(1969); (b) G. Porter and M. R. Topp, *Proc. R. Soc. London, Ser. A*, **315**, 163 (1970).
(17) (a) K. Sandros, *Acta Chem. Scand.*, **18**, 2355 (1964); (b) P. J. Wagner, *Mol. Photochem.*, **1**, 71 (1969); (c) A. A. Lamola, *J. Am. Chem. Soc.*, **92**, 5045 (1970).
(18) P. J. Wagner and T. Nakahira, *J. Am. Chem. Soc.*, **95**, 8474 (1973); **96**, 3668 (1974).
(19) R. W. Taft, Jr., and C. Lewis, *J. Am. Chem. Soc.*, **81**, 5343 (1959).
(20) P. J. Wagner, T. Jellinek, and A. E. Kemppainen, *J. Am. Chem. Soc.*, **94**, 7512 (1972).
(21) (a) P. J. Wagner, J. M. McGrath, and R. G. Zepp, *J. Am. Chem. Soc.*, **94**, 6883 (1972); (b) H. Kobashi, T. Morita, and N. Mataga, *Chem. Phys. Lett.*, **20**, 376 (1973).
(22) R. W. Anderson, *J. Chem. Phys.*, **61**, 2500 (1974).
(23) R. L. Livingston and C. N. R. Rao, *J. Phys. Chem.*, **64**, 756 (1960).
(24) H. E. O'Neal and S. W. Benson, *J. Phys. Chem.*, **71**, 2903 (1967).
(25) F. D. Lewis, R. W. Johnson, and D. R. Kory, *J. Am. Chem. Soc.*, **96**, 6100 (1974).
(26) W. S. Saunders, Jr., and A. W. Dimock, unpublished results; A. W. Dimock, Ph.D. Thesis, Rochester University, 1972.
(27) E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, **22**, 238 (1957).
(28) D. I. Stan, H. Bulbrook, and R. M. Hixon, *J. Am. Chem. Soc.*, **54**, 3971 (1932).
(29) A. E. Kemppainen, M. J. Thomas, and P. J. Wagner, *J. Org. Chem.*, **41**, 1294 (1976).
(30) (a) T. W. Thompson, *Chem. Commun.*, 532 (1968); (b) T. Severin and B. Bruch, *Chem. Ber.*, **98**, 3847 (1965); (c) R. A. Jones, *Aust. J. Chem.*, **16**, 93 (1963); (d) R. W. Guy and R. A. Jones, *Spectrochim. Acta*, **21**, 1011 (1965).
(31) R. Abramovitch and E. P. Kyba, *J. Am. Chem. Soc.*, **96**, 480 (1974).

Proton Transfers of Substituted Ammonium Salts. 14. The 1,*cis*-2,6-Trimethylpiperidinium Ion in Anhydrous Acidic Dimethyl Sulfoxide

Jean-Jacques Delpuech* and Bernard Bianchin

Contribution from the Laboratoire de Chimie Physique Organiqua, ERA CNRS 222, University of Nancy I, C.O. 140, F 54037 Nancy Cedex, France.
Received April 11, 1978

Abstract: The kinetics of nitrogen inversion of the title compound has been studied at 25 °C in acidic Me_2SO using variable pH (from −0.3 to 7.7) and piperidine concentrations C_0 (0.2–0.5 M). The two isomeric piperidinium cations AH^+ and BH^+, where the *N*-methyl is in equatorial or axial position, respectively, are observed either by DNMR using a solution of both isomers in equilibrium or by equilibration NMR using a solution initially containing one isomer (AH^+) only. In both cases, the interconversion (i) is brought to within the appropriate time scale through protonation of the nitrogen atom according to

$$AH^+ \underset{k_{NB}}{\overset{k_{NA}}{\rightleftharpoons}} BH^+ \text{ (i) } AH^+ \underset{k_p}{\overset{k_d}{\rightleftharpoons}} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \underset{k_d}{\overset{k_p}{\rightleftharpoons}} BH^+ \text{ (ii)}$$

the scheme in (ii). Three different laws are obtained: $k_{NA} + k_{NB} = 120.4 \times 10^{-7} C_0/[H^+]$ or 3×10^{-4} or $3.5 \times 10^{-4}/[H^+]$ (s^{-1}) according to the pH range investigated (pH >2 or 0 < pH < 2 or pH < 0, respectively). They can be accounted for when the deprotonation and reprotonation rates are taken into consideration: $k_d = k_3$ [piperidine] + k_1, and $k_p = k_3$[piperidinium ion] + k_{-1}, where $k_3 = 2.70 \times 10^4$ M^{-1} s^{-1}, $k_1 = 3 \times 10^4$ s^{-1}, and $k_{-1} = 6.7 \times 10^5$ M^{-1} s^{-1} refer to the reactions

$$AH^+ \text{ (or } BH^+) + (A + B \xrightarrow{k_3} A \text{ (or B)} + (AH^+ + BH^+) \text{ and } AH^+ \text{ (or } BH^+) + Me_2SO \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A \text{ (or B)} + Me_2SO\cdots H^+$$

Compared to previous data in aqueous solutions, the proton transfer and nitrogen inversion rates are respectively decreased and increased by four and three orders of magnitude. These results illustrate the importance of water as a small bridging molecule both allowing fast proton transfers within sterically hindered acid-base pairs and promoting the formation of associated species, $A\cdots H_2O\cdots AH^+$, which are not likely to undergo inversion.

Introduction

Studies of proton transfer in aprotic solvents have been performed mainly for the purpose of comparison with aqueous solutions. One of the objectives of such studies is to try to elucidate by comparison the role of the water molecule in these transfers.[1] On account of its amphoteric properties and of its small size, this molecule may be tentatively assumed to play the role of an intermediary proton vector between an acid AH and a base B, thus facilitating the exchange and increasing its rate according to the equation

$$AH + H{-}O{-}H + B \rightleftarrows A + H{-}O{-}H + HB$$

This assumed role could be of fundamental importance in biological media[2] where enzyme catalysis often involves the protonation and deprotonation of the active site in an aqueous environment at a fixed pH.

The enhancement of proton transfer by an interstitial water molecule has been clearly demonstrated for the first time by Grunwald and co-workers, using methylammonium ions (AH^+) in aqueous acidic solutions of variable pH.[3] The deprotonation of AH^+ was accounted for by the set of reactions

$$AH^+ + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A + H_3O^+ \quad \text{(R1)}$$

$$AH^+ + OH^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} A + H_2O \quad \text{(R2)}$$

$$AH^+ + A \underset{k_3}{\overset{k_3}{\rightleftharpoons}} A + AH^+ \quad \text{(R3)}$$

$$AH^+ + H{-}O{-}H + A \underset{k_{3'}}{\overset{k_{3'}}{\rightleftharpoons}} A + H{-}O{-}H + AH^+ \quad \text{(R'3)}$$

among which mechanism R'3 is of the type defined above (where B is replaced by the conjugate base A of AH^+). Mechanisms R3 and R'3 only were predominant in moderately acidic solutions (pH ≃ 3–5). The weight of reaction R'3 compared to that of R3 strongly depends on the structure of the ammonium salt, from about 10% (NH_4^+) to 50%

0002-7863/79/1501-0383$01.00/0

($MeNH_3^+$), 90% ($Me_2NH_2^+$), and more than 90% (Me_3NH^+). In the same time, the magnitude of k_3' decreases along the same series: $10^{-8}\,k_3' = 11.7, 4.0, 0.5$, and $0.3\ M^{-1}\ s^{-1}$, respectively. These results showed that sterically hindered ammonium ions can rapidly exchange their acidic proton with their conjugate base only in the presence of a bridging water molecule. These observations were extended to a series of protic solvents[4] on the one hand, and to a series of sterically hindered pyridinium salts[5] on the other hand, thus emphasizing the role of the solvent participation in proton transfer reactions of amines and their conjugate acids.

The present work aims at putting these conclusions on a firmer basis yet by using a sterically hindered amine, 1,*cis*-2,6-trimethylpiperidine (**3**), in a dipolar aprotic solvent, dimethyl sulfoxide (Me_2SO), in which the enhancement of the proton transfer by an interstitial water molecule should disappear. Dramatic changes from water to Me_2SO were indeed observed, which are worth mentioning in the following.

Choice of the Solvent and the Substrate

Dimethyl sulfoxide was chosen as the solvent because of its large dissolving and dissociating powers, its wide range of accessible pH and pK values, and its general use as an organic, inorganic, or biochemical medium. We have previously studied the deprotonation rate of the unsubstituted ammonium ion NH_4^+ in this solvent.[6] Three mechanisms may be envisaged in this medium according to the nature of the attacking base, namely, the solvent molecules or the conjugate base of either the solvent or the ammonium salt

$$AH^+ + Me_2SO \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A + Me_2SO\cdots H^+ \qquad (R4)$$

$$AH^+ + Me_2SO^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} A + Me_2SO \qquad (R5)$$

$$AH^+ + A \underset{k_3}{\overset{k_3}{\rightleftharpoons}} A + AH^+ \qquad (R3)$$

where Me_2SO^- is the methylsulfonylmethanide (dimsyl) anion $CH_2^-SOCH_3$. However, the wide difference of pK between Me_2SO and AH^+ (pK = 33.3 against 10.5[6]) results in the production of a negligible amount of dimsyl anion with respect to the concentration of base A, so that the contribution of reaction R5 can be neglected in the following. In th pH range where coalescence was obtained (pH 4.5–5.5), reaction R3 only was observed. The rate constant k_3 was found to be quite close to the one observed in aqueous solution: 1.17 against $1.21 \times 10^9\ M^{-1}\ s^{-1}$ for NH_4^+ at 25 °C, clearly showing that water has no special role in this transfer.[6] However, the contribution of reaction R4 is expected to become predominant as the acidity of the solution is increased and accordingly the concentration of base A is decreased. Taking into consideration reactions R4 and R3 thus yields the overall deprotonation rate k_d of AH^+ at any pH, or conversely the reprotonation rate k_p of A, as

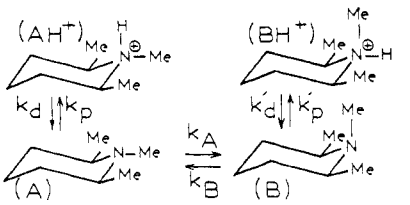
$$k_d = k_1 + k_3[A] \qquad (1)$$

$$k_p = k_{-1}[Me_2SO\cdots H^+] + k_3[AH^+] \qquad (2)$$

Piperidine (**3**) exists in two different geometric isomers A and B depending on whether the N-methyl substituent is in equatorial or axial position, respectively.[8] The experiments are performed in acidic solutions (pH −0.3 to 7.7). In these conditions, the isomeric amines are almost fully protonated (by more than 99%), and the cations AH^+ and BH^+ only are observed by NMR. Nitrogen inversion takes place on the very small amount of the free amines according to the general kinetic scheme[9,10] shown in Scheme I.

This sequence of balanced reactions is accompanied on the microscopic scale by NMR exchanges between the lines of four

Scheme I



species: AH^+, A, BH^+, and B. However, the pH of the solutions was kept well below the pK of the piperidinium salt in order to keep in turn the amount of bases A and B below the sensitivity level of the NMR method ($\lesssim$~1%). The NMR spectrum is thus restricted to the lines of the isomeric cations AH^+ and BH^+ (besides those of the solvent). NMR exchanges may be therefore classified as follows.[10]

(a) A proton transfer E_H on each individual isomer AH^+ (or BH^+) which results in a *separate* coalescence of AH^+ (or BH^+) lines only:

$$AH^+ + H^{+}* \underset{}{\overset{k_{HB}}{\rightleftharpoons}} AH^{+}* + H^+ \qquad (E_H)$$

and similarly

$$BH^+ + H^{+}* \underset{}{\overset{k_{HB}}{\rightleftharpoons}} BH^{+}* + H^+ \qquad (E_H)$$

where $H^{+}*$ indicates a proton coming from the solution, i.e., from $Me_2SO\cdots H^+$, AH^+, or BH^+, with a spin state ($\pm 1/2$) opposed to the one of the acidic proton of the piperidinium cation AH^+ (or BH^+) being deprotonated.

(b) A nitrogen inversion E_N which carries AH^+ into BH^+, and thus results in the coalescence of AH^+ and BH^+ lines *simultaneously* (cf. Experimental Section, no. 7):

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

Rate constants such as k_{HA} and k_{NA} are *macroscopic* NMR exchange probabilities (s^{-1}). k_{HA} represents the fraction of ions AH^+ being converted to $AH^{+}*$ per second through a deprotonation–reprotonation sequence:

$$AH^+ \xrightarrow{k_d} A + H^+ \text{ and } A + H^{+}* \xrightarrow{k_p} AH^+$$

Similarly k_{NA} is the fraction of cations AH^+, whatever may be the spin state of its acidic proton, converted to the isomeric cation BH^+ per second.

Applying steady-state equations to the above kinetic scheme of three consecutive pseudo-first-order reversible reactions[10-12] allows us to express k_{HA} or k_{NA} (and similarly k_{HB} and k_{NB}) as a function of the relevant microscopic rate constants k_A, k_B, k_{-1}, and k_3 according to the equations[7-9]

$$k_{HA} = k_p k_d (k'_p + k_B)/2D \text{ and } k_{HB} = k'_p k'_d (k_p + k_A)/2D \qquad (3)$$

$$k_{NA} = k_d k_A k'_p / D \text{ and } k_{NB}\, k_d k_B k_p / D = R k_{NA} \qquad (4)$$

where k_d and k_p (and similarly k'_d and k'_p) are given by eq 1 and 2. R is the equilibrium molar ratio $[AH^+]:[BH^+]$ and $D = k_p k_B + k_p k'_p + k'_p k_A$.

Both processes E_H and E_N depend on the pH of the solution. In water, we have shown that the pH ranges for coalescence are quite apart from each other for the two exchanges: pH 3.5–4.5 and 7.9–8.4 for E_H and E_N, respectively.[8,13] Alternatively, the latter process was studied by using an equilibration method.[14] It has been shown by X-ray crystallography[15] that hydrochloride **3** exists as the trans isomer AH^+ only in the solid state. An acidic solution of this salt contains initially this isomer only, which is then slowly converted to the isomer BH^+ so as to reach the equilibrium ratio R. Measuring the area $S(t)$ of

the signal of isomer BH^+ as a function of time t yields the probabilities k_{NA} and k_{NB} according to the equation

$$\log \frac{S(\infty)}{S(\infty) - S(t)} = (k_{NA} + k_{NB})t$$

Proton transfer rates in aqueous solution were found to be of the same order of magnitude as those previously measured by Grunwald[3,16] for trimethylamine: $(k_3 + k'_3) = 1.10 \times 10^8$ M^{-1} s^{-1} at 33 °C (compared to 0.34×10^8 M^{-1} s^{-1} at 25 °C). Nitrogen inversion rates were found to be abnormally low and concentration dependent: $k_A = 515$ s^{-1} for a 0.4 M solution at 25 °C.[8,14] These facts were tentatively assigned to the formation of a termolecular association which is not capable of inversion:

$$AH^+\cdots OH_2 + A \overset{K_{ass}}{\rightleftharpoons} AH^+\cdots H{-}O{-}H\cdots A \qquad (5)$$

where $K_{ass} \simeq 10^3$-10^4 M^{-1}.

We may therefore expect that both exchanges E_H and E_N are deeply altered on going from water to Me_2SO, thus making the investigated piperidine (**3**) a very convenient probe to test the role played by an interstitial water molecule in protonation-deprotonation processes.

Experimental Section

1. Materials. Dimethyl sulfoxide (Merck Uvasol) was left for 48 h on molecular sieves (Linde 3 Å), then distilled over calcium hydride under dry nitrogen at low pressure in an adiabatic fractionating column (1 m × 29 mm), with a reflux ratio of ca. 10, bp at 0.3 mmHg 27 °C. The water content of the purified solvent as found by Karl Fischer titration was $<5 \times 10^{-3}$ M. The role of this trace of water was found negligible by adding up to 5×10^{-3} M extra water to the initial solutions and observing no measurable variation of the exchange rates. 1,*cis*-2,6-Trimethylpiperidine (**3**) and its hydrochloride (**3'**) were prepared[17] by N-methylation of 2,6-dimethylpiperidine (Aldrich) according to Eschweiler-Clarke's procedure.[18] The hydrochloride was crystallized twice from acetone. Its structure was determined by X-ray crystallography.[15]

2. Solutions. Stock solutions of 0.5 M hydrochloride (**3'**) in Me_2SO were diluted to the desired concentration C_0. Aliquots were added either with piperidine (**3**) (in concentration $C_B = 1.5 \times 10^{-4}$ to 3.5×10^{-3} M) to obtain pH 6.3-7.7, or with a strong acid (HCl, CF_3SO_3H, or H_2SO_4) for experiments at pH <3. Gaseous HCl (Matheson) was dried through H_2SO_4 and made to bubble into anhydrous Me_2SO to obtain a stock solution of HCl in Me_2SO. All of these solutions were freshly prepared for immediate use.

3. Spectrophotometric pH Measurements. A Unicam SP 1800 spectrophotometer and a pair of 1-cm glass cells (Hellma 110-OS) with Teflon stoppers were used for all measurements. The Hammett indicators (Fluka) used for pH measurements were 2,5-dinitrophenol (pK = 7.7, ϵ 4.9×10^3, λ_{max} 490 nm, 2×10^{-4} M, pH 6.6-7.7), 4-chloro-2,6-dinitrophenol (pK = 3.5,[14] ϵ 9.7×10^3, λ_{max} 482 nm, 1.35×10^{-4} M, pH 2-4), 3-nitro- and 2,4-dichloroanilines (pK = 1.02 and 0.36,[15] ϵ 1.5 and 2.95×10^3, λ_{max} 398 and 313 nm, 7.3 and 6×10^{-4} M, pH −0.3 to 2).

4. pK Measurements. The pK of piperidine (**3**) was measured in Me_2SO both by spectrophotometry and potentiometry. The first method used either the pH value measured at half-neutralization with *p*-nitrophenol as an indicator (pK = 11.0[19]) or the pH measurements of Me_2SO solutions in the range pH 6.6-7.7 (see above) according to the equation

$$[H^+]^2 - [H^+](K + C_B) - C_0K = 0$$

which can be reduced to $[H^+]C_B - C_0K = 0$. A plot of $1/[H^+]$ vs. C_B/C_0 yields K and pK = 9.36 (in Me_2SO).

Potentiometric measurements are carried out with a Methrom EA 436 potentiometer equipped with a thermostated titration cell under dry nitrogen, a glass electrode (EA 109) and a reference Ag/AgCl electrode (EA 425). The glass electrode was calibrated using the salicylate buffer of pH 6.8.[19] The pK was derived from the neutralization curve according to a procedure described previously,[20] and was found in good agreement with the previous one: pK = 9.35. Activity coefficients γ were introduced to compute hydrogen ion concentrations according to Debye-Hückel theory[19]

$$\log \gamma = \frac{-1.12\sqrt{\mu}}{1 + 2.34\sqrt{\mu}} \text{ and } \log [H^+]^{-1} = pH + \log \gamma$$

where μ is the ionic strength. The quantity of free piperidine A was then computed as

$$[A] = \frac{K_A[AH^+]\gamma_{AH^+}}{[H^+]\gamma_{H^+}} \simeq \frac{K_AC_0}{[H^+]}$$

where K_A is the ionization constant of **3** and $\gamma_{AH^+} \simeq \gamma_{H^+} \simeq \gamma$. In very acidic Me_2SO (pH <2), we used a Hammett acidity function $H_0 = \log 1/h_0$ with indicators (3-nitroaniline and 2,4-dichloroaniline, pK = 1.02 and 0.36[21]) bearing the same electrical charge IH^+/I as the piperidinium/piperidine pair:

$$H_0 = pK_I + \log \frac{[I]}{]IH^+]}$$

and

$$[A] = K_AC_0/h_0$$

5. Conductometric Measurements. They use a Wayne-Kerr autobalance precision bridge B 331 (accuracy 0.01%), a Prolabo cell, and a Colora NB-DS ultrathermostat (temperature stability ±0.001 °C). The equivalent conductivity Λ is found to be a linear function of $\sqrt{C_0}$:

$$\Lambda = 38.4 - 186\sqrt{C_0} \ (\Omega^{-1} \text{ cm}^2 \text{ M}^{-1} \text{ at } 25 \text{ °C})$$

thus showing that the piperidinium chloride is completely dissociated in Me_2SO.

6. NMR Spectra. NMR spectra were taken with a JEOL C60-HL spectrometer at 60 MHz, or a JEOL PS-100 instrument at 100 MHz, both equipped with broad-band nitrogen-14 decoupling. Three sets of lines are used to distinguish isomers AH^+ and BH^+ in acidic Me_2SO. Each set consists of two groups of lines, one for each isomer, as follows.

(a) Two *C*-methyl doublets (Figure 1), δ 1.35 and 1.25 ppm, J = 6.3 and 6.8 Hz, with their intensities in the molar ratio $R = p_{AH}/p_{BH}$ = 1.63; these doublets are apart from each other at 100 MHz (Figure 1) and overlapping at 60 MHz (Figure 6).

(b) Two *N*-methyl doublets, δ 2.69 and 2.44 ppm, J = 5.0 and 5.6 Hz, with their intensities in the same ratio R; they can be observed only in Me_2SO-d_6.

(c) Two multiplets representing the acidic proton H_N of the piperidinium salt (Figure 2), δ 10.95 and 11.36 ppm. They can be observed only when decoupled from nitrogen-14. H_N is coupled with the two 2,6-methinic protons ($J_{aa} \simeq 10$ and $J_{ea} = 2.5$ Hz, according as H_N is axial in AH^+ or equatorial in BH^+) and with the three *N*-methylic protons ($J \simeq 5$ Hz). Two triplets of quadruplets are then expected for each isomer. In fact these quadruplets are partially overlapping owing to the fact that $J_{aa} \simeq J$ in AH^+ and $J_{ea} \simeq J/2$ in BH^+. For these reasons, the two multiplets are approximately composed of eight and nine broad lines, respectively (upfield and downfield), with the relative intensities $p_{AH}/32$, $3p_{AH}/32$, $5p_{AH}/32$, $7p_{AH}/32$, $7p_{AH}/32$, $5p_{AH}/32$, $3p_{AH}/32$, $p_{AH}/32$ (lines 1-8). $p_{BH}/32$, $2p_{BH}/32$, $4p_{BH}/32$, $6p_{BH}/32$, $6p_{BH}/32$, $6p_{BH}/32$, $4p_{BH}/32$, $2p_{BH}/32$, $p_{BH}/32$ (lines 10-17).

7. Exchange Rates in Moderately Acidic Me_2SO (6.3 < pH < 7.7). All of the three sets of lines suffer a coalescence within *the same pH range*, pH 6.3-7.7, in sharp contrast to what is observed in water.[8] The exchange rates are estimated by comparison of experimental spectra with simulated curves which are computed according to the theory of Kubo, Sack, and Anderson.[22] An important point of this theory consists of building a matrix, the so-called exchange matrix $||P||$, whose off-diagonal elements P_{ij} represent the probabilities for a nucleus to jump from site i to site j (diagonal elements are simply given by $P_{ii} = -\Sigma_{j \neq i} P_{ij}$). This matrix will be examined in each case in the following. A program TRECH has been written on this basis. All calculations are performed on a Texas Instruments 980 A minicomputer equipped with a digital plotter, Hewlett-Packard 7210 A. The quantities obtained from each group of lines successively and the conclusions drawn at each step are summarized for convenience in Table II.

(a) The *C*-methyl lines (1 and 2 on Figure 1) of isomer AH^+ are intramolecularly carried into those of isomer BH^+ (3 and 4) through nitrogen inversion E_N, without loss of the spin state of the tertiary coupled proton. Lines 1 and 3 on the one hand, and 2 and 4 on the other

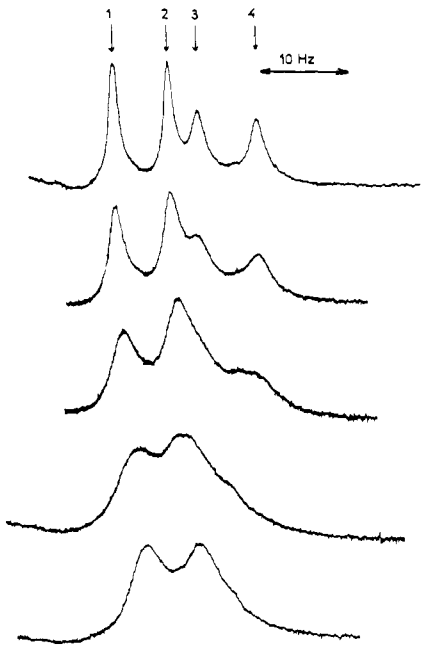


Figure 1. NMR line shapes of the *C*-methylic protons of the 1,*cis*-2,6-trimethylpiperidinium isomeric cations AH^+ (lines 1 and 2) and BH^+ (lines 3 and 4) as a function of the pH (6.30, 6.58, 6.84, 6.99, 7.31 from top to bottom) in a 0.5 M solution at 25 °C and 100 MHz.

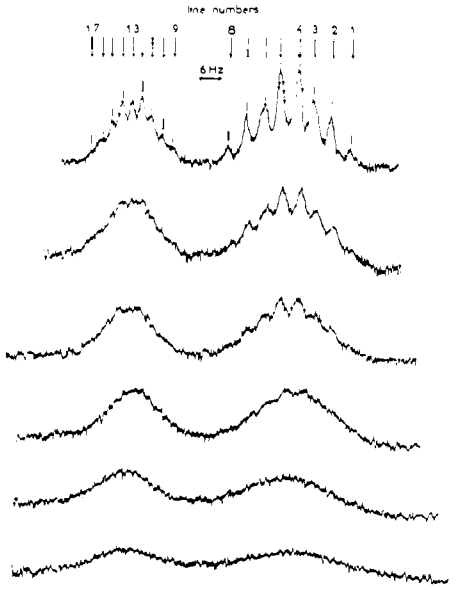


Figure 2. NMR line shapes of the acidic proton H_N $\{^{14}N\}$ of the 1,*cis*-2,6-trimethylpiperidinium cations AH^+ (lines 1-8) and BH^+ (lines 9-17) in the same conditions as in Figure 1 (pH 6.30, 6.58, 6.84, 6.99, 7.31 from top to bottom).

hand, are exchanging independently with rate constants k_{NA} and k_{NB}. A complete coalescence of these four lines into a sharp doublet is not observed in Figure 1. This is due to the limited pH range toward its basic end (pH $\leq$7.70) in order to prevent the production of significant amounts of piperidines A and B (see above). The exchange matrix is simply written (omitting the diagonal elements) as

$$\|P\| = \begin{vmatrix} 0 & k_{NA} & 0 & & \\ & 0 & k_{NA} & & \\ & & 0 & k_{NA} & \\ k_{NB} & & & 0 & \\ & k_{NB} & & 0 & \\ & & k_{NB} & & 0 \end{vmatrix} = k_N \begin{vmatrix} 0 & p_{BH} & 0 & & \\ & 0 & p_{BH} & & \\ & & 0 & p_{BH} & \\ p_{AH} & & & 0 & \\ & p_{AH} & & 0 & \\ & & p_{AH} & & 0 \end{vmatrix}$$

where $k_N = k_{NA} + k_{NA}(R + 1)$ and $p_{AH} = [AH^+]/([AH^+] + [BH^+]) = R/(R + 1) = k_{NA}/(k_{NA} + k_{NB})$.

The rate constants k_N were measured for four hydrochloride concentrations C_0 and for six pH values in each case (Table I). They fall along four straight lines A-D (Figure 3), one for each concentration, when they are plotted against $1/[H^+]$. A plot of the slopes p = 18.9, 27.0, 48.0, and 60.6 × 10^{-7} dm^3 mol^{-1} s^{-1} of A-D against C_0 again yields a straight line (Figure 4) with a slope p' = 120.45 × 10^{-7} s^{-1}. The k_N values are thus related to C_0 and $[H^+]$ through the equation

$$k_N = 120.4 \times 10^{-7} C_0/[H^+] \quad (6)$$

(b) The lines of the acidic protons H_N (1-17 in Figure 2) are coalescing as a result of the deprotonation of isomers AH^+ and BH^+. If we assume that the rate constants k_d and $k_{d'}$ are quite close together—as is observed in water[13] for reaction R3 a given proton H_N leaves one of the 17 sites (say i) at a rate of k_d, and then becomes randomly attached to any site j(j = 1-17). The off-diagonal elements of the 17 × 17 exchange matrix are thus written as $P_{ij} = k_d p_j$, where p_j is the aforementioned relative population of site j. The line shape of the H_N multiplets thus yields the deprotonation rate constant k_d in Me_2SO. Again a complete coalescence of the two H_N multiplets into a sharp singlet is not observed in Figure 2 on account of the limited pH range. The results (Table I) show that $k_N = k_d$ within experimental errors.

Table I. pH, k_N, and k_d Values for Various Concentrations C_0 and C_B of Hydrochloride (**3'**) and of Added Free Piperidine (**3**) at 25 °C

C_0, mol dm^{-3}	$C_B \times 10^4$, mol dm^{-3}	pH	k_N, s^{-1}	k_d, s^{-1}
0.19	1.52	6.60	4.0	5.0
	3.42	6.97	10.0	15
	6.84	7.25	20.0	25
	10.26	7.41	29.0	25
	18.69	7.52	37	30
	21.00	7.70	53	55
0.25	1.52	6.50	4.0	5.0
	3.42	6.80	9.5	9.0
	6.84	7.09	20.0	15
	10.26	7.24	27.5	22
	18.69	7.36	35	30
	21.00	7.55	54	50
0.38	1.52	6.30	5.0	5.0
	6.84	6.87	19.0	15
	10.26	7.14	30.0	30
	13.69	7.18	35	40
	21.00	7.35	56	55
	34.23	7.55	92	90
0.50	1.52	6.30	4.0	5.0
	3.42	6.58	9.5	9.0
	6.84	6.84	21.0	17
	10.26	6.99	27.5	23
	21.00	7.31	53	55
	34.23	7.44	91	95

Two hypotheses may account for this result: either (1) a proton transfer brings forth a nitrogen inversion simultaneously or (2) the reprotonation is so slow that the free amine obtained after deprotonation suffers a great number of nitrogen inversions before its reprotonation.

The distinction between these two assumptions results from the study of the coalescence of the two *N*-methyl doublets.

(c) The four *N*-methyl lines are simultaneously coalescing (Figure 5) as a result of both the deprotonation of each isomer (with rate constants k_{HA}, k_{HB}) and the nitrogen inversion (k_{NA}, k_{NB}). This is in sharp contrast with the behavior observed in water,[8] where each doublet is first coalesced into a singlet (pH 3-5) as a result of exchanges E_H independently occurring on each isomer, and then the two

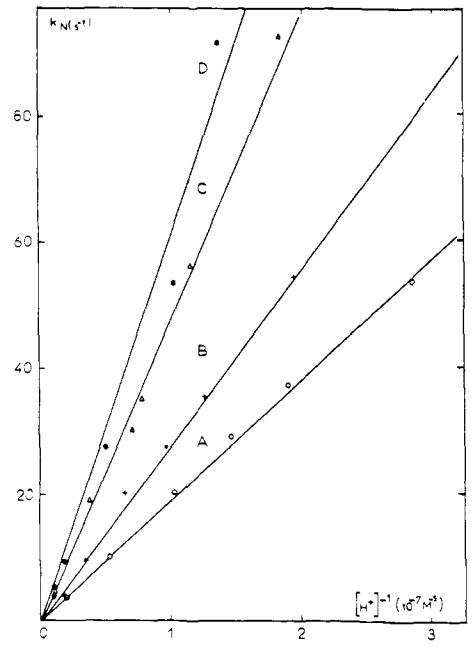


Figure 3. A plot of k_N (s^{-1}) vs. $[H^+]^{-1}$ in acidic Me_2SO at 25 °C for C_0 = 0.19 (○), 0.25 (+), 0.38 (△), and 0.50 M (●) (A, B, C, D, respectively).

Table II. A Summary of the Various NMR Coalescences and Exchange Processes, the Measured Rate Constants for Each Group of Lines, and the Conclusions Drawn at Each Successive Step

coalescing lines	exchange processes	measured rate constants	conclusions
C-methyl	E_N	$k_N = k_{NA} + k_{NB}$	k_{NA} and $k_{NB} = Rk_{NA}$
acidic protons	E_H	k_d	$k_N = k_d$
N-methyl	$E_N + E_H$	k_{HA}, k_{HB}, k_{NA}, k_{NB}	$2k_{HA} = k_{NB}$ $2k_{HB} = k_{NA}$

singlets are coalesced into a single line as a result of nitrogen inversion E_N (pH 7.9–8.4). Two different exchange matrices can be built using hypotheses (1) or (2), namely,

$$\begin{vmatrix} 0 & k_{NA}/2 & k_{NA}/2 \\ 0 & k_{NA}/2 & k_{NA}/2 \\ k_{NB}/2 & k_{NB}/2 & \\ k_{NB}/2 & k_{NB}/2 & 0 \end{vmatrix} \qquad \begin{vmatrix} k_{HA} & k_{NA}/2 & k_{NA}/2 \\ k_{HB} & k_{NA}/2 & k_{NA}/2 \\ k_{NB}/2 & k_{NB}/2 & k_{HB}/2 \\ k_{NB}/2 & k_{NB}/2 & k_{NB}/2 \end{vmatrix}$$

(1) (2)

In fact, the *N*-methylic spectrum is obscured by the Me_2SO line and the experiments should be performed in Me_2SO-d_6. As accurate pH and p*K* scales are unknown in this solvent, we have limited our investigations as follows. The spectra of both the *C*-methylic and the *N*-methylic protons were recorded for a convenient but unknown pH value. The rate constants k_{NA} and k_{NB} were extracted from the *C*-methyl lines as described above, and then were reported in the exchange matrices (1) or (2). No good fit between experimental and theoretical spectra of the *N*-methylic protons could be obtained when using matrix (1). On the contrary, a nice fit was observed (Figure 5) with matrix (2) when the parameters k_{HA} and k_{HB} were adjusted so

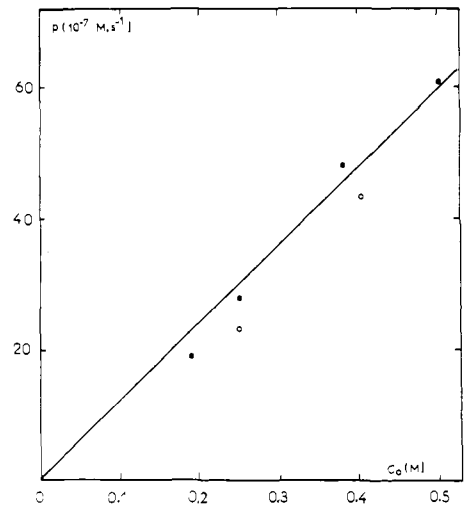


Figure 4. A plot of the slopes *p* of lines A–D from Figure 3 (●) and of those (○) derived from the data of Table II.

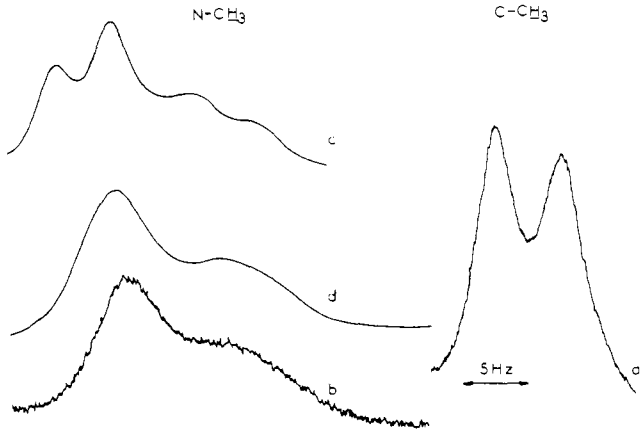


Figure 5. NMR line shapes of the *C*-methylic (a) and *N*-methylic (b) protons of hydrochloride (**3′**) in Me_2SO-d_6 together with the best fitting computed spectra of (b) assuming hypotheses (1) or (2) (curves c and d, respectively).

that $2k_{HA} = k_{NB}$ and $2k_{HB} = k_{NA}$. This is clear evidence for the validity of the assumption of a slow deprotonation and a fast nitrogen inversion (cf. Discussion).

8. Equilibration Rates in Acidic Me_2SO ($-0.27 < pH < 3.3$). Crystals of the pure hydrochloride AH^+Cl^- were dissolved in acidic Me_2SO. The appearance of the second isomer BH^+ was followed by measuring the area of the *C*-methyl doublets (Figure 6) at appropriate time intervals. Such a procedure is only feasible for relatively slow equilibration rates, i.e., for pH < ~3, where the time $t_{1/2}$ for appearance of half the BH^+ isomer is larger than ca. 5 min. Two acids were used to acidify the Me_2SO solutions: hydrochloric acid for pH >2 and trifluoromethanesulfonic acid for pH < 2. (It was checked that the results were independent of the chosen acid.) The accuracy on those measurements was rather poor, about 10% for pH (or H_0) > −0.2 and 20% for pH ≤ −0.2, on account of uncertainties in quantitative NMR measurements and in the use of Hammett acidity functions in very acidic medium.

The results (Table III) show that the variations of the rate constant k_N as a function of pH and concentration C_0 strongly depend on the pH range investigated. *For negative pH values*, k_N is found proportional to $[H^+]^{-1}$ (or h_0^{-1}) and independent of the salt concentration within experimental errors:

$$k_N = 3.5 \times i0^{-4}/[H^+] \qquad (7)$$

In the pH range 0 < pH < ~2, k_N is found independent of both the pH and the salt concentration:

$$k_N \simeq 3 \times 10^{-4}\ s^{-1} \qquad (8)$$

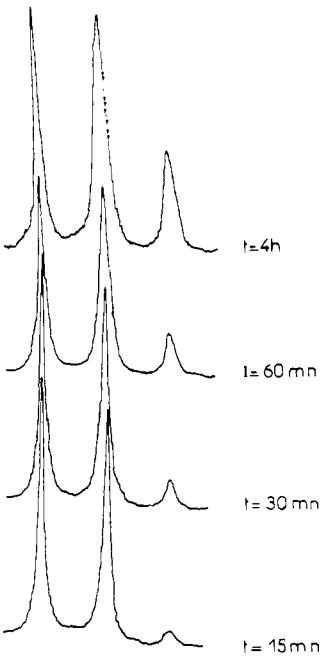


Figure 6. The *C*-methylic spectrum of a 0.5 M solution of 1,*cis*-2,6-trimethylpiperidinium crystals in acidic Me_2SO (pH 0) as a function of time *t*, showing the appearance of isomer BH^+ (right) at the expense of AH^+ (left), at 25 °C and 60 MHz.

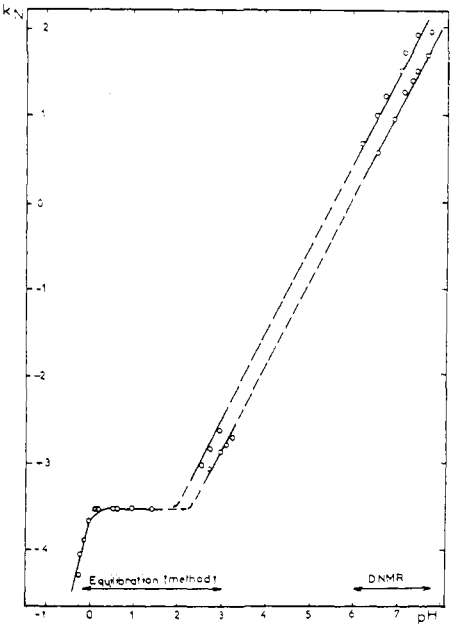


Figure 7. A plot of the rate constant $k_N = k_{NA} + k_{NB}$ (in log units) for the interchange of isomers AH^+ and BH^+ at 25 °C as a function of the pH, for two concentrations $C_0 = 0.5$ and 0.25 M (upper and lower lines, respectively).

Table III. Rate Constants k_N for the Appearance of the Second Isomer as a Function of the pH at 25 °C

salt concn C_0, M	pH or H_0	k_N, 10^{-4} s^{-1}
	pH <0	
0.40	−0.27	0.50
0.51	−0.23	0.85
0.26	−0.19	0.80
0.40	−0.10	1.35
0.40	+0.02	2.26
	0 ≤ pH < 2	
0.40	0.145	2.7
0.40	0.25	3.0
0.42	0.53	3.0
0.23	0.58	3.1
0.30	0.95	2.8
0.30	1.39	3.0
	pH ≥2	
0.40	2.39	7.4
0.40	2.85	14
0.40	2.98	28
0.25	2.89	9.6
0.25	2.92	13.4
0.25	3.05	20
0.25	3.21	24
0.25	3.31	28

For pH values larger than 2, k_N is proportional both to $[H^+]^{-1}$ and C_0, and the values obtained by this method are in good continuity (Figure 7) with those previously obtained by DNMR in the pH range of 6.3–7.7 (slopes of 43.2 and 22.9×10^{-7} M s^{-1} for $C_0 = 0.4$ and 0.25 M, to be compared to $p = 48.0$ and 27.7×10^{-7} M s^{-1}).

Discussion

The whole set of experimental data can be rationalized if we consider the relative magnitudes of rate constants k_A, k_B, and k_p, and the expressions (1) and (2) for the deprotonation and reprotonation rates written as

$$k_d = k_1 + k_3[\text{piperidine}] = k_1 + k_3K_AC_0/[H^+] \quad \text{or } k_1 + k_3K_AC_0/h_0 \quad (9)$$

$$k_p = k_{-1}[H^+] + k_3C_0 \quad (10)$$

assuming common values of k_d, k_p, and k_3 for both isomers).

(a) *From pH 2 to 7, the reprotonation rate* k_p *is much smaller* than the nitrogen inversion rate. Equations 4 can be simplified as follows:

$$k_{NA} = k_d \frac{k_A}{k_A + k_B} = 2k_{HB} \text{ and } k_{NB} = 2k_{HA}$$

thus accounting for the aforementioned coalescence pattern of the *N*-methylic protons. In this pH range, the interchange of isomers AH^+ and BH^+ is controlled by the rate of deprotonation

$$k_N = k_{NA} + k_{NB} = k_d$$

In turn, the deprotonation is predominantly performed through reaction R3, i.e.,

$$k_N = k_d \simeq k_3K_AC_0/[H^+] \quad (11)$$

Comparison of eq 6 and 11 brings

$$k_3K_A = 120.4 \times 10^{-7} \text{ or } k_3 = 2.70 \times 10^4 \text{ M}^{-1} \text{ s}^{-1} \text{ at } 25 \text{ °C}$$

(b) *From pH 0 to 2,* k_p is still smaller than k_A, but $k_1 \gg k_3K_AC_0/[H^+]$ in eq 9, and a *uniform rate of interchange of isomers* AH^+ *and* BH^+ *is observed in this pH range:*

$$k_N = k_d \simeq k_1 = 3 \times 10^{-4} \text{ s}^{-1} \text{ (from eq 8)}$$

and therefore

$$k_{-1} = K_A/k_1 = 6.71 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$$

(c) *For lower values of pH* (pH <0), *the rate of reprotonation becomes larger than that of nitrogen inversion.* We then have the same situation as with aqueous solutions of amines, first described by Saunders and Yamada.[9] Equations 4 can now be simplifed giving a third asymptotic law:

$$k_{NA} = \frac{k_d}{k_p} k_A = \frac{[A]}{[AH^+]} k_A = k_A K_A / h_0 \text{ and } k_{NB} = R k_{NA}$$

or $k_N = (k_A + k_B) K_A / h_0$.

From the experimental relationship (7), we deduce that $(k_A + k_B) = 3.5 \times 10^{-4}/K_A = 7.84 \times 10^5\ s^{-1}$, or, with $R = 1.63$, $k_A = 2.98 \times 10^5$ and $k_B = 4.86 \times 10^5\ s^{-1}$ at 25 °C.

A graph representing the variations of k_d, k_p, and K_N as a function of pH helps in understanding the whole set of our observations (Figure 8). Analogous plots with an inflection point had been observed previously by Leyden and Morgan[23] in aqueous solutions of various acyclic amines. They were accounted for by two mechanisms: an inversion promoted by proton transfer, and a kinetically controlled formation of a nonhydrated amine opposing to a hydrated species, the former only being capable of inversion. Alternatively it may be assumed that the reprotonation rate $k_p = k_{-1}[H_3O^+] + k_3$. [amine] (in aqueous solution) is smaller than k_A, k_B for pH $>\sim 3$. The interchange rate k_N is then identical with k_3. For lower pH, k_N should be written as

$$k_N = k_d \frac{k_A + k_B}{k_A + k_B + k_p} \text{ (from eq 4, assuming } k_p = k_p')$$

where k_d and k_p are given by expressions 9 and 10. From Figure 3 of ref 23, it may be inferred that $k_{-1} \simeq 5 \times 10^9\ M^{-1}\ s^{-1}$ (and therefore $k_1 \simeq 10\ s^{-1}$) and $k_A \simeq 10^8\ s^{-1}$ (for benzylmethylethanolamine). These two values are of an expected order of magnitude for both protonation rates of amines by hydronium ion and for nitrogen inversion of acyclic amines (contrary to the values $10^5\ s^{-1}$ first given by Saunders and Yamada[9]).

Finally, such an explanation cannot be envisaged to account for the abnormally lower nitrogen inversion of piperidine (**3**) itself in aqueous solution. Indeed no inflection point was observed from pH 2 to 8 and the interchange rate k_N was not found proportional to C_0.

Conclusion

These results illustrate clear-cut differences between aqueous and Me_2SO solutions.

(a) Very slow deprotonation and reprotonation rates within the piperidinium-piperidine pair are obtained in Me_2SO as compared to water (2.7×10^4 against $1.1 \times 10^8\ M^{-1}\ s^{-1}$), thus demonstrating the role of an intermediary bridging water molecule in the proton transfer (cf. Introduction).

(b) In water, an associated species $AH^+ \cdots OH_2 \cdots A$ may persist after proton transfer,[14] explaining an abnormally slow nitrogen inversion ($k_A + k_B$) $\sim 10^3\ s^{-1}$ against $10^6\ s^{-1}$ in Me_2SO (a value close to the one, $10^7\ s^{-1}$, observed in the pure piperidine from ultrasonic measurements[24]). The existence of such species is, however, not necessary to account for nitrogen inversion of acyclic amines, which invert at an expected rate of ca. $^{108}\ s^{-1}$ using our interpretation.

(c) The rate of deprotonation of piperidinium ion (**3'**) by Me_2SO is very slow too ($k_1 \simeq 3 \times 10^{-4}$ s) as compared to the values obtained in water ($10\text{-}50\ s^{-1}$) in spite of a greater basicity of Me_2SO. The same is true for the reprotonation of piperidine by the solvated proton $Me_2SO \cdots H^+$: $k_{-1} = 6.7 \times 10^5\ M^{-1}\ s^{-1}$ (against $10^9\text{-}10^{10}$ for H_3O^+). These facts may be assigned to either a steric hindrance to the approach of Me_2SO and piperidine (**3**) or to the possibility of transferring the acidic proton into the bulk solvent along a Grotthuss chain in the case of water. These views have been recently confirmed by Kreevoy and co-workers[25] as they measured the exchange rate of the acidic protons of a number of sterically hindered benzylammonium ions in anhydrous and moist dimethyl sulfoxide, showing that the exchange rate is strongly increased by progressive additions of water.

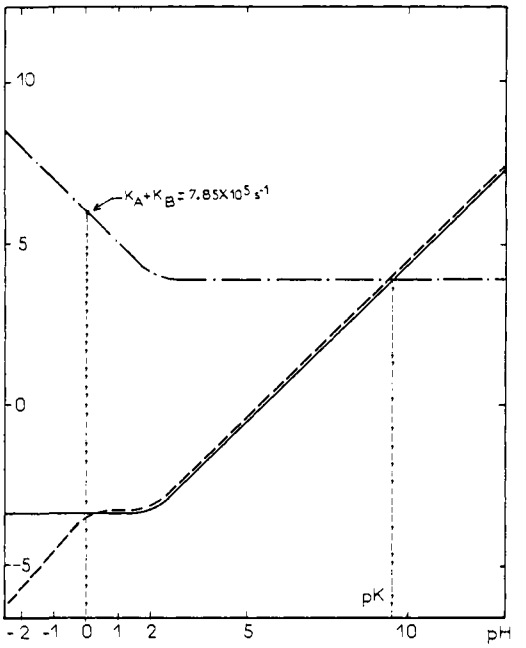


Figure 8. A schematic plot of rate constants k_p (-·-·-), k_d (—), and k_N (- - -) (in log units) as a function of pH.

Acknowledgments. We wish to thank Professor Baverez for the JEOL PS-100 spectrometer and the CNRS for financial support.

References and Notes

(1) E. Grunwald and D. Eustace in "Proton-Transfer Reactions", E. F. Caldin and V. Gold, Ed., Wiley, New York, N.Y., 1975, Chapter 5, p 121.
(2) P. Schuster, P. Wolschann, and K. Tortschanoff in "Chemical Relaxation in Molecular Biology", I. Pecht and R. Rigler, Ed., Springer-Verlag, West Berlin, 1977, p 107.
(3) E. Grunwald, A. Loewenstein, and S. Meiboom, *J. Chem. Phys.*, **27**, 630 (1957).
(4) E. Grunwald and M. Concivera, *Discuss. Faraday Soc.*, **39**, 105 (1965).
(5) M. Cocivera, *J. Chem. Phys.*, **72**, 2515, 2520 (1968).
(6) B. Bianchin and J-J. Delpuech, *Bull. Soc. Chim. Fr.*, **34**, (1973).
(7) J. Courtot-Coupex and M. Le Demezet, *C.R. Acad. Sci., Ser. C*, **266**, 1438 (1968); R. Stewart and J. R. Jones, *J. Am. Chem. Soc.*, **89**, 5069 (1967).
(8) J-J. Delpuech and M. N. Deschamps, *Chem. Commun.*, 1188 (1967).
(9) M. Saunders and F. Yamada, *J. Am. Chem. Soc.*, **85**, 1882 (1963).
(10) J-J. Delpuech, *Org. Magn. Reson.*, **2**, 91 (1970).
(11) S. W. Benson, "The Foundations of Chemical Kinetics", McGraw-Hill, New York, N.Y., 1960, p 225.
(12) C. D. Ritchie in "Solute-Solvent Interactions", Vol. 1, J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N.Y., 1969, p 246.
(13) J-J. Delpuech, F. Siriex, and M. N. Deschamps, *Org. Magn. Reson.*, **4**, 651 (1972).
(14) J-J. Delpuech and M. N. Deschamps, *Nouveau J. Chim.*, in press.
(15) C. Lecomte, J. Protas, B. Bianchin, and J-J. Delpuech, *Cryst. Struct. Commun.*, **4**, 477 (1975).
(16) A. Loewenstein and S. Meiboom, *J. Chem. Phys.*, **27**, 2208 (1963).
(17) J-J. Delpuech and M. N. Deschamps, *Tetrahedron*, **26**, 2723 (1970).
(18) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshans, *J. Am. Chem. Soc.*, **55**, 4571 (1933).
(19) I. M. Kolthoff, M. K. Chantooni, and S. Bhowmik, *J. Am. Chem. Soc.*, **90**, 23 (1968).
(20) J-J. Delpuech, M. N. Deschamps, and Y. Martinet, *J. Chim. Phys. Phys.-Chim. Biol.*, **66**, 232 (1969).
(21) A. G. Cook and G. W. Mason, *J. Inorg. Nucl. Chem.*, **28**, 2579 (1966).
(22) P. W. Anderson, *J. Phys. Soc. Jpn.*, **9**, 316 (1954); R. Kubo, *ibid.*, **9**, 935 (1954); R. A. Sack, *Mol. Phys.*, **1**, 163 (1958).
(23) W. R. Morgan and D. E. Leyden, *J. Am. Chem. Soc.*, **92**, 4527 (1970).
(24) V. M. Gittins, J. P., Heywood, and E. Wyn-Jones, *J. Chem. Soc., Perkin Trans. 2*, 1642 (1975).
(25) M. M. Kreevoy and Y. Wang, *J. Phys. Chem.*, **81**, 1924 (1977).