

Intramolecular Proton Transfer through Water in Diamine Monocations¹

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Abstract: Apparent second-order rate constants (k_{obsd}) for exchange of HCN protons catalyzed by diamine monocations were determined from the broadening of the proton NMR resonance of HCN. The absence of a large falloff in k_{obsd} when the pH is increased up to 6 is evidence that the diamine undergoes intramolecular proton transfer through one or more water molecules. This provides a mechanism for proton exchange between diamine monocations and solvent that is not present in monoamines. Acyclic diamine monocations can partition between intramolecular proton exchange with water or protonation by 1 M HCN. The rate constants for intramolecular proton transfer calculated from this partitioning at 20 °C, ionic strength 1.0 M (KCl) in 10% D₂O, are the following: *N,N,N',N'*-tetramethylethylenediamine, $\geq 10^{7.2}$ s⁻¹; *N,N,N',N'*-tetramethyl-1,3-propanediamine, $\geq 10^{7.4}$ s⁻¹; *N,N,N',N'*-tetramethyl-1,3-diamino-2-propanol, $10^{6.5}$ s⁻¹; *N,N,N',N'*-tetramethyl-1,4-butanediamine, $< 10^{7.0}$ s⁻¹; ethylenediamine, $10^{6.8}$ s⁻¹. The absence of detectable intramolecular solvent-mediated proton transfer for piperazine and 2,6-dimethylpiperazine monocations and for imidazole sets upper limits on the rate constants for these compounds of $10^{5.2}$, $10^{4.8}$, and $10^{5.5}$ s⁻¹, respectively. A rate constant of $10^{7.6}$ M⁻¹ s⁻¹ was obtained for the symmetrical intramolecular proton transfer between cholamine and its conjugate acid through a water molecule(s).

In the previous paper,² we showed that proton transfer from HCN to a base catalyst occurs directly. In this paper we show that a number of diamine monocations, unlike monoamines, do not exhibit a large fall-off of k_{obsd} for catalysis of the exchange of HCN protons, relative to k_{TX} for transfer of protons from HCN, as the pH is increased. This result means that there must be a mechanism for the exchange of the protons of protonated diamines with solvent that is not available to monoamines. This mechanism involves removal of one of the protons by CN⁻ to form the monocation, followed by a rapid intramolecular proton transfer through one or more water molecules that results in the exchange of its protons with water. The partitioning of the diamine monocation between protonation by HCN ($k_a[\text{HCN}]$) and intramolecular proton transfer (k_c) provides a method of measuring these rate constants.

Results

Rate constants for the exchange of HCN protons with solvent in the presence of buffers were determined by NMR measurements with the methods described in the previous papers.^{2,3} The broadening of the HCN resonance line in the presence of increasing concentrations of buffer was used to obtain a second-order rate constant for proton exchange, k_{obsd} .³ The rate constant k_{obsd} is defined by eq 1, in which $\Delta f_{1/2}$ is the increase in width (in Hz) of the HCN resonance at half-height caused by the added buffer.

$$k_{\text{obsd}} = \frac{\pi \Delta f_{1/2}}{[\text{total buffer}]} \quad (1)$$


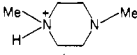

Figure 1 shows the dependence on pH of log ($k_{\text{obsd}}[\text{HCN}]$) for catalysis of the broadening of the HCN resonance by *N,N,N',N'*-tetramethylethylenediamine. The dashed line labeled $k_{\text{TX}}[\text{HCN}]$ indicates the rate constant for proton transfer from HCN to the amine buffer, according to the rate law of eq 2. These first-order rate constants are numerically equal to the second-order

$$\text{Rate} = k_{\text{TX}}[\text{HCN}][\text{total buffer}] \quad (2)$$

rate constants k_{obsd} and k_{TX} because the concentration of HCN is 1 M; first-order rate constants are shown in the figure to permit comparison with k_{soln} (see below). The rate constant k_{TX} increases by a factor of 10 for each unit increase in pH because it is proportional to the concentration of the monoprotonated diamine, which is only a small fraction of the total diamine concentration in this pH range.⁴

The value of k_{TX} was calculated from the values of k_{obsd} below pH 3. At this pH value HCN and the diprotonated diamine are

Table I. Rate Constants for Cyclic Proton Transfer through Water^a

catalyst	pK ^b	pH	($k_{\text{obsd}}/k_{\text{TX}}$) ^c	k_a , ^d M ⁻¹ s ⁻¹	k_c , ^e s ⁻¹
H ₃ N ⁺ CH ₂ CH ₂ NH ₂	7.5 ^f	6.0	0.26	10 ^{7.17}	10 ^{6.8}
Me ₃ N ⁺ CH ₂ CH ₂ NH ₂	7.32 ^g	5.75	0.016	10 ^{7.13}	<i>h</i>
	6.01 ⁱ	5.91	0.047	10 ^{6.36}	<10 ^{5.2}
	4.64 ^g	6.0	0.19	10 ^{5.15}	<10 ^{4.8}
Me ₂ N ⁺ H(CH ₂) ₂ NMe ₂	6.47 ^g	6.0	0.50	10 ^{6.87}	$\geq 10^{7.2}$
	7.24 ^j	5.9	0.049	10 ^{6.78}	>10 ^{5.5}
Me ₂ N ⁺ HCH ₂ CH ₂ CH ₂ NMe ₂	8.39 ^g	5.9	0.30	10 ^{7.48}	$\geq 10^{7.4}$
Me ₂ N ⁺ HCH ₂ CH(OH)-CH ₂ NMe ₂	8.01 ^g	5.9	0.05	10 ^{7.72}	10 ^{6.5}
Me ₂ N ⁺ H(CH ₂) ₄ NMe ₂	9.24 ^g	5.9	<0.44	10 ^{7.46}	<10 ^{7.0k}

^a At 20 °C and ionic strength 1.0 M (KCl) in 10% D₂O. ^b For the protonated form of catalyst at 25 °C and ionic strength 1.0 M (KCl). ^c At the indicated pH. Additional data are given in the supplementary material of the first paper in this series.³ ^d Obtained as described previously.³ ^e Calculated as described in the text. The value of k_{soln} was obtained from eq 5 of the previous paper² by using $k_{\text{HOH}} = 10^{(10.3 - \text{p}K_{\text{BH}^+})}$ s⁻¹, $k_{\text{OH}} = 2 \times 10^{10}$ M⁻¹ s⁻¹, and $k_{\text{B}} = 10^8$ M⁻¹ s⁻¹. ^f Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 572-580. ^g This work. ^h Cyclic proton transfer is not possible with this compound. The data are fit with $k_c = 0$ and $k_{\text{B}} = 10^{(7.6 \pm 0.2)}$ M⁻¹ s⁻¹ (see Figure 3). ⁱ Jencks, W. P.; Gilchrist, M. J. *Am. Chem. Soc.* **1968**, *90*, 2622-2637. ^j Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6353-6361. ^k Calculated from eq 3-5 by using a limiting value of $\alpha < 0.71$; α was calculated as described previously.²

in slow exchange on the NMR time scale and, therefore, the broadening of the HCN resonance is sensitive to all proton transfers from HCN.^{2,3} At pH >4 the value of log k_{obsd} is con-

(1) Supported in part by grants from the National Institutes of Health (GM 20888 and GM 20168) and the National Science Foundation (PCM 81-17816). Dr. Bednar was supported by a fellowship from the National Institutes of Health (AM 06911).

(2) Bednar, R. A.; Jencks, W. P. *J. Am. Chem. Soc.*, previous paper in this series.

(3) Bednar, R. A.; Jencks, W. P. *J. Am. Chem. Soc.*, first paper in this series.

(4) The free base diamine does not contribute to the observed catalysis of proton removal from HCN because it is present in very small concentrations at the pH values used in this study. The log of the concentration of free diamine decreases with a slope of -2 at pH values below the pK of the monocation.

(5) Grunwald, E.; Fong, D.-W. *J. Am. Chem. Soc.* **1972**, *94*, 7371-7377. Chang, K. C.; Grunwald, E.; Robinson, L. R. *J. Am. Chem. Soc.* **1977**, *99*, 3794-3796.

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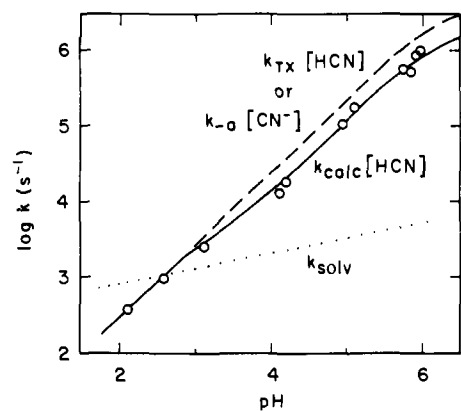


Figure 1. The dependence on pH of $\log k_{\text{obsd}}[\text{HCN}]$ catalyzed by *N,N,N',N'*-tetramethylethylenediamine buffers at 20 °C, ionic strength 1.0 M (KCl), 1 M HCN, and 10% D₂O. The dashed line, labeled $k_{\text{TX}}[\text{HCN}]$ or $k_{-\text{o}}[\text{CN}^-]$, indicates the pH dependence of the rate constant for proton transfer from HCN (eq 2). The dotted line, labeled k_{solv} , is the sum of the first-order rate constants for removal of a proton from the diprotonated diamine by H₂O, OH⁻, or the monoprotonated diamine through a water molecule (Scheme I). The solid line was calculated from eq 3, with $\beta = 1$ and $\gamma = 0.5$; α was calculated as described previously² by using $\delta = 10^{3.79}$ rad/s.

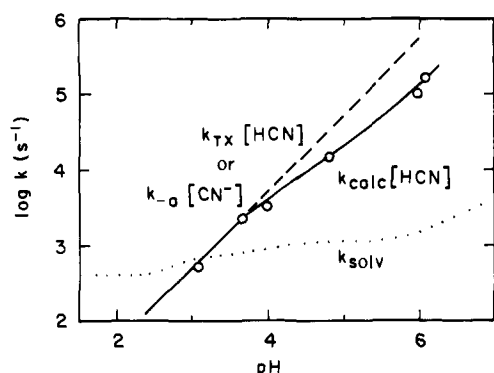


Figure 2. The dependence of pH of $\log k_{\text{obsd}}[\text{HCN}]$ determined from the broadening of the HCN resonance catalyzed by ethylenediamine buffers at 20 °C, ionic strength 1.0 M (KCl), 1 M HCN, and 10% D₂O. See the legend of Figure 1 for an explanation of the lines. The solid line was calculated from eq 3 with $\beta = 1$, α was calculated as described previously² by using $\delta = 10^{3.63}$ rad/s, and γ was obtained from eq 4 and 6 with $k_{\text{c}} = 10^{6.8}$ s⁻¹. The value of k_{solv} was obtained from eq 5 of the previous paper² by using $k_{\text{HOH}} = 10^{2.8}$ s⁻¹, $k_{\text{OH}} = 2 \times 10^{10}$ M⁻¹ s⁻¹, and $k_{\text{B}} = 10^8$ M⁻¹ s⁻¹.

sistently 0.30 unit lower than k_{TX} . This difference is significantly larger than the experimental error of the data. The dotted line, labeled k_{solv} , is the sum of the first-order rate constants for removal of a proton from the diprotonated diamine by H₂O, OH⁻, or the monoprotonated diamine through a water molecule under the conditions of the experiment.²

Qualitatively similar results are shown for ethylenediamine in Figure 2. At pH 6, k_{obsd} is 0.58 log units lower than k_{TX} . A significantly larger fall-off in k_{obsd} with increasing pH is seen with cholamine (Figure 3), which is an analogue of ethylenediamine monocation with three methyl groups instead of protons on one nitrogen atom. At pH 5.75, k_{obsd} is smaller than k_{TX} by a factor of $\sim 10^{1.8}$.

The results of similar experiments with a series of diamines are summarized in Table I. The ratio $k_{\text{obsd}}/k_{\text{TX}}$ for the highest pH measured is indicated; complete data for other pH values are given in the supplementary material for the first paper in this series.³ The rate constant k_{a} , for the removal of a proton from HCN by the diamine monocation, was obtained by dividing k_{TX} by the fraction of total buffer in the monoprotonated form.⁴ The rate constant k_{c} , for cyclic intramolecular proton transfer through a water molecule in monoprotonated diamines (Table I; see Schemes II and III), was calculated as described in the Discussion section.

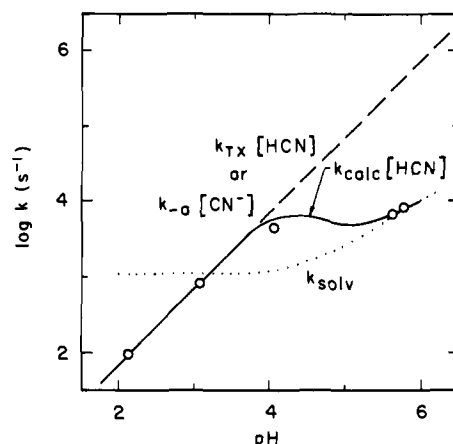
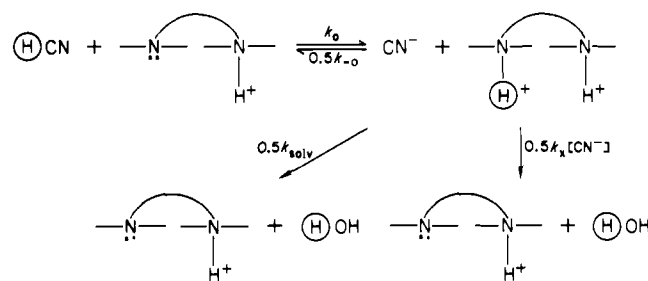
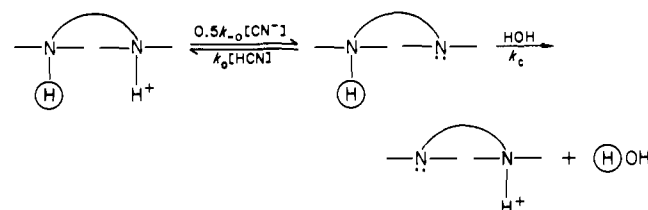


Figure 3. The dependence on pH of $\log k_{\text{obsd}}[\text{HCN}]$ determined from the broadening of the HCN resonance catalyzed by cholamine at 20 °C, ionic strength 1.0 M (KCl), 1 M HCN, and 10% D₂O. The solid line was calculated as described previously² from $\delta = 10^{3.66}$ rad/s, $k_{\text{HOH}} = 10^3$ s⁻¹, $k_{\text{OH}} = 2 \times 10^{10}$ M⁻¹ s⁻¹, a value of $k_{\text{B}} = 10^{7.6}$ M⁻¹ s⁻¹, and the average concentration of monoprotonated diamine used in the determination of each k_{obsd} .

Scheme I



Scheme II



Discussion

Scheme I describes the fate of a proton on HCN that is removed by a monoprotonated tertiary diamine. The labeled proton on the diprotonated diamine will be returned to CN⁻ with a first-order rate constant of $0.5k_{-\text{o}}[\text{CN}^-]$. Alternatively, it will exchange with solvent with a first-order rate constant of $0.5k_{\text{solv}}$. (The 0.5 is required because only one of the two protons is removed.) When HCN and the diprotonated diamine are in fast exchange on the NMR time scale (this occurs at high pH, see below or the previous paper²), proton transfers between HCN and the monoprotonated diamine do not cause broadening of the HCN line if the same proton is returned. The proton transfer is detected as line broadening only if the "labeled" proton is exchanged for a solvent proton ($0.5k_{\text{solv}}$) before return to CN⁻ ($0.5k_{-\text{o}}[\text{CN}^-]$). Since HCN and water are in slow exchange on the NMR time scale, the exchange of an HCN proton for a water proton will be fully reflected in the broadening of the HCN resonance. The fast return of labeled protons back to CN⁻ relative to exchange with solvent at high pH accounts for the large fall-off in k_{obsd} , compared with k_{TX} , that is observed with monoamines and phenolate ions when the pH is increased.²

We were initially surprised to find that the expected large drop-off in k_{obsd} does not occur with diamines (Figure 1 and 2). The absence of this large drop-off shows that the protonated diamine has an additional mechanism for exchange of its protons

with solvent that is not available for monoamines or alcohols. This mechanism is indicated by the rate constant k_X in Scheme I.

Scheme II describes a mechanism by which diprotonated diamines can exchange protons with solvent ($0.5k_X[\text{CN}^-]$ in Scheme I). A similar mechanism has been suggested by Grunwald and co-workers to explain the base-catalyzed exchange of the protons of protonated hexamine platinum and 1,4,7,10-tetraazocyclododecane with solvent.⁵ When CN^- removes an unlabeled proton from the diprotonated diamine, it produces a monoprotated diamine containing a labeled proton. This monoprotated diamine can now exchange its labeled proton with solvent by an intramolecular proton transfer through one or more water molecules, with a rate constant k_c . Other bases besides CN^- can remove the unlabeled proton from the diprotonated diamine. However, at higher pH values the concentration of free CN^- increases and the rate constant for removal of the unlabeled proton by CN^- ($0.5k_a[\text{CN}^-]$) is much larger than that for removal by solvent ($0.5k_{\text{solv}}$). This is shown by the dashed and dotted lines in Figure 1-3, which are explained below. The rate constant k_c for the intramolecular cyclic proton transfer in a monoprotated diamine was determined from the partitioning of the labeled monoprotated diamine between cyclic proton transfer (k_c) or protonation by HCN ($k_a[\text{HCN}]$). The quantitative aspects of these measurements are as follows.

The relationship between the rate constants k_{obsd} , determined from the broadening of the HCN resonance line, and k_{TX} , defined by eq 2, was derived in the previous paper² and is given in eq 3.

$$k_{\text{obsd}}/k_{\text{TX}} = 1 - \alpha\beta^2\gamma \quad (3)$$

The parameter α indicates whether HCN and the protons on diamine dications are in fast ($\alpha = 1$) or in slow ($\alpha = 0$) exchange on the NMR time scale. The parameter β is the fraction of proton transfer that occurs directly, as opposed to transfer through solvent. Evidence presented in the previous paper² indicates that proton transfer between HCN and several nitrogen and oxygen bases occurs directly ($\beta = 1.0$). The parameter γ , the partition fraction for return of a proton to CN^- ($k_a[\text{CN}^-]$) vs. exchange of the proton with solvent ($k_{\text{solv}} + k_X[\text{CN}^-]$), is defined in eq 4.

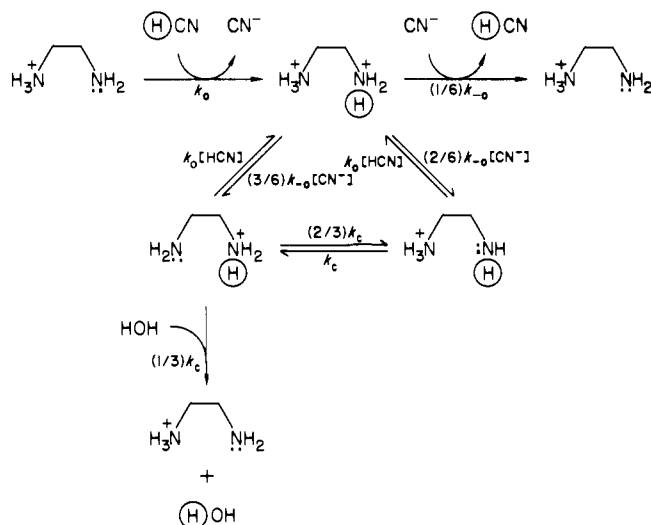
$$\gamma = \frac{k_a[\text{CN}^-]}{k_a[\text{CN}^-] + (k_{\text{solv}} + k_X[\text{CN}^-])} \quad (4)$$

Consider the broadening of the HCN resonance caused by N,N,N',N' -tetramethylethylenediamine (TMEDA) buffer (Figure 1). The dashed line in Figure 1 shows the dependence on pH of $k_{\text{TX}}[\text{HCN}]$ and $k_a[\text{CN}^-]$. The rate constant k_{TX} is expressed in terms of total buffer concentration (eq 2) and is equal to k_a divided by the fraction of monoprotated diamine. The rate constant k_a is defined in Scheme I. Since the NMR measurements are made under equilibrium conditions, the rate of the forward reaction equals the rate of the reverse reaction. The concentration of total buffer is approximately equal to the concentration of diprotonated diamine at the pH values used in this study, so that $k_{\text{TX}}[\text{HCN}]$ is equal to $k_a[\text{CN}^-]$.

The observed difference, δ , between the resonance frequencies of HCN and the diprotonated TMEDA ion is $10^{3.79}$ rad/s. At pH < 3, where $0.5k_a[\text{CN}^-] < 10^{3.79} \text{ s}^{-1}$, return of the proton to CN^- ($0.5k_a[\text{CN}^-]$) is slow compared with the difference in the resonance frequencies of the two exchanging species. Therefore, HCN and the diprotonated diamine are in slow exchange on the NMR time scale and the NMR line broadening is sensitive to all proton transfers between HCN and the monoprotated TMEDA ($\alpha = 0$). At pH > 4, where $0.5k_a[\text{CN}^-] > 10^{3.79} \text{ s}^{-1}$, return of the proton to CN^- ($0.5k_a[\text{CN}^-]$) is fast compared with the difference in the resonance frequencies of the two exchanging species. Therefore, HCN and the diprotonated diamine are in fast exchange on the NMR time scale, and the HCN resonance line is not broadened by proton transfer to monoprotated TMEDA if the same proton is returned to CN^- without exchanging with solvent; i.e., $\alpha = 1$.

The dotted line in Figure 1 describes k_{solv} , the sum of the first-order rate constants for the removal of a proton on the

Scheme III



diprotonated diamine by H_2O , by OH^- , and by a second-order reaction with monoprotated diamine through an intermediate water molecule. These were estimated by the procedure described in the previous paper.² At pH > 2.5 the return of a proton to CN^- (dashed line, $k_a[\text{CN}^-]$) is faster than the loss of a proton from the diprotonated diamine to solvent (dotted line, k_{solv}). Equation 4 shows that γ would then be expected to approach 1.0 at the higher pH values if k_{solv} describes the only pathway for proton exchange with solvent. Since α and β are also equal to 1, eq 3 would then require that k_{obsd} should be much less than k_{TX} . Substitution of eq 4 into eq 3 and of $k_{\text{TX}}[\text{HCN}]$ for $k_a[\text{CN}^-]$ shows that $k_{\text{obsd}}[\text{HCN}]$ should be approximately equal to k_{solv} under these conditions. However, k_{obsd} is only 0.3 log units lower than k_{TX} instead of the 2.5 log units predicted.

This discrepancy means that there is an additional pathway, indicated by $0.5k_X[\text{CN}^-]$ in Scheme I, for exchange of a proton of a diprotonated diamine with solvent. The exchange with solvent that is described by $0.5k_X[\text{CN}^-]$ occurs by intramolecular proton transfer through water in the monocation, with the rate constant k_c (Scheme II). The drop of 0.3 log unit in $k_{\text{obsd}}/k_{\text{TX}}$ (a factor of 2) indicates that γ must really be 0.5 (eq 3, $\alpha = 1, \beta = 1$). The rate constant $0.5k_X[\text{CN}^-]$ for exchange of a proton on the diprotonated diamine with solvent is therefore equal to the rate constant for return of the labeled proton to CN^- , $0.5k_a[\text{CN}^-]$, as described by eq 4 when k_{solv} is small. The value of k_c was calculated from eq 5, which was derived from Scheme II by applying the steady-state assumption to the concentration of the labeled monoprotated diamine.

$$k_X[\text{CN}^-] = k_a[\text{CN}^-] \frac{k_c}{k_c + k_a[\text{HCN}]} \quad (5)$$

In the limit when $k_c \gg k_a[\text{HCN}]$, the first step in Scheme II, removal of the unlabeled proton from the diprotonated diamine, is rate limiting for exchange of the labeled proton with solvent. That is, every time the unlabeled proton is removed from the diprotonated diamine with a rate constant $0.5k_a[\text{CN}^-]$, a rapid cyclic proton transfer through water causes loss of the labeled proton to solvent. Since CN^- will remove the labeled and unlabeled proton with equal probability, the rate constants for return of the labeled proton to CN^- and for its exchange with solvent are equal; therefore, $\gamma = 0.5$. The ratio of proton exchange to proton transfer, $k_{\text{obsd}}/k_{\text{TX}}$, is 0.5, which corresponds to a drop of 0.3 log unit. This is precisely what is observed with TMEDA (Figure 1). In this way a limit can be placed on the rate constant for the cyclic proton transfer via water, k_c , because $k_c \gg k_a[\text{HCN}]$. Therefore, k_c for TMEDA is $\gg 10^{6.87} \text{ s}^{-1}$. Consideration of the uncertainty in the data gives a value of $k_c \geq 10^{7.2} \text{ s}^{-1}$ (Table I).

A similar analysis can be applied to the data for ethylenediamine. Scheme III illustrates the more complicated pathways by which primary diamine dications can exchange their protons

with solvent. The removal of protons from the dication by water, hydroxide ion, and the monocation of the diamine, k_{soliv} , is much slower than removal by CN^- ($k_{-\text{a}}[\text{CN}^-]$) and is not included in Scheme III. In the limit when cyclic proton exchange with solvent is much faster than protonation of the monocation by HCN ($k_{\text{c}} \gg k_{\text{a}}[\text{HCN}]$), every time a proton is removed from the dication all the protons on the newly formed monocation will exchange rapidly with solvent. Only one time in six will CN^- remove the labeled proton from the dication. This gives $\gamma = 1/6$, which corresponds to a drop of 0.08 log unit in k_{obsd} relative to k_{TX} . When the drop-off of k_{obsd} is greater than 0.08 log unit it is possible to calculate a value for k_{c} . The contribution of cyclic proton transfer to the washout of "labeled" protons can be calculated by treating both of the labeled monocation species in Scheme III as steady-state intermediates. Equation 6 gives the expression for the exchange of a labeled proton from a primary diamine dication ($k_{\text{X}}[\text{CN}^-]$).

$$k_{\text{X}}[\text{CN}^-] = k_{-\text{a}}[\text{CN}^-] \frac{2k_{\text{c}}(1/2k_{\text{a}}[\text{HCN}] + 5/6k_{\text{c}})}{(k_{\text{a}}[\text{HCN}])^2 + 1/3k_{\text{c}}^2 + 2k_{\text{c}}k_{\text{a}}[\text{HCN}]} \quad (6)$$

The experimentally-determined ratio of $k_{\text{obsd}}/k_{\text{TX}}$ yields a value of γ (eq 3). The value of k_{X} can be calculated from γ by using eq 4. The rate constant for the intramolecular cyclic proton transfer (k_{c}) can then be calculated by using eq 5 for tertiary diamines and eq 6 for primary diamines. The solid line in Figure 2 was calculated by using a rate constant of $k_{\text{c}} = 10^{6.8} \text{ s}^{-1}$ for the intramolecular cyclic proton transfer in ethylenediamine monocation.

Additional evidence that the cyclic proton transfer is responsible for the absence of a large drop-off in k_{obsd} relative to k_{TX} for diamines was obtained with cholamine. Cholamine is an analogue of ethylenediamine in which one nitrogen atom is quaternary and the cyclic proton-transfer mechanism is not possible. Indeed, a large drop in k_{obsd} of 1.8 log units is observed at pH 5.75 with this compound (Figure 3). The absence of such a large drop with ethylenediamine (Figure 2) is due to the cyclic transfer mechanism, which provides the diamine dication with a rapid pathway for exchange of protons with solvent (Scheme III).

A value for the *intermolecular* symmetrical proton transfer through water of $k_{\text{B}} = 10^{(7.6 \pm 0.2)} \text{ M}^{-1} \text{ s}^{-1}$ was calculated for cholamine mono- and dications from the observed drop-off of k_{obsd} with increasing pH, as described in the previous paper.² This rate constant is slightly smaller than that for other symmetrical transfer reactions of primary amines.⁶ It is possible that a small electrostatic effect slows the reaction of the monocation with the dication.

The dotted line in Figure 3 shows the contribution of k_{soliv} , from proton transfer to water and hydroxide ion and from intermolecular symmetrical proton transfer, to the exchange of ammonium ion protons with solvent. The solid line was calculated from eq 3 as described in the previous paper.² The hump in this line arises from the change from slow exchange on the NMR time scale between HCN and the ammonium ion at low pH ($\alpha = 1$) to fast exchange at high pH ($\alpha = 0$). This change occurs in the region in which $k_{-\text{a}}[\text{CN}^-]$ is approximately equal to the frequency difference of the two exchanging species ($\delta = 10^{3.66} \text{ rad/s}$ for cholamine).

Rate Constants for Intramolecular Proton Transfer. Values or limits of the rate constants for intramolecular cyclic proton transfer in a series of diamine monocations, k_{c} , are tabulated in Table I.

These rate constants were calculated from the ratio $k_{\text{obsd}}/k_{\text{TX}}$ and k_{a} . At the pH values for which $k_{\text{obsd}}/k_{\text{TX}}$ is reported in Table I, HCN and the diammonium ions are in fast exchange ($\alpha = 1$) for all compounds except $\text{Me}_2\text{N}(\text{CH}_2)_4\text{NMe}_2\text{H}^+$. The value of β is 1.0 because proton transfers between HCN and bases occur directly and are not mediated via water.²

These rate constants for intramolecular proton transfer are in the range reported previously for reactions of this type.^{7,8} The value obtained for ethylenediamine of $10^{6.8} \text{ s}^{-1}$ at 20 °C probably does not differ significantly from the value of $10^{7.3} \text{ s}^{-1}$, at 25 °C obtained by Ralph and co-workers⁹ and the limit of $\geq 10^{7.2} \text{ s}^{-1}$ at 20 °C for *N,N,N',N'*-tetramethylethylenediamine may be compared with an observed rate constant of $10^{7.2}$ at 25 °C for *N,N,N',N'*-tetraethylethylenediamine obtained by Ralph and co-workers.⁹ It has been suggested that exchange of bridging water molecules with the solvent is kinetically significant for *N,N,N',N'*-tetraethylethylenediamine,⁹ however, it is unlikely to be rate limiting for ethylenediamine because the observed rate constant is smaller and desolvation is considerably faster for primary amines than for tertiary amines.^{6a}

The rate constant for cyclic proton transfer in *N,N,N',N'*-tetramethyl-1,3-propanediamine monocation is $\geq 10^{7.4} \text{ s}^{-1}$. The addition of a hydroxyl group on the central methylene group, in *N,N,N',N'*-tetramethyl-1,3-diamino-2-propanol, causes a decrease of $\geq 10^{0.9}$ in this rate constant (Table I). The OH group may interfere with the reaction by hydrogen bonding to one or both of the nitrogen atoms, possibly through an intervening water molecule(s). The present techniques do not allow us to determine if an intramolecular proton transfer also occurs directly through this hydroxyl group because exchange of the hydroxyl proton with solvent is probably slower than the observed intramolecular proton transfer, so that the same proton would be transferred back and forth. The hydroxyl group may also decrease the exchange rate of intervening water molecules with the bulk solvent. The rate decrease of >8-fold suggests that ΔG° for formation of the hydrogen bond responsible for this inhibition is at least -1 kcal/mol .

Constraining the flexibility of TMEDA by placing a covalent bond between two methyl groups to form piperazine and *N,N'*-dimethylpiperazine causes decreases in the rate of intramolecular transfer through water by factors of >400. Inspection of molecular models indicates that intramolecular proton transfer through 1–2 water molecules with these cyclic compounds is possible only with the boat conformation and an axial electron pair. Similarly, Dubois et al. have found only slow or no intramolecular proton transfer with tautomeric molecules that have little tendency to form a cyclic system, such as the imidazole ring of adenine and the pyrimidine ring of cytosine and isocytosine.⁷ Chang and Grunwald have reported a rate constant of $10^{6.2} \text{ s}^{-1}$ for OH proton exchange of water associated with intramolecular proton exchange between the two nitrogen atoms of imidazole at 30 °C.¹⁰ This is somewhat larger than the upper limit of $k_{\text{c}} < 10^{5.5} \text{ s}^{-1}$ for imidazole at 20 °C reported here; however, the k_{c} process measures only NH proton exchange and could correspond to exchange of several OH protons.

Registry No. HCN, 74-90-8; $\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2\text{H}^+$, 26265-69-0; $\text{Me}_3\text{N}^+\text{CH}_2\text{CH}_2\text{NH}_2$, 38170-37-5; $\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2\text{H}^+$, 71889-99-1; $\text{Me}_2\text{N}(\text{CH}_2)_3\text{NMe}_2\text{H}^+$, 98678-00-3; $\text{Me}_2\text{NCH}_2\text{CH}(\text{OH})\text{CH}_2\text{NMe}_2\text{H}^+$, 98677-99-7; $\text{Me}_2\text{N}(\text{CH}_2)_4\text{NMe}_2\text{H}^+$, 98678-01-4; piperazine- H^+ , 22044-09-3; 1,4-dimethylpiperazine- H^+ , 98688-76-7; imidazole, 288-32-4.

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