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HYDROXYL PROTON COUPLING IN CYCLOHEXANOLS.
ROTAMER POPULATIONS OF THE HYDROXYL GROUP

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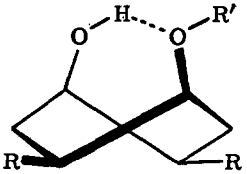
When the hydroxyl hydrogen or oxygen is engaged in intermolecular hydrogen bonding, steric effects exerted upon its partner may control rotamer populations for the hydroxyl group. For example, such steric effects may be expected for alcohols in dimethyl sulfoxide solution (2-4). However, we suggest that hydroxyl rotamer populations are probably not influenced greatly by steric repulsions exerted by alkyl groups upon the hydroxyl hydrogen when the oxygen-alkyl hydrogen internuclear distance exceeds 2.5 Å. Hence, we must challenge the prevailing assumption (2-5) that the anti rotamer ($\theta = 180°$) is populated negligibly for an axial hydroxyl group of cyclohexanol, because of "steric interactions of the axial 3,5-hydrogens with the hydroxyl hydrogen" (6). The claim that infrared studies (6) support this assumption is questioned (7). Our feeling that this assumption should be tested further is based upon the results presented below.

Because the hydrogen bond tends to hold the ring in a twist conformation, and the hydroxyl group near a particular rotational position, cis,cis,cis-2,5-di-t-butyl-4-methoxycyclohexanol (I) may be useful as a "conformationally homogeneous" model compound, both in studies of nonchair conformations, and in studies of hydroxyl group rotamers (8).



I R = $C(CH_3)_3$, R′ = CH_3

II R = $C(CH_3)_3$, R′ = H

TABLE I

Concentration Dependence of J_{HCOH} for I and II in Carbon Tetrachloride Solution at 30°.*

Compound I		Diol II	
Concentration moles/liter	J_{HCOH} Hz	Concentration moles/liter	J_{HCOH} Hz
0.43	11.3 ± 0.2	0.086	7.0 ± 0.2
0.074	11.4 ± 0.2	0.016	6.9 ± 0.2
0.005	11.4 ± 0.3	0.005	7.0 ± 0.3
1/∞	11.4 (extrapolated)	1/∞	7.0 (extrapolated)

*Nmr spectra were recorded by use of a Varian A-60A spectrometer. At the lowest concentrations, hundreds of spectral scans were averaged by use of a C-1024 computer. Dried CCl_4, passed through alumina, was not exposed to light.

The hydroxyl proton-carbinol proton coupling constant, J_{HCOH}, in nmr spectra of cyclohexanols (and related alcohols) is undoubtedly a function of the dihedral angle, θ, about the carbon-oxygen bond (2-4). The energy barrier for rotation about that bond is too small (4) to permit nmr observations of individual rotamers in solution at accessible temperatures. Therefore, the coupling constant, observed under conditions of slow proton exchange, would be the weighted average: $J_{HCOH} = \sum N_\theta J_\theta$, where J_θ is the specific hydroxyl coupling constant (N_θ is the mole fraction) of rotamer with dihedral angle θ, and $\sum N_\theta = 1$. In the case of the model compound (I), a small range of rotamers is made significantly more stable than all others by the preferred geometry of the transannular hydrogen bond; projection from a Dreiding molecular model of I gives θ as 167 ± 2°. As θ is increased or decreased from 167° by rotation about the carbon-oxygen bond, strength of the hydrogen bond and stability of the rotamer are decreased rapidly (9). A hypothetical plot of rotamer free energy vs. θ is given for model compound I as compared to methanol in Fig. I. To be consistent with the infrared spectrum of I (8), N_θ must be negligible except for a small range of θ near 167°. Furthermore, $N_\theta J_\theta$ also should be negligible except for a small range of θ near 167°, since $J_{167°}$ is near the maximum expected value of J_θ (see below).

In carbon tetrachloride solution (0.005 M), the model compound (I) gives J_{HCOH}, 11.4 Hz. This value remains the same up to 80 times greater concentration (Table I), indicating that for I, intermolecular hydrogen bonding does not compete effectively with intramolecular hydrogen bonding, a fact that supports the conformational homogeneity of I, as

FIG. I. Hypothetical rotamer free energies for I and II.

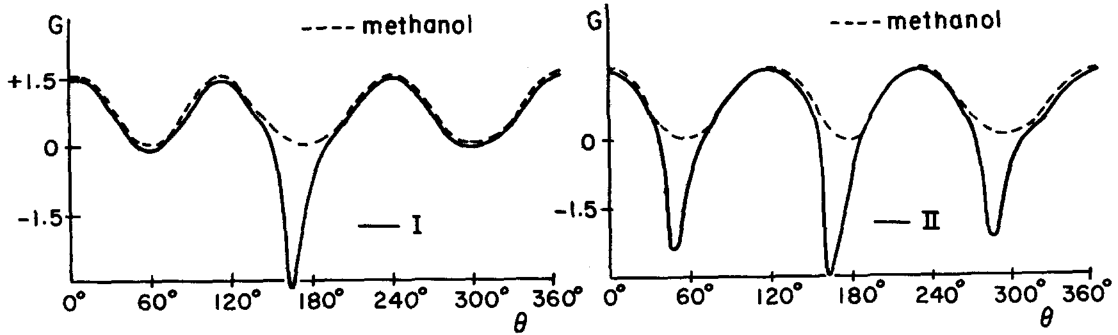
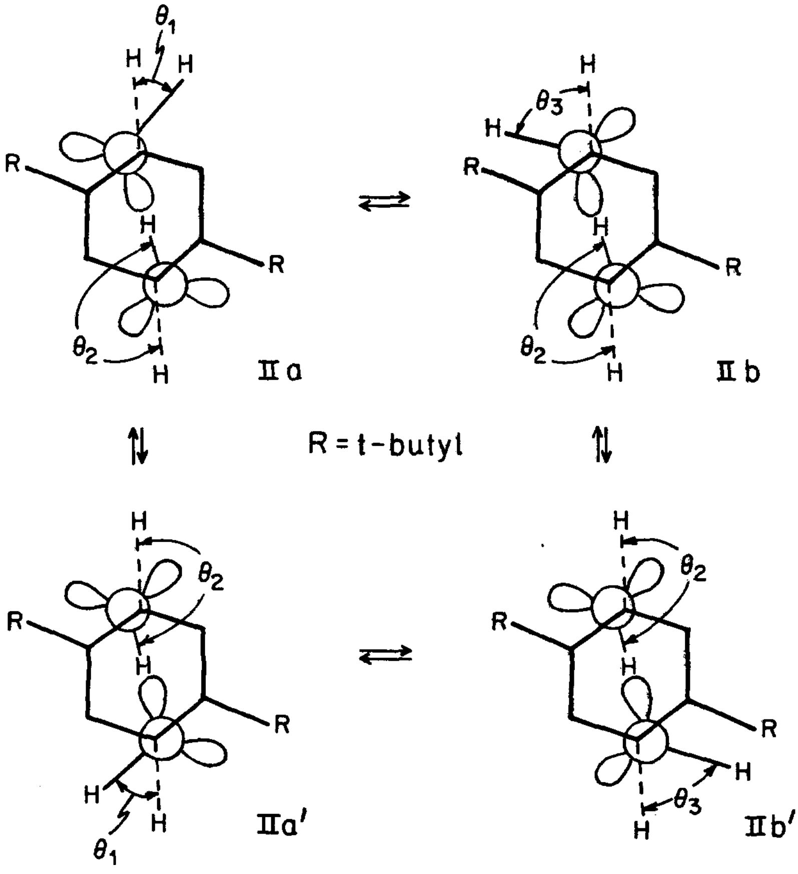


FIG. II. The two pairs of equivalent conformations of II showing the HCOH dihedral angles (θ) in projections from above the ring.



hypothesized in Fig. I. Therefore, we conclude that $J_{HCOH} = 11.4$ Hz for $\theta \sim 167°$ in model compound I and in closely related secondary alcohols.

Compare model compound I with cis, cis, cis-2, 5-di-t-butyl-1, 4-cyclohexanediol (II) in carbon tetrachloride solution at 30° (Table I). Diol II is not "conformationally homogeneous;" its infrared spectrum has been interpreted in terms of two pairs of equivalent intramolecularly hydrogen bonded conformations, interconverting rapidly by rotation about the carbon-oxygen bonds (8). For diol II, a hypothetical plot of rotamer free energy vs. θ for a single hydroxyl group (allowing θ' for the second hydroxyl group, which becomes equivalent to the first by rotamer interconversion, to take the value which minimizes the total free energy for each value of θ) would be expected to exhibit three minima (Fig. I). Therefore for II,

$$J_{HCOH} = N_{\theta_1}J_{\theta_1} + N_{\theta_2}J_{\theta_2} + N_{\theta_3}J_{\theta_3} \quad (1)$$

where each subscript number refers to the value of θ at one minimum. If diol II retains a hydrogen bond in all populated rotamers (8), each hydroxyl proton would be hydrogen bonded (as in I) half of the time. Therefore, for II, setting θ_2 at 167° (as for compound I), J_{θ_2} = 11.4 Hz, $N_{\theta_2} = 0.50$, and $N_{\theta_1} + N_{\theta_3} = 0.50$. For diol II, $J_{HCOH} = 7.0$ Hz (Table I). Substitution into eq. 1 gives eq. 2, which when solved for N_{θ_1}, yields eq. 3.

$$J_{HCOH} = 7.0 = N_{\theta_1}J_{\theta_1} + 0.50(11.4) + (0.50 - N_{\theta_1})J_{\theta_3} \quad (2)$$

$$N_{\theta_1} = (1.3 - 0.5J_{\theta_3})/(J_{\theta_1} - J_{\theta_3}) \quad (3)$$

If θ_1 and θ_3 could be determined, and if J_{θ_1} and J_{θ_3} could then be predicted, evaluation of N_{θ_1} (and N_{θ_3}) would be possible. The relative populations of the two rotamers would give the free energy difference between the two environments for the free hydroxyl hydrogen (IIa and IIb in Fig. II). In IIb, that hydrogen is much closer to a t-butyl group than in IIa, while an oxygen lone pair of electrons may be much closer to the t-butyl group in IIa than in IIb (Fig. II). The problem is significant. It may offer an opportunity to evaluate the effective steric size of a hydroxyl oxygen, as compared to the hydrogen on that oxygen, for the specific environment found in II (Fig. II) (10).

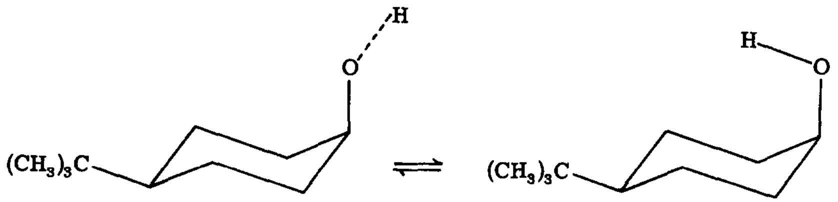
As a crude approximation to a solution of the problem, one might assume first, tetrahedral sp^3 hybridization of oxygen orbitals. Then the hydrogen bond can be represented as a hydroxyl hydrogen directed in space toward a pair of electrons in an oxygen sp^3 orbital, as illustrated in Fig. II, so that $\theta_1 = \theta_2 - 120° \sim 47°$, and $\theta_3 = (360° - \theta_2) - 120° \sim 73°$.

Continuing the crude approximation, one might assume next a Karplus-type relationship exists (2-4), of the form (11):

$$J_{HCOH} = A\cos^2\theta - B\cos\theta. \qquad (4)$$

Then one can estimate $J_{180°} = 12.0$ Hz, (based on model compound I, by substituting θ, 167°; J_{HCOH}, 11.4 Hz; $B \sim 0$). Next one can estimate $J_{60°} = 1.9$ Hz (based upon methanol in carbon tetrachloride solution (2), for which $J_{HCOH} = 5.3 \text{ Hz} = \frac{1}{3}[2J_{60°} + J_{180°}]$). Then, evaluating the constants, $A = 10.6$ and $B = 1.4$. Approximate values may now be calculated for J_{HCOH} at any dihedral angle, θ. Thus, $J_{47°} \sim 4.0$ Hz and $J_{73°} \sim 0.5$ Hz, when substituted into eq. 3 as J_{θ_1} and J_{θ_3}, respectively, would yield $N_{\theta_1} \sim 0.3$. Since $N_{\theta_3} = 0.50 - N_{\theta_1} \sim 0.2$, rotamers IIa and IIb would have comparable populations, a result consistent with an earlier interpretation of infrared spectra of II (8), but inconsistent with the concept of much stronger steric repulsions between an alkyl group and a hydroxyl hydrogen than between an alkyl group and a hydroxyl oxygen (2-6) when the oxygen-alkyl hydrogen internuclear distance exceeds 2.5 Å.

Although molecular models show similarity between the steric environments of hydroxyl groups in IIIa and IIa, and in IIIb and IIb (assuming the *t*-butyl-hydroxyl interaction in IIb is relaxed, the favored *t*-butyl rotamer being intermediate between staggered and eclipsed), the hydrogen bond in II may alter the hybridization of the hydroxyl oxygen, relative to that of a free hydroxyl group. Therefore, the analogy between II and III is tentative. Direct measurement of



IIIa (gauche) IIIb (anti)

J_{HCOH} for cis-4-t-butylcyclohexanol (III) (or other suitable model compound) at < 0.004 M concentration in carbon tetrachloride (or other relatively nonassociating solvent), to our knowledge, has not yet been carried out successfully because slow exchange is difficult to achieve under such conditions, in the absence of hydrogen bonding. We suspect that use of scrupulously purified materials and samples prepared by vacuum line techniques may overcome this experimental difficulty.

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(9) The dihedral angle, θ, is not changed significantly by small changes in the ring conformation.

(10) Justifiable criticism leveled against the concept of a "size" for an electron lone pair has led us to avoid such language. Nevertheless, the steric "size" of a hydroxyl oxygen is no less vague a concept, since steric "size" is largely an electronic phenomenon. See N. L. Allinger, J. A. Hirsch, and M. A. Miller, Tetrahedron Letters, 3729 (1967); J. B. Lambert, R. G. Keske, and D. K. Weary, J. Am. Chem. Soc., **89**, 5921 (1967).

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(12) NOTE ADDED, March 22, 1968: N. L. Bauld and Y. S. Rim, J. Org. Chem., **33**, 1303 (1968), report $J_{180°} = 12.5$ Hz for a conformationally homogeneous diarylcarbinol in carbon tetrachloride solution. The electron attracting aryl substituents in this compound would be expected (2) to increase $J_{180°}$ slightly, compared to I (12.0 Hz).