

# Conformational Analysis by Nuclear Magnetic Resonance. Shift Reagent Studies on Acyclic Alcohols. $^1\text{H}$ and $^{13}\text{C}$ Spectra of the Six-Carbon Aliphatic Alcohols

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**Abstract:** The proton spectra of all 18 possible six-carbon aliphatic alcohols have been examined with ten increasing concentrations of  $\text{Eu}(\text{dpm})_3$  and the  $^{13}\text{C}$  spectra examined with four increasing concentrations of  $\text{Yb}(\text{dpm})_3$ . Utilizing the McConnell–Robertson equation, the average solution conformations of these alcohols in  $\text{CS}_2$  have been determined by both methods of spectroscopy and have been found to be the same. Experimentally, the use of  $\text{Yb}(\text{dpm})_3$  and  $^{13}\text{C}$  spectroscopy has several advantages. The problem of distortion of the substrate by the shift reagent is considered in detail. The many pitfalls of this type of analysis are discussed. A linear regression analysis of the  $^{13}\text{C}$  chemical shifts of the 95 nonequivalent resonances in the 18 alcohols has been performed. Large correction factors in the  $^{13}\text{C}$  shifts are indicated for adjacent tertiary and quaternary carbons. Comparisons are made between the  $^{13}\text{C}$  chemical shifts of these alcohols and conformationally similar fragments of cyclohexanols. The  $^{13}\text{C}$  shifts of diastereotopic methyl groups are considered in detail.

Methods for the determination of conformations of acyclic molecules in solution are relatively few in number. Where cyclic compounds, especially cyclohexane derivatives, have received much attention the acyclic compounds have, by comparison, been neglected. Since Hinckley's discovery of lanthanide induced shifts (LIS) of nmr spectra<sup>2</sup> it has become abundantly clear that careful analysis of LIS data with the aid of the McConnell–Robertson equation<sup>3</sup> holds great promise for conformational analysis. It is also clear from the multitude of reports appearing in the last 2 years, that there are many pitfalls to be avoided in this analysis.

The object of the work reported here is to compare the results of an LIS study on a large group of closely related molecules using both proton and carbon-13 spectroscopy and two different shift reagents: tris(dipivaloylmethanato)europium(III) ( $\text{Eu}(\text{dpm})_3$ ) (for protons) and tris(dipivaloylmethanato)ytterbium(III) ( $\text{Yb}(\text{dpm})_3$ ) (for C-13). We have chosen to examine all of the 18 possible isomers of the saturated six-carbon alcohols. These alcohols are simple enough to be amenable to complete, unambiguous analysis of their proton and C-13 spectra yet complex enough to afford a wide variety of conformational situations involving eight primary, eight secondary, and two tertiary alcohols. It should be emphasized at the outset that the "conformations" calculated for these molecules are the weighted-average geometries of these substrates interacting with lanthanide shift reagents and that they do not necessarily represent the weighted-average conformations of the free substrates. In fact one of the questions to which we have directed our attention is: to what extent does interaction of the substrate with different shift reagents change the geometry of the substrate and/or the position of the equilibrium between two conformations of nearly equal energy?

We also sought to compare the two different approaches (proton spectroscopy using  $\text{Eu}(\text{dpm})_3$  and  $^{13}\text{C}$  spectroscopy using  $\text{Yb}(\text{dpm})_3$ ) to the same problem in terms of accuracy of data obtained, ease of data acquisition, and ease of analysis of results.

## Experimental Section

**Proton spectra** were run on a Varian T-60 nmr spectrometer at ambient temperature. Samples were made up at an alcohol concentration of 0.4 M in 0.5 ml of carbon disulfide containing 4% tetramethylsilane (TMS). The solvent containing TMS was stored over molecular sieves. Except where noted each alcohol was run alone and then in solution with nine increasing incremental concentrations of  $\text{Eu}(\text{dpm})_3$  in the range 0.0008–0.4 M.  $\text{Eu}(\text{dpm})_3$  was added in small increments to the alcohol sample. Lack of  $\text{Eu}(\text{dpm})_3$  solubility with solutions of three alcohols permitted only six different  $\text{Eu}(\text{dpm})_3$  concentrations for 1-hexanol and eight for 2,3-dimethyl-1-butanol and 3,3-dimethyl-1-butanol.

Spectra were obtained over the entire proton chemical shift range by adjustment of the Coarse Sweep Zero Control which was calibrated by the audio side-band method. The accuracy of the chemical shift measurement depended on the multiplet structure of the lines being measured.

**Carbon-13 spectra** were obtained on a Varian HA-100–Digilab NMR-3 pulsed Fourier transform nmr spectrometer in 5-mm sample tubes containing 1.2 mm diameter coaxial capillaries filled with hexafluorobenzene. Samples were made up at an alcohol concentration of 1.0 M in carbon disulfide containing 10% TMS. The solvent containing TMS was stored over molecular sieves. All alcohols were run alone and with four increasing concentrations of  $\text{Yb}(\text{dpm})_3$  in the range 0.05–0.12 M. Separate samples were prepared for each concentration of shift reagent, unlike the proton samples above.

Each spectrum was noise decoupled at 100 MHz to eliminate  $^{13}\text{C}$ – $^1\text{H}$  coupling. Since the Varian V-3512A decoupler does not provide sufficient power over the entire range of proton frequencies encountered with shift reagent present, it was necessary to run two  $^{13}\text{C}$  spectra at each  $\text{Yb}(\text{dpm})_3$  concentration in order to obtain sharp  $^{13}\text{C}$  resonances.

Spectra were collected with a 1-sec repetition rate, a pulse width of 42.5  $\mu\text{sec}$  (corresponding to a 90° flip of the nuclear magnetization) and a high spinning speed. Between 1000 and 6000 pulses (depending on  $\text{Yb}(\text{dpm})_3$  concentration) were taken to obtain good spectra.

Chemical shifts were measured relative to TMS or occasionally to carbon disulfide, which has a shift of 192.360 ppm downfield from TMS (a value found to be independent of  $\text{Yb}(\text{dpm})_3$  concentration). Chemical shifts for all lines are accurate to  $\pm 0.054$  ppm.

(1) Petroleum Research Fund Scholars and NSF Undergraduate Research Participants.

(2) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969).

(3) H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, **29**, 1361 (1958).

Alcohols were obtained from the Chemical Samples Co., are said to be 98–99% pure, and came sealed in 2-ml ampoules under argon.  $^{13}\text{C}$  and  $^1\text{H}$  spectra did not reveal any extra peaks which might have come from impurities. Compounds **8** and **9** are a mixture of erythro and threo isomers.

Shift reagents were synthesized according to modifications of the procedure of Eisentraut and Sievers.<sup>4</sup>  $\text{Eu}(\text{dpm})_3$  was prepared in 63% yield and after vacuum sublimation had mp 183–188°.  $\text{Yb}(\text{dpm})_3$  was prepared in similar yield and had mp 165–165.5° after sublimation. The reagents were stored in a desiccator over phosphorus pentoxide. From time to time the reagents were resublimed with no noticeable effect on appearance or properties.

**Analysis of Spectra and Treatment of Data.** Proton chemical shifts for each peak relative to internal TMS were measured at each concentration of  $\text{Eu}(\text{dpm})_3$ . Measurements were made only when peaks could be clearly distinguished; thus for some peaks of particular alcohols measurements at only five concentrations were possible. Measurements are considered to be accurate to  $\pm 1.0$  Hz in most cases.

A plot of chemical shifts downfield from TMS vs. the mole ratio of shift reagent to alcohol was made for each proton or group of equivalent protons. From the slope and intercept of the least-squares line through these experimental points the chemical shift at zero shift reagent concentration and at a 1:1 mole ratio of shift reagent to alcohol were determined giving  $\Delta H_i/H$ , the total shift induced at a 1:1 mole ratio. Peak assignments were made by integration and extensive double resonance experiments. An oxygen–europium distance of 3.0 Å and a carbon–oxygen–europium bond angle of 130° were assumed.

A manual search was then made, using Dreiding models rendered semirigid by crimping, for conformations for which the europium–hydrogen internuclear distances when plotted against the corresponding  $\Delta H_i/H$  values on full logarithmic coordinates, gave a straight line with a slope reasonably close to  $-3$  and a correlation coefficient of 0.950 or better. This served as an efficient and rapid screening technique for conformations for which the strongly influential inverse  $r^{-3}$  relationship holds.

Again, using just Dreiding models and a ruler, measurements of the oxygen–hydrogen distances for all conformations passing the above screening were made. Knowing the europium–proton distance, the oxygen–proton distance and the europium–oxygen distance (1.30 Å in all cases), and applying the law of cosines give the oxygen–europium–hydrogen angle,  $\theta_i$ , which then allows calculation of the complete geometric term  $(3 \cos^2/\theta_i - 1)r_i^{-3}$ . The geometric parameters for methyl groups were determined by measurement of  $r$  and  $\theta$  values for each proton, the methyl protons being staggered with respect to adjacent atoms. The term  $(3 \cos^2 \theta_i - 1)r_i^{-3}$  for each methyl proton was then calculated and the three values obtained for the methyl protons then arithmetically averaged.

Usually six or seven trial conformations that met the first screening test were calculated. The conformation giving the best correlation coefficient for the plot of  $\Delta H_i/\Delta H$  vs.  $(3 \cos^2 \theta_i - 1)r_i^{-3}$  is reported.

To reduce the possibility for error in the measurement of internuclear distances the Modelbuilder<sup>5</sup> computer program was used to calculate the  $X$ ,  $Y$ , and  $Z$  coordinates for all atoms in a given conformation, and then  $r_i$  and  $\theta_i$ . The program accepts as input bond angles, bond lengths, and dihedral angles. Tetrahedral angles for all carbons and bond distances of 1.541 Å for C–C, 1.43 Å for C–O, and 1.091 Å for C–H bonds were assumed.

Carbon-13 peaks were assigned to particular atoms by use of the procedure of Grant and Paul<sup>6</sup> using parameters for alcohols determined by Roberts, *et al.*,<sup>7</sup> by relative peak intensities, by off-resonance decoupling, by selective heteronuclear decoupling, by the change in chemical shifts of the carbons induced by the lanthanide as a function of distance, or by calculation of the geometric factor when this difference did not make the assignment obvious. Chemical shifts of carbon peaks are reported in ppm downfield from in-

ternal TMS and are accurate to  $\pm 0.054$  ppm. The error in the molar ratios is estimated to be  $\pm 0.0004$ .

The ratio of shift reagent to alcohol did not exceed 0.12. The slope of the least-squares line through these four values was extrapolated to a ratio of 0.5. The standard deviation on the slope of the  $\Delta H_i/H$  vs. shift reagent/alcohol ratio plots varied from 0.85 to 1.25, employing chemical shift errors of 0.054 ppm for the 18 alcohols. Only the four points representing shift reagent to alcohol ratios of 0.008–0.12 were used; at lower values of this ratio the plot deviated from linearity, presumably due to very small quantities of water competing for the shift reagent.

## Results and Discussion

The best weighted average conformations for each of the 18 alcohols are given in Figure 1.<sup>8</sup> Correlation coefficients are reported in Table IV. Within the limits

Table IV. Correlations between Lanthanide Induced Shifts and Geometric Factors for the Six-Carbon Alcohols

| Alcohol                         | Correlation coefficients |                          |
|---------------------------------|--------------------------|--------------------------|
|                                 | Proton data <sup>a</sup> | Carbon data <sup>b</sup> |
| 1-Hexanol (1)                   | 0.991                    | 0.999                    |
| 2-Hexanol (2)                   | 0.993                    | 0.9995                   |
| 3-Hexanol (3)                   | 0.979                    | 0.9974                   |
| 2-Methyl-1-pentanol (4)         | 0.979                    | 0.9992                   |
| 3-Methyl-1-pentanol (5)         | 0.986                    | 0.9994                   |
| 4-Methyl-1-pentanol (6)         | 0.986                    | 0.9991                   |
| 2-Methyl-2-pentanol (7)         | 0.932                    | 0.9971                   |
| erythro-3-Methyl-2-pentanol (8) | 0.9654                   | 0.9993                   |
| threo-3-Methyl-2-pentanol (9)   | 0.9731                   | 0.9969                   |
| 4-Methyl-2-pentanol (10)        | 0.9969                   | 0.9990                   |
| 2-Methyl-3-pentanol (11)        | 0.9664                   | 0.9974                   |
| 3-Methyl-3-pentanol (12)        | 0.9980                   | 0.9975                   |
| 2-Ethyl-1-butanol (13)          | 0.973                    | 0.9975                   |
| 2,2-Dimethyl-1-butanol (14)     | 0.980                    | 0.9880                   |
| 2,3-Dimethyl-1-butanol (15)     | 0.985                    | 0.9987                   |
| 3,3-Dimethyl-1-butanol (16)     | 1.00                     | 0.9997                   |
| 2,3-Dimethyl-2-butanol (17)     | 0.973                    | 0.9998                   |
| 3,3-Dimethyl-2-butanol (18)     | 1.00                     | 0.9960                   |

<sup>a</sup> Correlation coefficients between  $\Delta H_i/\Delta H$  and  $3(\cos^2 \theta_i - 1)r_i^{-3}$  using proton chemical shift data.<sup>8</sup> <sup>b</sup> Correlation coefficients between  $\Delta H_i/\Delta H$  and  $3(\cos^2 \theta_i - 1)r_i^{-3}$  using carbon chemical shift data.<sup>8</sup>

of our analysis the conformations derived from proton spectroscopy using  $\text{Eu}(\text{dpm})_3$  and the conformations derived from  $^{13}\text{C}$  spectroscopy using  $\text{Yb}(\text{dpm})_3$  are the same; in no case could we find one conformation which fit the proton data and a substantially different conformation which fit the carbon data (as judged by high correlation coefficients). The correlation coefficients from  $^{13}\text{C}$  spectroscopy are consistently better than those from the proton data. At low shift reagent concentrations overlapping patterns of lines make accurate chemical shift measurements of proton data difficult. At high shift reagent concentrations line broadening leads to some lack of precision. It would require much effort to improve this situation involving the use of a high field spectrometer and some partial numerical analysis of spectra. By contrast the noise-decoupled carbon spectra are single sharp lines not significantly broadened by Yb. Chemical shift measurements at all shift reagent concentrations are equally accurate and, in our Fourier transform system, calculated by an unbiased computer. Furthermore the

(8) Tables I–III can be found in the microfilm edition of this journal; see paragraph at end of paper regarding supplementary material which defines these conformations and gives the experimental data from which these conformations were derived.

(4) K. J. Eisentraut and R. E. Sievers, *J. Amer. Chem. Soc.*, **87**, 5254 (1965).

(5) M. S. Gordon, Modelbuilder (MBLD), Program #135, Quantum Chemistry Program Exchange, Indiana University, Bloomington, Ind.

(6) D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, **86**, 2984 (1964).

(7) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, **92**, 1338 (1970).

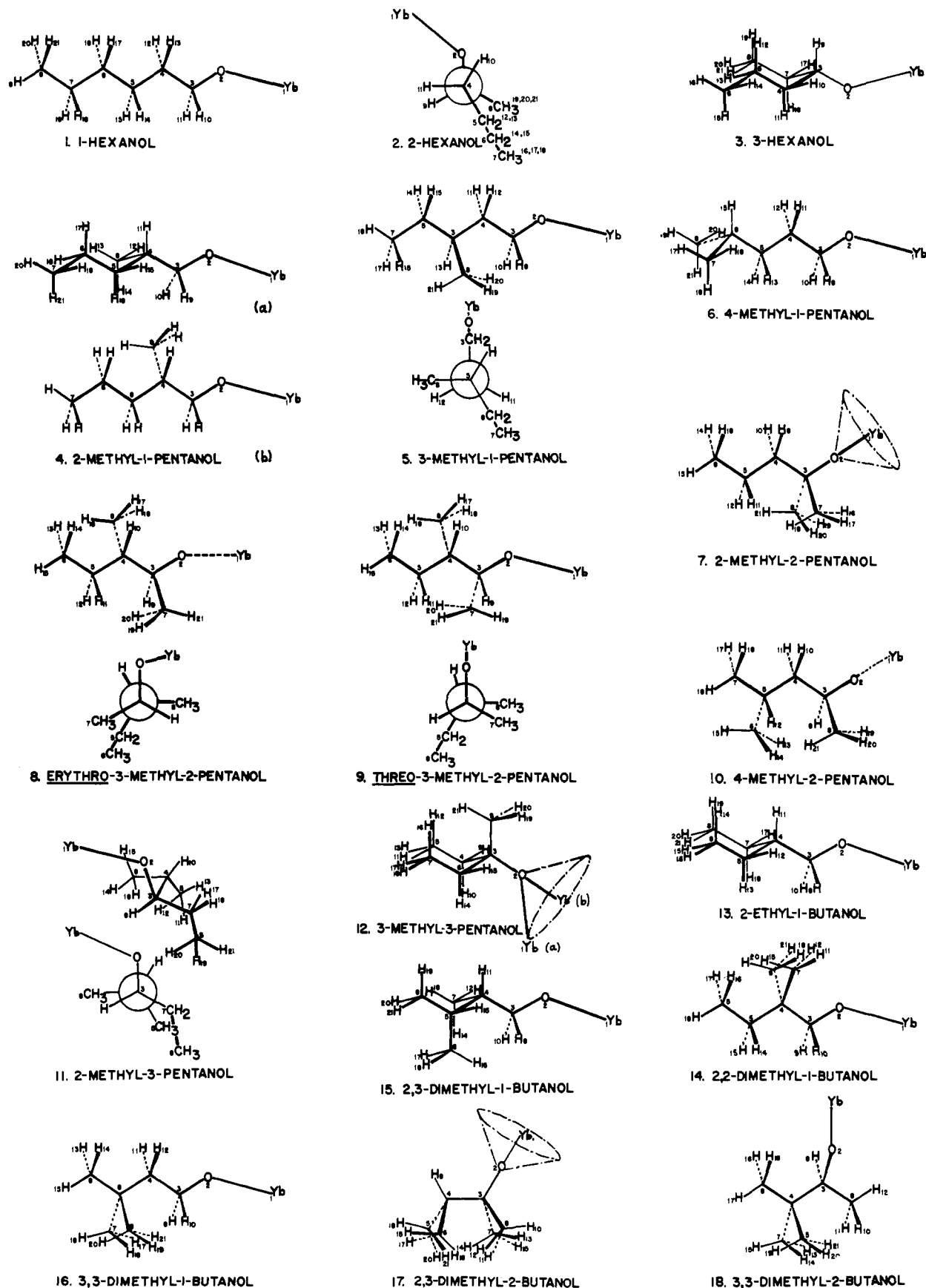


Figure 1. Average solution conformations for the six-carbon alcohols. Although Yb(dpm)<sub>3</sub> is the lanthanide shown these conformations are exactly the same for Eu(dpm)<sub>3</sub>.

carbon shifts in this system could be calculated fairly well (see below), making assignments straightforward.

While many proton spectra could be assigned by inspection, others require extensive decoupling experi-

ments to confirm assignments. In short,  $^{13}\text{C}$  spectroscopy using low concentrations of  $\text{Yb}(\text{dpm})_3$  proved to be much easier than proton spectroscopy using  $\text{Eu}(\text{dpm})_3$  in this work.

A large number of assumptions go into the application of the McConnell–Robertson equation to a spectral analysis of this type. Since the primary object of this work was to compare proton and carbon spectroscopy and the use of  $\text{Eu}(\text{dpm})_3$  and  $\text{Yb}(\text{dpm})_3$  applied to a large number of closely related compounds, we have made some seemingly arbitrary choices of parameters based on the experiences of previous workers in order to put some bounds on this investigation.

We chose  $\text{Eu}(\text{dpm})_3$  as the proton shift reagent because it induces large downfield shifts without causing excessive line broadening.<sup>9</sup> We chose  $\text{Yb}(\text{dpm})_3$  as the carbon shift reagent because Gansow, *et al.*,<sup>10</sup> have recently demonstrated this lanthanide causes the least contact shift effect. We have assumed that the principal magnetic axis of the complex lies along the lanthanide–oxygen bond because Roberts, *et al.*,<sup>11</sup> found in a recent quantitative study that borneol and isoborneol shift reagent complexes are effectively axially symmetric. We have for reasons of expediency assumed that the oxygen–lanthanide distance is 3 Å and the carbon–oxygen–lanthanide angle is 130°. We do not pretend that these values are the correct ones for each compound under study here. In their study cited above Roberts, *et al.*,<sup>11</sup> used the rigid borneol skeleton to maximize the fit of experimental and calculated proton and  $^{13}\text{C}$  shifts in a computer program to find the optimum bond lengths and angles. They found angles ranging from 129.5 to 133° and oxygen–lanthanide distances ranging from 2.4 to 2.7 Å with  $\text{Pr}(\text{fod})_3$  and  $\text{Eu}(\text{fod})_3$  as the shift reagents. Using their program PDIGM Willcott and Davis, *et al.*,<sup>12</sup> found the best fit of  $\text{Eu}(\text{dpm})_3$  with borneol at an angle of 130° and a distance of 3.2 Å. In keeping with Willcott's findings we also have found our correlations to be quite insensitive to the values assumed for the lanthanide–oxygen distance. Farid, *et al.*,<sup>13</sup> in a similar analysis obtained an oxygen–europium distance of 3.0 Å and an angle of 128° for adamantan-2-ol, and a distance of 2.3 Å and an angle of 139° for *trans*-4-*tert*-butylcyclohexanol.

Both Robert's and Willcott's computer programs are designed to find the best location of lanthanide in relation to a rigid molecule.<sup>14</sup> Danyluk, *et al.*,<sup>15</sup> have used this method in the determination of the conformation of the antimalarial, chloroquine. First they found the best location of the lanthanide in relation to a rigid

(9) N. Ahmad, N. S. Bhacca, J. Selbin, and J. D. Wander, *J. Amer. Chem. Soc.*, **93**, 2564 (1971); W. DeW. Horrocks, Jr., and J. P. Sipe, *ibid.*, **93**, 6800 (1971).

(10) O. A. Gansow, P. A. Loeffler, R. E. Davis, M. R. Willcott, III, and R. E. Lenkinski, *J. Amer. Chem. Soc.*, **95**, 3389, 3390 (1973). See also G. E. Hawkes, C. Martin, S. R. Johns, and J. D. Roberts, *ibid.*, **95**, 1661 (1973).

(11) G. E. Hawkes, D. Leibfruits, D. W. Roberts, and J. D. Roberts, *J. Amer. Chem. Soc.*, **95**, 1659 (1973).

(12) M. R. Willcott, III, R. E. Lenkinski, and R. E. Davis, *J. Amer. Chem. Soc.*, **94**, 1742 (1972); R. E. Davis and M. R. Willcott, III, *ibid.*, **94**, 1744 (1972). See also I. M. Armitage, L. D. Hall, A. G. Marshall, and L. G. Werbelow, *ibid.*, **95**, 1437 (1973).

(13) S. Farid, A. Ateya, and M. Maggio, *Chem. Commun.*, 1285 (1971).

(14) See also J. Briggs, F. A. Hart, and G. P. Moss, *Chem. Commun.*, 1506 (1970), and ref 12 who use the same approach.

(15) N. S. Angerman, S. S. Danyluk, and T. A. Victor, *J. Amer. Chem. Soc.*, **94**, 7137 (1972).

quinoline ring system, and then they used this rigid framework to define the conformation of a 32 atom side chain. They concluded that the conformation thus derived was probably not significantly different from the free molecule with no shift reagent present.

Similarly, Ammon, *et al.*,<sup>16</sup> having defined the positions of 12 protons on a rigid framework by X-ray analysis, used this information to fix the location of the lanthanide in a complex. Having specified lanthanide–substrate geometry in the rigid part of their system, they determined the conformation of a mobile ethoxy group attached to their molecule. These workers also determined the conformation of a methoxy group in their system and found the methoxy group to be in essentially the same place as determined by X-ray analysis.

The most extensive search for a good fit of induced shifts with conformations was that of Williams, *et al.*,<sup>17</sup> who picked out 12 acceptable conformations of AMP from  $64 \times 10^6$  possibilities.

The present work is one of the first attempts to define the stereochemistry of a number of completely acyclic molecules in which it is not possible to fix the location of the lanthanide in relation to any rigid part of the molecule. As Roberts<sup>18</sup> has shown, there are a variety of bond angles and oxygen–lanthanide bond lengths which will fit the induced shift of just one or two atoms near the lanthanide. It is for this reason we have chosen to use throughout this work a carbon–oxygen–lanthanide angle of 130° and an oxygen–lanthanide distance of 3.0 Å.

The question remains: to what extent does interaction of the substrate with shift reagent change the conformation of the substrate? This is, of course, most easily manifest in systems equilibrating between two conformers of nearly equal energy.

As indicated in the Experimental Section we found it possible to “zero in” quickly on most of the conformations in Figure 1 using Dreiding models and a ruler along with plots of the geometric factor *vs.* induced shift before resorting to more extensive calculations. In doing this, it was readily apparent that certain of the average conformations represented in Figure 1 conform to shallow minima in the potential energy well; a number of closely related conformations will fit the data almost as well as the best one. For example, in Figure 2 we show the correlation coefficient between the induced carbon shifts,  $\Delta H_i/H$ , and the geometric factor,  $(3 \cos^2 \theta_i - 1)r_i^{-3}$ , for *threo*-3-methyl-2-pentanol (9) as a function of rotation about the oxygen–carbon bond, the geometry of the remainder of the molecule remaining as defined<sup>8</sup> and depicted in Figure 1. The correlation coefficient is  $>0.99$  from *ca.* 100 to 280°, whereas in 2-methyl-3-pentanol (11) (Figure 3) the correlation coefficient is  $>0.99$  only between *ca.* 150 and 210°, a much narrower region.

In the present work we find the coupling of the diastereotopic protons 9 and 10 with proton 11 in 4 (Figure 1) to be unchanged on addition of shift re-

(16) H. L. Ammon, P. H. Mazzocchi, W. K. Kopecky, Jr., H. J. Tamburin, and P. H. Watts, Jr., *J. Amer. Chem. Soc.*, **95**, 1968 (1973).

(17) C. D. Barry, A. C. T. North, J. A. Glasel, R. J. P. Williams, and A. V. Xavier, *Nature (London)*, **232**, 236 (1971).

(18) J. D. Roberts, 165th National Meeting of the American Chemical Society, Dallas, Texas, Apr 1973.

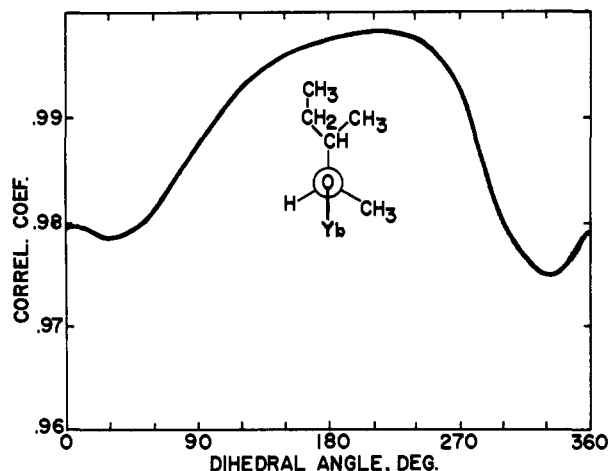


Figure 2. Correlation coefficient (between  $\Delta H_i/H$  and  $(3 \cos^2 \theta_i - 1)r_i^{-3}$ ) vs. angle of rotation around the oxygen-C-3 bond for *threo*-3-methyl-2-pentanol (9). The geometry of all other atoms is the same as that given in Table I and depicted in Figure 1.

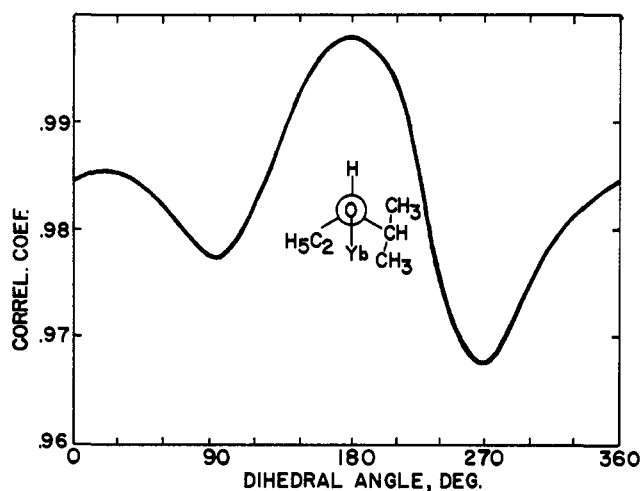
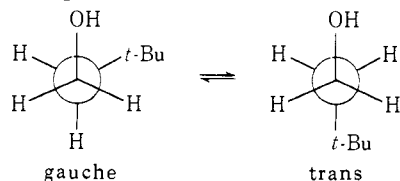


Figure 3. Correlation coefficient (between  $\Delta H_i/H$  and  $(3 \cos^2 \theta_i - 1)r_i^{-3}$ ) vs. angle of rotation around the oxygen-C-3 bond for 2-methyl-3-pentanol (11). The geometry of all other atoms is the same as that given in Table I and depicted in Figure 1.

agent.<sup>19</sup> The same is true for 15. Also no change in the coupling of the isochronous 9 and 10 protons with proton 11 in 13 is observed indicating that at least part of the molecule is conformationally unperturbed by adding shift reagent. But in 3,3-dimethyl-1-butanol (16) there is a change in the coupling of protons 9 and 10 to 11 and 12. In the absence of shift reagent  $J_{AX+AX'}$  is 16.8 Hz (Figure 4). Upon the addition of the first small increment of  $\text{Eu}(\text{dpm})_3$   $J_{AX+AX'}$  decreases to 15.0 Hz and remains essentially unchanged on further addition of the shift reagent. This is evidence for a change in the equilibrium between the *trans* and *gauche*



forms of the pure alcohol toward the *trans* conformer in the complexed alcohol. We estimate the equilibrium

(19) Throughout this paper carbon and proton numbers refer to those seen in Figure 1.

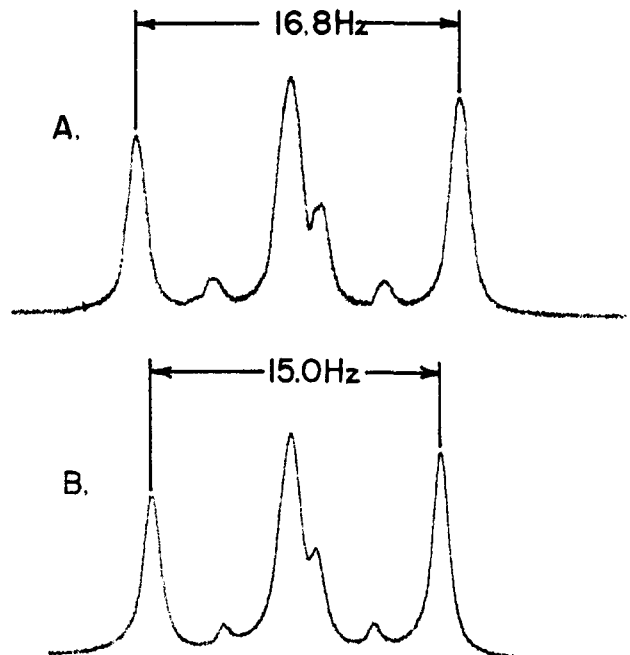


Figure 4.  $J_{AX+AX'}$  in the low-field portion (protons 9 and 10) of the AA'XX' spectrum from 3,3-dimethyl-1-butanol (16): (A) the pure alcohol; (B) the alcohol plus 0.1 molar equiv of  $\text{Eu}(\text{dpm})_3$ . Alcohol concentration 0.4 M in carbon disulfide.

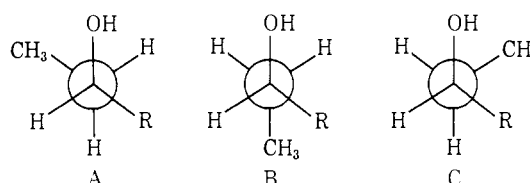


Figure 5. Rotamers of secondary alcohols.

has gone from about a 75:25 *trans*:*gauche* ratio to >90% *trans*.<sup>20</sup>

The addition of a shift reagent has, through an analysis of coupling constants, been shown to shift the equilibrium between equatorial and axial *tert*-butyl to the axial conformer in a *tert*-butyl dioxaphosphorinane.<sup>21</sup> So there is little question that the shift reagent can sometimes perturb the conformations of the substrate. The extent to which this is probably occurring we will take up in the next section where we consider the alcohols one by one.

**1-Hexanol (1)** has the expected staggered straight chain conformation with the oxygen and lanthanide lying in the plane of the carbon skeleton. Lack of solubility of  $\text{Eu}(\text{dpm})_3$  in the 0.4 M solution of the alcohol in  $\text{CS}_2$  precluded going above a mole ratio of alcohol to lanthanide of 0.813. **2-Hexanol (2)** is an example of a molecule for which a variety of conformations near that depicted in Figure 1 will give a good correlation coefficient. The conformation shown has the lanthanide, oxygen, C-3 and H-9 coplanar and C-4, -5, -6, and -6 in a staggered straight chain. This average conformation might be compared to that of 2-butanol ( $R = \text{Me}$ ) (Figure 5) which has been shown by Jack-

(20) A similar observation has been made by Hawkes and Roberts for neohexylamine.<sup>11</sup>

(21) W. G. Bentrude, H.-W. Tan, and K. C. Yee, *J. Amer. Chem. Soc.*, **94**, 3264 (1972).

Table V. C-13 Shifts for Six-Carbon Alcohols<sup>a</sup>

| Alcohol                                 | $\alpha$ | $\beta$     | $\gamma$    | $\delta$  | $\epsilon$ | $\zeta$ |
|---|----------|-------------|-------------|-----------|------------|---------|
| 1-Hexanol (1)                           | 62.11    | 32.89       | 25.77       | 31.92     | 23.02      | 14.23   |
| 2-Hexanol (2)                           | 67.23    | 39.19 (4)   | 28.20       | 23.16     | 14.29      |         |
|   |          | 23.45 (8)   |             |           |            |         |
| 3-Hexanol (3)                           | 72.24    | 39.36 (4)   | 19.19 (5)   | 14.34     |            |         |
|   |          | 30.46 (7)   | 10.14 (8)   |           |            |         |
| 2-Methyl-1-pentanol (4)                 | 67.55    | 35.69       | 35.53 (5)   | 20.49     | 14.61      |         |
|   |          |             | 16.71 (8)   |           |            |         |
| 3-Methyl-1-pentanol (5)                 | 60.33    | 39.57       | 31.22       | 29.92 (6) | 11.48      |         |
|   |          |             |             | 19.25 (8) |            |         |
| 4-Methyl-1-pentanol (6)                 | 62.32    | 30.67       | 35.15       | 28.04     | 22.59      |         |
| 2-Methyl-2-pentanol (7)                 | 69.98    | 46.47 (4)   | 17.79       | 14.88     |            |         |
|   |          | 29.12 (7,8) |             |           |            |         |
| <i>erythro</i> -3-Methyl-2-pentanol (8) | 70.68    | 41.84 (4)   | 25.61 (5)   | 11.86     |            |         |
|   |          | 19.24 (7)   | 14.12 (8)   |           |            |         |
| <i>threo</i> -3-Methyl-2-pentanol (9)   | 70.36    | 41.84 (4)   | 25.55 (5)   | 12.02     |            |         |
|   |          | 20.22 (7)   | 14.02 (8)   |           |            |         |
| 4-Methyl-2-pentanol (10)                | 65.23    | 48.63 (4)   | 24.75       | 23.24 (6) |            |         |
|   |          | 24.05 (8)   |             | 22.37 (7) |            |         |
| 2-Methyl-3-pentanol (11)                | 77.58    | 27.28 (7)   | 19.09 (6)   |           |            |         |
|   |          | 33.37 (4)   | 17.25 (5)   |           |            |         |
|   |          |             | 10.57 (8)   |           |            |         |
| 3-Methyl-3-pentanol (12)                | 72.04    | 34.02 (4,6) | 8.36 (5,7)  |           |            |         |
|   |          | 25.77 (8)   |             |           |            |         |
| 2-Ethyl-1-butanol (13)                  | 63.99    | 43.62       | 23.24       | 11.32     |            |         |
| 2,2-Dimethyl-1-butanol (14)             | 70.89    | 34.77       | 31.11 (5)   | 8.36      |            |         |
|   |          |             | 23.40 (7,8) |           |            |         |
| 2,3-Dimethyl-1-butanol (15)             | 65.67    | 41.46       | 29.01 (5)   | 20.70 (8) |            |         |
|   |          |             | 12.67 (7)   | 18.06 (6) |            |         |
| 3,3-Dimethyl-1-butanol (16)             | 58.98    | 46.20       | 29.44       | 29.71     |            |         |
| 2,3-Dimethyl-2-butanol (17)             | 72.14    | 38.70 (5,6) | 17.68       |           |            |         |
|   |          | 26.47 (7,8) |             |           |            |         |
| 3,3-Dimethyl-2-butanol (18)             | 74.94    | 34.61 (4)   | 25.50       |           |            |         |
|   |          | 18.01 (8)   |             |           |            |         |

<sup>a</sup> Ppm downfield from TMS, 1.0 M in CS<sub>2</sub>. For numbering of carbons (in parentheses), see Figure 1.

Table VI. Regression Analysis of Chemical Shift Parameters in Six-Carbon Alcohols

Number of observations: 95  
 Number of independent variables: 15  
 Multiple correlation coefficient *R* squared: 0.9966  
 Standard deviation in predicted chemical shifts:  $\pm 1.11$  ppm  
 Constant term:  $0.64 \pm 0.91$  ppm

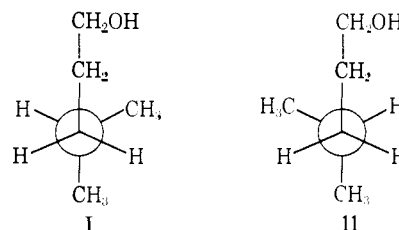
| Variable and coefficients             | Observations affected by variable no. | Student <i>T</i> ratio |
|---------------------------------------|---------------------------------------|------------------------|
| $\alpha$ 9.58 $\pm$ 0.42              | 95                                    | 22.8                   |
| $\beta$ 6.95 $\pm$ 0.25               | 95                                    | 28.2                   |
| $\gamma$ -2.68 $\pm$ 0.24             | 76                                    | 11.1                   |
| Corrective terms                      |                                       |                        |
| to hydroxyl                           |                                       |                        |
| $\alpha$ 47.98 $\pm$ 0.49             | 18                                    | 98.7                   |
| $\beta$ 8.26 $\pm$ 0.36               | 20                                    | 22.9                   |
| $\gamma$ -4.46 $\pm$ 0.35             | 26                                    | 12.9                   |
| 1°(3°) 0.61 $\pm$ 0.38                | 18                                    | 1.6                    |
| 2°(3°) -1.09 $\pm$ 0.47               | 14                                    | 2.3                    |
| 2°(4°) -4.20 $\pm$ 0.71               | 5                                     | 6.0                    |
| 3°(2°) -5.95 $\pm$ 0.76               | 8                                     | 7.8                    |
| 3°(3°) -9.49 $\pm$ 0.80               | 8                                     | 11.8                   |
| 3°(4°) -13.27 $\pm$ 1.10              | 2                                     | 12.1                   |
| 4°(2°) <sup>a</sup> -11.84 $\pm$ 1.30 | 2                                     | 9.1                    |
| 4°(2°) <sup>b</sup> -18.97 $\pm$ 1.33 | 2                                     | 14.3                   |
| 4°(3°) -19.35 $\pm$ 1.33              | 2                                     | 14.6                   |

<sup>a</sup> Quaternary carbon adjacent to one methylene group. <sup>b</sup> Quaternary carbon adjacent to two methylene groups.

man and Kelly<sup>22</sup> to be 97% A and B and 3% C by an analysis of coupling constants, but of course, such an analysis cannot indicate whether A or B predominates at equilibrium whereas our work indicates it is B.

(22) L. M. Jackman and D. P. Kelly, *J. Chem. Soc. B*, 102 (1970).

**3-Hexanol (3)** has an average conformation resembling part of a cyclohexane ring system. Note that protons 10 and 17 are 3 ppm downfield from protons 11 and 18 at a 1:1 mole ratio of alcohol to Eu(dpm)<sub>3</sub>. Here again this average conformation can be compared to Jackman's<sup>22</sup> for 3-pentanol (*R* = Et) (Figure 5) where he finds A and B make up 87% of the population and C 13%. Our conformation corresponds to B. **2-Methyl-1-pentanol (4)** is another example of a molecule with more than one conformation of closely similar energy. The data in Tables V and VI correspond to conformation A which has a correlation coefficient for the carbon spectra of 0.9992. However, conformation B gives a carbon correlation coefficient of 0.9973 and a proton correlation coefficient of 0.967. **3-Methyl-1-pentanol (5)** has an average conformation which in Newman projection along the C-4, C-5 bond is seen to be 30° away from the gauche-trans conformer. **4-Methyl-1-pentanol (6)** has an average conformation in which C-7 and -8 are eclipsed with H-13 and -14. This, of course, implies that this alcohol is an equilibrium mixture of conformers I and II. **2-Methyl-2-pentanol (7)** can only be described by an average conformation which averages the position of the lanthanide with



respect to C-4, -7, and -8. Because of nearly equal steric hindrance presented by the hydrogens of the three carbons adjacent to the hydroxyl carbon no single locus of the lanthanide will give as good a correlation coefficient as the average of all possible loci which corresponds to the center of the base of the cone swept out by the lanthanide atom. This geometric average gives an oxygen-lanthanide distance of 1.928 Å along a line coaxial with the carbon-oxygen bond. **erythro-3-Methyl-2-pentanol (8)** was run as a mixture with the threo isomer (**9**). Fortunately the equilibrium constants for complexation with the lanthanide were almost exactly the same for these two isomers as evidenced by the linear relationship between  $\Delta H_i/H$  and mole ratio of alcohol to lanthanide.<sup>23</sup> The proton spectrum of the mixture of isomers without shift reagent has been assigned by Bucci and Rossi.<sup>24</sup> On the basis of non-spectroscopic evidence they assign the higher field peaks to the threo isomers (which made up about 45% of our sample). These isomers were among the most difficult to find average conformations for. They have in common the fact that C-3, -4, -5, and -6 are coplanar and the dihedral angle between oxygen and C-8 is 90°. Shifted spectra (carbon or hydrogen) would not be a reliable way to distinguish between these two isomers, but the unshifted C-13 spectrum might be (see below). **4-Methyl-2-pentanol (10)** has the lanthanide oxygen, C-3, and H-9 coplanar. The conformation of C-4, -5, -6, and -7 in this molecule can be contrasted with the conformation of C-5, -6, -7, and -8 in **6**. In **10** the average position of the terminal isopropyl group avoids proximity to the C-8 methyl. **2-Methyl-3-pentanol (11)** is another molecule with a rather irregular average conformation. The lanthanide, oxygen, C-3, and H-9 are coplanar. The correlation coefficients as a function of rotation around the C-O bond have been discussed above; the C-13 shifts of the diastereotopic methyls are discussed in the next section. **3-Methyl-3-pentanol (12)** to our surprise gives the best correlation coefficient with the lanthanide at position a (carbon correlation coefficient 0.9975). When the geometric average position b is used the correlation coefficient is 0.9800. It is not readily apparent why position a for the lanthanide between the two large ethyl groups on C-3 should be preferred to a position closer to C-8. **2-Ethyl-1-butanol (13)** has an average conformation resembling cyclohexylmethanol. The C-6 and C-8 carbons in this conformation (like C-5 and -7 in **12**, and C-5 and -8 in **3**) are as close together as 1,3-diaxial methyl groups would be in a cyclohexane ring system. Since these are average conformations these atoms are of course rarely in these positions simultaneously. **2,2-Dimethyl-1-butanol (14)** has an average conformation which one might predict with the hydroxyl gauche to the two methyls and trans to the ethyl group. **2,3-Dimethyl-1-butanol (15)** has a very regular average conformation resembling part of a cyclohexylmethyl ring system. **3,3-Dimethyl-1-butanol (16)** gives the best correlation coefficient with the hydroxyl trans to the *tert*-butyl group. As has been noted above the uncomplexed alcohol exists as a 75:25 mixture of trans

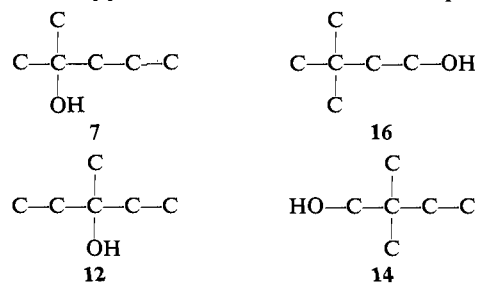
and gauche rotamers. **2,3-Dimethyl-2-butanol (17)** has an average conformation in which all four methyl groups are eclipsed, indicating libration between the two adjacent gauche conformers. The best correlation coefficient was obtained using the geometric average position for the lanthanide as indicated in Figure 1. **3,3-Dimethyl-2-butanol (18)** has a very regular average conformation with the lanthanide, oxygen, C-3, and H-9 coplanar. It might be expected the lanthanide would favor proximity to the C-8 methyl in order to avoid contact with the *tert*-butyl group (C-4, -5, -6, and -7), but it will be noted in Table III that the C-4 carbon has a slightly larger induced shift than C-8.

**Stoichiometry.** Perhaps no aspect of the use of shift reagents has received more attention than the stoichiometry of the complexes involved.<sup>25</sup> In the present work we have noted the complete linearity of the induced shifts *vs.* the alcohol/shift reagent ratio and we have assumed a 1:1 ratio of Eu(dpm)<sub>3</sub> to alcohol for the proton work and a 0.5:1 ratio of Yb(dpm)<sub>3</sub> to alcohol at the concentrations employed for the C-13 measurements. The obvious way to investigate these equilibria is by vapor pressure osmometry as has been recently reported by Shriver, Marks, and Porter.<sup>26,27</sup>

**Carbon-13 Chemical Shifts of the Pure Alcohols.** Since it has been possible to identify positively each of the 95 magnetically nonequivalent carbon atoms in these 18 alcohols and determine their C-13 chemical shifts (Table V) we have performed a linear multiple regression analysis (Table VI) of the same type initially reported by Grant and Paul<sup>6</sup> for alkanes. The C-13 chemical shift values for the carbons in all of these alcohols can be described by the linear equation

$$S_c(k) = B + \sum_l A_l n_{kl} + C + D$$

where  $S_c(k)$  is the chemical shift of the  $k$ th carbon,  $B$  is a constant,  $n_{kl}$  is the number of carbon atoms in the  $l$ th position relative to the  $k$ th carbon,  $A_l$  is the additive chemical shift parameter assigned to the  $l$ th carbon atom,  $C$  is the additive chemical shift parameter describing the relationship of the  $k$ th carbon to the hydroxyl group ( $\alpha$ ,  $\beta$ , or  $\gamma$ ), and  $D$  is the term which describes the relationship of the  $k$ th carbon to its most highly branched neighbor, *e.g.*, 1°(3°) a  $k$ th methyl group adjacent to a tertiary carbon, 2°(4°) a  $k$ th methylene group adjacent to a quaternary carbon, etc. Two different terms are needed to correct for a quaternary carbon adjacent to a secondary carbon, 4°(2°):  $D = -11.84 \pm 1.3$  ppm for **7** and **16** in which the quaternary



(25) B. L. Shapiro and M. D. Johnston, Jr., *J. Amer. Chem. Soc.*, **94**, 8185 (1972); J. K. M. Sanders, S. W. Hanson, and D. H. Williams, *ibid.*, **94**, 5325 (1972), and references cited therein.

(26) R. Porter, T. J. Marks, and D. F. Shriver, *J. Amer. Chem. Soc.*, **95**, 3548 (1973).

(27) A report of the stoichiometry of Eu(dpm)<sub>3</sub> and Yb(dpm)<sub>3</sub> in the presence and absence of these alcohols as determined by vapor pressure osmometry will be the subject of a future communication.

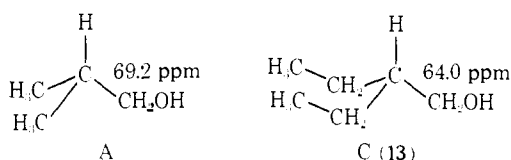
(23) See J. K. M. Sanders, S. W. Hanson, and D. H. Williams, *J. Amer. Chem. Soc.*, **94**, 5325 (1972), for a discussion of substrate mixtures.

(24) P. Bucci and R. Rossi, "NMR in Chemistry," Academic Press, New York, N. Y., 1965, p 140.

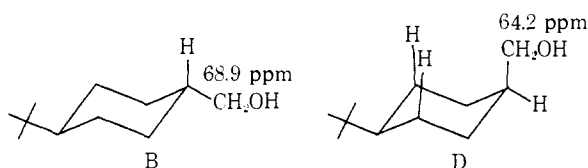
carbon is adjacent to only one methylene group and  $-18.97 \pm 1.33$  ppm for **12** and **14** in which the quaternary carbon is adjacent to two methylene groups.

This regression analysis is interesting from a number of points. The additive chemical shift parameters and corrective terms all come directly from the analysis; they are not added on to the hydrocarbon parameters determined by Grant and Paul.<sup>6</sup> We found a better overall standard deviation by leaving out corrective terms for 1°(4°) and 4°(1°). The very large corrective terms for a tertiary carbon adjacent to a quaternary carbon and a quaternary adjacent to a secondary or tertiary (from 11.8 to 19.3 ppm  $\pm$  1.3 ppm) are noteworthy. Even though all these corrective terms have stereochemical implications due to the  $\gamma$  effect, stereochemistry, as such, does not enter into this regression analysis. We are unable, just on the basis of these terms, to make stereochemical deductions for these alcohols as has recently been done by Djerassi and Eggert for the aliphatic amines;<sup>28</sup> however, some interesting comparisons with other C-13 chemical shifts can be made.

Stothers, *et al.*,<sup>29</sup> have previously noted the close similarity in chemical shifts of the carbonyl carbon in isobutyl alcohol (A) and *trans*-4-*tert*-butylcyclohexyl-

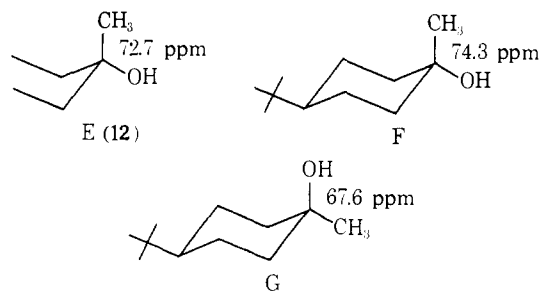


methanol (B). They cite this as evidence that the



carbonyl carbon in *cis*-4-*tert*-butylcyclohexylmethanol (D) has been shielded by a 1,3-diaxial interaction with the two cyclohexane hydrogens. We would like to point out by contrast the great similarity between the chemical shift of the carbonyl carbons of C (13) and D. Even though we have found the average conformation of 13 resembles B the chemical shift obviously is the same as D. We interpret this as another example of the  $\gamma$  effect. The terminal methyls (C-6 and C-8) in 13 are gauche to the carbonyl often enough to cause a shielding almost identical with D. This also points up the fact that the conformations found in this work are indeed *average* conformations.

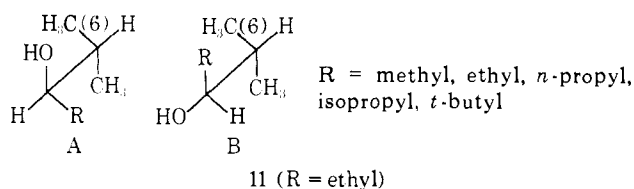
Along these same lines we would like to compare the chemical shifts of the carbonyl carbon in **12** (E) with F<sup>29</sup> and G.<sup>29</sup> Our shift reagent studies indicate E has the average conformation shown which resembles part of the *tert*-butylcyclohexanol, F. The similarities of the carbonyl chemical shifts in these two molecules, E and F ( $\Delta = 5.1$  ppm), we regard as confirmatory evidence that **12** (E) does indeed resemble more closely the average conformation shown than the alternative with an "axial" hydroxyl and "equatorial" methyl. This



is not what one might expect offhand on the basis of the conformational free energies of equatorial and axial methyls and hydroxyls in cyclohexanes.<sup>30</sup>

Similarly the average conformation of 3-hexanol (**3**) resembles part of a cyclohexanol ring system with an equatorial hydroxyl. The chemical shift of the carbonyl carbon in **3** (72.2 ppm) resembles that of the carbonyl carbon in a cyclohexanol with an equatorial hydroxyl (70.4 ppm) more closely than a cyclohexanol carbonyl carbon bearing on axial hydroxyl (65.0 ppm).<sup>31</sup>

2-Methyl-3-pentanol (**11**) was examined in 1969 by



Roberts, *et al.*,<sup>32</sup> as one of a series of alcohols bearing enantiotopic methyl groups. The methyl groups, A and B, are magnetically nonequivalent by 0.2 ppm when R = methyl and this difference increases to 6.0 ppm when R = *tert*-butyl. In **11** (R = ethyl) we find, in agreement with Roberts, the methyls are nonequivalent by 1.84 ppm. Roberts noted the shift of one methyl group remained constant at *ca.* 17.5 ppm when R was changed from methyl to *tert*-butyl, while the other *increased* to 24 ppm. To rationalize the latter observation these workers assign B as the favored conformation and invoke a rarely observed 1,5 CH<sub>3</sub>-CH<sub>3</sub> interaction which produces a *downfield* shift. In this way then they can assign the high-field shift to C-5 and the low-field shift to C-6, since the C-6 shift increases as the size of R increases.

In the present work our assignment of the methyls is the same as that of Roberts, *et al.*, but we find A (actually a slightly distorted version of A; see Figure 1) to be the average conformation. This may, of course, be a reflection of changed rotamer populations as a result of interaction of the alcohol with the bulky lanthanide. In our regression analysis of the C-13 chemical shifts we did not assign separate correction factors for the diastereotopic methyls in **10**, **11**, and **15** and since these methyls are magnetically nonequivalent they are not precisely predicted by our regression parameters. The calculated value for the methyls in **11** is 17.59 ppm, close to that found for C-5 (17.25 ppm) but 1.5 ppm upfield from that found for C-6 (19.09 ppm). So from this point of view the C-6 chemical shift seems to be the anomalous one.

However, we do not favor a 1,5 CH<sub>3</sub>-CH<sub>3</sub> downfield

(28) C. Djerassi and H. Eggert, *J. Amer. Chem. Soc.*, **95**, 3710 (1973).

(29) G. W. Buchanan, J. B. Stothers, and S.-T. Wu, *Can. J. Chem.*, **47**, 3113 (1969).

(30) J. A. Hirsch, *Top. Stereochem.*, **1**, 188 (1967).

(31) Chemical shifts found for *trans*- and *cis*-4-*tert*-butylcyclohexanol.<sup>7</sup>

(32) J. I. Kroschwitz, M. Winokur, H. J. Reich, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 5927 (1969).



interaction to rationalize this result because in **15**, where the two diastereotopic methyls differ in chemical shift by 2.6 ppm, a 1,5  $CH_3-CH_3$  interaction is impossible. In both **11** and **15**, despite the uncertainties of the average conformation we have deduced, we note that the sterically crowded C-5 methyl in **11** is the upfield one, and in **15** the C-8 methyl (gauche to two carbons, 3 and 7) is upfield from C-6 (gauche only to C-7), both manifestations of the familiar  $\gamma$  effect. In **10** the two diastereotopic methyls are only 0.9 ppm apart and the apparently more crowded (6) appears at low field.

### Conclusion

Valuable information on the average solution conformations of acyclic molecules can be obtained by the use of  $^1H$  and  $^{13}C$  shift reagents. The reagents are complementary, but  $Yb(dpm)_3$  and  $^{13}C$  spectroscopy are more readily utilized than  $Eu(dpm)_3$  and proton spectroscopy. Great caution must be used in interpreting the results because the shift reagent can distort the conformation of the substrate being examined. Diastereotopic atoms can be assigned with assurance.

**Acknowledgment.** Support of this work through grants from the National Institutes of Health (GM-10224-11), the National Science Foundation, and the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. We would also like to thank Professors Paul A. Dobosh and John Durso for help with computer programs.

**Supplementary Material Available.** Three tables of data will appear following these pages in the microfilm edition of this volume of the journal. Table I gives the dihedral angles and torsion angles used to define the conformations of the 18 alcohols as well as the lanthanide-hydrogen and lanthanide-carbon internuclear distances and the lanthanide-oxygen-atom angles for the 21 atoms in each alcohol. Tables II and III give the proton and carbon chemical shifts and assignments for a 1:1 mole ratio of  $Eu(dpm)_3$  to alcohol, the calculated geometric factor using the conformations from Table I, and the calculated correlation coefficient for the geometric factor vs. induced shift. Photocopies of the supplementary material from this paper only or microfilm (105  $\times$  148 mm, 24 $\times$  reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for \$4.00 for photocopy or \$2.00 for microfiche, referring to code number JACS-74-1471.

## Conformational Aspects of Polypeptide Structure. XLV. Nuclear Magnetic Resonance Study of Trans-Cis Isomerization in an *N*-Methyl-L-alanine Derivative

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Contribution from the Department of Chemistry, University of California, San Diego, La Jolla, California 92037. Received September 10, 1973

**Abstract:** Trans-cis isomerism of *N*-acetyl-*N*-methyl-L-alanine methyl ester was studied by using nmr spectroscopy. Kinetic as well as thermodynamic parameters for trans-cis dynamic exchange in various solvents were obtained from computer simulations of the observed resonances at different temperatures. The estimated activation energies as well as enthalpy differences between the two isomers in various solvent systems are similar to those obtained for the other *N,N*-disubstituted amides. The effects of solvents on the chemical nonequivalence between the trans and cis isomers are also discussed.

Because of the restricted rotation about the C-N amide bond, *N*-substituted amides exist in two different rotational isomers. During the past decades, nmr spectroscopy has been used to characterize the nature of the restricted rotations of *N*-alkylated derivatives of formamides as well as acetamides.<sup>2-5</sup> Most of the studies were concerned with cases of equal populations for which kinetic treatments are relatively simple. However, in a few of the amide systems having different amide substituents, nonequivalent populations of the rotational isomers were found.<sup>6-8</sup>

(1) (a) This work was carried out by F. C. as partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of California, San Diego. (b) Postdoctoral research fellow, Department of Chemistry, University of California, San Diego.

(2) R. C. Neuman, Jr., D. N. Roark, and V. Jonas, *J. Amer. Chem. Soc.*, **89**, 3412 (1967).

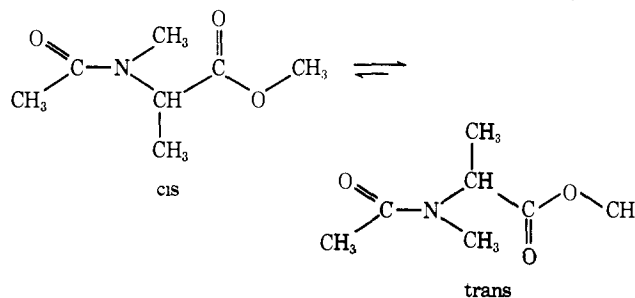
(3) G. Binsch, *Top. Stereochem.*, **3**, 97 (1968).

(4) W. E. Stewart and T. H. Siddall III, *Chem. Rev.*, **70**, 517 (1970).

(5) M. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970).

(6) J. A. Weil, A. Blum, A. H. Heiss, and J. K. Kinnaird, *J. Chem. Phys.*, **46**, 3132 (1967).

The existence of the distinctive, nonequivalent trans-cis rotational conformers of *N*-acetyl-*N*-methyl-L-alanine methyl ester (I) has been reported by this



*N*-acetyl-*N*-methyl-L-alanine methyl ester (I) laboratory.<sup>9</sup> We have also shown that the polymer,

(7) R. C. Neuman, Jr., V. Jonas, K. Anderson, and R. Barry, *Biochem. Biophys. Res. Commun.*, **44**, 1156 (1971).

(8) M. Sisido, Y. Imanishi, and T. Higashimura, *Biopolymers*, **11**, 399 (1972).

(9) M. Goodman and M. Fried, *J. Amer. Chem. Soc.*, **89**, 1264 (1967).