 48 energy levels are divided into two submatrices, with submatrix I consisting of 32 energy levels and submatrix II of 16 energy levels. Transitions may only arise within a given submatrix. The program also calculates the allowed transitions among the 48 energy levels, their frequencies (line positions), and their intensities. It is then possible to construct a spectral plot from the output data for the AB, X and C regions. In order to do this accurately, it is necessary to make use of the calibration curve. It is possible to reproduce, with the aid of this curve, small downfield or upfield errors

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[d]For a look at a typical analysis of the AB region in depth, see "High Resolution NMR," Edwin Becker, 1972, p 157.

in line positions caused by non-linearity in the sweep pot of the HA-100. In essence, spectral plots show incorrect line positions to duplicate inherent non-linear errors of the HA-100 sweep pot. These plots are then compared with the actual 100 Hz sweep width spectra of the compound to check the accuracy of the input data. This completes the first half of the computer analysis.

In the second stage of the computer analysis, it is necessary to obtain a minimum of N-1 line positions, where N is equal to the number of energy levels in a submatrix, for each submatrix, and correct the calculated frequencies to give agreement with the observed spectrum. The computer program may then calculate a new set of energy levels using as input data the observed line positions (frequencies) of the spectrum, and the energy levels associated with these lines as obtained from NMRIT(0). Unless a line is isolated from its neighbors, or highly characterized by its intensity, it is possible to misassign energy levels at this stage, and this step must normally be repeated several times. These corrected line positions and energy levels are used as input data for the NMREN stage of the program. From these the computer constructs a new set of energy levels which, if they exist, give rise to transitions coinciding with those observed in the spectrum. The final stage of the program, NMRIT>0, takes the original coupling constants and chemical shifts used as input data for NMRIT(0), and alters them in an iterative fashion to generate an additional set of energy levels which converge on the new set constructed by NMREN. After convergence, new transition frequencies and their corresponding intensities are calculated. Using the new transitions another spectral plot is

constructed and compared to the observed spectrum. In all steps of this analysis, it is always necessary to use the calibration curve. If spectral plots are to be constructed from computer output, then it is necessary to introduce upfield or downfield errors as caused by non-linearity in the HA-100 sweep pot. Likewise, whenever transitions are supplied as input data for computer analysis, these aforementioned errors must be negated by use of the calibration curve. If proper correlation is not obtained, the above sequence is repeated until a constructed plot is superimposable with the observed spectrum. After this is accomplished a set of spectral parameters are obtained as shown on page 27. Figures 1 and 2 (pages 20 and 21) show the observed and computed spectra for the AB and X regions of 2,2-dimethyl-3-pentanol.

5. C-13 Analysis

In order to investigate possible inductive effects caused by the presence of a hydroxyl group in the model compounds, C-13 spectra of 2-butanol were analyzed.[e] 2-Butanol was selected since conformational changes are known to occur with variation in concentration. By examination of line position, as sample concentration and consequently effective hydroxyl group size were varied, a correlation between concentration and the inductive effect of the hydroxyl group was investigated. Table II shows that no direct relationship between variation in concentration (effective hydroxyl size and extent of hydrogen-bonding) and an inductive effect as reflected by changes in line positions at carbon 1 exist.

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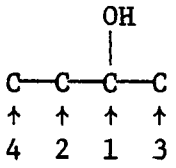
[e]Spectra were analyzed using a Nicolet TT-14.

TABLE II




C-13 DATA FOR 2-BUTANOL

| Concentration | Carbon 1 | Carbon 2 | Carbon 3 | Carbon 4 |
|---|---|---|---|---|
| 94.0[f] | 1034.8[g] | 478.6 | 336.2 | 143.6 |
| 90.1 | 1032.9 | 478.4 | 336.7 | 144.7 |
| 12.9 | 1032.7 | 478.9 | 340.8 | 146.4 |
| 1.2 | 1034.7 | 482.5 | 347.3 | 147.1 |

[f]Sample concentration in mole %.

[g]All values in Hertz.

## B. Accuracy of Data

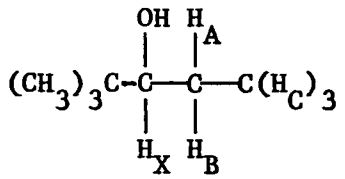
The accuracy of values determined by computer analysis was believed to be a function of two factors. The first factor is the inherent inaccuracy of the HA-100 spectrometer. According to specifications of the instrument, accuracy is listed as being ±0.3 Hz. The second factor influencing accuracy of reported values was the possibility of human error in assigning line positions. Line positions were measured to the nearest 0.1 Hz, and in a typical computer run, the average deviation between observed and calculated line positions was 0.2 Hz, with a maximum deviation of 0.4 Hz. Thus, it is probable that errors in chemical shifts and coupling constants should not exceed 0.3 Hz, the level of inaccuracy of the HA-100.

## C. Summary

Tables III-VI list computed chemical shift values associated with protons A, B, C, and X of the various compounds. The chemical shift of the methylene proton $H_B$ varies only slightly ($\Delta\nu_B \tilde{=} 1.0$ Hz) with change in sample concentration. Meanwhile, it is evident that the chemical shift of the methylene proton $H_A$ is quite concentration dependent, varying as much as 10.8 Hz upon sample dilution.

The coupling constants $J_{AX}$, $J_{BX}$, $J_{AB}$, $J_{AC}$, and $J_{BC}$ are shown to vary only slightly with change in concentration. The proton with the larger coupling constant to X, has arbitrarily been designated as "A", thus proton $H_A$ must be predominately "anti" to proton $H_X$ while proton $H_B$ must be predominately "gauche" to $H_X$. The coupling constants determined for $J_{AB}$ are fairly typical of geminal coupling constants.

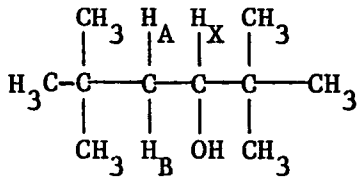
TABLE III



SPECTRAL PARAMETERS (IN Hz) FOR 2,2 DIMETHYL-3-PENTANOL (100 MHz)

| Mole Percent | $\nu_A$ | $\nu_B$ | $\nu_X$ | $J_{AB}$ | $J_{AX}$ | $J_{BX}$ | $\nu_{OH}$ | $\nu_C$ | $J_{AC}$ | $J_{BC}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 5.89 | 119.5 | 153.2 | 300.0 | -13.6 | 10.4 | 1.9 | 168 | 97.3 | 7.2 | 6.9 |
| 73.4 | 121.9 | 153.1 | 300.2 | -13.7 | 10.5 | 1.9 | 424 | 99.3 | 7.3 | 7.2 |

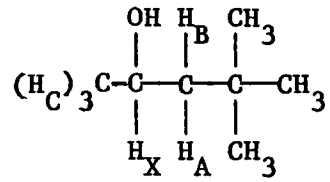
TABLE IV



SPECTRAL PARAMETERS (IN Hz) FOR 2,2,5,5 TETRAMETHYL-3-HEXANOL (100 MHz)

| Mole Percent | $\nu_A$ | $\nu_B$ | $\nu_X$ | $J_{AB}$ | $J_{AX}$ | $J_{BX}$ | $\nu_{OH}$ |
|---|---|---|---|---|---|---|---|
| 5.75 | 111.3 | 142.2 | 325.0 | -14.5 | 8.8 | 1.2 | 117 |
| 61.0 | 115.1 | 143.4 | 327.5 | -14.7 | 8.5 | 1.3 | 206 |

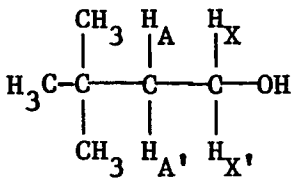
TABLE V



SPECTRAL PARAMETERS (IN Hz) FOR 4,4 DIMETHYL-2-PENTANOL (100 MHz)

| Mole Percent | $\nu_A$ | $\nu_B$ | $\nu_X$ | $J_{AB}$ | $J_{AX}$ | $J_{BX}$ | $\nu_{OH}$ | $\nu_C$ | $J_{CX}$ |
|---|---|---|---|---|---|---|---|---|---|
| 5.59 | 136.5 | 126.2 | 387.2 | -14.1 | 8.2 | 2.7 | 175 | 112.7 | 6.1 |
| 74.0 | 147.3 | 124.4 | 389.7 | -14.0 | 7.9 | 3.9 | 424 | 114.9 | 6.2 |

TABLE VI



SPECTRAL PARAMETERS (IN Hz) FOR 3,3 DIMETHYL-1-BUTANOL (100 MHz)

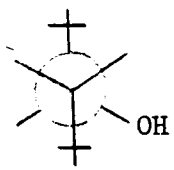
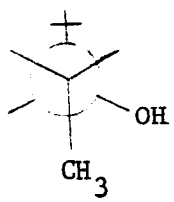
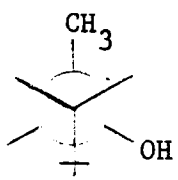
| Mole Percent | $\nu_A$ | $\nu_B$ | $\nu_X$ | $J_{AX'}$ | $J_{AX}$ | $\nu_{OH'}$ |
|---|---|---|---|---|---|---|
| 5.20 | 146.7 | 146.7 | 358.6 | 9.5 | 5.4 | 302 |
| 74.3 | 150.2 | 150.2 | 359.8 | 10.2 | 5.5 | 500 |

# CHAPTER IV

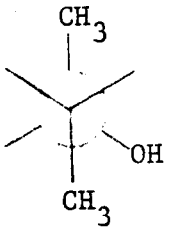
## DISCUSSION AND RESULTS

### A. Relative Importance of Alkyl-Alkyl and Alkyl-Hydroxyl Interactions

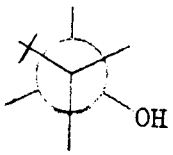
It is deemed informative first to comment on the resonance frequencies of the hydroxyl protons since a consideration of these frequencies reveal certain structural features of the molecules which have been studied. Following is a summary of the compounds which were experimentally analyzed and their respective hydroxyl resonance frequencies.

| Molecule | Hydroxyl Resonance Frequency in ppm's | |
|---|---|---|
| | Conc. $\sim$ 75 mole % | Dilute $\sim$ 5.0 mole % |
|  | 2.06[a] | 1.17 |
|  | 4.24 | 1.68 |
|  | 4.24 | 1.75 |

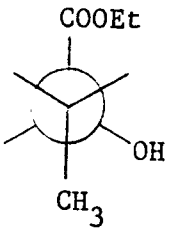
[a]The concentration here was approximately 60 mole %. Due to the nature of the dilution curve, little difference is noted between 75 and 60 mole %.




5.00 1.65

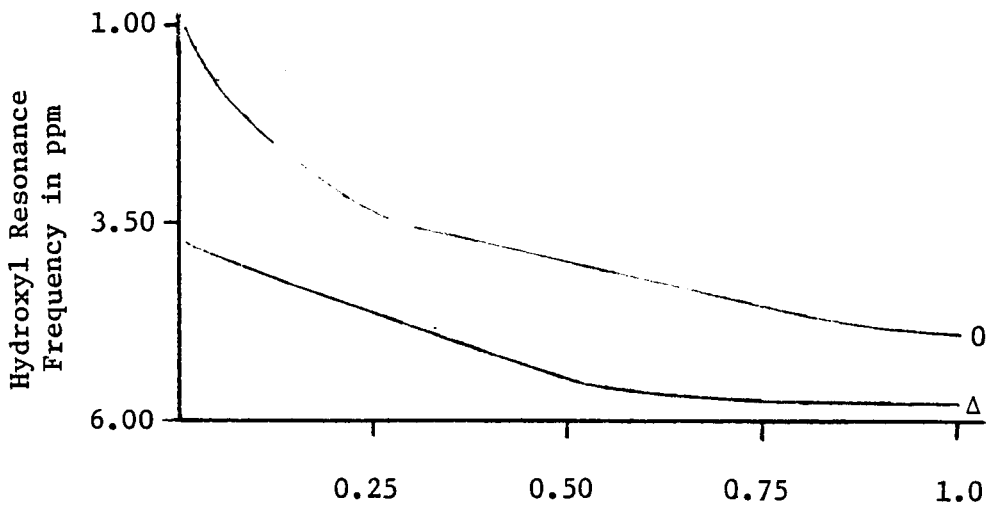



5.00 3.02




3.80 2.70

It is informative to consider dilution curves for a primary and secondary alcohol. Following are typical dilution curves for a primary and secondary alcohol.




Mole Fraction of Ethanol[c] (Δ) and 2-Butanol[d] (0)

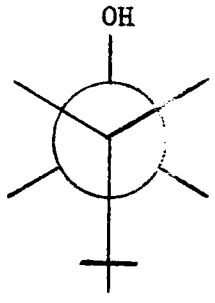
[c]See Becker, Liddel and Shoolery, J. Mol. Phys. Spectroscopy, 2, 1 (1958).

[d]See Jackman and Bowman, J. Am. Chem. Soc., 88, 5565 (1966).

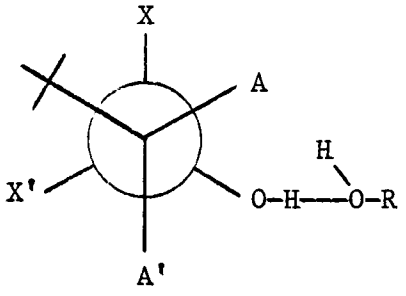
Other alcohols and phenols give similar curves.

Mathematical analyses of a number of hydroxyl bearing compounds reveal that the hydroxyl proton frequency is related to the degree of association as a consequence of hydrogen bonding.[23] The frequency of the monomeric alcohol is obtained by extrapolation to infinite dilution, and the equilibrium present beyond the reversal of curvature (∿3 mole percent above) is presumably between dimer and monomer.

In considering the above molecules, one is struck by the hydroxyl frequency of two molecules. The following molecule

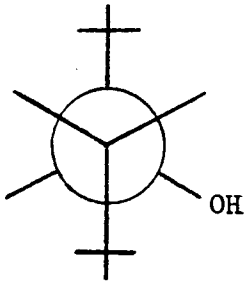



has a very high hydroxyl frequency at low concentrations; the highest of any molecule given, and similar to that of ethanol. This is suggestive of a strong tendency to hydrogen bond even in dilute solution and would imply the below conformation in which there is little steric interaction between the tert-butyl of the alcohol and the hydroxyl group which is presumably bonded to a rather bulky neighbor. This conforamtion is furthermore supported by the value of the coupling constants ($J_{AX'}$ = 10.2, $J_{AX}$ = 5.5).

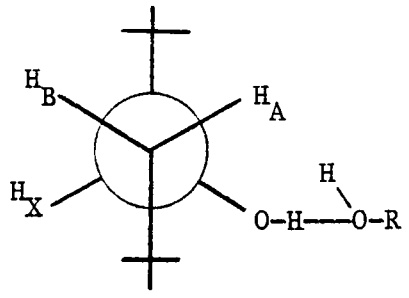



The remaining alcohols, being secondary, must have at least one alkyl-alkyl, or alkyl-hydroxyl interaction no matter what conformer they adopt.

The following molecule on the other hand

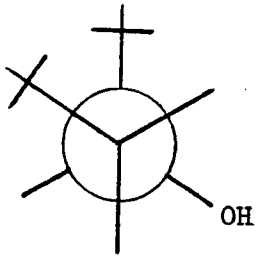



shows a very high field resonance frequency for the hydroxyl proton both in concentrated and particularly in dilute solutions, indicative of limited hydrogen bonding in all concentrations. The very low values of $J_{BX}$ in both concentrated and dilute solutions (1.3 Hz and 1.2 Hz) indicate the below conformation is preferred at all concentrations.




In this conformation there is a highly unfavorable gauche tert-butyl-hydroxyl interaction, especially if the hydroxyl group is an effectively much bulkier group because of hydrogen bonding.

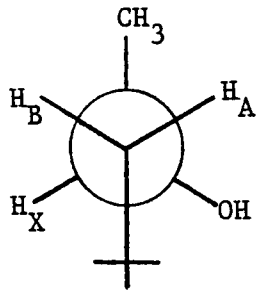
To alleviate this interaction, the molecule could adopt the below conformation which would allow hydrogen bonding to be less sterically inhibited.



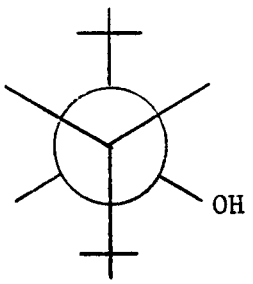

This, however, would now lead to an unfavorable gauche tert-butyl-tert-butyl interaction. In view of the small and constant value of $J_{BX}$, this conformer is apparently less energetically favorable overall

even though there should be increased stability due to formation of hydrogen bonds. This finding is consistent with the conformation proposed for 3,3-dimethyl-1-butanol, since strong hydrogen bonding may take place without tert-butyl gauche interactions between either hydroxyl or alkyl groups.

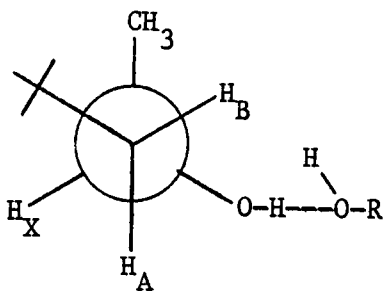
If a tert-butyl gauche to a hydroxyl group prevents, or at least hinders hydrogen bonding, the following molecule would be expected to exhibit similar properties with respect to the resonance frequency of the hydroxyl group.




However, this is not found to be the case. As a matter of fact, the hydroxyl frequencies associated with the above molecule are quite similar to 2-butanol where there is a much smaller methyl-hydroxyl gauche interaction. It would appear from this as well as from the coupling constant data (larger $J_{BX}$, smaller $J_{AX}$), that in this case the tert-butyl group is not in as close proximity to the hydroxyl group as in the molecule



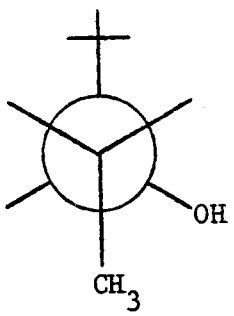

The tendency of 4,4-dimethyl-2-pentanol to hydrogen bond in spite of a potential gauche tert-butyl-hydroxyl interaction can be accounted for if the molecule adopts the conformation below which minimizes gauche interactions with the hydroxyl group allowing it to hydrogen bond with neighbors.



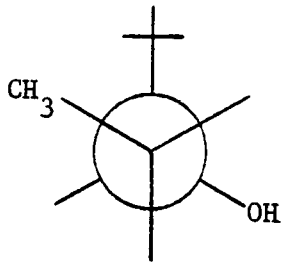

This conformation being occupied to at least some extent would also account for the difference in coupling constants $J_{AX}$ and $J_{BX}$ between this molecule and 2,2,5,5-tetramethyl-3-hexanol. This in turn would mean that while a gauche tert-butyl-methyl interaction may not be

favorable, it is, not surprisingly, not as unfavorable as a gauche tert-butyl-tert-butyl interaction. The steric values given by Eliel[24] for tert-butyl, methyl and hydroxyl groups are >4.4, 1.7 and 0.6 respectively, where the larger value represents a larger potential steric interaction. These values would indicate that interaction with a methyl group is less sterically favored than a monomeric hydroxyl group. However, this less favorable dialkyl interaction is apparently not so large that it cannot be accommodated in order to gain the additional energy associated as a consequence of hydrogen bond formation.

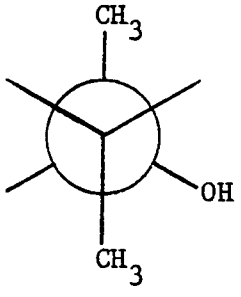
In considering the following molecule



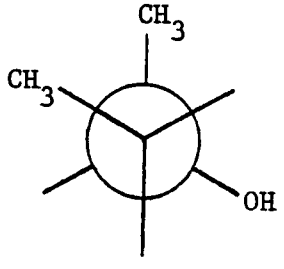

the hydroxyl frequency values indicate rather strong hydrogen bonding in both concentrated and dilute solutions, comparable to that of 2-butanol. The invariance of $J_{AX}$ and $J_{BX}$ on dilution however, and especially the very small value for $J_{BX}$ would imply a very strong preference for the above conformation and a very low population of the conformation below.




In order to give a steric interpretation that is consistent with both the observed values of vicinal coupling constants ($J_{AX}$ and $J_{BX}$) and hydroxyl frequencies, it would be necessary to suppose that while a gauche methyl-hydroxyl interaction may be unfavorable when the hydroxyl group is hydrogen bonded, it is not as unfavorable as a gauche methyl-tert-butyl interaction. This is in agreement with the earlier reported conclusion that the favored conformation of 2-butanol is VII rather than VIII.




VII




VIII

From the previously mentioned studies of Eliel, one would suppose that for the monomeric alcohol, a gauche interaction of a methyl group with a hydroxyl is always favored over that of a methyl with another methyl or tert-butyl group.

The aforementioned findings regarding the relative importance of various alkyl-alkyl and alkyl-hydroxyl interactions, relative conformer populations, and conformational changes on dilution in alcohols are deemed valid independent of the origin of nonequivalence displayed by the methylene protons $H_A$ and $H_B$, and represent the beginnings of an understanding of the factors determining conformational changes on dilution, to what extent these various factors are important, and possible empirical predictions of conformational population as these factors are changed either as a consequence of structure or of concentrations. Additionally, these results indicate that the organic chemist's tendency to estimate the importance of various conformations by a consideration of only the steric factors present in an isolated molecule is a gross oversimplification which will, in many cases, lead to incorrect conclusions.

## B. The Chemical Shift

When a hydrogen atom in a molecule such as methane is replaced by another atom or group of atoms G, the resonance frequency of the protons

$$H\text{-}CH_3 \qquad\qquad G\text{-}C(H_A)_3$$

$H_A$ is, in general, not the same as the protons of methane itself. This is the well known chemical shift which has made NMR such a useful tool to organic chemists.

Since the discovery of the chemical shift, its origin has been the subject of extensive theoretical and experimental investigation, and has been shown to arise from a number of causes. Quantum mechanics has been used in a quantitative attack on this problem. Due to the extreme complexity of the problem, even the simplest organic molecule, methane, cannot be treated without a vast number of assumptions and approximations. While there is disagreement among theoreticians as to the quantitative approach to the chemical shift, there is considerably better accord as to its various qualitative origins. These various factors can be found in many references dealing with the theory of magnetic resonance, and will not be detailed at this time since not all are involved in the present work. However, there are three factors which will bear considerable importance to the presentation of the results of this study, and these will be emphasized at this time.

First is the concept of inductive effects. If G releases electrons relative to H, the electron density around the carbon is increased, and the attached protons are more shielded than in methane itself. This is normally observed only in cases where G is an atom with a lesser electronegativity than H. If G is an electron-releasing group of atoms, there are normally additional deshielding perturbations on the chemical shift of the protons in question other than the electronegativity alone. These are usually of greater importance than the electronegative effects, and consequently most methyl resonances are found downfield from methane. Of course if G is electron-withdrawing, the effect will be to deshield the attached protons.

The second effect, single α-bond anisotropy, may be illustrated

by the following (Figure 3).

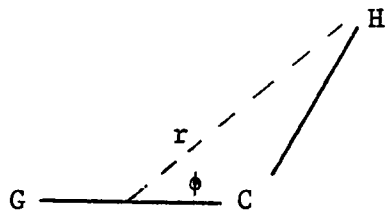



Figure 3. Single bond anisotropy.

C-G bonds would be expected to have different longitudinal and transverse magnetic susceptibilities, and thus tend to shield or deshield neighboring atoms such as H above. The sign and magnitude of shielding are related to the angle, $\phi$, and the distance, r.

The third effect to be considered is the anisotropy of group G. Since G itself may be anisotropic or may contain certain more remote anisotropic bonds or groups which shield or deshield protons, the extent of this effect will again be related to angle and distance. One example of such an effect is the case of the rather low field methyl protons (2.62 ppm) of ethyl benzene. Here the methyl protons lie in a deshielding region of a rather remote benzene ring, thus accounting for their downfield appearance.

In 1958, J. N. Shoolery[25] observed that a simple relationship exists between electronegativity of substituents and the proton chemical shifts in alkyl derivatives. In 1955, in a study he conducted with Dailey,[26] further modifications were made in the overly simplistic idea of a one-to-one correlation between electronegativity and alkyl proton chemical shift values. Finally in 1959, Shoolery published a set of shielding constants, $\sigma$,[27] which not only incorporated inductive effects, but also the shielding due to any anisotropic effects as well.

Using molecules of the type

$$CH_3X \qquad XCH_2Y \qquad \begin{matrix} & Y & \\ & | & \\ XCHZ & & \end{matrix}$$

Shoolery noted it was possible to estimate proton resonance frequencies from a knowledge of X, Y, and Z. In terms of the δ scale, the calculated chemical shift of the proton in question is given by equation 7

$$\delta = + 0.233 + \sum_i \sigma_i \text{ eff} \qquad (7)$$

where 0.233 is the δ value of methane. As an example using his values of $\sigma_{Cl} = 2.53$ and $\sigma_{Br} = 2.33$, the below agreement is obtained:

| molecule | calculated frequency | observed frequency | error |
|---|---|---|---|
| $CH_3Cl$ | 2.76 | 3.05 | -0.29 |
| $CH_3Br$ | 2.56 | 2.68 | -0.12 |
| $CH_2Br_2$ | 4.89 | 4.94 | -0.05 |
| $CH_2Cl_2$ | 5.29 | 5.34 | -0.05 |
| $CH_2ClBr$ | 5.09 | 5.16 | -0.07 |
| $CHCl_3$ | 7.82 | 7.21 | +0.61 |

As the above data suggest, the shielding effects are not totally additive. It should be noted that the best agreement between Shoolery's values and observed shifts is obtained in the disubstituted cases, which they were primarily designed to do.

The possible existence of long-range, remote shielding effects has led Jackman[22] to comment that the surprising factor about the Shoolery rules is that they work as well as they do, since any anisotropic effects will vary with both distance and angle between the site

of shielding and the proton being shielded. Thus the shielding of H by X might be expected to be conformationally dependent, and would vary between a gauche and anti interaction.

Since Shoolery's original publication, many other workers have expanded and refined his results.[28-32] Emsley, Feeney and Sutcliffe[33] pointed out that there is no known theoretical basis for the additivity of substituent effects. Primas[34] by considering the extensive data of Tiers, devised a computer program to generate optimum values for effective shielding constants.

## C. Single Bond Anisotropy

Long-range shielding effects (double bonds, carbonyl groups and aromatic rings as examples) can at least in part be interpreted in terms of difference in the polarizability of multiple bonds parallel and perpendicular to the magnetic field. McConnell[35] has developed an approximate relation

$$\sigma_G = \frac{(3\cos^2\phi - 1)(X_L - X_T)}{3r^3}$$

where $\sigma_G$ is the shielding contribution which arises from some specific group electrons associated with G within a molecule, $\phi$ is the angle illustrated by Figure 3, r is the distance between the proton and the electrical center of the bond and $(X_L - X_T)$ is defined as the difference in the transverse and longitudinal magnetic susceptibilities of the C-G bond.

A few early studies[36-37] indicated that in rigid cyclohexyl and related systems, axial protons are more shielded and appear at higher

fields than equatorial protons. In 1960, Jensen[38] showed this to be true for cyclohexane as well.

Jackman and Wiley[22] using the $(X_L - X_T)$ value of Bothner-By and Naar-Colin,[39] proposed that the difference of axial and equatorial proton resonances at $C_1$ in cyclohexyl systems, was due to the anisotropy of the $C_{2-3}$ and $C_{5-6}$ bonds. From calculations using the McConnell equation, they determined that the effect of the $C_{2-3}$ and $C_{5-6}$ bonds should give a resonance frequency difference between axial and equatorial protons of 0.40 ppm. Similar considerations were also made by Musher[40] in his cyclohexyl systems.

There has been much questioning in the literature of Jackman's interpretations. J. W. Ap Simon[41] for example has demonstrated that the anisotropy of a C-H bond is comparable to that of a C-C bond: this in direct disagreement with contentions of Jackman and Wiley who assumed C-H bond anisotropies were negligible. Eliel,[42] in a study of 26 substituted cyclohexanols, has commented that while the unequal shielding by gauche and anti substituents in the $C_2$ position as they affect the $C_1$ protons is real, it is impossible to explain this effect in terms of simple C-C bond anisotropies. It was also Eliel's contention that more remote carbons ($C_3$ and $C_5$) should make significant contributions.

All of the systems mentioned previously are rigid where presumably the effect is that measured on a single conformer and assuming that no complicating factors such as changes in bond angles or conformer population occur. Lemieux and co-workers[36] and Shoolery and Rogers[43] in studying cyclohexane derivatives observed that in all cases the axial

proton in question resonated at higher fields than the corresponding equatorial proton, however the difference varied from 0.10 ppm to 0.68 ppm. If one ascribed this difference (as Jackman does) to the 0.40 ppm difference in long-range shielding of the $C_{2-3}$ and $C_{5-6}$ bonds, this leads to an $|\delta_{obs.} - \delta_{calc.}|$ error of between 0.30 and 0.28 ppm. Eliel on the other hand obtained a value of +0.20 ppm (deshielding) solely for an anti (1,2-diaxial) interaction of a methyl group, and, depending on whether a gauche 1,2 interaction was equatorial-axial, di-equatorial, or axial-equatorial, obtained values varying from -0.28 to -0.47 ppm (shielding).

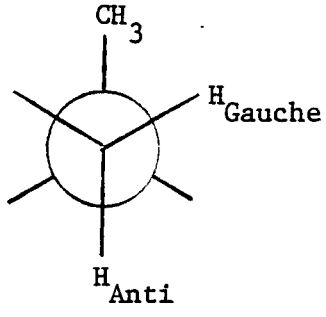
It is arguable that Eliel's choice of cyclohexanols was a particularly unfortunate one. The advantage of easy determination of chemical shift of the proton alpha to the hydroxyl group is obvious due to its large downfield shift. However, it is also apparent the hydroxyl group possibly introduces a complicating factor. The long-range shielding of a hydroxyl group is supposedly related to its electric dipole.[44] Meanwhile, the direction and magnitude of this dipole is unknown. It will be shown later, however, that in our calculations, which involved alcohols it was possible to ignore this aspect of the hydroxyl group if indeed it exists. Perhaps were the extent of the error thus introduced by neglecting this factor known, both our calculations and Eliel's could have achieved better agreement between observed and calculated values.

It was deemed important to mention the lack of agreement of Eliel and Jackman's data since they might be taken as representing the limitations of any simplified treatment where the shielding by a group

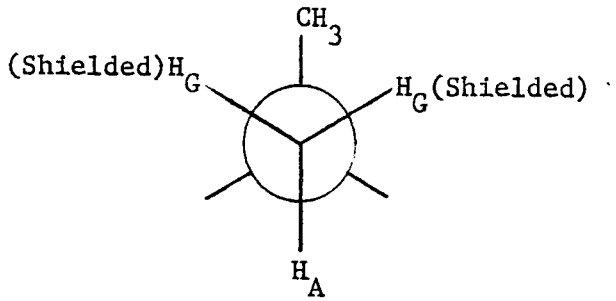
on neighboring protons is treated as though it were a constant. Since it was our intention to apply a similar treatment to our acyclic system in an effort to determine conformations and qualitative information about relative conformer populations, it was desirable that our predicted chemical shifts would be qualitatively correct, and the errors between the calculated and observed chemical shifts would not be greater than those found in rigid systems by other workers; this is, approximately ±0.25 ppm as has been previously noted.

### D. Anomalies in the Methyl System

In considering the work of Jackman, Eliel and others, it is observed that the methyl group below is expected to shield a gauche proton and deshield an anti proton in a cyclohexyl or similar rigid system.




If this argument is extended to an acyclic molecule propane, it might be expected that the two gauche protons would be shielded and the

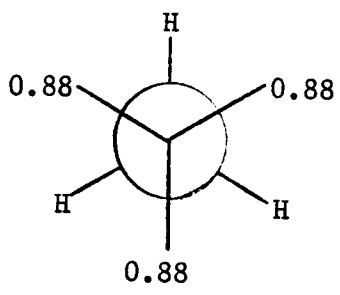


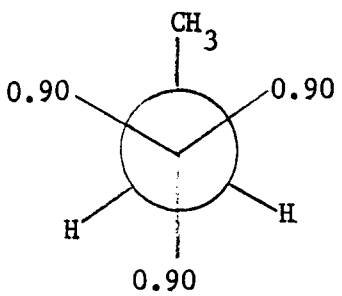

(Deshielded)

anti proton deshielded. Due to rapid rotation of the methyl group, it would not be expected to see two different kinds of methyl protons. One way[45] of handling this problem is to calculate the $\nu_{obs.}$ as the time-averaged value of the three conformers,

$$\nu_{obs} = 2/3\ \nu_G + 1/3\ \nu_A \qquad (8)$$

If it is assumed for the moment that the shielding is due to the anisotropy of the C-$CH_3$ bond, then our expectation would be that any difference in shielding of the methyl protons between ethane and propane might arise as a consequence of this anisotropy. However, in actual fact there is no significant difference.



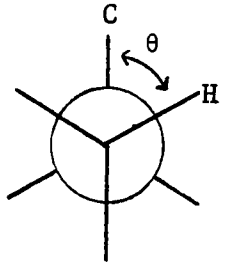
Using equation 8, one would obtain

$$2/3\ \Delta\nu_G + 1/3\ \Delta\nu_A \simeq 0 \qquad (9)$$

$$\text{or } \Delta\nu_G = -1/2\ \Delta\nu_A$$

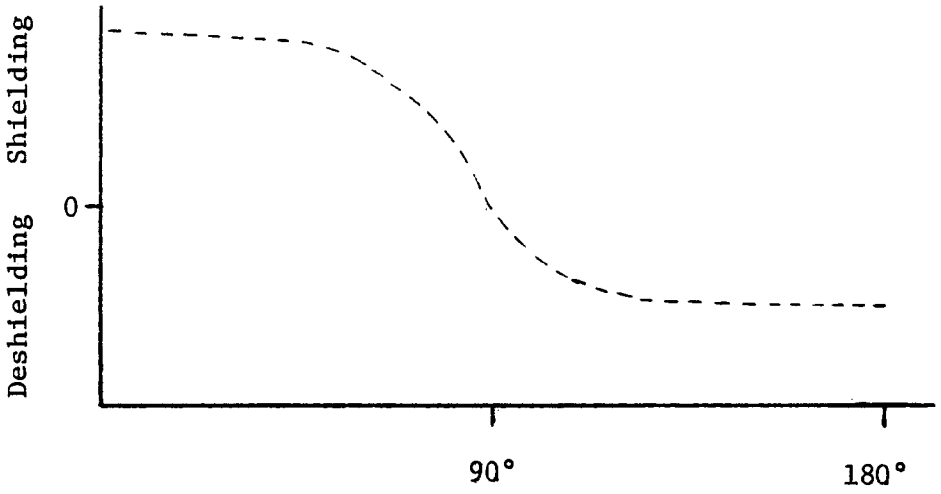
where $\Delta\nu$ is the change in frequency from 0.88 as a consequence of the long-range shielding by methyl. This is in disagreement with Eliel's data and the McConnell equation as well which, while predicting that the $\Delta\nu$'s are opposite in sign (gauche-shielding, anti-deshielding), gives a value for the shielding parameter approximately twice that of the deshielding parameter rather than the other way around.

Through use of the McConnell equation, it is possible to develop a curve relating the dihedral angle $\theta$




where $\theta = 0° \rightarrow 180°$

to shielding or deshielding magnitude as seen below



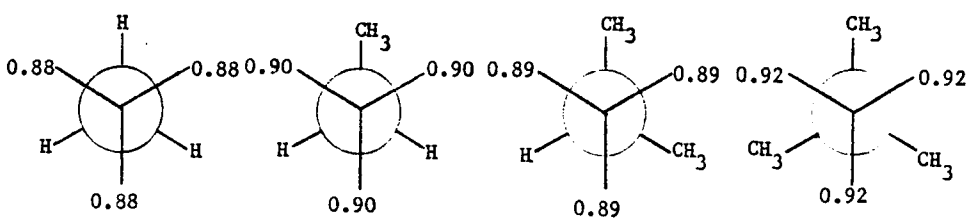

An argument may be put forward that rapid rotation shows no highly preferred conformation, and thus the integrated value of the curve between 0° and 360° should be used rather than the value for only three individual conformers as employed in equation 9.

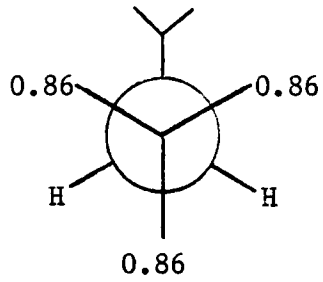
Upon integration of the shielding curve, it is noted that a net shielding would occur. The magnitude of this net shielding is difficult to estimate due to the confusion in the literature as to the exact value to ascribe to $(X_L - X_T)$.[39-41,46-47] Referring back to the ethane-propane example, it is noted that upon addition of a methyl group to ethane, a very small (+0.02 ppm) <u>deshielding</u> is observed. Here theory of C-C single bond anisotropy once again does not support the experimental observation, since integration of the curve (assuming rapid rotation) predicts a small shielding and not deshielding as actually observed.

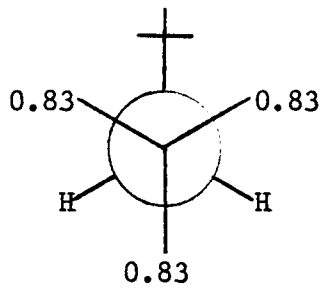
Eliel, while disagreeing with Jackman as to the origin of the methyl shielding, is in qualitative agreement with him, and finds that gauche methyl shielding effects ($\sim$ -0.4 ppm) are larger than that of anti deshielding (+0.2 ppm), so again the Pople treatment would fail to account for the results.

While Eliel does not present a curve showing a dependence of shielding on dihedral angle or distance, it is reasonable to suppose that one might exist, and if there is an inherent shielding by a methyl group regardless of its origin, it would be difficult to reason why the magnitude of this shielding should not at least superficially resemble that described by the McConnell equation in which a positive shielding at 60° is smoothly converted to a deshielding at 180°. It would be very fortuitous indeed if such a curve existed whose integration just happened to equal zero as would be necessary to explain the methyl frequencies in propane.

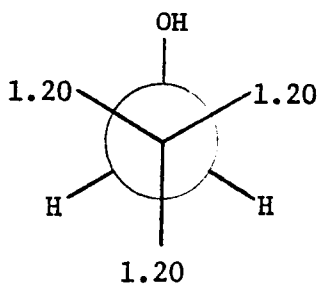
Additionally, the number or nature of substituents at $C_2$ seems to make little difference in the chemical shift of the three methyl protons at $C_1$. This fact can be illustrated by use of the following Newman projections.

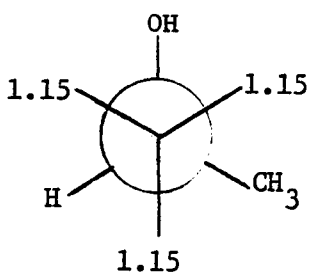


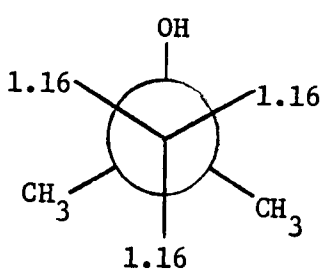


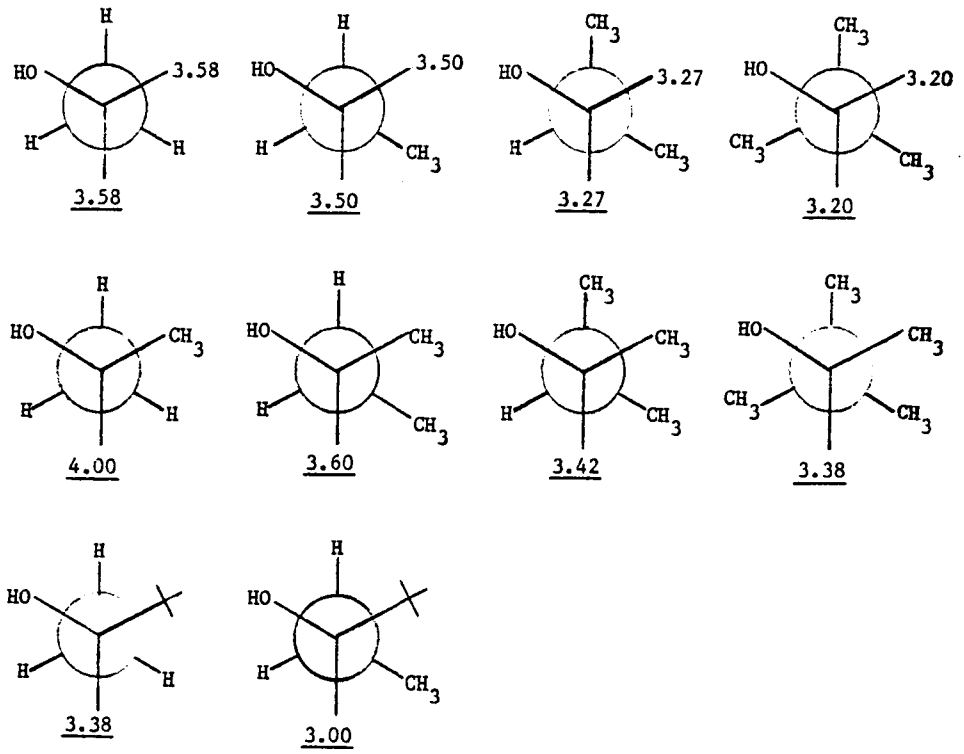

If a hydroxyl group is substituted at $C_2$, it is still observed that additional methyl substituents at $C_2$ again do not appreciably affect the methyl proton resonances at $C_1$.



However, if substituents are located on both $C_1$ and $C_2$, it would appear that the supposed shielding effects become greater and increase as the number and size of substituents increase. This effect, as seen below, is especially pronounced if one of the substituents is a hydroxyl group.



In view of the data just presented for alkanes and alcohols, it would appear that long-range shielding is evident only when substituents other than hydrogen are located at both $C_1$ and $C_2$. In such cases, there is an increasing effect on the $C_1$ proton resonances as the number of substituents is increased at $C_2$. The reason for this is not clear, but could be interpreted as indicating that long-range shielding requires a single conformation, or an equilibrium between conformations, and is increasingly manifested as the rotational barriers are heightened.

In anticipation of our own findings to be presented later, our data would seem to cast doubts on an "inherent" shielding associated with any group such as methyl (whether due to single bond anisotropies or otherwise) and whose contribution to the various chemical shifts of neighboring protons can be determined from a knowledge of the geometry alone. It is felt, however, that for a given molecule, the "shielding effect" of a group such as methyl would indeed show a dependence on the dihedral angle, $\theta$.

## E. Purpose of This Study

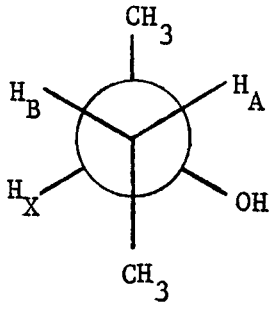
It was the purpose of this study to attempt to gain an understanding of the apparently anomalous results obtained in the study of 2-butanol and ethyl α-hydroxylbutyrate, the results of which are summarized in Table 7.[13,16]

One striking feature of the above data is the change in chemical shift of proton $H_A$ on dilution compared to the much smaller change for $H_B$ for both molecules. In the original work of Jackman and Bowman, this was interpreted as arising from a higher population of conformer X

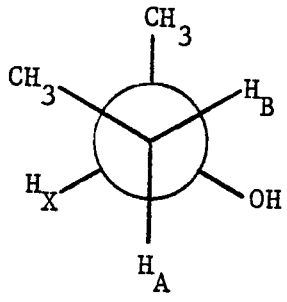
TABLE VII

SPECTRAL PARAMETERS (In Hz) FOR 2-BUTANOL AND ETHYL α-HYDROXYBUTRATE (100 MHz)

| Molecule | Mole fraction | $\nu_X$ | $\nu_A$ | $\nu_B$ | $J_{AX}$ | $J_{BX}$ | $\nu_{OH}$ |
|---|---|---|---|---|---|---|---|
| 2-Butanol | 1.00 | 361.8 | 148.1 | 137.1 | 6.5 | 5.8 | 500 |
| | 0.03 | 359.3 | 140.6 | 137.8 | 7.1 | 5.4 | 165 |
| Ethyl α-hydroxybutyrate | 0.847 | 408.2 | 164.0 | 175.9 | 7.1 | 4.4 | 390.1 |
| | 0.075 | 400.6 | 161.0 | 176.6 | 7.0 | 4.3 | 291.7 |




IX




X

in concentrated solution than dilute due to greater steric repulsion between the methyl and hydroxyl when hydrogen bonded extensively (concentrated). It was noted that $H_A$ in IX is shielded by the gauche methyl while in X it is deshielded according to both Jackman and Eliel's findings. This conclusion was supported by a change in coupling constants $J_{AX}$ and $J_{BX}$ which indicates there is increasing gauche character of $H_B$ on dilution which is accompanied by an increasing anti character in $H_A$.

The ester, ethyl α-hydroxybutyrate, was also extensively studied and likewise exhibited an upfield shift on dilution of $H_A$ analogous to that of 2-butanol. The coupling constants, however, remained unaltered over the concentration range studied, thus the origin of this dilution shift in $\nu_A$ could not arise as a consequence of changes in conformer populations such as was proposed for 2-butanol. There were other disturbing differences as well. The hydroxyl proton of the ester exhibited an unusually high resonance frequency in dilute

solution. In 2-butanol, $H_A$ was observed at higher field than $H_B$, while in the ester these relative frequencies were reversed.

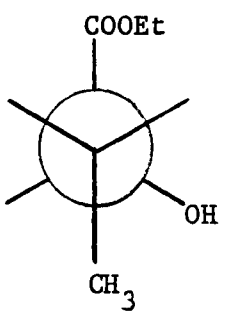
There were however, factors associated with the ester which, if understood and their relative contributions known, might account for these differences, or similarities. If, for example, one takes into account the fact that the carbethoxy group is sterically a much larger group than the methyl, then this might well lead to a low conformer population where the methyl group is gauche to the carbethoxy or perhaps even preclude it. This would at least qualitatively account for the invariance of the coupling constants $J_{AX}$ and $J_{BX}$ on dilution as well as their absolute magnitude.

Secondly, the carbethoxy group contains a highly anisotropic carbonyl group. It is expected that protons ($H_A$ and $H_B$ for example) in the vicinity of this group might be shielded and give rise to resonance frequencies quite different than those observed in 2-butanol, and, depending on the orientation of the carbonyl group, might shield $H_A$ and $H_B$ differently even though both protons are gauche to the carbonyl.

Thirdly, since it is known that a carbonyl-hydroxyl hydrogen bond is stronger than a hydroxyl-hydroxyl hydrogen bond, this would suggest the possibility of a number of consequences. For example at comparable concentrations in the same solvent, the fraction of monomeric molecules in the ester might be expected to be considerably less than that of 2-butanol. It is viewed that the change in proton frequency of a hydroxyl group on dilution measures the change in involvement in hydrogen bonding. The relatively small difference in resonance

frequency of the ester's hydroxyl proton on dilution can be taken as indicating strong hydrogen bonding compared to 2-butanol. The extensive hydrogen bonding experienced by ethyl α-hydroxybutyrate, appears to be attributable to the stronger hydrogen bond (carbonyl-hydroxyl). However, the observed values are suspect as to whether they measure solely the extent of hydrogen bonding of the hydroxyl proton since the hydroxyl proton must also feel the anisotropy of the carbonyl group.

Finally, because of hydrogen bonding at the carbonyl carbon of the ester, one would expect that in concentrated solutions of the ester both the carbethoxy and hydroxyl groups are hydrogen bonded to neighbors unlike the 2-butanol case where only the hydroxyl group is involved. This would seem to impress an even more unfavorable gauche carbethoxy-methyl interaction than has already been considered, and again suggests that comparable conformer populations of the two molecules in question at similar concentration could not reasonably be expected. It also makes less surprising the invariance of the vicinal coupling constants ($J_{AX}$ and $J_{BX}$) of the ester at all concentrations, and makes reasonable the below conformation to be preferred at all concentrations.



The complexities associated with the ester were thus many and varied. In view of this, it was elected to study a series of alcohols in concentrated and dilute solutions in hopes of unraveling some of the factors that lead both to magnetic nonequivalence of these protons as well as their unequal behavior on dilution, if indeed this was observed in other cases.

One of the initial factors to which our attention was directed was the upfield shift of $H_A$ in both the 2-butanol and the ester on dilution. In the case of the ester this was not due to changes in conformational populations as had been proposed for 2-butanol. Perhaps then this was also not the origin in 2-butanol itself, as put forth by Jackman and Bowman. If this is not the origin, three ad hoc explanations seemed reasonable.

I) Molecules hydrogen bonded to the hydroxyl group deshield protons in their vicinity. As the hydrogen bonds are broken on dilution, this dishielding effect disappears with a consequent upfield shift of the originally deshielded protons. Since $H_A$ is in closer proximity to the hydroxyl group, it will be affected to a greater extent than $H_B$ (it is now proposed that this effect, if it exists, is small, and contributes at the most 0.02 or 0.03 ppm).

II) The upfield shift of $H_A$ parallels that of the hydroxyl proton. One could theorize an inductive effect transmitted and attenuated by sigma bonds to $H_A$ and $H_B$. The reason for $H_A$ and $H_B$ being unequally affected gives rise to the necessity of subsequent investigations.

III) One cannot totally rule out the possibility that the

change in chemical shift of $H_A$ has its origin in the change of orientation of the hydroxyl group as the hydrogen bonds are broken. If this is the case, one might reasonably expect that since this preferred orientation of this group should be dependent on the molecular structure as a whole, it would vary with the molecule being studied, and no clear pattern should arise.

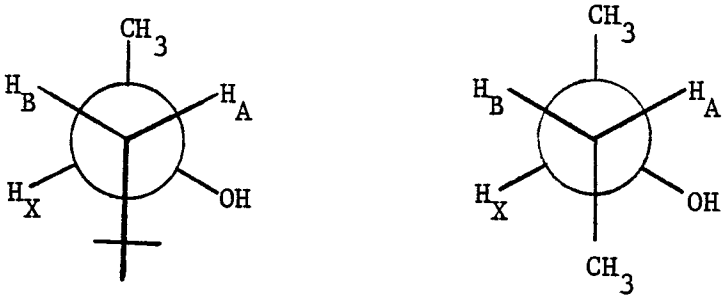
The second premise did not seem totally reasonable since the upfield shift of the hydroxyl on rupture of hydrogen bonds is presumably a consequence of the shortening of the hydroxyl bond rather than due to an increase in electron density about oxygen. To check this possibility, data were obtained on $C^{13}$ spectra of 2-butanol at different concentrations. These results which are given in Chapter III show relatively no change in the chemical shift of the $H_A$- and $H_B$-bearing carbon and none at all to the carbon directly bonded to the hydroxyl group. This would tend to rule out an inductive effect being responsible for any dilution effect felt by proton $H_A$ and $H_B$.

Regarding the third premise, fortunately this was not found experimentally to be the case, because if the change in chemical shift of $H_A$ were primarily the result of this effect, no predictions concerning the behavior of such protons or estimates of conformational populations could be made.

## F. Classification of Compounds

In considering the chemical shifts of the protons $H_A$ and $H_B$, the molecules studied fall into two classes.

Class I



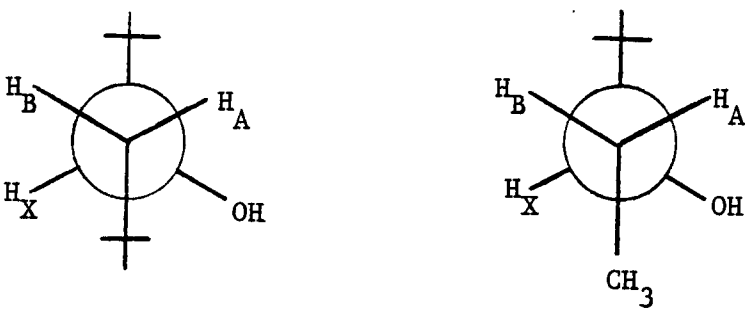

Class I is characterized by:

1) proton $H_A$ appearing at lower fields than $H_B$

2) proton $H_A$ undergoing a large shift on dilution (0.08 ppm - 0.10 ppm)

3) coupling constants $J_{AX}$ and $J_{BX}$ changing as the concentration changes (see Tables V and VII, pages 27 and 55).

Class II



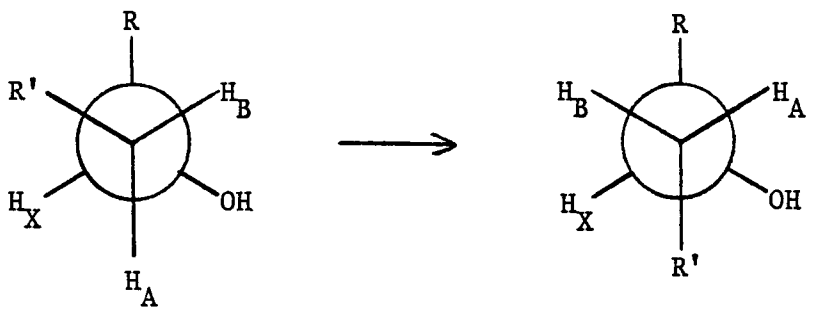
Class II is characterized by:

1) the proton $H_A$ appears at higher fields than $H_B$.

2) the change in chemical shift associated with $H_A$ on dilution is small (0.02 ppm - 0.04 ppm).

3) the coupling constants $J_{AX}$ and $J_{BX}$ are unaltered by dilution (see Tables III and IV, pages 25 and 26).

In considering solely the behavior of the coupling constants $J_{AX}$ and $J_{BX}$, on dilution a shift of equilibrium to the right must occur for those molecules in Class I as seen below.




At the same time, the molecules of Class II must exist only in the conformer where the R groups are anti to each other (or dominantly so).

It is noted that this is the same argument as originally put forth in the 2-butanol case. If this premise is accepted, it is then argued that changes in conformation or lack thereof arise as a consequence of gauche or potential gauche interactions.

## G. Shielding Parameters

The work of Shoolery, McConnell, Jackman, Eliel and others

relating proton chemical shifts to substituent groups and conformations has been mentioned earlier. The only previous efforts to account for proton nonequivalence (e.g. axial and equatorial protons in cyclohexane) in terms of conformation have involved rigid ring systems with locked conformations. No reported effort has been made to conduct similar calculations in acyclic systems where the possibility of free or limited rotation might exist.

It was hoped that the data available from the alcohols involved in this study might lend themselves to such treatment, and if successful might contribute the following:

1) Account for the magnetic nonequivalence of $H_A$ and $H_B$ in terms of conformation

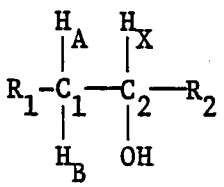
2) Account for the changes in this nonequivalence on dilution

3) Allow for estimates as to population of conformations

4) Yield a set of "shielding parameters" that would have wide applicability and could be extended to a host of molecules outside this study

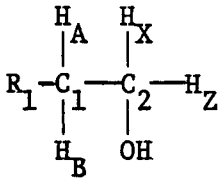
5) Indicate the theoretical possibility of gaining conformational information concerning any molecule from its experimental chemical shifts and a set of predetermined shielding parameters.

The compounds used in this investigation have had the following general structure.

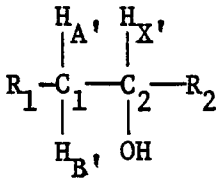


An effort was made to calculate the chemical shifts of $H_A$, $H_B$, and $H_X$,

and to incorporate into these calculations values which would yield information of conformational preferences of the molecule in question. To do this a model compound was selected whose chemical shifts were known. One such set of model compounds were the primary alcohols.



From the known chemical shifts of $H_A$, $H_B$ and $H_X$, an attempt was made to predict what the corresponding values would be in the below molecule where $H_Z$ in the reference compound had been replaced by $R_2$. The predicted results were then compared to the experimental.



$R_2$ was presumed to possibly exert three effects on the original shifts of $H_A$, $H_B$, and $H_X$

1) an "inductive effect" on $H_X$ similar to that found by Shoolery

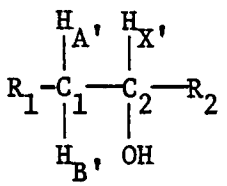
2) a smaller "inductive effect" on $H_A$ and $H_B$, and which in certain cases was assigned the value of zero. Both effects 1) and 2) are independent of conformation about the $C_{1-2}$ bond.

3) A "long-range shielding" of $R_2$ on $H_A$ and $H_B$ and which in keeping with Jackman's, Eliel's, and other findings differ with gauche and anti interactions.

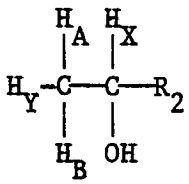
It should be stressed, however that in designating these effects as "inductive" or "long-range shielding" there is nothing in this study that sheds light on their origin, resolves the question as to the

nature of their cause, or the validity of inherent shielding values of various groups. Thus it might well be expected, for example, that what is termed an "inductive effect" may incorporate long-range shielding as well from more remote parts of $R_2$. In the same vein, what is described as a "gauche shielding of tert-butyl", may not be due to the tert-butyl at all, but due to some other cause, and a gauche tert-butyl interaction just happens to be one of several ways of describing the conformation of the molecule. Besides predictions based on the reference molecule given above, two other references have been used with known chemical shifts.

Shifts of of $H_{A'}$, $H_{B'}$, and $H_{X'}$ were predicted for the molecule



using the known values of certain methyl carbinols

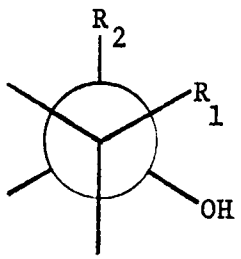


Values similar to those described for $R_2$, are thus assigned to $R_1$ as it is considered replacing $H_Y$ in the reference compound.

Finally shifts of $H_{A'}$, $H_{B'}$, and $H_{X'}$ were predicted from the chemical shifts of ethanol. Here corrections were introduced for the effects of $R_1$ and $R_2$ and were numerically identical to the values of $R_1$ and $R_2$ that had been used in the previous two sets of calculations described above.

It was thus necessary to assign parameters associated with

methyl, tert-butyl, and hydroxyl. Wherever possible, an attempt was made to arrive at these parameters from a consideration of chemical shifts found in the literature. In some cases such data were lacking, and in these instances values were determined from molecules included in this study. The following describes the various effects, their magnitudes, and the method by which they were determined. In determining estimates of chemical shifts, it was assumed that the following conformer does not exist, or exists in percentages small enough to make trivial its inclusion in all calculations.




This assumption is deemed reasonable due to the 2 gauche (alkyl-alkyl and alkyl-hydroxyl) interactions.

1. $R_1 = CH_3 = +0.46$ ppm (added to $\delta H_A$ and $\delta H_B$)

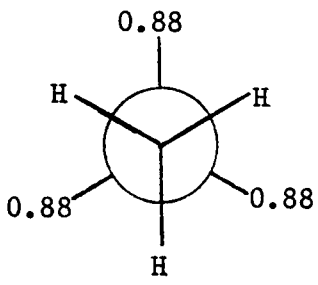
An "inductive effect" on $H_A$ and $H_B$ of +0.46 ppm is observed. No effect is produced at $H_X$. This value is very close to the Shoolery value of +0.47 ppm. The value 0.46 was arrived at as follows: In the sequence of methyl frequencies $CH_4$ = 0.23 ppm, $CH_3CH_3$ = 0.88 ppm and $CH_3CH_2CH_3$ = 1.34 ppm, the introduction of the first methyl produces an effect of +0.65 ppm (0.88-0.23) and the second an effect of +0.46 ppm (1.34-0.88). The second value, which represents the difference

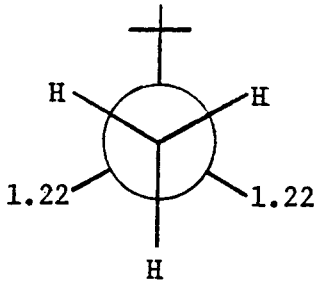
between a monosubstituted and disubstituted molecule was chosen since this was representative of the type of substitution involved in all calculations conducted in this work.

2. $R_1$ = Tert-butyl = +0.36 ppm (added to $\delta H_A$ and $\delta H_B$)

It is noted that upon introduction of a tert-butyl group protons $H_A$ and $H_B$ are shifted to lower fields by +0.36 ppm. No correction has been made for $\delta H_X$. In the Shoolery table no specific value is given for a tert-butyl group other than a generalization that alkyl groups in general give approximately the same shielding parameter, σ eff, and thus would be expected to resemble that of a methyl group.

From the data below for whatever reason or combination of reasons




it would appear that the tert-butyl group produces a downfield shift of approximately 0.12 ppm less than a methyl group (+0.46 ppm). Our own data support this, and it was found that using +0.36 ppm gives better agreement than +0.34 ppm.

3. $R_2$ = Me = +0.41 (added to $\delta H_X$), +0.17 (added to $\delta H_A$ and $\delta H_B$)

The replacement of a hydrogen at $C_2$ by an alkyl group results in

trisubstitution at $C_2$(OH, $R_1CH_2$, $R_2$). Use of Shoolery values in such cases give notoriously unreliable values. Again there are relatively few model compounds which can be used to determine these values without simultaneously introducing the complicating factors of "long range shielding" due to conformational preference. Two such cases are

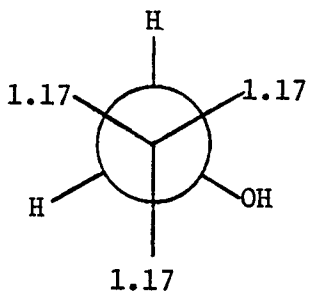
$$\underset{3.47}{\underline{CH_3OH}} \qquad CH_3 \rightarrow \underset{3.58}{\underline{CH_2OH}} \qquad CH_3 = +0.11$$

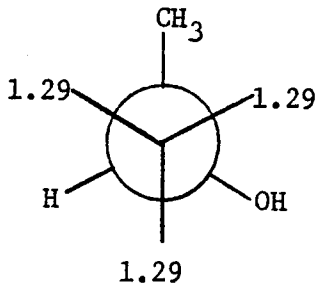
$$CH_3 \rightarrow \underset{3.58}{\underline{CH_2OH}} \qquad CH_3 \rightarrow \underset{\underset{3.99}{\underline{H}}}{\overset{\overset{OH}{|}}{C}} \leftarrow CH_3 \qquad CH_3 = +0.41$$

The lack of agreement in these two values again points out the difference between disubstitution and trisubstition. The latter value (+0.41 ppm) was chosen since this value is obtained in converting a disubstituted to a trisubstituted methane, as all our compounds were, rather than a monosubstituted to disubstituted as in the case of +0.11 ppm.

In addition, a correction of +0.17 ppm was included for hydrogen atoms attached to $C_1$($H_A$ and $H_B$). This value might be attributed to a change in the inductive effect of the hydroxyl group felt at $C_1$ as electron releasing groups are added to $C_2$. Our reason for ascribing this as an inductive effect of the hydroxyl group rather than an inductive effect of the methyl itself is that no corresponding change is noted in the alkanes, nor in the case of the alcohols do we note a corresponding effect at $H_X$ when a methyl group replaces a hydrogen at $C_1$. While it is possible that this interpretation is wrong, the effect at $C_1$ felt equally by all hydrogens attached to this carbon is real.

The necessity for this correction is illustrated by the below two compounds where the value of +0.12 has been modified to +0.17 to achieve a more consistent data set.




4. $R_2$ = tert-butyl = −0.20 (added to $\delta H_X$), −0.06 (added to $\delta H_A$ and $\delta H_B$)

The change of tert-butyl from +0.36 ppm for disubstitution to −0.20 ppm for trisubstitution is again indicative of the magnitude of errors that result if a single shielding parameter is used for mono-, di-, and trisubstituted methanes, and again emphasize the unreliability often encountered in attempting to apply the Shoolery values to estimate proton chemical shifts for molecules of the type CXYZH.

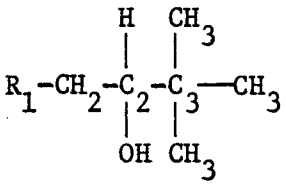
Once more there are a limited number of model compounds which can be used to estimate these effects. To cite two such cases

$\underset{3.47}{CH_3OH}$ tert-butyl → $\underset{3.20}{CH_2OH}$ (tert-butyl) = −0.27 ppm

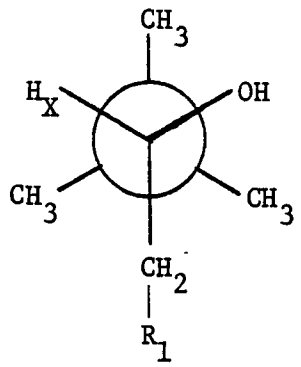
$CH_3 \rightarrow \underset{3.58}{CH_2OH}$ $CH_3 \rightarrow \underset{\underset{3.38}{H}}{\overset{\overset{OH}{|}}{C}} \leftarrow$ tert-butyl (tert-butyl) = −0.20 ppm

Unlike the methyl substituted alcohols these two values are in fair agreement and the latter value was selected (-0.20 ppm) since the final product in this case was a trisubstituted methane.

It is possible that this value (-0.20 ppm) may incorporate two terms: an inductive effect, and a more remote methyl shielding effect. The compounds now under consideration have the general structure

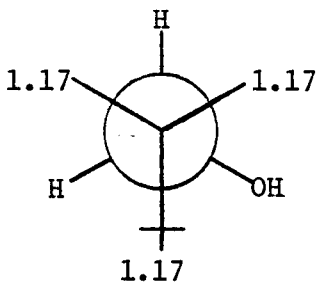


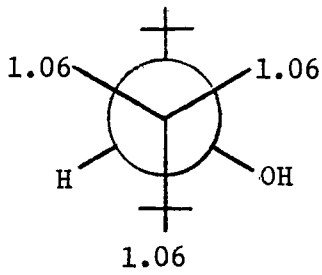
and in a Newman projection, citing along the $C_2$-$C_3$ bond, the following is observed



It could be argued that due to the methyl interactions with $RCH_2$ and the hydroxyl group, rotation is hindered. It was pointed out on page 54 that in the absence of hindered rotation "long-range shielding effects" by methyl groups are apparently not observed.

Finally, as already been noted, tert-butyl substitution at $C_2$ produces an upfield shift on $H_A$ and $H_B$ at $C_1$ of -0.06 ppm. As evidence for this value the following case is cited.



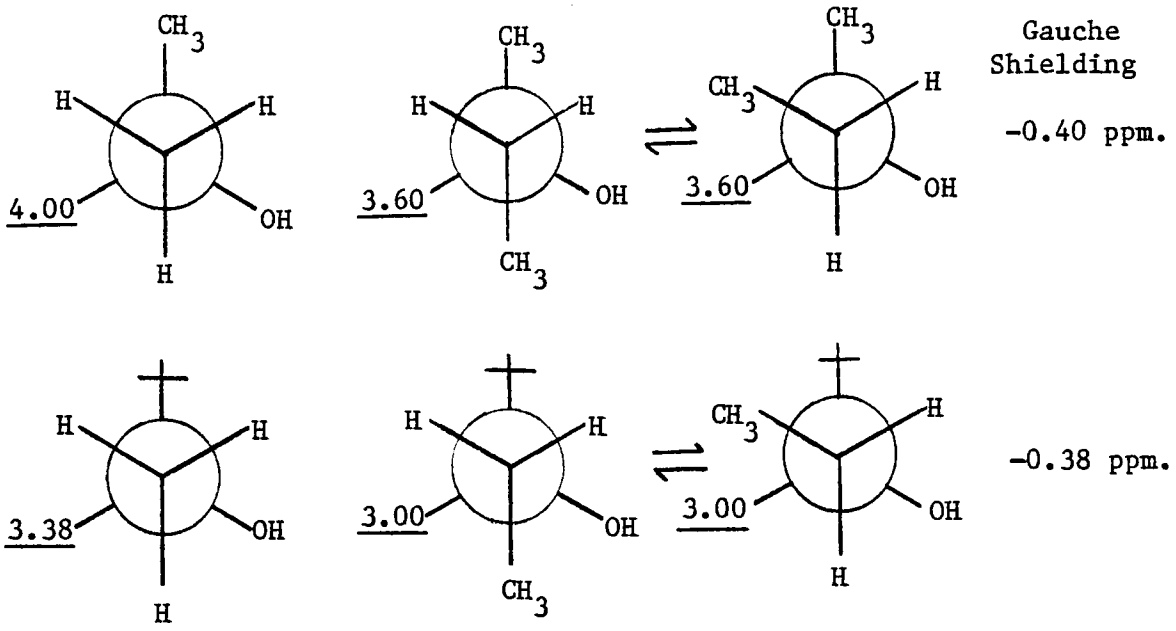

(tert-butyl) = -0.11 ppm.

However, it was found later that a value of -0.06 ppm gives better agreement with our data.

5. $R_1$, $R_2$ = $CH_3$ Gauche = -0.38 ppm (added to $\delta H_A$, $\delta H_B$ and $\delta H_X$), Anti = +0.22 ppm (added to $\delta H_A$)

As has been noted earlier, it would appear that if "inherent" shielding is associated with a methyl group, this type of long range shielding exists only in rigid molecules or those in which there is restricted rotation. Values for this shielding are already present in the literature. Eliel as mentioned previously, determined a value of +0.20 ppm for an anti diaxial interaction in substituted cyclohexanols, and values of -0.47, -0.28 and -0.40 ppm for various gauche-methyl shieldings.

From the following set of model compounds, if one assumes that upon methyl substitution for a hydrogen, an individual conformer or an equilibrium of two conformers result, it is noted that one gauche interaction ($CH_3$-$H_X$) results and the following shielding values are observed

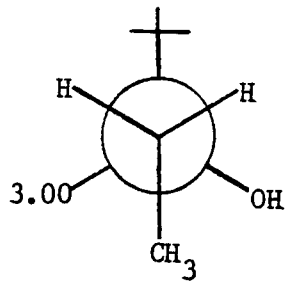


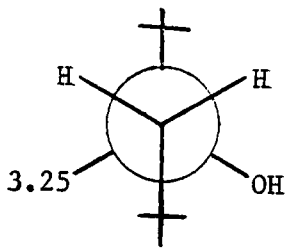

The preceding examples indicate a gauche shielding value of approximately -0.39 ppm. Modification of this value to -0.38 ppm and the anti (deshielding) value to +0.22 ppm gave slightly better results.

6. $R_1$, $R_2$ = tert-butyl Gauche = -0.13 ppm (added to $\delta H_A$, $\delta H_B$ and $\delta H_X$) Anti = Not Used

No clear cases were found in the literature for estimation of this value. Eliel does cite two cases involving a tert-butyl group, wherein one gauche interaction produces a small negative shielding, and in the other a small positive shielding. Our own estimation of this value was made from the following two examples.

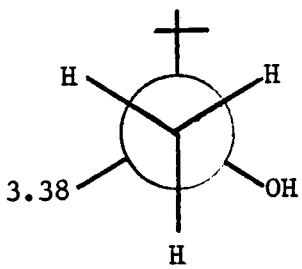
If it is assumed that the following conformers are rigid,

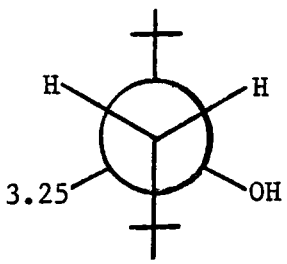



which is supported by the value of the coupling constants $J_{AX}$ and $J_{BX}$, this would suggest that the gauche tert-butyl interaction is 0.25 ppm less in shielding than a methyl group. Since a methyl shielding of -0.38 ppm has already been determined, this leads to a gauche shielding for a tert-butyl group of -0.13 ppm. [-0.38-(-.25)]

One additional example which should be noted is the following,

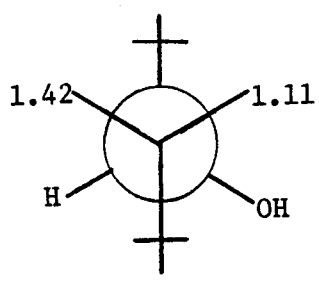


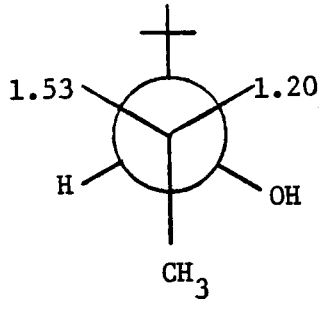




wherein upon addition of a tert-butyl group, a shielding of -0.13 ppm is observed.

7. Hydroxyl Shielding (added to $\delta H_A$, $\delta H_B$) Gauche = -0.17 ppm, Anti = +0.14 ppm

No value of hydroxyl shielding could be found in literature, and the theoretical difficulties of estimating this value are complicated by the supposed dependence of this shielding on the direction and magnitude of the electric dipole associated with the hydroxyl group. It was also noted that cases in the literature were not readily found which would allow estimation of shielding values. It was therefore necessary to use our own data, and then determine which values gave the best result. A striking observation was made on the two molecules below whose widely different coupling constants, $J_{AX}$ and $J_{BX}$, which remained unchanged on dilution suggested the rigid conformations below.




The rather constant difference in the chemical shift of the non-equivalent protons (0.31 and 0.33 ppm) was interpreted as representing the difference in shielding of a proton gauche and anti to a hydroxyl group. The best data fit was then obtained using the values of gauche (-0.17 ppm) and anti (+0.14 ppm).

## H. Calculations

In the following is a summary of parameters used in making chemical shift predictions.

"Inductive" Effects - α

α Me (monosubstituted) = +0.46 ppm

α Me (disubstituted) = +0.41 ppm

α tert-butyl (monosubstituted) = +0.41 ppm

α tert-butyl (disubstituted) = -0.20 ppm

The above values represent "inductive" effects experienced by protons on the substituted carbon.

"Long Range Shielding" Effects - β

β tert-butyl (Gauche) = -0.13 ppm

β tert-butyl (Anti) = Not Used

β Me (Gauche) = -0.38 ppm

β Me (Anti) = +0.22 ppm

β OH (Gauche) = -0.17 ppm

β OH (Anti) = +0.14 ppm

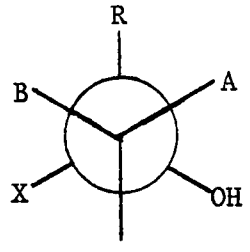
β Me (substitution at $C_2$ - "inductive" at $C_1$) = +0.17 ppm

β tert-butyl (substitution at $C_2$ - "inductive" at $C_1$) = -0.06 ppm

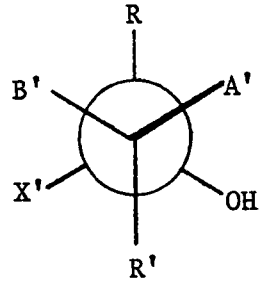
The preceeding parameters are ascribed to "shielding" effects which are felt alpha (vicinal) to the substituted carbon.

### 1. Method I

In the calculations of method I the reference compound is a methyl carbinol of the type




in which there is assumed to be in the reference compound no long range shielding of A and B due to R- or -OH. Calculations are then made for a new compound which is now of the form




All estimates in this and following sections involve comparison against dilute solutions (∿5.0 mole %).

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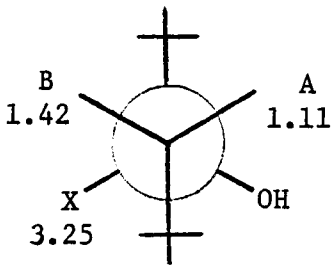
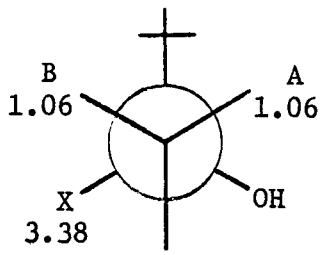



REFERENCE

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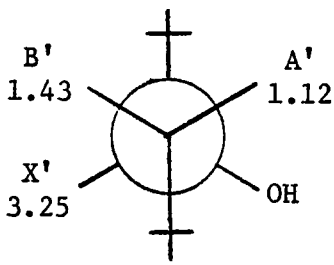


| X | A | B |
|---|---|---|
| 3.38 | 1.06 | 1.06 |
| − .13 | + .36 | + .36 |
| X' = 3.25 | − .13 | − .13 |
| | − .17 | + .14 |
| | A' = 1.12 | 1.43 = B' |

The details of arriving at the predicted values 1.43, 1.12, and 3.25 is given as follows: In predicting a value of A', an initial or reference value must be obtained. In this case a value of 1.06 ppm was used. After substitution of the tert-butyl group on $C_1$ a value of +0.36 ppm is ascribed to an "inductive" effect associated with this group. Additionally, a value of -0.13 ppm is ascribed to the "long range shielding" of the tert-butyl group at $C_2$ which is gauche to $H_A$. Finally, a correction attributed to the gauche hydroxyl of

-0.17 ppm is included. The summation of these values gives a prediction of A' (1.12 ppm). All other predicted chemical shifts in this and subsequent molecules were carried out in a similar manner.

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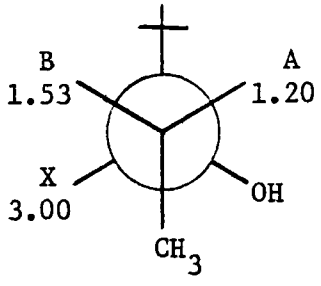


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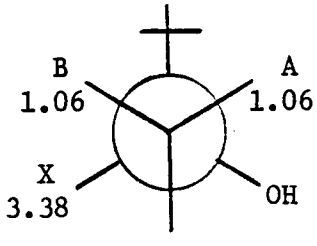
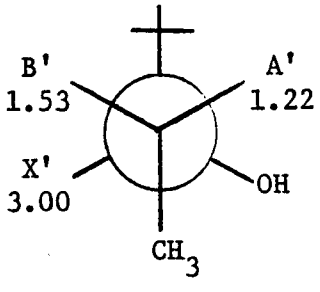
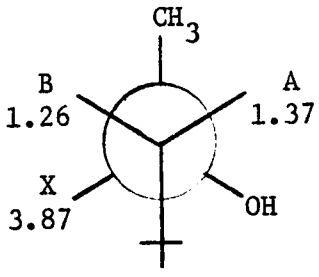



PREDICTED

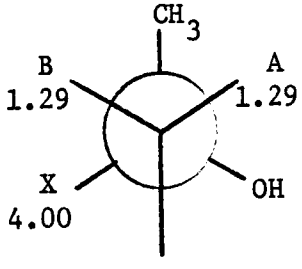



| X | A | B |
|---|---|---|
| 3.38 | 1.06 | 1.06 |
| - .38 | + .46 | + .46 |
| 3.00 | - .13 | - .13 |
| | - .17 | + .14 |
| | A' = 1.22 | 1.53 = B' |

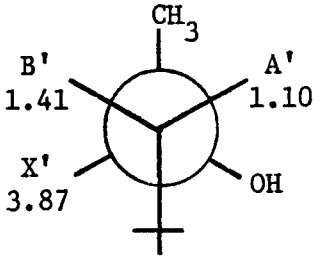
OBSERVED




REFERENCE




PREDICTED

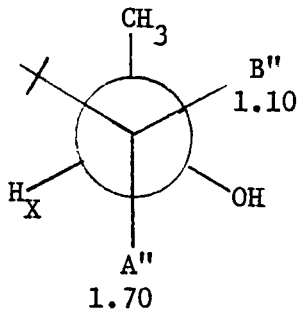



| X | A | B |
|---|---|---|
| 4.00 | 1.29 | 1.29 |
| - .13 | + .36 | + .36 |
| X' = 3.87 | - .38 | - .38 |
| | - .17 | + .14 |
| | A' = 1.10 | B' = 1.41 |

The values predicted here for protons A and B are in very poor agreement with the observed values. This is really as expected since the observed coupling constants do not support the conformer predicted and are suggestive of the possibility of an equilibrium between two conformers. By the same token the value predicted for X, X', would be expected to agree with the observed value, since an equilibrium of conformers would have no effect. This is exactly as observed.

Since the below conformer is the additional conformer existing

in equilibrium,




it should be possible to calculate the chemical shift experienced by a proton anti to the $C_2$ methyl group.

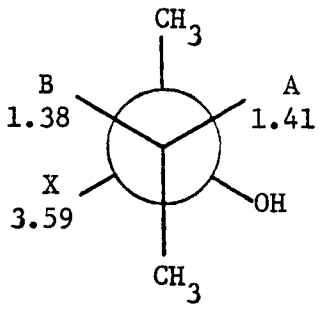
B" = A' = 1.10

and

A" = 1.29 + .36 + .22 − .17 = 1.70

Using the above values for A', B', and A" and B", it is possible to calculate semiquantitatively, the percentage of anti (i.e. anti $CH_3$-tert-butyl) and gauche (i.e. gauche $CH_3$-tert-butyl) conformers. Calculations comparing the observed frequency of proton A (1.37 ppm) with the predicted values of 1.10 ppm and 1.70 ppm for the individual conformer lead to a percentage of gauche conformer of 45% and anti conformer of 55%. Using the observed value of proton B (1.26 ppm) in a similar set of calculations gives values of 48% gauche and 52% anti conformer population. The above percentages, while not in exact agreement, are nevertheless reasonably close.

OBSERVED

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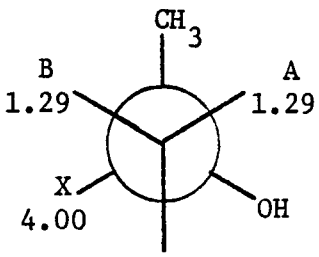
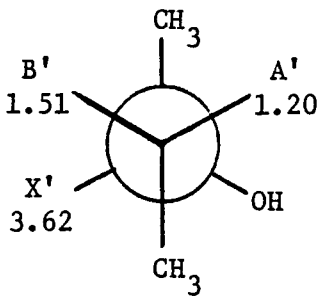
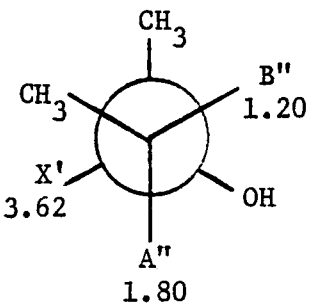



PREDICTED




| X | A | B | A |
|---|---|---|---|
| 4.00 | 1.29 | 1.29 | 1.29 |
| − .38 | + .46 | + .46 | + .46 |
| X' = 3.62 | − .38 | − .38 | + .22 |
| | − .17 | + .14 | − .17 |
| | A' = 1.20 | B' = 1.51 | A" = 1.80 |
| | B" = 1.20 | | |

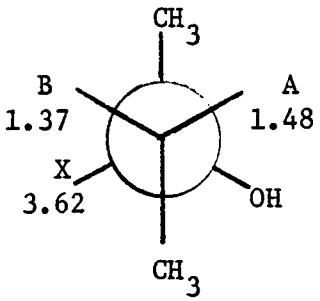



Calculations in which the conformer population is estimated as for the previous molecule by comparing the observed shifts of $H_A$ and $H_B$ with those predicted for the two conformations given yield the following results.

| | Gauche % ($CH_3$-$CH_3$) | Anti % ($CH_3$-$CH_3$) |
|---|---|---|
| A-proton | 35 | 65 |
| B-proton | 40 | 60 |

If the observed data for concentrated solution (∿75 mole %) are also considered, it would be expected that in going from dilute to concentrated the calculations that would reveal the percentage of anti conformer decreases. The following data illustrates this point.

OBSERVED




| | Gauche % ($CH_3$–$CH_3$) | Anti % ($CH_3$–$CH_3$) |
|---|---|---|
| A proton | 47 | 53 |
| B proton | 45 | 55 |

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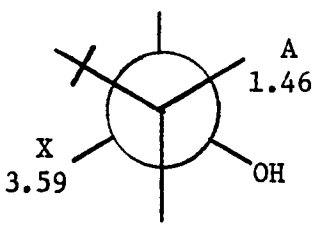
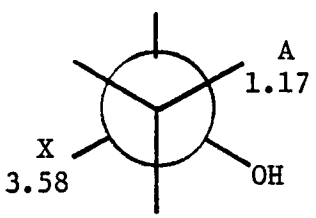
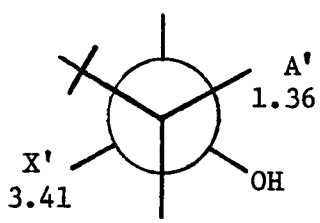
OBSERVED




REFERENCE




PREDICTED

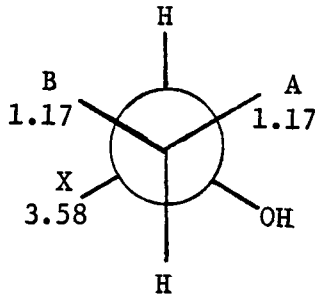



$$A' = \begin{array}{r} A \\ 1.17 \\ +\ .36 \\ -\ .17 \\ \hline 1.36 \end{array} \qquad \begin{array}{r} 3.58 \\ -\ .17 \\ \hline 3.41 = X' \end{array}$$

It is noted that the predicted values are quite poor. It was assumed that a somewhat rigid conformer existed due to the tert-butyl group. If no "inherent" shielding is attributed to the hydroxyl and tert-butyl groups, the following values arise, $A' = 1.53$ and $X' = 3.58$. These values, in much better agreement with the observed values, casts additional doubt on the concept of "inherent" shielding. This discovery, that apparently there is no intrinsic long-range shielding in symmetrical molecules even though they show strong conformational preference, is the single most significant outcome of these calculations.

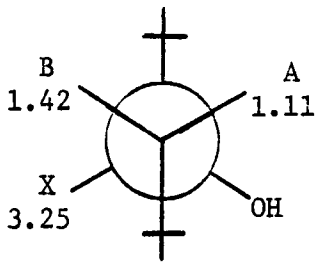
2. Method II

In this method, ethanol was used as reference.




This led to the following predicted chemical shifts.

OBSERVED

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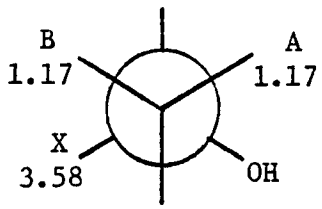


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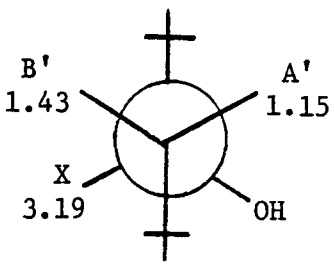


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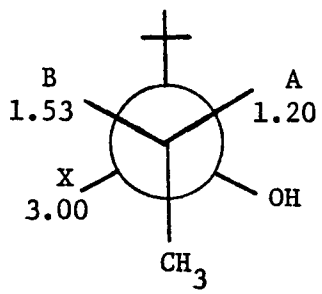


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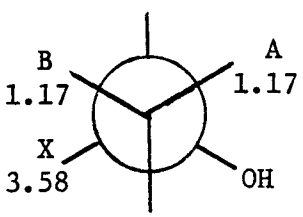


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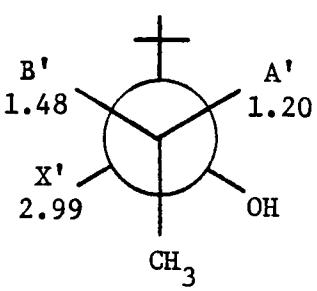

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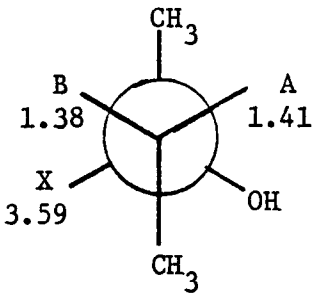


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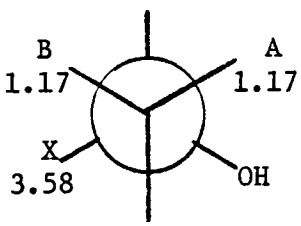


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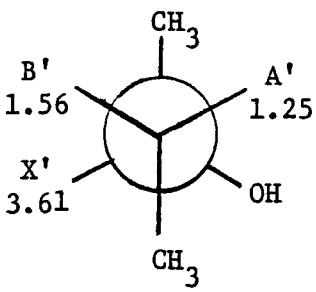
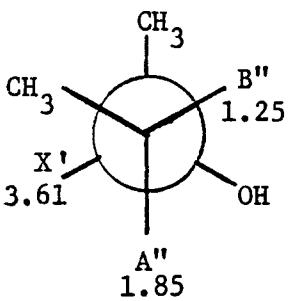
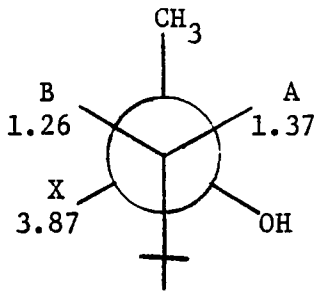


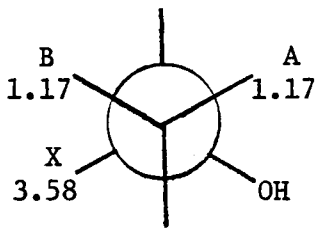




| | Gauche % ($CH_3$–$CH_3$) | Anti % ($CH_3$–$CH_3$) |
|---|---|---|
| A proton | 27 | 73 |
| B proton | 58 | 42 |

OBSERVED




REFERENCE

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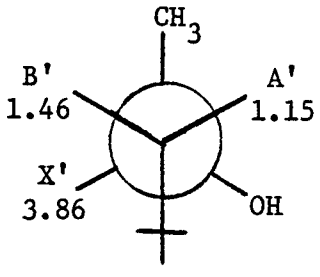
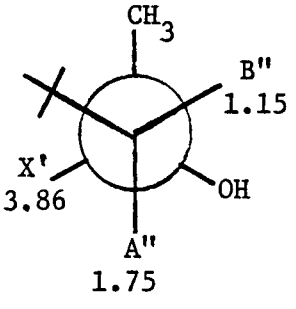
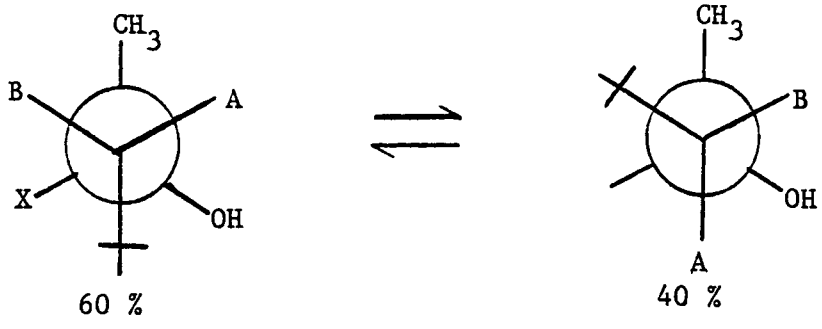



| | Gauche % ($CH_3$-<u>tert</u>-butyl) | Anti % ($CH_3$-<u>tert</u>-butyl) |
|---|---|---|
| A proton | 37 | 63 |
| B proton | 64 | 36 |

The last two sets of calculations (percentages) are not in particularly good quantitative agreement. It should be noted that small errors in chemical shift values lead to very large changes in calculations of conformer populations. This is illustrated by the following. If it is assumed that the population is 40% gauche and 60% anti, the below results are obtained.

PREDICTED

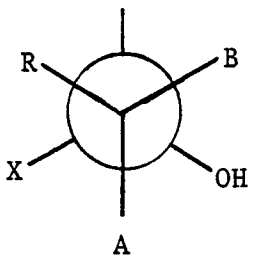



| Calculated | Error |
|---|---|
| A = 1.34 | -0.03 ppm |
| B = 1.28 | +0.02 ppm |
| X = 3.87 | +0.00 ppm |

Though the difference in the errors associated with protons A and B between calculated and observed are -0.03 and +0.02 ppm. respectively and thus quite small, these percentages (60%, 40%) are markedly different from those determined previously using the observed frequencies of $H_A$ and $H_B$ as the basis of calculation.

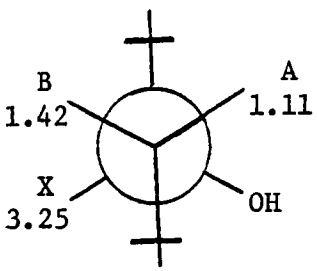
3. Method III

Calculations of predicted chemical shifts were made using the below compound.




It was also assumed that the values for A, B and X in the reference compound include no contribution due to long range shielding of the hydroxyl groups on A and B or the R group on X.

OBSERVED

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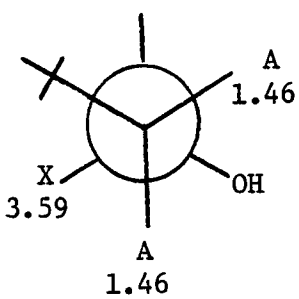


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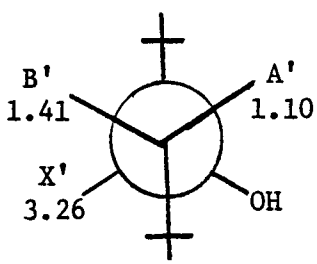

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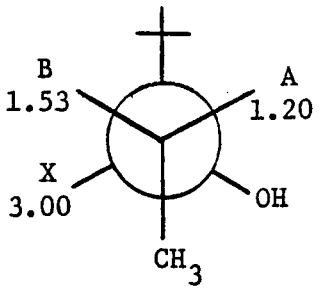


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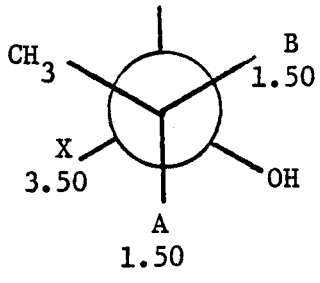
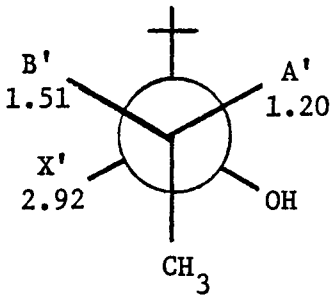



PREDICTED



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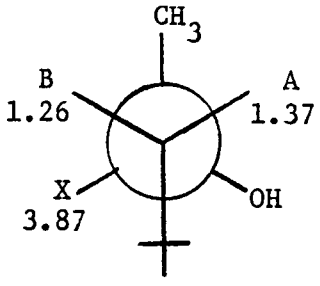


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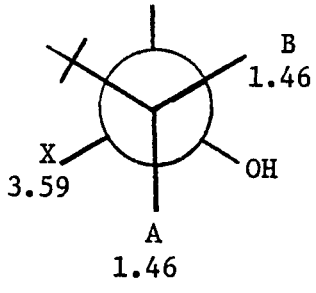


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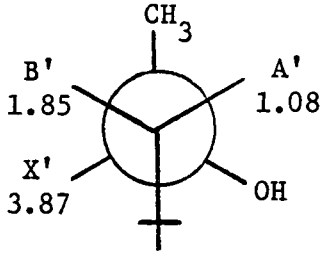
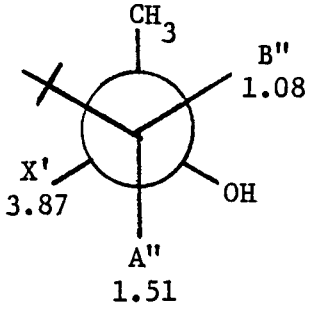
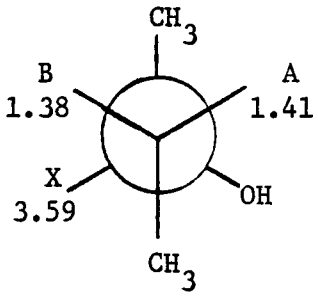



| | Gauche % ($CH_3$-<u>tert</u>-butyl) | Anti % ($CH_3$-<u>tert</u>-butyl) |
|---|---|---|
| A-proton | 67 | 33 |
| B-proton | 77 | 23 |

OBSERVED

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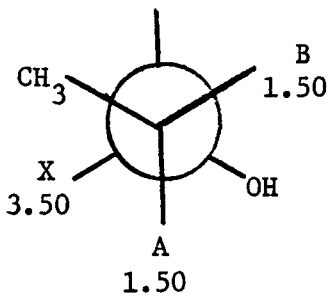
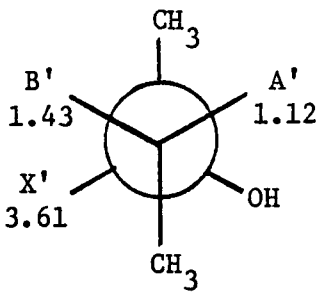
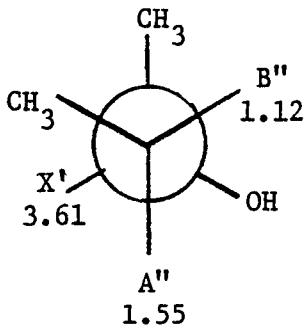



PREDICTED



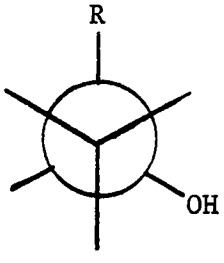




| | Gauche % ($CH_3$-$CH_3$) | Anti % ($CH_3$-$CH_3$) |
|---|---|---|
| A-proton | 67 | 33 |
| B-proton | 16 | 84 |

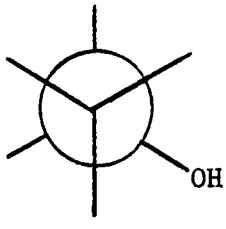
4. Summary of Values

Three methods were used in calculation of predicted shifts. A summary of the three methods used are shown below where the structure of the reference compound is given.

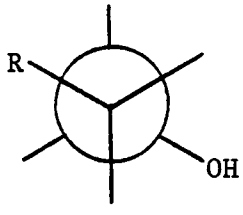
Method I




Method II




Method III




The following is a listing of predicted values from each method, and the actual observed values.

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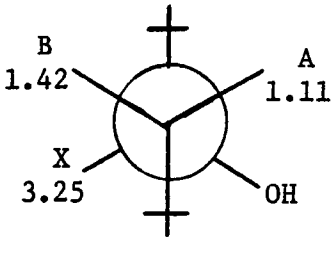


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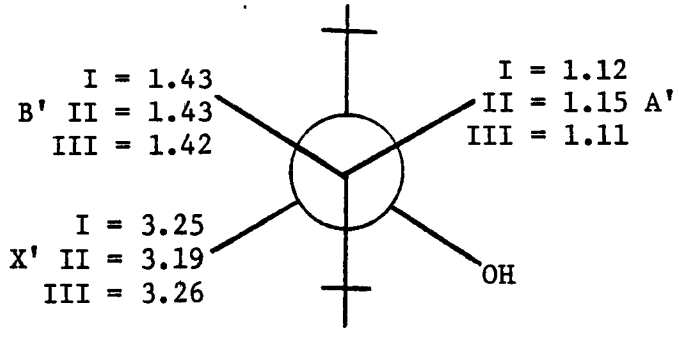

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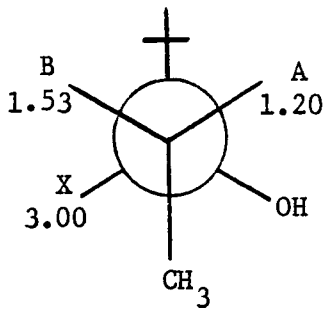


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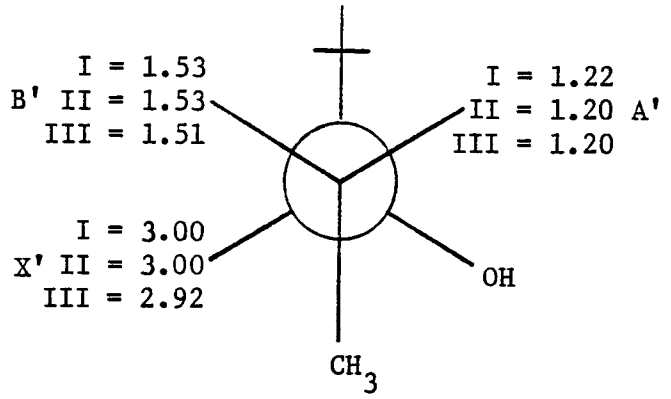


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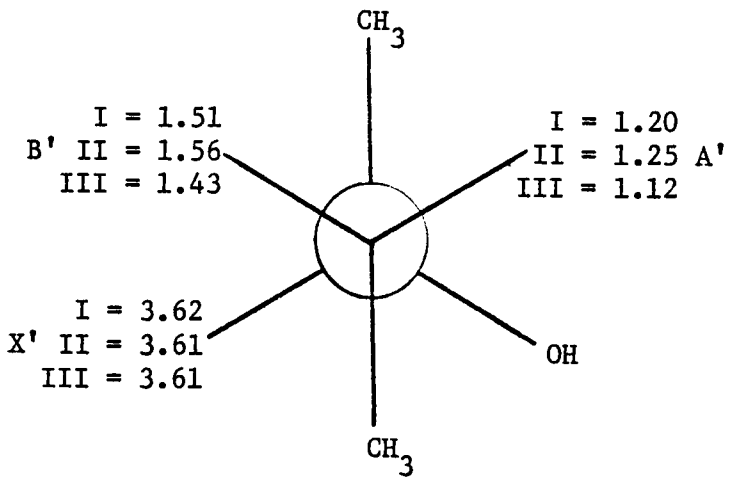


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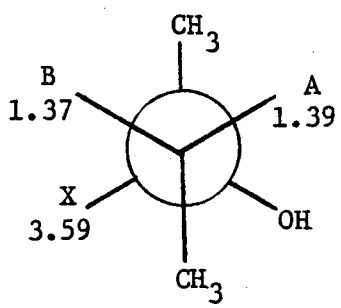


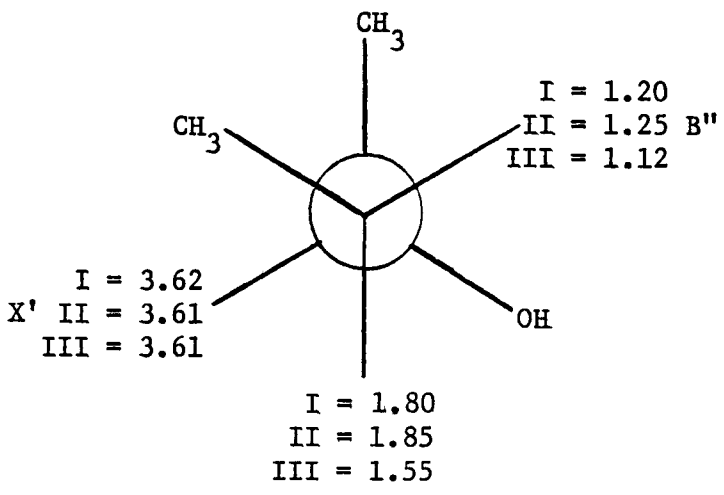

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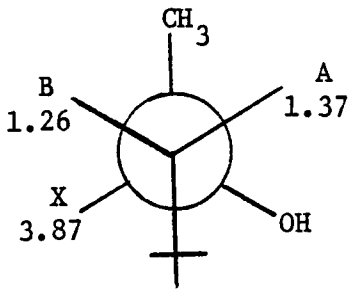


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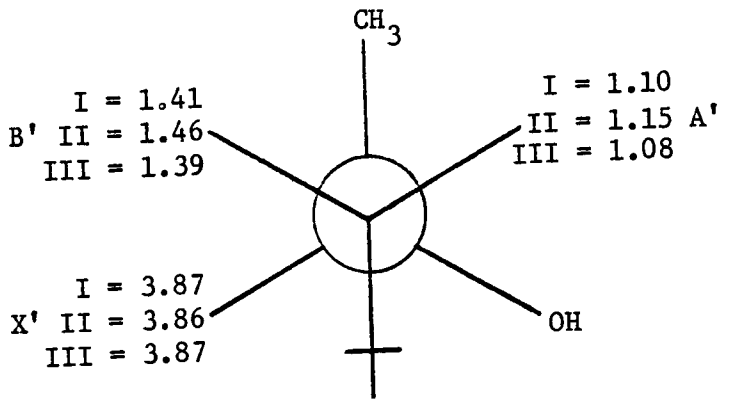


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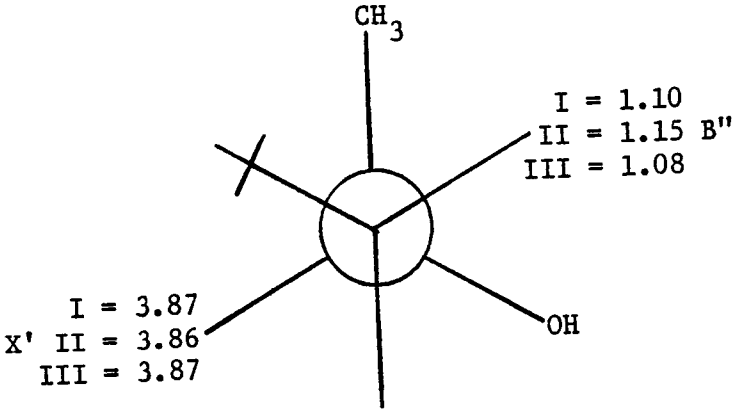
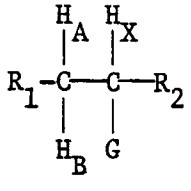



A"

## I. Comments

Over 50 chemical shifts using three different types of model compounds were calculated. Intercomparing calculated with observed values, in those compounds in which coupling constants are indicative of a rigid conformer, the average deviation is better than ±0.02 ppm. In molecules where an equilibrium of conformers is suspected to exist from a consideration of the variance of the vicinal coupling constants $J_{AX}$ and $J_{BX}$, it is impossible to ascertain the accuracy of the values determined since this would be a function of the conformer populations which is an unknown quantity. However, the precision of the values determined is quite good.

It is also believed that the shielding parameters chosen for $R_1$ and $R_2$ apply only to the system,




where G = OH

It is suspected that if G were some other atom, or group of atoms, the same values of shielding parameters used in this study would not necessarily apply. Since studies which might support this premise have not been made, the certainty of this point can only be speculated on at present.

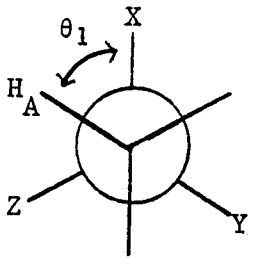
Many of the values used in this study bear a striking resemblance to those of Eliel's. It is believed this was at least partly the result of a structural similarity between the two systems. It is reasonable to suppose that $R_1$ and $R_2$ may be extended to groups other than methyl and tert-butyl and still allow prediction of chemical shifts,

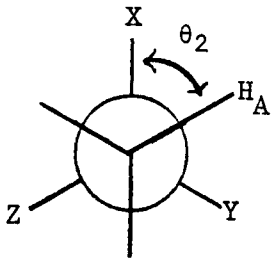
and in certain cases, semi-quantitative estimates of conformer populations. Eliel's compounds would then be examples where $R_1$ and $R_2$ were the cyclohexyl ring itself.

It would be remiss at this point not to discuss a possible source of errors and a number of assumptions involved in making the calculations of predicted chemical shifts. Poor agreement between observed and calculated results may be a consequence of numerical errors of the shielding values used rather than an error in principle of handling the data. On the other hand agreement may be open to other interpretations than the assumptions made.

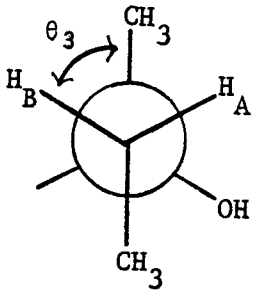
First, in making estimates of shielding parameters it has been necessary to rely on spectral parameters found in literature. Various spectral catalogues have been used (Varian, Sadtler and API) as well as the original literature itself. It has been attempted, wherever possible, to use the most recent values determined in dilute carbon tetrachloride, run at the highest oscillator frequency possible. In many cases such data were not available. To indicate the difficulty and magnitude of error that might be introduced using literature values, the following example is cited. On examination of the $C_1$ protons of the very simple and common molecule 1-propanol, values of 3.58, 3.50 and 3.41 ppm are noted in Varian, Sadtler and API catalogues respectively.

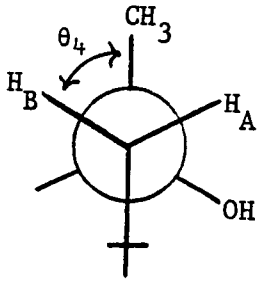
Secondly, it was assumed that in the structure below, shieldings are additive and that $H_A$ for example is equally shielded by X in the below conformers.




If it is imagined that there is an inherent and constant shielding at the site of the methyl group, then implicit in this assumption is that not only must $\theta_1 = \theta_2$, but indeed in all cases must equal 60°. Thus for example, it must be assumed that the shielding by methyl on $H_A$ and $H_B$ was identical in both conformers below and furthermore that $\theta_3 = \theta_4 = 60°$.




One would more reasonably suppose that both $\theta_3$ and $\theta_4 < 60°$ and furthermore that $\theta_4 < \theta_3$ due to the nature of the variation of alkyl interactions with the hydroxyl group. As has already been mentioned,

whatever the origin of the long range shielding of the methyl group, it is expected to follow the same general behavior as predicted by the McConnell equation, thus it should vary with the angle, $\alpha$, and the distance, r. Since both of these change as $\theta$ changes, it would appear to be unreasonable to suppose that in all compounds the various groups such as methyl shield all gauche protons or deshield all anti protons equally.

# CHAPTER V

## CONCLUSION

At this time certain conclusions based on the findings of this research and which have been touched on previously should be re-emphasized. Initially, an examination of certain alkyl-alkyl and alkyl-hydroxyl steric interactions was made. Through correlation of vicinal coupling constants and hydroxyl group resonance frequencies, a definite hierarchy regarding the relative importance of various alkyl-alkyl and alkyl-hydroxyl interactions was found. These results allow predictions not only as to preferred conformations in certain molecules, but also the extent to which such molecules might be expected to participate in intermolecular hydrogen bonding, since the ability to hydrogen bond has been demonstrated to be related to the magnitude of gauche hydroxyl interactions and the ability of the molecule to adopt conformations which minimize this interaction.

Additionally, the results of this study regarding the aspects of shielding seem to cast doubts concerning an "inherent" shielding associated with any group such as tert-butyl or methyl. This would appear to be true regardless of the origin (e.g., single bond anisotropies) of the shielding. In attempting to make chemical shift predictions for our compounds using alcohols of type $RCH_2CH_2OH$ as reference, it was noted that inclusion of shielding values (on $H_A$, $H_B$ and $H_X$) with respect to the substituted groups (methyl, tert-butyl, and hydroxyl) already present in the reference compound caused the predicted chemical shift values to be in quite poor agreement with those

observed. However if no inherent shielding due to the aforementioned groups is assumed for the reference compound itself, it was noted that the agreement between observed and predicted chemical shifts was quite good. Thus it is concluded that inherent "long range shielding" parameters which vary with gauche and anti interactions, and which have been used to account for geminal magnetic nonequivalence are not manifested in symmetrical molecules, and arise only when there is assymetry associated with the molecule itself. This cast doubts on previous explanations as to the origin of such nonequivalence and the concept of inherent shieldings associated with various groups.

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# VITA

Duane Allen Hall was born in Albuquerque, New Mexico on November 27, 1953. In 1963, he moved to Cleveland, Tennessee, from Atlanta, Georgia. After graduating from Cleveland High School in 1971, he attended Lee College. In 1975, upon receiving a B.A. in Chemistry, he accepted an instructing position from the United States Tennis Association for the city of Athens, Tennessee. In the fall of 1975 he enrolled in the Graduate School of the University of Tennessee. He held a teaching assistantship from September of 1975 to June, 1979. Upon obtaining his Master of Science degree in Chemistry in December of 1979, he accepted a position with Texaco.