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PROTON TRANSFERS OF SUBSTITUTED AMMONIUM SALTS—XIII

N-INVERSION OF PIPERIDINES IN AQUEOUS ACIDIC SOLUTIONS

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Abstract—The kinetics of the nitrogen inversion of 1,2-dimethyl-(2); 1,4-dimethyl-(8); 1-*trans*(2,6)-trimethyl-(4); 1,4-*cis*(2,6)-tetramethyl-(7) and 1,2,2,6,6-pentamethyl-(5) piperidines have been inveatigated in aqueous acidic solution (pH ≈ 6.5–8.5) at 33° by dynamic NMR. In all cases, two isomeric cations AH^+ and BH^+ are observed in acidic conditions (pH < ~6), and the nitrogen inversion is brought to the NMR time scale as a result of a progressive deprotonation of the cations into their conjugate amines on increasing the pH. Low rate constants k_A are obtained for α-substituted or unsubstituted compounds ($k_A \simeq 10^3\ s^{-1}$), except for piperidine 5 where the rate constant $k_A = 4.3 \times 10^5\ s^{-1}$ is of the same order of magnitude as the one found for tertiary acyclic amines.

Pyramidal inversion on N, P and S atoms has been the subject of many experimental and theoretical studies.[1] Nitrogen inversion has some important aspects in spectroscopy and in organic synthesis: the splitting of the vibration levels of ammonia[2] used to advantage in the first atomic clock, the impossibility of resolving the optical isomers of most tertiary amines at room temperature for example. The dynamics of nitrogen inversion for the latter compounds has been mainly studied by ^1H or ^{13}C NMR.[1,3] The tertiary amines were used as a neat liquid or dissolved in a low-melting solvent. These amines should possess either diastereotopic non-equivalent protons that are interchanged through nitrogen inversion (as in dibenzylmethylamine[4,5]) or exist under two interconverting stereoisomers A and B,[6] as in the N-methylpiperidines which are examined in this paper. Low temperatures are indeed necessary in most cases to bring the exchange of nuclei to the NMR time-scale. This means that aqueous solutions are not convenient for most amines. This medium however is a very important one, especially in biological systems, for which nitrogen inversion could be a significant dynamic process. Fortunately another method has been described by Saunders and Yamada[5,7] using aqueous acidic solutions and measuring nuclear exchange as a function of the pH. In these conditions the isomeric amines A and B are almost fully protonated (by *ca* 99% or more), and the cations AH^+ and BH^+ only are detected by NMR. Nitrogen inversion takes place on the very small amount of the free amines according to the general kinetic Scheme 1:

$$AH^+ \underset{k_p}{\overset{k_d}{\rightleftharpoons}} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \underset{k_d}{\overset{k_p}{\rightleftharpoons}} BH^+. \qquad (1)$$

The nuclear site exchange probabilities k_{NA}, k_{NB}:

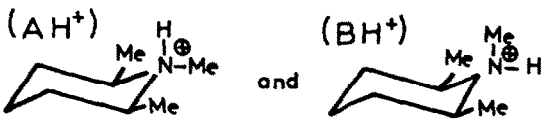
$$AH^+ \underset{k_{NB}}{\overset{k_{NA}}{\rightleftharpoons}} BH^+ \qquad (2)$$

may be related to the nitrogen inversion rates k_A, k_B by the following equations[8]

$$k_{NA} = k_A[A]/[AH^+] = k_A K_i \gamma / a_{H^+}$$
$$k_{NB} = k_B[B]/[BH^+] = R k_{NA}$$

where $a_{H^+} = e^{-2.303\,pH}$ is the activity of the hydronium ion, γ the activity coefficient of a monoelectrolyte, K_i the ionization constant of the ammonium salt and R the equilibrium ratio: $R = [AH^+]/[BH^+]$.

We have already described[6,9,10] a study of the 1,(*cis*2,6)-trimethylpiperidine (3) in which the isomers AH^+ and BH^+ are written as



The present paper extends this work to five more piperidines, the 1-*cis* 2,4,6-tetramethyl-(7), the 1,2-dimethyl-(2), the 1-*trans* 2,6-trimethyl-(4), the 1,2,2,6,6-pentamethyl-(5), the 1,4-dimethyl (8) piperidines.

Experimental procedures and results

The preparation of the products and solutions,[9] and the measurement of pH's and pK's[11] have been described in previous publications. Rate constants k_A, k_B result from pH values in a 0.4 molar aqueous acidic solution of each amine at 33°. NMR spectra of compounds 2, 3 and 4 were recorded at 60 MHz on a Jeol C60 HL spectrometer. A Varian HA-100 apparatus (100 MHz) was used for the other amines. The exchange probabilities were derived from a total lineshape analysis applied to the coalescence of a symmetrical (5) or unsymmetrical (2, 3, 7, 8, 9) doublet, or of the sum of two symmetrical doublets (4). The pK's of the amines, the pH range for coalescence, the ratio of the two isomers R, the nitrogen inversion rate constants, k_A, k_B, and the related free energies are displayed in Table 1. Two analogous amines, the piperidine (3)[6,9] and the 1,4-*cis* 2,6-tetramethylpiperazine (9)[12] are also reported for convenience.

DISCUSSION

The data relative to piperidine 7 confirm our earlier statement concerning piperidine 3:[6] nitrogen inversion is slow as compared to the rate measured for tertiary acyclic amines in similar conditions:[5,7] $2 \times 10^5\ s^{-1}$ for dibenzylmethylamine (10) at 25° for example, or for amines in non-aqueous solvents ($10^8\ s^{-1}$ for a solution of

Table 1. Nitrogen inversion rates of various N-methylpiperidines in 0.4 molar aqueous acidic solution at 33°C

Amine	pK	Nature of the observed signals with their chemical shift difference	pH range for coalescence	ratio R of the two isomers (ΔG, kcal.mole^{-1} on the 2nd line)	k_A and k_B ($\Delta G_A^{\ddagger}$, $\Delta G_B^{\ddagger}$, kcal.mole^{-1} on the 2nd line)	
	10.47	N-methyle (0.25 ppm)	8-8.3	2.33 0.51	810 13.86	1892 13.34
	10.54	N-methyle (0.27 ppm)	7.6-8.0	2.41 0.53	660 13.99	1537 13.47
	4.13	N-methyle (0.19 ppm)	1.5-2.3	5.26 1.00	1.47×10^5 10.70	7.73×10^5 9.70
	10.29	N-methyle (0.08 ppm)	7.6-7.95	4.44 0.91	1270 13.52	5590 12.63
	10.79	C-methyle (0.03 ppm)	7.4-8.1	1 0	5100 12.74	5100 12.74
	11.13	C-methyle (0.04 ppm)	6.7-7.6	1 0	4.28×10^5 10.05	4.28×10^5 10.05
	10.05	N-methyle (0.04 ppm)	6.6-6.9	~8.4 ~1.30	1040 13.71	~8740 ~12.41

amine 10 in vinyl chloride,[4] or 10^6–$10^7\ s^{-1}$ for piperidine 3 in dimethyl sulphoxide[13] or as the neat liquid[14]). We have assigned this phenomenon to a non-inverting association of the free amine with its conjugate cation: $AH^+ \cdots O\text{–}H \cdots A$ on the basis of an observed proportionality of k_A to the reciprocal of the concentration of the piperidinium salt.[13] If we turn to the analogous piperazinium monocation 9,[12] we observe a much higher inversion rate $k_A = 1.47$ against $0.0066 \times 10^5\ s^{-1}$, a point which may be easily rationalized. The observed spectrum is indeed relative to the piperazinium dication. The inverting monocation should associate with this dication, which is highly unlikely on account of a strong electrostatic repulsion between the two positively charged species.

If we now examine the other piperidines of the table, an additional feature arises from a cyclohexane-like ring inversion superimposed to the nitrogen inversion. However this process remains fast on the NMR time scale since no line-broadening was observed using acidic solutions of piperidines in methanol at low temperatures (up to −80°). Nitrogen inversion thus carries one mixture of two chair conformers (AH^+) into another one (BH^+), and the rates k_A, k_B observed result from a weighted mean of those relative to each stereoisomer of the corresponding mixture (AH^+ and BH^+, respectively).

The main component of 2-AH^+ (Fig. 1) is the diequatorial (ee) isomer, and k_A is close to the rate $k_{eq.}$ at which a N-Me substituent is brought from an equatorial to an axial position (the rate for the reverse process is called $k_{ax.}$ in the following). We observe that the rate constant $k_{eq.} = 1.27 \times 10^3\ s^{-1}$ is of the same order of magnitude as the corresponding value for piperidine 3. The alternative mixture 2-BH^+ contains approximatively equal contents of the N-equatorial-C-axial (ea) and N-axial-C-equatorial (AE) stereoisomers. If we assume that the rate constant $k_{eq.}$ is not modified from AH^+ to BH^+, we may derive the rate constant $k_{ax.}$ (relative to the ae isomer) from $k_B = (k_{eq.} + k_{ax.})/2$, whence $k_{ax.} = 9.91 \times 10^3\ s^{-1}$. A similar analysis can be performed with piperidine 8 (Fig. 2), where $k_{eq.} = 1.04 \times 10^3$ and $k_{ax.} = 1.64 \times 10^4\ s^{-1}$. Again we observe that the equatorial rate constant $k_{eq.}$ is not sensitive to the degree of α-substitution.

The solution of piperidine 4 contains two pairs of optical stereoisomers (Fig. 3), in which the N-methyle substituent is either equatorial (75% of each mixture, AH^+ and BH^+) or axial (25%).[9] The two equally abundant mixture AH^+ and BH^+ give rise to a single N-Me signal and two C-Me symmetrical doublets of equal intensities. Nitrogen inversion brings about the coalescence of these two doublets into a single one. The apparent rate constant k_A ($= k_B$) results from a weighted mean $k_A = 0.75k_{eq.} + 0.25k_{ax.}$. This relationship allows to compute $k_{ax.} = 16{,}800\ s^{-1}$ if we assume $k_{eq.} = 1270\ s^{-1}$ as in piperidine 2.

At last the acidic solutions of piperidine 5 contain two mixtures of conformers (Fig. 4). Although identical on a chemical point of view, these two mixtures give rise to

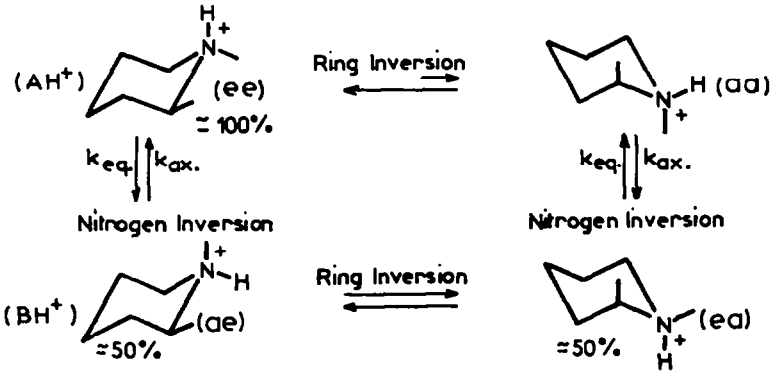


Fig. 1. Nitrogen and ring inversion in the 1,2-dimethyl-piperidinium cation (2).

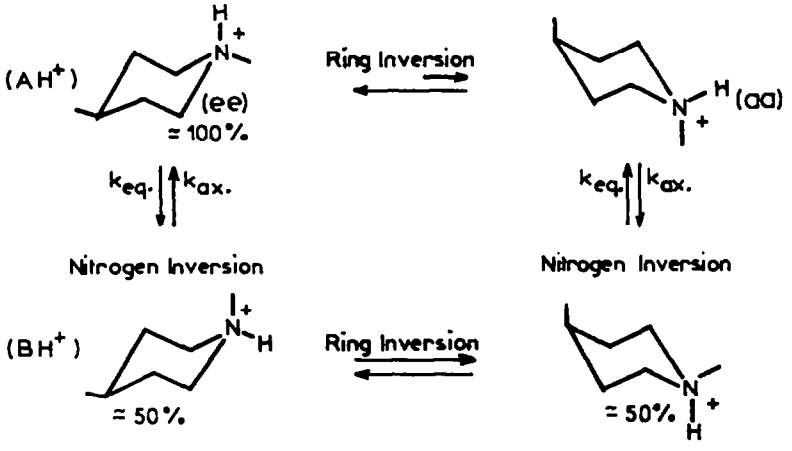


Fig. 2. Nitrogen and ring inversion in the 1,4-dimethyl-piperidinium cation (3).

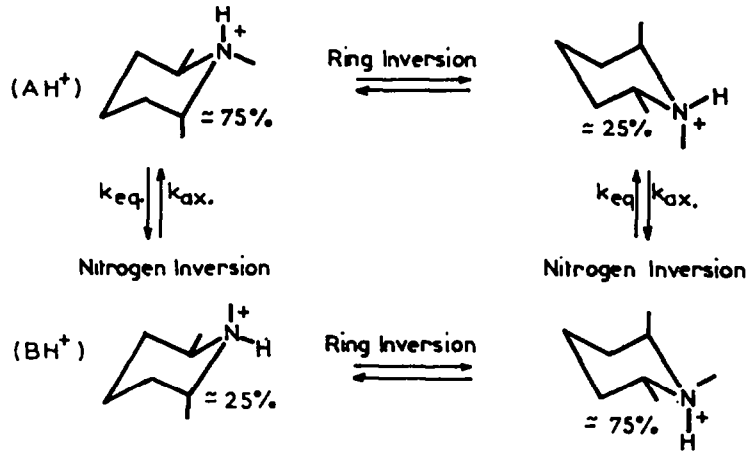


Fig. 3. Nitrogen and ring inversion in the 1-(*trans* 2,6)-trimethylpiperidinium cation (4).

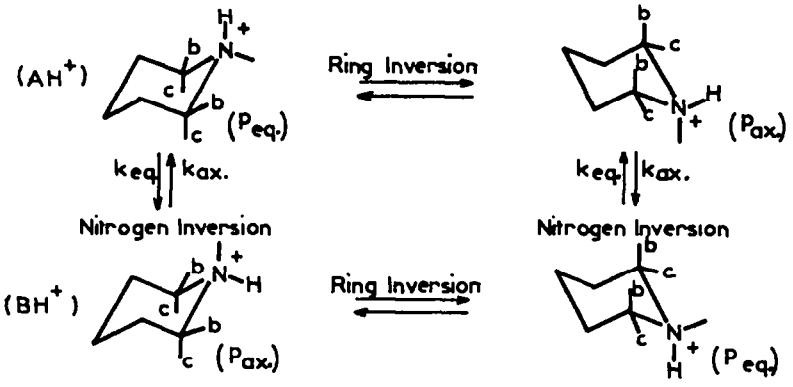


Fig. 4. Nitrogen and ring inversion in the 1,2,2,6,6-pentamethylpiperidinium cation (5).

different chemical shifts for the individual C-Me groups (b and c on the figure) as a result of two unequal weighted means of equatorial and axial chemical shifts. Two closely spaced singlets of equal intensities are thus observed which are coalescing into a single line as the pH is raised up to *ca* 7 units. The apparent rate constant k_A ($=k_B$) again is a weighted mean

$$k_A = p_{ax.}k_{ax.} + p_{eq.}k_{eq.}$$

where $p_{ax.}$ and $p_{eq.}$ are the unknown proportions of the two stereoisomers where the N-Me substituent is either axial or equatorial respectively. The equatorial isomer is likely to be predominant, so that $k_{eq.}$ has an order of magnitude of 10^5, a value which is much larger than those obtained for all the other piperidines investigated. The overall rate constant $k_A = 4.3 \times 10^5\ s^{-1}$ is close to the one observed for piperazine **9**, thus suggesting that the association of the piperidine **5** with its conjugate cation is again impossible, presumably on account of steric hindrance around the N atom. Another reason could be the flatness of the piperidinium ring, which may be quantitatively characterized by the angle $C_2C_3C_4 = 111.5°$ and 112.9° for the N-methylpiperidinium[16] and the 3-AH^+ cations,[17] and 113.5°, 114.4°[18] for analogues of **5**. This flatness reveals an increase in the energy of the pyramide structure as a result of steric interactions, whereas little change has been predicted in the energy of the planar intermediate structure.[3,20] An enhancement of nitrogen inversion could thus accompany the flattening of the piperidinium ring. Such an explanation however is not consistent with a decrease of the nitrogen inversion rate from **8** to **3**.

CONCLUSION

The N-heterocyclic analogues of cyclohexane suffer an abnormally slow nitrogen inversion in aqueous solutions ($k_{eq.} \simeq 10^3\ s^{-1}$), except if the presumed association of the amine with its conjugate cation is forbidden for steric or electrostatic grounds ($k_{eq.} \simeq 10^5\ s^{-1}$). The inversion rate of a N-Me substituent is smaller and relatively constant when this substituent is initially equatorial, this rate is faster and variable with α-substitution for the reverse process—as a result, presumably, of strong 1–3 and 1–5 diaxial interactions. The presence of α-Me substituents or of a simultaneous cyclohexane-like ring inversion do not seem to be very important factors. At last nitrogen inversion seems to be faster when it carries one isomer or a mixture of stereoisomers into another one of the same energy content (**4** and **5** faster than **2** and **3**).

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