Nitrogen Inversion Rate of Substituted Piperazinium Chlorides and Relative Acidities of their two Ammonium Groups

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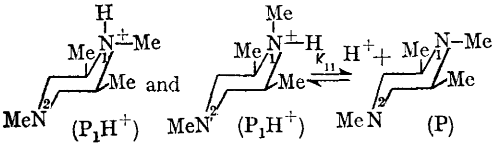
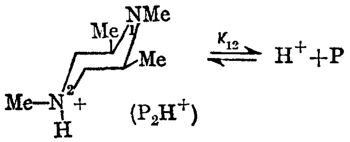
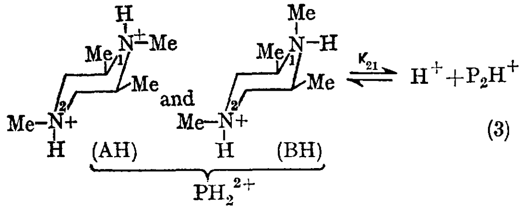
AN unequivocal nitrogen inversion rate of piperazinium monochloride has been determined by a method previously described for piperidine.[1] The n.m.r. spectrum of the *cis*-2,4-isomer of 1,2,4,6-tetramethylpiperazine (P) is observed at 33·3° in 0·4 molar hydrochloric solutions from pH = 10·75 to 0. The predominant species are a mixture of P and the mono-cation PH^+ (pH 10·75—6), or a mixture of PH^+ and the dication PH_2^{2+} (pH 6—3), or PH_2^{2+} alone (pH 2—0). The complex behaviour of n.m.r. signals of the methyl group (Figure 1)† can be rationalised by assuming equilibria (1), (2), (3), (4), where we attribute the same symbol for species giving one averaged line for any pH, and where any basic N-Me may also be axial:



(1)



(2)



(3)

$$PH_2^{2+} \text{ (i.e. AH and BH) } \underset{}{\overset{K_{22}}{\rightleftharpoons}} H^+ + P_1H^+ \quad (4)$$

The apparent first and second ionisation constants:

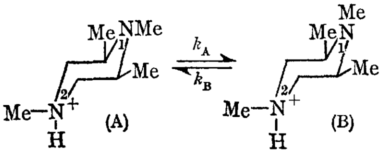
$$K_1 = 3{\cdot}04 \times 10^{-9} \text{ and } K_2 = 5{\cdot}77 \times 10^{-5}$$

measured by potentiometric titration at 25° in 0·04 molar aqueous solution, are related to the K_{ij} by the equations:

$$\frac{K_{21}}{K_2} = \frac{K_1}{K_{12}} = \frac{[P_2H^+]}{[PH^+]} \quad (=\lambda_2), \text{ and}$$

$$\frac{K_{22}}{K_2} = \frac{K_1}{K_{11}} = \frac{[P_1H^+]}{[PH^+]} \quad (=\lambda_1 = 1 - \lambda_2)$$

Proton exchange between the different species (and water also) is so fast that no spin decoupling of N–Me signals with the N–H acidic protons occurs in this pH range. At pH = 0, AH and BH display two doublets [Figure 1 (f)] for the C–Me groups, as in 1,2,6-trimethylpiperidine[1] (PP) at 60 Mz, and an apparent triplet[2] at 100 Mz; the relative areas of its outer components yield the ratio: [AH]/[BH] = 84/16. The *N*-methyls are represented by a small line (δ_3) due to N(1)-Me of BH, and a larger one (δ'_2) ,downfield, for N(1)-Me of AH *plus* N(2)-Me of AH *and* BH, as evidenced by their area ratio (184/16), which implies that N(2)-Me should assume only an equatorial position with the same chemical shift as an equatorial N(1)-Me. From pH = 0 to 2 [Figure 1 (d), (e), and (f)], an inversion of N(1) *specifically* is observable, bringing AH into BH, by means of equilibria (3), and (5) between conformers A and B of P_2H^+:



(5)

The C–Me quartet therefore merges into a doublet, while, *simultaneously*, the *N*-methyls display a complex spectrum originating from the addition of a fixed line (a) at δ'_2 for N(2)–Me of AH and BH, *plus* a broad line (b) at δ'_1 resulting itself from the coalescence of previous lines (pH = 0) for N(1)–Me of AH (δ'_2) and BH(δ_3), as evidenced by the ratio:

$$\frac{\delta'_1 - \delta_3}{\delta'_2 - \delta'_1} \sim \frac{84}{16}$$

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† 100 MHz spectra were kindly supplied by Professor Gagnaire's Laboratory.

(δ'_1 is actually measured before complete coalescence because of appearance of PH^+ for pH > 2). At pH $= 2$, it is possible to deduce line (b) by substraction, therefore to compute the lifetimes[1] τ_{AH} and τ_{BH}, then the rate constant k_A, according to the formula[1]:

$$k_A = \frac{1}{\tau_{AH}} \cdot \frac{[H^+]}{K_{21}} = 1{\cdot}51\ 10^{-4}\ \text{sec.}^{-1},$$

a value about 70 times larger and 10 times smaller than for PP and 1,4-dimethylpiperazinium chloride[4] respectively. The second result may prove a steric hindrance of α-methyls to nitrogen inversion; the first one shows that this inversion in piperidine is made easier by replacement of a saturated carbon in position 4 by an equally tetragonal nitrogen (that remains actually so during inversion of the reference nitrogen, preventing any synchronous motion[5]), which could be interpreted by an improved flexibility of the cycle, thus promoting the planar trigonal transition state.

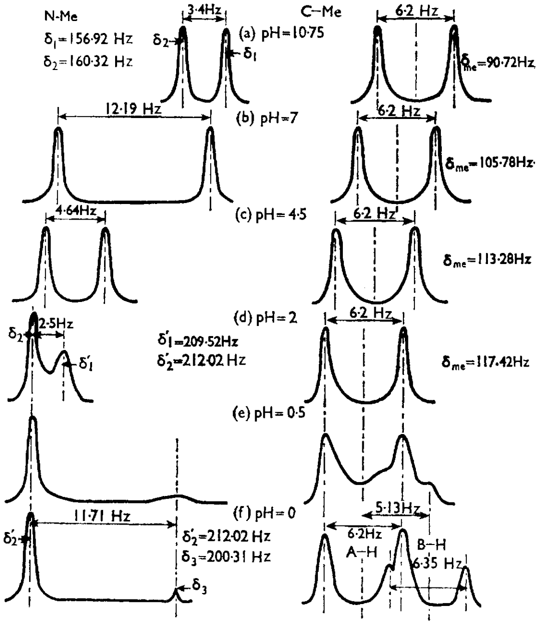

FIGURE 1. *N.m.r. spectrum of aqueous solutions of* 1,2,4,6-*tetramethylpiperazine, at* 33·3°, *as a function of the* pH (Me_4Si *as an external reference*).

In basic medium (pH $= 10{\cdot}75$), P displays one line (δ_1) for N(1)–Me, and another equal one (δ_2) for N(2)–Me, *downfield*, for it corresponds to δ'_2 on account of continuity from pH $= 2$. These lines (as well as $\delta_{C\text{-}Me}$) shift progressively downfield (pH 10·75—6), because each kind of methyl give a separate averaged signal (from P, P_1H^+ and P_2H^+), that can be computed from δ_1, δ_2, δ'_1, δ'_2 and λ_2. The distance δ between N(1)–Me and N(2)–Me lines grow from 3·4 Hz to a maximum of 12·19 Hz at pH 7 [Figure 1 (b)], according to formula:

$$\delta = \delta_2 - \delta_1 + \frac{[RH]}{0{\cdot}4}\,[\lambda_2(\delta'_2 - \delta_2) - \lambda_1(\delta'_1 - \delta_1)],$$

whose validity is shown in Figure 2 (a) yielding: $\lambda_2 = 0{\cdot}59 \pm 0{\cdot}01$, which means that:

$$\frac{K_{12}}{K_{11}} = \frac{K_{22}}{K_{21}} = \frac{\lambda_1}{\lambda_2} \simeq \frac{2}{3}$$

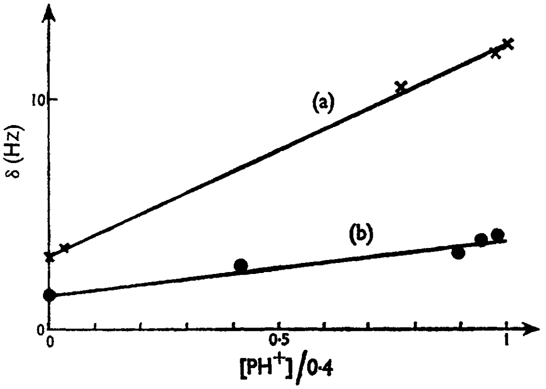

FIGURE 2. *Plot of* δ *versus* [PH].

For the first time, the relative basicities of an unsymmetrical diamine is thus obtained: the $\alpha\alpha'$-disubstituted nitrogen N(1) is truly the least *basic*, or its conjugated ammonium acid the stronger one ($\Delta pK = +\,0{\cdot}17$). This is confirmed by our first results in the study of 1,2,4-trimethylpiperazine [Figure 2 (b)], where $\lambda_2 = 0{\cdot}52$ and $\Delta pK = +0{\cdot}035$, an intermediate value for one α-methylation.

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