The Conformational Equilibrium in Piperidine

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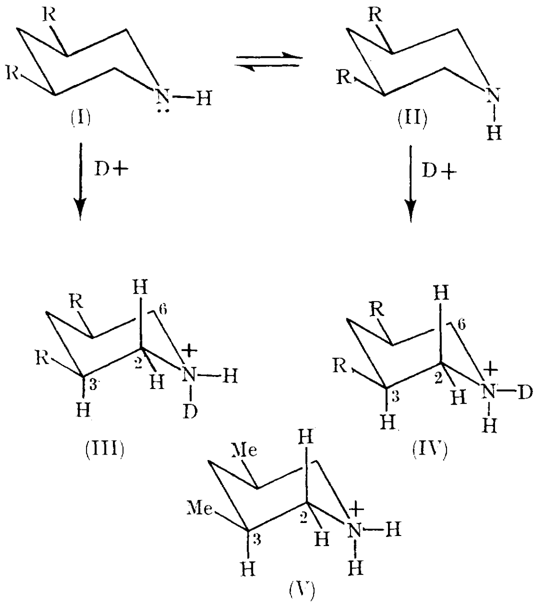
THE position of conformational equilibrium in piperidine (I $\rightleftharpoons$ II; R = H) has been investigated by many methods, leading to widely differing results.[1] Two papers[2] have employed ^{1}H n.m.r. measurements, but the arguments used are open to serious objections. This work also uses ^{1}H n.m.r. spectroscopy and shows that the steric requirements of nitrogen lone-pair and nitrogen-attached hydrogen, in neat piperidine, are almost identical.

In the spectrum of *cis*-3,5-dimethylpiperidine (V) in trifluoroacetic acid the 2,6-axial protons appear at τ 7·30 as a quartet, separations *ca.* 12 c./sec., due to approximately equal couplings with the 1-axial, 2,6-equatorial, and 3,5-axial protons. Each peak is broadened by coupling with the 1-equatorial proton and, probably, by coupling with ^{14}N. The spectrum of pure, dry *cis*-3,5-dimethylpiperidine (I $\rightleftharpoons$ II; R = Me) (50 mg.) in deuteriotrifluoroacetic acid (CF_3CO_2D) (850 mg.)



is unchanged after 2 days, and shows at τ 7·30 a group of seven lines (Figure), consisting of a triplet and a quartet with identical chemical shifts. The triplet (separations *ca.* 12 c./sec.) is due to the 2,6-axial protons of (III), which are coupled, about equally, to the 2,6-equatorial and 3,5-axial protons; the lines are broadened by additional couplings with the 1-equatorial proton and the 1-axial deuterium. The quartet (separations *ca.* 12 c./sec.) is due to the 2,6-axial protons of (IV), which are coupled, about equally, to the 1-axial, 2,6-equatorial, and 3,5-axial protons; the lines are broadened by additional coupling with the 1-equatorial deuterium. From this seven-line resonance, it is concluded that the rate of loss of H^+ or D^+ from (III) and (IV), whether to free base or solvent, is extremely slow under the conditions employed. (The phenomenon is not confined to piperidines: the spectrum of trimethylamine hydrochloride in $CF_3 \cdot CO_2D$ is unchanged after 7 days, and shows a doublet, J *ca.* 5 c./sec., for the methyl protons.) The explanation was confirmed when the use of a different concentration (25 mg. base in 850 mg. CF_3CO_2D) yielded an identical spectrum.

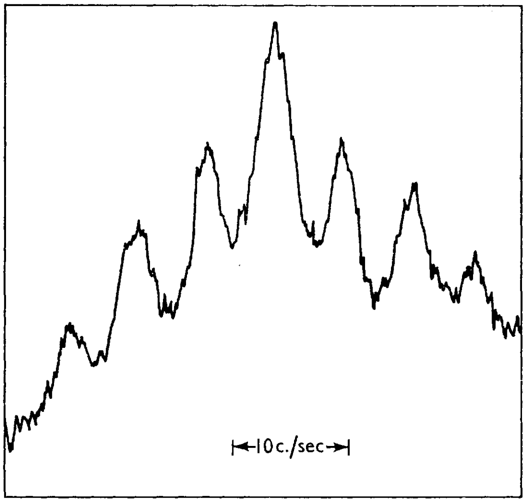


FIGURE. *Resonance of 2,6-axial protons in spectrum of* cis-*3,5-dimethylpiperidine in* CF_3CO_2D.

The relative areas of triplet and quartet, obtained by use of the Du Pont 310 Curve Resolver showed that the mixture of (III) and (IV) contained 54% (III) and 46% (IV) (9 measurements on 3 different spectra, reproducibility ±2%). Since the rate of reaction of base with D^+ is almost certainly much greater than the rate of nitrogen inversion,[3] it follows that *cis*-3,5-dimethylpiperidine (I $\rightleftharpoons$ II; R = Me) contains 54% (I) and 46% (II), the free-energy difference ΔG between (I) and (II) being only *ca.* 0·1 kcal./mole.

It is probable that this conclusion holds for piperidine itself. The result applies to the conformational equilibrium in neat liquid; the effect of solvents remains to be investigated.

(*Received, May* 10*th,* 1968; *Com.* 589.)

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[2] J. B. Lambert, R. G. Keske, R. E. Carhart and A. P. Jovanovitch, *J. Amer. Chem. Soc.*, 1967, **89**, 3761; M. J. T. Robinson, *Tetrahedron Letters*, 1968, 1153.

[3] *cf.* M. Saunders and F. Yamada, *J. Amer. Chem. Soc.*, 1963, **85**, 1882; J. J. Delpuech and (Mrs.) M. N. Deschamps, *Chem. Comm.*, 1967, 1188.