Nuclear Magnetic Resonance Spectroscopy: Nitrogen Inversion Rate of 1,2,6-Trimethylpiperidine

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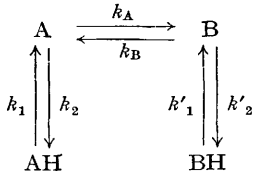
THE n.m.r. determination of nitrogen inversion rates of *N*-heterocyclic amines has two difficulties: the high rate values and the ambiguity between ring and nitrogen inversion. Only heavily strained cycles (*i.e.*, aziridines[1]), and some systems with restrictions resulting presumably from simultaneous nitrogen inversions,[2] or steric hindrance[3] have been studied, generally at low temperatures. By an extension of Saunders's method,[4] we have determined the nitrogen inversion rate of amines, for certain piperidinic compounds. The substrate 1,2,6-trimethylpiperidine, with 2,6-methyls in the *cis*-position, has been chosen, as it exists in two different observable geometric isomers when completely protonated,[5,6] the former AH is completely *cis*, and the latter BH with its methyl groups *trans*. In progressively basic aqueous solutions (pH = 0—9), nitrogen inversion occurs in the very small amount of free amine, according to the following scheme:



This inversion carries AH into BH (A and B do not intervene in the spectrum, owing to their small concentrations), thus bringing a coalescence of AH and BH lines. The value of k_A and k_B is then approximately:

$$\frac{1}{\tau_{AH}} = \frac{k_A K_1}{[H^+]} \text{ and } \frac{1}{\tau_{BH}} = \frac{k_B K_1}{[H^+]} \quad (1)$$

τ_{AH} and τ_{BH} being the life-time of isomers AH and BH, as determined by n.m.r. line-broadening, and K_1 ($=10^{-10\cdot21}$) the acid dissociation constant of AH, as long as the ratio A/AH (or B/BH) is small ($\leqslant 10^{-2}$).

The spectrum was observed and an order of magnitude of *nitrogen inversion* determined at 33° (the temperature of the probe of the Perkin-Elmer R-10 spectrometer). At pH = 0, each isomer, as described earlier in formic acid,[5] displays a N-Me and a C-Me doublet [Figure (a)]. The attribution of the different doublets to the same isomer (I) (the most abundant) or (II) is made easily by means of the population ratio (*ca.* 2 : 1), (I) and (II) being either AH and BH, or, alternatively, BH and AH, the choice being immaterial for our purpose, [with presumably (I) = BH,[6] *i.e.*, the triequatorial isomer, the ratio AH/BH corresponding effectively here to thermodynamic equilibrium].

When deprotonation occurs at a sufficient rate (pH ~ 3—4) we observe the expected coalescence of each N-Me doublet into a single line[5] while the C-Me doublets remain unchanged [Figure (b)]. This clearly means that process A $\rightleftarrows$ B is too slow on the n.m.r. time scale. This situation prevails till pH ~ 8: the lifetime of transient free amine

A or B then becomes long enough to ensure nitrogen inversion. We observe a progressive *simultaneous* coalescence [Figure (c)] of the two N-Me peaks into a single one, and of the two C-Me doublets into a unique one [Figure (d)], at pH $\simeq$ 9.

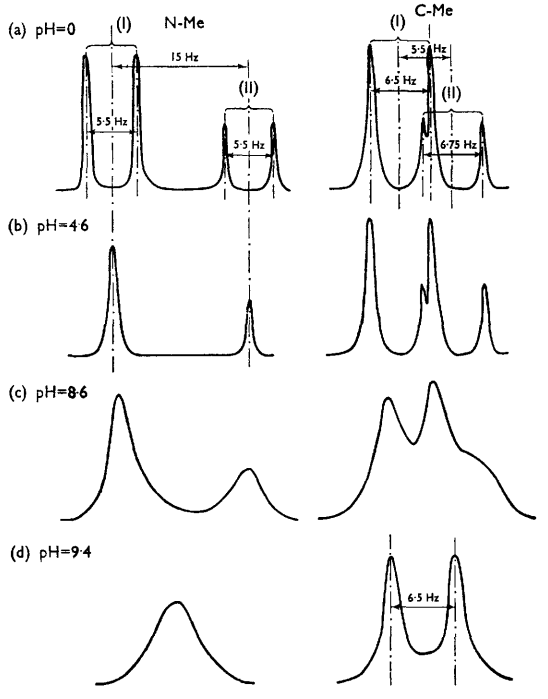


FIGURE. *N.m.r. spectrum of aqueous solutions of* 1,2,6-*trimethylpiperidine at* 33°, *as a function of the* pH.

Although more elaborate numerical methods of line-shape analysis will be devised, we give here the order of magnitude of k_A (or k_B). Using the two N-Me peaks at pH = 8·35, for which A/AH $\simeq$ 0·011 a simple comparison between the experimental curve and a set of theoretical spectra computed for a series of τ_{AH} (or τ_{BH}) values, yields the following approximate values of k_A and k_B:

$$k_A = 220 \pm 20 \text{ sec.}^{-1}$$

$$k_B = 500 \pm 40 \text{ sec.}^{-1}$$

This value which refers to an actual nitrogen *inversion* proves to be much slower, by a factor of $\simeq 10^3$, than for tertiary acyclic amine (2×10^5 sec.$^{-1}$ at 25° for dibenzylmethylamine).[4] Whether this low value is due intrinsically to the piperidine ring, or to steric hindrance by C-Me groups, will be examined later by comparison of progressively substituted *N*-methylpiperidines.[5] While variable-temperature experiments still remain to be performed, this rate could reveal, on the basis of an activation barrier of about 5—15 kcal./mole,[7] a very slow process at low temperatures, which would lead to the reconsideration of the generally accepted assumption that nitrogen inversion is fast as compared to ring inversion in *N*-heterocyclic amines.

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[1] See for example, A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.*, 1958, **80**, 5203; T. J. Bardos, C. Szantay, and C. K. Navada, *ibid.*, 1965, **87**, 5796; F. A. L. Anet and J. M. Osyany, *ibid.*, 1967, **89**, 352; S. J. Brois, *ibid.*, p. 4243.
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