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HYDROXYL PROTON MAGNETIC RESONANCE STUDY OF CYCLIC ALCOHOLS IN DIMETHYL SULFOXIDE

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As part of another project, in order to determine stereochemistry and the effect of ring size on hydrogenation of cyclic allylic alcohols, it was of concern to develop a direct method for assigning configurations to unknown epimeric cyclanols under study.

In extremely low concentration of acids or bases which catalyze O-H proton exchange, proton magnetic resonance (pmr) spectra of alcohols exhibit spin-spin coupling[1]. It is more difficult to observe the coupling in non-polar solvents than in polar ones which can donate an electron pair to the hydroxyl group. In dimethyl sulfoxide (DMSO) solution strong hydrogen bonding to the solvent decreases the rate of proton exchange appreciably to allow observation of hydroxyl proton splitting[1b]. Therefore DMSO has proved to be an extremely valuable solvent for the study of hydroxyl pmr spectra of alcohols. Furthermore, in dilute DMSO, the O-H proton resonance occurs in the τ 5.5-6.3 region, a portion of the spectrum relatively free from peaks due to other protons[2a]. Finally, hydroxyl proton chemical shifts are very sensitive to both temperature and concentration, due to the critical effect of hydrogen bond formation on chemical shift[2a].

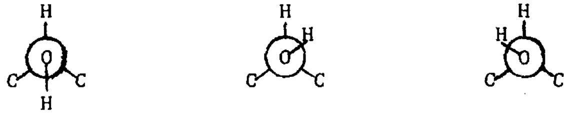
For a series of sets of epimeric alcohols pmr spectra of the O-H proton were obtained in DMSO, in the dilute concentration region in which the chemical shift had been established as invariant (Table 1). The expected doublet was always obtained (in the case of cis-2-cyclopentylcyclopentanol the doublet was not discernible), since the fine structure was sufficiently well resolved to allow both the determination of the magnitude of the coupling constant and chemical shift. The observed values give the clear correlation that in every epimeric set the axial O-H proton is found at significantly higher field (0.14-0.31) than its equatorial counterpart. The coupling constant data also lend themselves to ready correlation with conformation. In each set of epimers of the five-membered systems the equatorial alcohol coupling constant is 1.2 cps greater than that of its axial epimer. In each set of epimers of the six-membered systems the

Table 1 Hydroxyl Proton Chemical Shifts and Coupling Constants of Epimeric Cyclanols in DMSO

	Axial Alcohol (Cis Configuration)		Equatorial Alcohol (Trans Configuration)	
	Chemical Shift τ	Coupling Constant J(cps)	Chemical Shift τ	Coupling Constant J(cps)
2-Benzylcyclopentanol	5.74	3.6	5.54	4.8
2-Hexahydrobenzyl-cyclopentanol	5.95	3.6	5.67	4.8
2-Benzylcyclohexanol	5.81	3.6	5.50	6.6
2-Hexahydrobenzyl-cyclohexanol	5.99	3.0	5.74	4.8
2-Benzylcycloheptanol	5.76	4.8	5.51	4.8
2-Hexahydrobenzyl-cycloheptanol	5.98	4.8	5.84	4.8
2-Butylcyclopentanol	5.945	4.2	5.645	5.4
2-Butylcyclohexanol	5.96	4.8	5.73	6.0
2-Butylcycloheptanol	5.96	4.8	5.81	4.8
2-Cyclopentylcyclo-pentanol	6.015	—	5.745	5.4

equatorial alcohol coupling constant is 1.2-3.0 cps greater than that of its axial epimer.

The difference between the hydroxyl-carbinol coupling constants for epimeric cyclohexanols may be understood from a consideration of the isomers resulting from rotation about the C-O bond[2]. The O-H may be staggered either between the two C-C bonds (a) or between the C-H bond and a C-C one (b and c).



(a) anti (b) gauche (c) gauche

Assuming H-C-O-H coupling constants to vary with dihedral angle in a manner similar to that for H-C-C-H systems, C. P. Rader was led to the conclusion that an equatorial alcohol should have a larger J than its axial epimer, due to the greater contribution of the anti-conformer (a) in the former[2a]. The difference between the hydroxyl-carbinol coupling constants for epimeric cyclopentanols may be attributed similarly to the contribution of the anti-conformer to the equatorial alcohol and consequently the equatorial alcohol has a larger J than its axial epimer. However, no difference is observed between the hydroxyl-carbinol coupling constants for epimeric cycloheptanols. This is likely due to the seven-membered systems being conformationally more mobile[3].

The chemical shift difference between the epimeric alcohols may be related to solute-solvent hydrogen bonding. Hydrogen bonding is known to influence profoundly the chemical shift of a participating proton. Qualitatively at least, the proton resonance is shifted to lower field as the strength of the bond increases[4]. However, solute-solute hydrogen bonds may be neglected due to the invariance of the chemical shift with concentration in the region of interest.

It is logical to presume that the relative strength of the axial and equatorial O-H---- solvent hydrogen bonds will be determined primarily by steric effects, since polar contributions to the bond strengths should be nearly the same. Therefore one could predict that with a given electron donor the equatorial alcohol forms a stronger hydrogen bond than its epimer, due to its greater steric accessibility[5]. Relative glc retention data of epimeric five-, six-, and seven-membered ring alcohols on polar substrates with which the hydroxyl hydrogen can bond support this conclusion[6]. One might conclude that a hydrogen-bonded equatorial hydroxyl proton should resonate at significantly lower field than its axial counterpart. All of the above chemical shift data clearly agree with this. One might also expect the chemical shift difference for the epimeric cycloheptanols to be less than for five- or six-membered epimers, because of the conformational flexibility of seven-membered epimers and consequently the axial alcohol will be only slightly sterically less accessible for hydrogen bond formation. This is indeed observed in the cases of 2-butylcycloheptanol and 2-hexahydrobenzylcycloheptanol (the difference is only 0.15 and 0.14 respectively).

Factors other than the relative strength of the axial and equatorial O-H----DMSO hydrogen bonds also appear to influence the chemical shift difference of axial and equatorial O-H protons in DMSO. One of these factors is likely the differences in O-H proton shielding experienced by the various rotational conformers, as a result of the magnetic anisotropy of the C-C bonds. Such shielding differences certainly affect the relative chemical shifts of axial and equatorial carbinol protons bonded directly to the ring[7].

It is significant that in view of the characteristic chemical shift differences and coupling constants the nmr technique can be used to distinguish not only six-membered but five- and seven-membered ring epimers. These observations appear to provide direct experimental evidence for the configurations and conformations of these epimers.

Experimental. All alcohol samples were prepared by hydrogenating five-, six-, and seven-membered 2-butylidene and 2-benzylidene cyclanols[8] which in turn were prepared by lithium aluminium hydride reduction of the respective cyclanone. All proton magnetic resonance spectra were obtained on a Perkin Elmer R 10 spectrometer at 60 Mc./sec. Tetramethylsilane was used as internal standard. The reported spectral data are the result of several independent measurements using different batches of solvent and chromatographically pure sample. The water concentration in the DMSO varied from about 1% to less than 0.3%. DMSO was dried by heating over calcium hydride and distilling from calcium hydride under reduced pressure (bp ca.80°).

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