Nuclear Magnetic Resonance Studies of Proton Exchange Rate, Nitrogen Inversion Rate, and Relative "Size" of Methyl Groups and –NH$^+$ Protons in N,N'-Dimethylpiperazine Hydrochlorides[1]

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Abstract: N,N'-Dimethylpiperazine in aqueous hydrochloric acid is studied by nuclear magnetic resonance as a function of pH and temperature. The rate of proton exchange of the *trans*-dihydrochloride is 50–100 times slower than those for comparable acyclic amine hydrochlorides. The nitrogen inversion rates for the *trans*- and *cis*-monohydrochlorides are $2.0 \pm 0.6 \times 10^5$ and $1.6 \pm 0.5 \times 10^6$ sec^{-1}, respectively. The *trans–cis* conversion of the dihydrochloride at 25° is accompanied by changes of $\Delta G = 1.16 \pm 0.1$ kcal/mole, $\Delta H = 0.3 \pm 0.3$ kcal/mole, and $\Delta S = -3.1 \pm 0.1$ eu. The small value of ΔG substantiates the view that the effective "size" of –NH$^+$ protons is increased by the presence of tightly held water molecules of hydration.

Saunders and Yamada[2] showed that proton exchange rates and nitrogen inversion rates of suitable amines in acidic aqueous solution can be determined by nuclear magnetic resonance (nmr) spectroscopy. By this method, proton exchange and nitrogen inversion rates of a heterocyclic amine are determined for the first time in the present work.

The ring inversion rate of N,N'-dimethylpiperazine (P) has been determined at low temperatures by nmr spectroscopy.[3] Reeves and Strømme,[3a] using both coalescence point and fast exchange approximation methods, found a value of $E_a = 13.3$ kcal/mole for the chair–chair inversion. A reexamination of this work by Harris and Spragg,[3b] using the coalescence point method, yielded a value of $E_a = 12.6$ kcal/mole. Recent investigation[4] of N,N,N,'N'-tetramethylpiperazine dichloride at low temperature in liquid sulfur dioxide yielded values of $\Delta H^{\ddagger} = 9.3 \pm 1.2$ kcal/mole and $\Delta S^{\ddagger} = -13.5 \pm 5.6$ eu for the chair–boat conversion at 0°.

Nitrogen inversion rates in P remain rapid at low temperatures and at the lowest temperature reported to date ($-56°$) the axial and equatorial methyl groups are observed as a single time-averaged resonance. In the present work, however, direct observation of axial and equatorial methyl resonances has been possible at room temperature and higher, merely by maintaining low pH.

Measurement of the relative areas of axial and equatorial methyl resonances at various temperatures yields ΔG, ΔH, and ΔS of the reaction *trans*-$H_2P^{2+} \rightarrow$ *cis*-H_2P^{2+}. The ΔG value is particularly interesting as a measure of the "size" of –NH$^+$ protons in relation to N-methyl groups. Because water molecules of hydration are more strongly held by positively charged –NH$^+$ protons than by uncharged –NH protons,[5] it is expected that this difference in effective size may be reflected in ΔG values. It has been shown previously[6] that in cyclohexane derivatives, the –NH_3^+ group has a larger ΔG value than the –NH_2 group and thus the former is larger with respect to the –CH proton. This combined steric–solvent effect is important in conformational analysis of amino acids at various pH values[7] and in biochemistry generally.

In order to make the comparison between the sizes of –NH$^+$ and –NH protons, however, knowledge of the relative size of N-methyl groups and uncharged –NH protons is required. By dipole measurements of piperazine and piperidine derivatives, Allinger and co-workers[8] found ΔG values of 1.7 and 0.4 kcal/mole for N-methyl groups and uncharged –NH protons, respectively, both relative to the lone electron pair on nitrogen. From these results a ΔG value of 1.3 kcal/mole would be derived, relating the size of the N-methyl group to that of the uncharged –NH protons. However, the validity of these results, yielding the steric order $CH_3 >$ H $>$ lone pair, has been thrown into question by recent studies[9] indicating the steric order $CH_3 >$ lone pair $>$ H, based on interpretation of chemical shift values. This finding constitutes a partial return to the first report on this subject by Aroney and LeFevre,[10] who deduced the steric order $CH_3 \approx$ lone pair $>$ H from Kerr constant measurements.

Because of the lack of reliable data as to the relative size of N-methyl groups and uncharged –NH protons, we are forced to ignore the nitrogen atoms and will use ΔG values from cyclohexane derivatives for comparison purposes. Literature values for ΔG of methyl groups in cyclohexane derivatives vary from 1.5 to 2.1 kcal/mole, with 1.7 kcal/mole being the recommended value.[11]

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(1) (a) This research was supported by the National Institutes of Health Grant No. 1-RO1-AM-10889; (b) presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(2) M. Saunders and F. Yamada, *J. Am. Chem. Soc.*, **85**, 1882 (1963).

(3) (a) L. W. Reeves and K. O. Strømme, *J. Chem. Phys.*, **34**, 1711 (1961); (b) R. K. Harris and R. A. Spragg, *Chem. Commun.*, 314 (1966).

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(6) E. L. Eliel, E. W. Della, and T. H. Williams, *Tetrahedron Letters*, 831 (1963).

(7) See, for example, F. Taddei and L. Pratt, *J. Chem. Soc.*, 1553 (1964), and K. G. R. Pachler, *Spectrochim. Acta*, **19**, 2085 (1963).

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Experimental Section

The spectra were measured using a Varian A-60 nmr spectrometer with variable-temperature probe. Temperatures were measured by the usual calibration with ethylene glycol and methanol and are estimated accurate to within ±1°. The ambient temperature of the probe sample compartment was found to be 44°. Chemical shifts were measured relative to *t*-butyl alcohol internal standard, which is chemically shifted 1.233 ppm downfield of 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt (TMS*). No attempt was made to remove oxygen from the samples before recording their spectra. Line-width measurements were carried out at a sweep width of 1 cm = 2 cps (estimated accurate to within ±0.1 cps). The sweep rate was 0.2 cps^2 and the radiofrequency field strength (0.02 mgauss) was maintained below the saturation level. The magnetic field homogeneity was checked after each line-width measurement to ensure that no degeneration had taken place during the measurement and all line-width measurements were carried out at essentially constant homogeneity.

N,N′-Dimethylpiperazine, obtained from Aldrich Chemical Co., was purified by distillation. Gas chromatographic analysis on a special column for diamines[12] revealed the presence of no resolvable impurities in greater than trace amounts. N-Methylpiperazine, a potential contaminant which could easily be resolved from P in synthetic mixture, was not present in detectable amounts. Reagent grade J. T. Baker hydrochloric acid was used and all solutions were prepared from deionized or doubly glass-distilled water.

Results and Discussion

N,N′-Dimethylpiperazine (P) is a base capable of accepting two protons, forming the monohydrochloride (HP^+) and the dihydrochloride (H_2P^{2+}), as described by equilibria 1 and 2.

$$H_2P^{2+} = HP^+ + H^+;\ K_1 = \frac{[H^+][HP^+]}{[H_2P^{2+}]} = 2.82 \pm 0.06 \times 10^{-5} \quad (1)$$

$$HP^+ = P + H^+;\ K_2 = \frac{[H^+][P]}{[HP^+]} = 3.98 \pm 0.08 \times 10^{-9} \quad (2)$$

The values of acid dissociation constants K_1 and K_2 were determined by potentiometric titration of 0.74 *M* P in 1.0 *M* potassium nitrate at 25°. The ionic strength thus varies somewhat during the titration, but is quite high, corresponding roughly to the conditions of the nmr experiments.

The nmr spectrum of P (at pH 9.6) consists of singlets at 2.50 and 2.23 ppm *vs.* TMS* having relative areas 4:3. The low-field singlet, attributed to the methylene protons, has a half-width (width at half-amplitude) of 2.0 cps and the high-field singlet, attributed to the methyl protons, has a half-width of 1.0 cps. As the pH is decreased to 3.0, where H_2P^{2+} is the predominant species, both singlets undergo downfield shifts, as expected.[13] Figure 1 shows the nmr spectrum of H_2P^{2+} at pH 3.0. The methylene and methyl protons at pH 3.0 and below have chemical shifts of 3.70 and 3.03 ppm *vs.* TMS* and their half-widths at pH 3.0 are 0.8 and 0.8 cps, respectively.

As the pH is further decreased, the methylene resonance broadens and eventually (in 0.80 *M* HCl) splits into an AA′BB′ pattern, as shown in Figure 1b. This indicates a decrease in the rate of interconversion of *trans*- and *cis*-H_2P^{2+} and an equilibrium mixture of these species becomes observable.

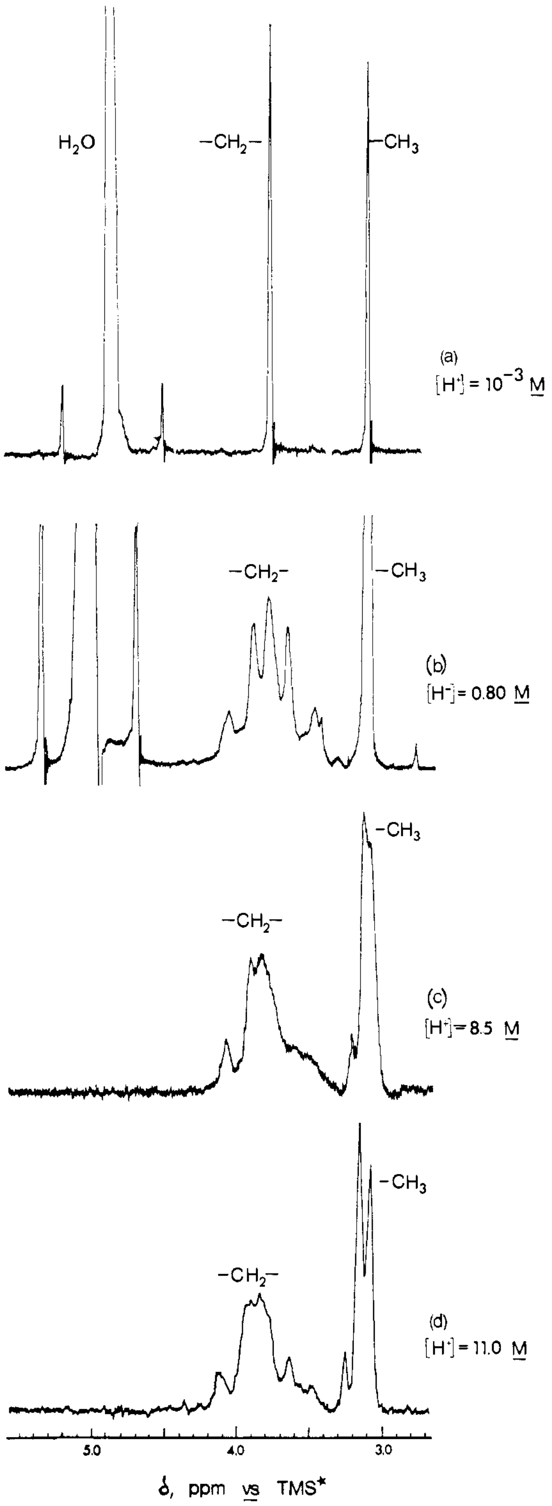

Figure 1. Nmr spectra of N,N′-dimethylpiperazine at various values of [H$^+$].

The *cis* isomer has one axial and one equatorial methyl group in the chair conformation and, being less stable than the *trans* isomer, is only about 11% abundant at room temperature. Although there is little evidence of *cis* isomer in 0.80 *M* HCl, resolution of the *cis* methyl resonance is achieved in stronger HCl.

In 8.5 *M* HCl, the methyl singlet begins to split into a doublet, as shown in Figure 1c, and the methylene

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(11) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 44.

(12) E. D. Smith and R. D. Radford, *Anal. Chem.*, 33, 1160 (1961).

(13) E. Grunwald, A. Loewenstein, and S. Meiboom, *J. Chem. Phys.*, 27, 641 (1957).

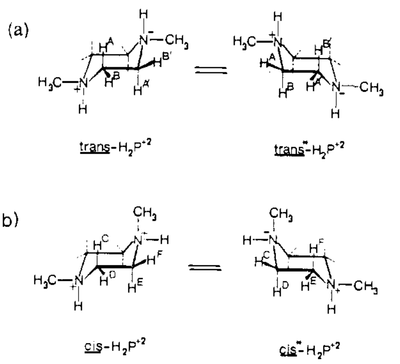

Figure 2. Structure of N,N′-dimethylpiperazine dihydrochlorides.

AA′BB′ pattern becomes more highly split, particularly on the high-field side. Spin coupling of –CH protons by neighboring $-NH^+$ protons is well known,[14] and is caused by the increased lifetime of $-NH^+$ protons in strongly acidic solution. If the higher field portion of the methylene resonance is assigned to axial protons labeled A in Figure 2a, and the lower field portion to equatorial protons labeled B, then the unsymmetrical splitting in Figure 1c suggests that vicinal coupling constants in aliphatic HCNH systems depend upon the dihedral angle in a manner similar to that described by Karplus and co-workers[15] for aliphatic HCCH systems, as previously reported[16] for aminocarboxylate chelates of Co(III). That is, for a dihedral angle of 180°, the vicinal coupling constant is several times larger than for a dihedral angle of 60°.

Proton Exchange Rate. When the concentration of HCl is increased to 11.0 *M*, the methyl singlet becomes fully split into a doublet (J = 5.0 cps), as shown in Figure 1d. A second doublet, assigned to *cis*-H_2P^{2+}, appears at slightly lower magnetic field strength. The high-field member of the *cis* doublet is superimposed on the low-field member of the *trans* doublet. In spite of this, sufficient resolution is obtained to permit determination of the relative abundances of the isomers and the line shapes of the *trans*-methyl doublet at various stages of collapse.

A series of spectra at various pH values were obtained, showing the *trans*-methyl resonance in various stages ranging from the singlet of Figure 1b to the doublet of Figure 1d. Determination of proton exchange rates from line shapes of multiplets caused by spin coupling to $-NH^+$ protons is well known.[14] Theoretical curves[14b] were employed, relating proton exchange rates to the peak-to-valley ratios of lines having multiplet character and to half-widths of lines having only singlet character.

The following reactions are considered as possible mechanisms for exchange of protons from *trans*-H_2P^{2+}, abbreviated t-H_2P^{2+} (although water–bridge mechanisms parallel to those in eq 5 and 6 are not separately designated, previous studies[14b,14c] indicate that for acyclic tertiary amines, the water–bridge mechanism is predominant).

$$t\text{-H}_2\text{P}^{2+} + \text{H}_2\text{O} \overset{k_1}{\rightleftharpoons} t\text{-HP}^+ + \text{H}_3\text{O}^+ \qquad (3)$$

$$t\text{-H}_2\text{P}^{2+} + \text{OH}^- \overset{k_2}{\rightleftharpoons} t\text{-HP}^+ + \text{H}_2\text{O} \qquad (4)$$

$$t\text{-H}_2\text{P}^{2+} + \text{HP}^+ \overset{k_3}{\rightleftharpoons} t\text{-HP}^+ + \text{H}_2\text{P}^{2+} \qquad (5)$$

$$t\text{-H}_2\text{P}^{2+} + \text{P} \overset{k_4}{\rightleftharpoons} t\text{-HP}^+ + \text{HP}^+ \qquad (6)$$

The over-all proton exchange rate is given by

$$\text{rate} = k_1[t\text{-H}_2\text{P}^+][\text{H}_2\text{O}] + k_2[t\text{-H}_2\text{P}^{2+}][\text{OH}^-] + k_3[t\text{-H}_2\text{P}^{2+}][\text{HP}] + k_4[t\text{-H}_2\text{P}^{2+}][\text{P}] \qquad (7)$$

Equation 7 can be rearranged and set equal to the reciprocal $-NH^+$ proton lifetime yielded by the nmr experiment

$$\frac{1}{\tau_\text{H}} = \frac{\text{rate}}{[t\text{-H}_2\text{P}^{2+}]} = k_1[\text{H}_2\text{O}] + k_2[\text{OH}^-] + k_3[\text{HP}^+] + k_4[\text{P}] \qquad (8)$$

Substituting in terms of $[H^+]$, K_1, K_2, and K_w, the autoprotolysis constant of water ($K_w = 10^{-14}$), we obtain

$$\frac{1}{\tau_\text{H}} = k_1[\text{H}_2\text{O}] + \frac{k_2K_\text{w}}{[\text{H}^+]} + \frac{k_3K_1[\text{H}_2\text{P}^{2+}]}{[\text{H}^+]} + \frac{k_4K_1K_2[\text{H}_2\text{P}^{2+}]}{[\text{H}^+]^2} \qquad (9)$$

The lowest concentration of HCl for which a proton exchange rate could be measured was 8.2 *M*. The values of $[H_2P^{2+}]$ ranged from 0.3 to 1.2 *M*. Because the rates are probably not ascertainable to better than ±1 sec $^{-1}$, the second and fourth terms in eq 9 cannot be significant unless $k_2 \geq 8.2 \times 10^{14}$ l. mole^{-1} sec^{-1} or $k_4 \geq 4.6 \times 10^{14}$ l. mole^{-1} sec^{-1}, both of which are faster than the theoretical maximum for diffusion-controlled reactions in solution.[17] Eliminating the second and fourth terms, we obtain

$$\frac{1}{\tau_\text{H}} = k_1[\text{H}_2\text{O}] + \frac{k_3K_1[\text{H}_2\text{P}^{2+}]}{[\text{H}^+]} \qquad (10)$$

Plotting $1/\tau_H$ *vs.* $[H_2P^{+2}]/[H^+]$ as shown in Figure 3, we obtain a slope of $1.7 \pm 0.1 \times 10^2$ sec^{-1}. Therefore, $k_3 = 6.1 \pm 0.4 \times 10^6$ l. mole^{-1} sec^{-1}. This is approximately 50 times slower than the corresponding proton exchange rate constant of trimethylammonium chloride[14b] and 100 times slower than that of dibenzylmethylammonium chloride,[2] which may be caused by steric hindrance of neighboring axial protons. The intercept (0.12 ± 0.42) is within experimental error of zero and thus $k_1 \leqslant 1.0 \times 10^{-2}$ l. mole^{-1} sec^{-1}, in reasonable agreement with results obtained for acyclic amines.[14b]

Nitrogen Inversion Rate. The methylenic resonance shown in Figure 1b consists primarily of an AA′BB′ attributable to *trans*-H_2P^{2+}. The *cis* isomer is expected to undergo rapid chair–chair interconversion at room temperature. As shown in Figure 2b, this will cause averaging of the magnetic environments of C with F and D with E, resulting in a different pattern (CC′DD′) from that of the *trans* isomer. Superimpo-

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(14) (a) E. Grunwald, A. Loewenstein, and S. Meiboom, *J. Chem. Phys.* 27, 630 (1957); (b) A. Loewenstein and S. Meiboom, *ibid.*, 27, 1067 (1957); (c) Z. Luz and S. Meiboom, *ibid.*, **39**, 366 (1963).

(15) M. Karplus, *J. Am. Chem. Soc.*, 85, 2870 (1963); H. S. Gutowsky, M. Karplus, and D. M. Grant, *J. Chem. Phys.*, **31**, 1278 (1959).

(16) J. I. Legg and D. W. Cooke, *Inorg. Chem.*, **5**, 594 (1966).

(17) See, for example, S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Chapter 15.

Table I. Methylenic Line Widths and Reciprocal Lifetimes of *trans*-H_2P^{2+}

pH	W, cps	ΔW, cps	$1/\tau_A \times 10^{-2}$, sec^{-1}	$[H^+]^2/\tau_A \times 10^3$, sec^{-1}
3.00 ± 0.01	0.8 ± 0.1	0.0 ± 0.1	∞	∞
2.60 ± 0.01	1.3 ± 0.1	0.5 ± 0.1	16.0 ± 19.0	10.0 ± 12.0
2.40 ± 0.01	2.3 ± 0.1	1.5 ± 0.1	5.2 ± 4.4	8.2 ± 7.0
2.20 ± 0.01	2.4 ± 0.1	1.6 ± 0.1	4.8 ± 4.1	19.0 ± 16.0
2.00 ± 0.01	3.6 ± 0.1	2.8 ± 0.1	2.8 ± 2.3	28.0 ± 23.0

sition of the *cis*- and *trans*-methylene resonances, however, makes separate observation impossible.

For *trans*-H_2P^{2+}, the diequatorial–diaxial equilibrium favors the former by greater than 98%. The process which is principally responsible for the observed coalescence of an AA′BB′ pattern (Figure 1b) into a singlet (Figure 1a) must be that shown in Figure 2a. This process, allowing interconversion of a particular diequatorial *trans*-H_2P^{2+} molecule and its mirror image, *trans**-H_2P^{2+}, is more than a simple ring inversion, involving inversion of both nitrogen atoms as well. In Figure 2a the labeling of individual protons A, A′, B, and B′ is preserved during the *trans–trans** conversion, just as in the nmr experiment spin-labeling of individual protons is preserved during the conversion time. Because of interchange of the magnetic environments of all A's and B's, only rapid *trans–trans** interconversion can account for the observed averaging of methylene proton chemical shifts at pH values of 3.0 and higher.

Because nitrogen atoms do not undergo inversion while tetrahedrally bonded, the *trans–trans** conversion must involve intermediates in which one or both $-NH^+$ protons are removed, namely *t*-HP^+ and/or *t*-P. For the *t*-HP^+ intermediate, the sequence of steps (eq 5, 11, and 5) in the *trans–trans** conversion is considered.

$$t\text{-}H_2P^{2+} + HP^+ \underset{}{\overset{k_3}{\rightleftarrows}} t\text{-}HP^+ + H_2P^{2+} \tag{5}$$

$$t\text{-}HP^+ \overset{k_5}{\rightleftarrows} t^*\text{-}HP^+ \tag{11}$$

$$t^*\text{-}HP^+ + H_2P^{2+} \overset{k_3}{\rightleftarrows} t^*\text{-}H_2P^{2+} + HP^+ \tag{5a}$$

The rate of *trans–trans** conversion (abbreviated *t–t** rate) resulting from intermediate *t*-HP^+ is given by

$$t\text{–}t^* \text{ rate} = k_5[t\text{-}HP^+] \tag{12}$$

As will be shown, the rate of the reaction in eq 5 is rapid compared to the observed *t–t** rate and equilibrium constant K_1 may then be substituted for [*t*-HP^+] in eq 12 as

$$t\text{–}t^* \text{ rate} = \frac{k_5K_1[t\text{-}H_2P^{2+}]}{[H^+]} \tag{13}$$

If *t*-P is an intermediate in the *trans–trans** conversion, the following sequence of steps must be considered

$$t\text{-}H_2P^{2+} + HP^+ \overset{k_3}{\rightleftarrows} t\text{-}HP^+ + H_2P^{2+} \tag{5}$$

$$t\text{-}HP^+ + HP^+ \underset{k_4}{\overset{k_{-4}}{\rightleftarrows}} t\text{-}P + H_2P^{2+} \tag{6a}$$

$$t\text{-}P \overset{k_7}{\rightleftarrows} t^*\text{-}P \tag{14}$$

$$t^*\text{-}P + H_2P^{2+} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} t^*\text{-}HP^+ + HP^+ \tag{6b}$$

$$t^*\text{-}HP^+ + H_2P^{2+} \overset{k_3}{\rightleftharpoons} t^*\text{-}H_2P^{2+} + HP^+ \tag{5a}$$

Equation 6a is derived by analogy with proton exchange studies described herein and elsewhere.[14] That is, the proton acceptor which would probably contribute most toward the rate of conversion of *t*-HP^+ to *t*-P is assumed to be HP^+.

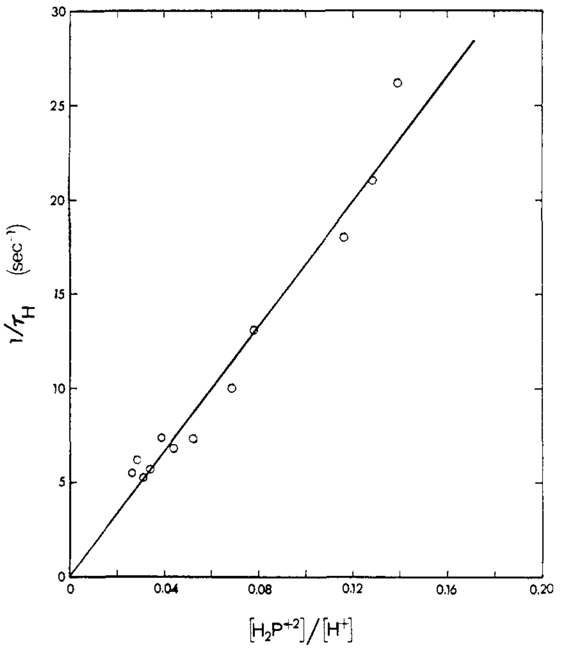

Figure 3. Exchange rate of $-NH^+$ protons at various values of $[H_2P^{2+}]/[H^+]$.

In order for P to make an appreciable contribution as an intermediate

$$k_7[P] \approx k_5[HP^+] \text{ or} \tag{15}$$

$$k_7 \approx (2.5 \times 10^6)k_5 \tag{16}$$

If the conditions given in eq 17 and 18 are satisfied

$$k_{-4}[HP^+]^2 > k_7[P], \text{ or } k_{-4} > (2 \times 10^{-4})k_7 \tag{17}$$

$$k_4[H_2P^{2+}][P] > k_7[P], \text{ or } k_4 > k_7 \tag{18}$$

then P is in rapid equilibrium with HP^+ and the total *trans–trans** conversion rate is given by

$$t\text{–}t^* \text{ rate} = \frac{k_5K_1[t\text{-}H_2P^{2+}]}{[H^+]} + \frac{k_7K_1K_2[t\text{-}H_2P^{2+}]}{[H^+]^2} \tag{19}$$

Dividing through by [*t*-H_2P^{2+}], we obtain the fractional rate yielded by the nmr experiment, equal to $1/\tau_A$, the reciprocal lifetime of a particular proton A (or the lifetime of a particular *trans*-H_2P^{2+} configuration)

$$\frac{1}{\tau_A} = \frac{t\text{–}t^* \text{ rate}}{[t\text{-}H_2P^{2+}]} = \frac{k_5K_1}{[H^+]} + \frac{k_7K_1K_2}{[H^+]^2} \tag{20}$$

Table I gives W, the half-width of the methylenic resonance in 0.67 *M* H_2P^{2+} at various pH values.

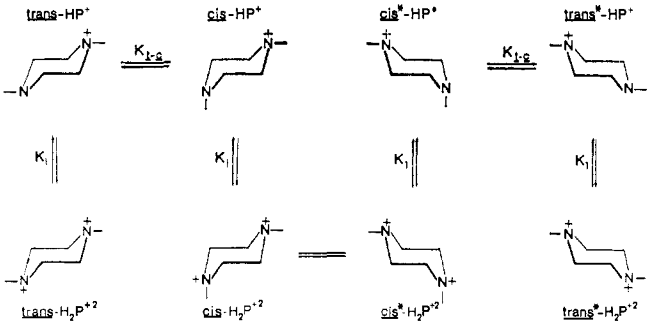

Figure 4. Proposed mechanism of conversion of *trans*-H_2P^{2+} to *trans**-H_2P^{2+}.

The half-width at pH 3.00 is the minimum value observed and is taken to represent W_0, the half-width in the absence of chemical exchange. W_0 is the sum of contributions of magnetic field inhomogeneity $(1/\pi T_2')$ and natural line width $(1/\pi T_2)$. Table I gives ΔW, the increase in half-width W caused by chemical exchange $(\Delta W = W - W_0)$. In the fast-exchange limit, $1/\tau_A$ is given by[18]

$$\frac{1}{\tau_A} = \frac{\pi \Delta \nu_{AB}^2}{2\Delta W} \tag{21}$$

The chemical shift separation $\Delta\nu_{AB}$ between protons A and B was determined to be 22 ± 4 cps by second moment analysis[19] of the AA′BB′ pattern shown in Figure 1b. The rather large uncertainty in $\Delta\nu_{AB}$ is estimated because of the potential distortion of the superimposed methylene resonance of *cis*-H_2P^{2+}, comprising ~11% of the total intensity. Because $\Delta\nu_{AB}$ enters eq 21 as the second power, uncertainties in individual values of $1/\tau$ are large. However, $\Delta\nu_{AB}^2$ is a constant for all values of $1/\tau_A$ and its error contribution is applied to the common slope and intercept arising from a linear function of $1/\tau_A$. Multiplying eq 20 by $[H^+]^2$, we obtain

$$[H^+]^2/\tau_A = k_5K_1[H^+] + k_7K_1K_2 \tag{22}$$

Least-squares analysis of a plot of $[H^+]^2/\tau_A$ *vs.* $[H^+]$ yields a slope of 2.7 ± 0.5 and an intercept of $1.1 \pm 1.5 \times 10^{-3}$, the standard deviations reflecting only random errors in ΔW and $[H^+]$. Applying the additional error contribution of $\Delta\nu_{AB}^2$, we obtain a slope of 2.7 ± 0.9 and an intercept of $1.1 \pm 1.5 \times 10^{-3}$. From these results we determine values of $k_5 = 1.0 \pm 0.3 \times 10^5$ sec^{-1} and $k_7 = 1.0 \pm 1.4 \times 10^{10}$ sec^{-1}. Little significance is attached to the value of k_7 and, in any event, the contribution of the second term in eq 22 is very small; therefore *t*-HP^+ is the predominant intermediate in the *trans–trans** conversion.

Because the methylene line shapes are determined by the rate of *trans–trans** conversion, we observe only those processes which lead to complete conversion of *trans*-H_2P^{2+} all the way to *trans**-H_2P^{2+}, a process requiring inversion of the ring and inversion of both nitrogen atoms. Because inversion of six-membered rings is rapid at room temperature,[3,4,18b] the rate of *trans–cis* conversion of H_2P^{2+} must determine the *trans–trans** conversion rate. As shown in Figure 4, after one nitrogen atom in *trans*-HP^+ has undergone inversion, forming *cis*-HP^+, the probability of reprotonation, forming *cis*-H_2P^{2+}, is expected to be large, considering the large ratio of $[H_2P^{2+}]$ to $[HP^+]$ and the large value of k_3 ($6.1 \pm 0.4 \times 10^6$ l. mole^{-1} sec^{-1}). Thus when a particular molecule of *trans*-H_2P^{2+} has undergone conversion to *cis*-H_2P^{2+}, which is expected to undergo rapid chair–chair inversion at room temperature, it may with equal probability undergo conversion to either *trans**-H_2P^{2+} or to the original *trans*-H_2P^{2+} configuration. The nitrogen inversion rate must therefore equal twice the observed *trans–trans** conversion rate, and k_{t-c}, the nitrogen inversion rate of *t*-HP^+ at 44°, is given by

$$k_{t-c} = 2k_5 = 2.0 \pm 0.6 \times 10^5 \text{ sec}^{-1} \tag{23}$$

This is in excellent agreement with the nitrogen inversion rate of $2 \pm 1 \times 10^5$ sec^{-1} found by Saunders and Yamada[2] for dibenzylmethylamine.

Because *trans*-HP^+ and *cis*-HP^+ are in steady-state equilibrium, we can write that

$$t_{t-c}[t\text{-HP}^+] = k_{c-t}[c\text{-HP}^+] \tag{24}$$

and

$$k_{c-t} = k_{t-c}\frac{[t\text{-HP}^+]}{[c\text{-HP}^+]} = k_{t-c}\frac{[t\text{-H}_2\text{P}^{2+}]}{[c\text{-H}_2\text{P}^{2+}]} = k_{t-c}/K_{t-c} \tag{25}$$

where k_{c-t} is the nitrogen inversion rate of *cis*-HP^+ (and where it is assumed that the same value of K_1 applies to the *trans* and *cis* subspecies). Using a value of equilibrium constant $K_{t-c} = 0.126 \pm 0.013$, obtained from data given below, a value of $k_{c-t} = 1.6 \pm 0.5 \times 10^6$ sec^{-1} at 44° is calculated.

The number of proton exchanges per nitrogen inversion of *t*-H_2P^{2+} is given by the ratio (eq 26) derived from eq 10 and 20.

$$\frac{1/\tau_H}{2/\tau_A} = \frac{k_3[t\text{-H}_2\text{P}^{2+}]}{k_{t-c}} = 30 \pm 10[t\text{-H}_2\text{P}^{2+}] \tag{26}$$

Because all steps following the first nitrogen inversion are rapid, one cannot distinguish between the proposed mechanism of *trans–trans** conversion shown in Figure 4 and several variations. If the conversion of *cis*-HP^+ to *cis**-HP^+ takes place in three steps as proposed, the sequence is unknown and it is possible, for example, that ring inversion could take place first, followed by the gain of a second proton and subsequent loss of the first proton. An attractive possibility which cannot be ruled out is the direct conversion of *cis*-HP^+ to *cis**-HP^+ *via* concerted ring inversion and intramolecular proton exchange.

With regard to the ring inversion rate of *cis*-H_2P^{2+}, we can state only that it must be greater than the greatest observed rate of *trans–trans** conversion. Assuming $\Delta S^{\ddagger} = 0.0$, it can be shown from the data in Table I that $E_a < 14.6$ kcal/mole for the *cis–cis** inversion of H_2P^{2+}.

Equilibrium of *trans*- and *cis*-H_2P^{2+}. The relative abundance of *cis*-H_2P^{2+} was determined by electronic integration of peak areas and found to be 11.2 ± 1% at 44°. That is, the small peak at lowest field strength in Figure 5b contains 11.2% of the combined areas of

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[18] (a) A. Loewenstein and T. M. Connor, *Ber. Bunsenges. Physik. Chem.*, **67**, 280 (1963) (note that the τ in eq 12b of this paper is related to our τ_A by the expression $\tau^{-1} = \tau_A^{-1} + \tau_B^{-1} = 2\tau_A^{-1}$); (b) F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, **89**, 760 (1967).

[19] W. A. Anderson and H. M. McConnell, *J. Chem. Phys.*, **26**, 1496 (1957).

the lowest and highest field peaks. It follows that the *trans* to *cis* conversion is accompanied by $\Delta G = 1.23 \pm 0.1$ kcal/mole at 44°.

The observation that the *cis*-methyl resonance, formed by averaging equatorial and axial methyl groups, lies 5 cps downfield of the *trans*-methyl resonance differs from chemical shift data for 1,4-dimethylcyclohexanes[20] (where the *cis*-methyl resonance lies 7.2 cps upfield of the *trans*-methyl resonance), and suggests that the axial methyl groups are shifted 10 cps downfield of the equatorial methyl groups in *cis*-H_2P^{2+}.

Upon decreasing the temperature to 12° (Figure 5a), no significant increase in the population of the *cis* isomer is found. Upon raising the temperature to 95° (Figure 5c), the *cis*- and *trans*-methyl doublets coalesce into two singlets, indicating increased proton exchange rates, and an increase of 1.3% in the abundance of the *cis* isomer is observed, barely significant with respect to experimental error. Thus ΔH for the *trans–cis* isomerization is small, a value of 0.3 ± 0.3 kcal/mole being determined by least-squares analysis. It follows that $\Delta S = -3.1 \pm 1.0$ eu and $\Delta G = 1.16 \pm 0.1$ kcal/mole at 25°.

This value of ΔG, representing the difference in size of $-NH^+$ protons and N-methyl groups, is smaller than any ΔG value[11] reported for the difference in size of –CH protons and methyl groups in cyclohexane derivatives (1.5–2.1 kcal/mole), which supports the contention that a sphere of tightly bound solvent increases the effective size of a substituent, in agreement with previous findings.[6]

The value of ΔS is lower than expected by 4.5 eu because the *trans* and *cis* isomers have symmetry numbers of 2 and 1, leading to a theoretical ΔS value of $R \ln 2$ or +1.38 eu. This smaller ΔS value could arise from loss of translational entropy of water owing to the accommodation of an additional water molecule in the primary hydration sphere of the less hindered equatorial $-NH^+$ proton of the *cis* isomer, as shown in the reaction

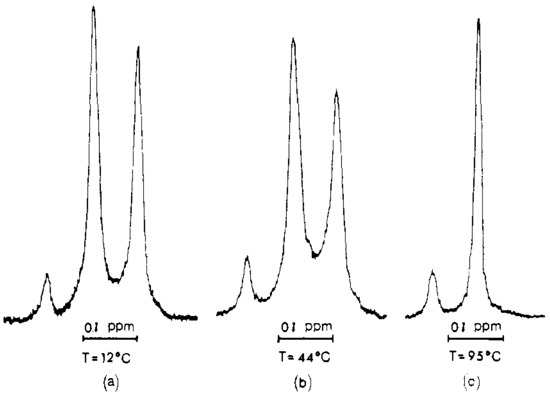

Figure 5. Methyl resonances of *trans*-H_2P^{2+} and *cis*-H_2P^{2+} at various temperatures.

$$H_2O + trans\text{-}H_2P^{2+}(H_2O)_n = cis\text{-}H_2P^{2+}(H_2O)_{n+1} \quad (27)$$

This explanation is supported by potentiometric data[5a] for the acid dissociation constants of the methylammonium ion series, which indicate that incorporation of a single water molecule in the primary hydration sphere of an ion is accompanied by the loss of 4.9 ± 0.8 eu.

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(20) S. Brownstein and R. Miller, *J. Org. Chem.*, **24**, 1886 (1959).