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THE FREE ENERGY DIFFERENCE BETWEEN THE AXIAL AND THE EQUATORIAL DISPOSITIONS OF THE HYDROXYL GROUP IN N-METHYL-4-PIPERIDINOL BY PROTON MAGNETIC RESONANCE SPECTROSCOPY

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The free energy difference ($-\Delta G^{o}$) between the equatorial and the axial conformers of cyclohexanol has been studied, during the last decade or so, by various physical methods (1). However, corresponding attention has not been given to those six-membered, saturated rings which contain hetero-atoms. In view of the similarities between a cyclohexane and a piperidine ring, and the importance of conformational studies of 4-piperidinol rings to natural product chemistry, it seems that an investigation into the free energy difference between the axial and the equatorial dispositions of the hydroxyl group on a 4-piperidinol ring should be in order. We have therefore examined the proton magnetic resonance spectra of N-methyl-4-piperidinol (2) as a solute in various media.

Unlike cyclohexanol, where the C_1 proton gives rise to a rather diffused band and where, therefore, band-width must be relied on to calculate the free energy difference (3), N-methyl-4-piperidinol in most solvents exhibits a symmetric septet, from which 2(J* + Jae) - for definition of J*, see ref. (3) - can be measured with an accuracy of ± 0.2 c./sec, by taking the average of four consecutive runs. The pertinent information is listed as Table 1; a typical spectrum of the C_4 proton is given as <u>Fig</u>. 1.

TABLE 1

The p.m.r. Signal of the C_4 Proton of
N-Methyl-4-piperidinol in Various Media

Solvent	C_4 proton chemical shift (τ) [(2J* + 2Jae) c./sec]	
	at 40°	at 80°
CS_2	6.57 (26.5)	6.52 (25.5)
C_6H_6	6.34 (——)*	6.45 (25.6)
$CDCl_3$**	6.40 (27.0)	6.30 (25.7)
$(CD_3)_2SO$	6.55 (26.9)	6.44 (25.6)
D_2O	6.31 (27.4)	6.22 (26.5)

* Signal too broad and diffused to allow an accurate estimation of 2(J* + Jae).

** Dilution to 0.05 molar does not change the (2J* + 2Jae) observed.

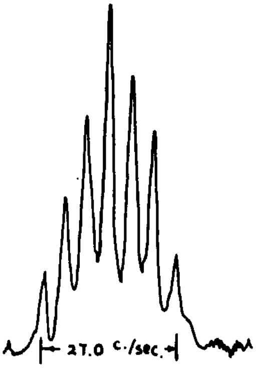
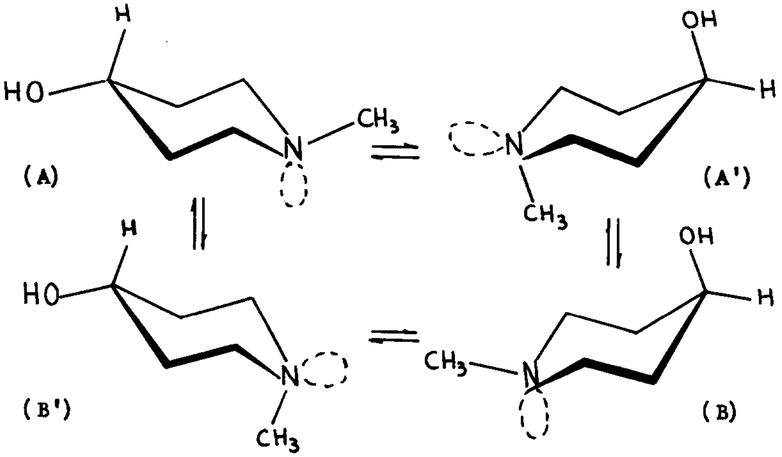


FIG. 1

A typical spectrum of the C_4 proton of N-methyl-4-piperidinol (Solvent: $CDCl_3$; temp. +40°)

Theoretically N-methyl-4-piperidinol can exist in a number of extreme conformations as follow:



Nevertheless, high inversion rates about the nitrogen atom (4) and the relatively large free energy needed for the N-methyl group to assume an axial disposition (5), rule out any appreciable participation of (A') and (B') in the conformational equilibria of N-methyl-4-piperidinol when present as a solute. Non-chair conformations are not considered here as their energies are high compared with those for chair forms (see also ref. 5).

Therefore, the state of dissolved N-methyl-4-piperidinol may effectively be regarded as an equilibrium between conformers (A) and (B), so that the equilibrium constants (K) between (A) and (B), should give the free energy difference ($-\Delta G^o$) between the axial and the equatorial dispositions of the hydroxyl group.

To estimate, from $2(J^* + Jae)$, the molar fraction (X) of the conformer (A) in the equilibrium $(A) \rightleftharpoons (B)$, we need the relevant coupling constants on a 4-piperidinol ring; these are (6):

$Jaa = 11.2$ c./sec., $Jae = 4.1$ c./sec., and

$Jea \cong Jee = 2.5$ c./sec.

From them, and the separations between the terminal lines observed for the C_4 proton - which should equal to $2(J^* + Jae)$ - we calculate the thermodynamic data shown as Table 2.

TABLE 2

Free energy difference observed between the axial and the equatorial dispositions of the hydroxyl group of N-methyl-4-piperidinol in various media

Solvent	X		K		$-\Delta G^{*}(40^{\circ})$	$-\Delta G(80^{\circ})$	ΔG^{**}
	at 40°	at 80°	40°	80°			
CS_2	0.76	0.71	3.17	2.45	0.72	0.63	0.09
C_6H_6	-	0.71	-	2.45	-	0.63	-
$CDCl_3$	0.79	0.72	3.76	2.57	0.82	0.66	0.16
$(CD_3)_2SO$	0.79	0.71	3.76	2.45	0.82	0.63	0.19
D_2O	0.82	0.76	4.56	3.17	0.94	0.81	0.13

* $-\Delta G$'s in kcal./mole; the uncertainties in $-\Delta G$'s correspond to an uncertainty of ± 0.2 c./sec. in $2(J^{*} + Jae)$ should not be more than ± 0.05 kcal./mole.

** ΔG is defined as $-\Delta G(80^{\circ}) - \left[-\Delta G(40^{\circ})\right]$.

From Tables 1 and 2, the following conclusions may be drawn:

a) Solute-solute interactions are not important in determining $-\Delta G^{\circ}$ values for the hydroxyl group in N-methyl-4-piperidinol - see also ref. (7).

b) For an inert solvent, such as CS_2, $\Delta S_x^{\circ} \cong 0$; but for solvents which are capable of interacting with the hydroxyl group, $\Delta S_x^{\circ} \neq 0$; this may either be due to the breaking up of the solute-solvent interactions at higher temperatures, or to the asymmetry of the solvated hydroxyl group.

c) The $-\Delta G^o$ value for the hydroxyl group on a 4-piperidinol ring is very similar to that of cyclohexanol (1) - which further demonstrates that the principles of conformational analysis as applied to cyclohexane systems can be carried over to six-membered, saturated rings containing hetero atoms. The change in ($-\Delta G^o$) in passing from D_2O to CS_2 for N-methyl-4-piperidinol (0.22 kcal./mole at 40°) is almost identical with that reported for cyclohexanol (8) in passing from D_2O to CCl_4 at 28°; this suggests that, despite the differences between $>$NMe and $>CH_2$ groups, the hydroxyl groups in N-methyl-4-piperidinol and cyclohexanol behave similarly under like circumstances.

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2. The N-methyl-4-piperidinol used was a commercial sample from Fluka AG, Switzerland. The twice re-distilled compound had b.p. 78-80°/2.2 mm Hg. All the p.m.r. spectra were

taken on a Varian A-60 spectrometer. The concentrations of the solutions used were all *ca*. 0.5 molar; these, except that in D_2O, were shaken with D_2O before the spectra were run. TMS (tetramethylsilane) was used as internal reference with the organic solvents; with D_2O, TMPS (3-trimethylsilylpropane-1-sulphonic acid sodium salt) was used instead.

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