isotope effect on the transfer of HCN from water to deuterium oxide, so that $\phi_{HCN} = 1.0$ (note that ϕ_{HCN} refers only to HCN, which is observed by NMR, not to LCN).[68,69] Values of ϕ_{CN^-} = 0.65 and 0.79 can then be calculated from the observed deuterium isotope effect of $K_{HCN}/K_{DCN} = \phi_{LCN}/(\phi_{L_3O^+}\phi_{CN^-}) = 2.3$ for the ionization of LCN and estimates of ϕ_{LCN} obtained from the vibration frequencies of LCN and from the ratio of the fractionation factors for LCN and methane.[29,70] These values of ϕ_{CN^-} suggest that there is a significant isotope effect from interaction of the CN⁻ ion with the solvent, analogous to that observed for alkoxide and thiol anions.[71] They give calculated values of $k_{H_2O}/k_{D_2O} = 4.2$ and 3.4 for the direct transfer mech-

anism (eq 19 and 20) and 6.1 and 5.0 for transfer through solvent (eq 21 and 22). The observed isotope effect of $k_{H_2O}/k_{D_2O} = 4.5$ is consistent with either of these values.

Acknowledgment. We are most grateful to Drs. E. Grunwald, A. Redfield, and S. Roy for invaluable assistance with the NMR and discussions regarding the experiments described in this and the accompanying papers.

Supplementary Material Available: Tables showing data for general base catalyzed broadening of the HCN resonance and rate constants for exchange of HCN protons in strong acid media (11 pages). Ordering information is given on any current masthead page.

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(68) The assumption that $\phi_{HCN} = 1.0$ is supported by the value of $\phi_{HA} = 1.0$ for acetic acid,[69] a stronger acid.

(69) Cleland, W. W.; O'Leary, M. H.; Northrop, D. B., Eds. "Isotope Effects on Enzyme-Catalyzed Reactions"; University Park Press: Baltimore, 1977; pp 11 and 70.

(70) The deuterium isotope effect for the ionization of HCN and DCN in H₂O and D₂O, respectively, is given by eq 23.[66] The difference between the

$$K_{HCN}/K_{DCN} = \phi_{LCN}/l^3\phi_{CN^-} \qquad (23)$$

vibration frequencies of HCN and ROH gives an estimated value of $\phi_{LCN} = 10^{-0.31} = 0.49$.[29] The observed isotope effect[29] of $K_{HCN}/K_{DCN} = 2.3$ then gives $\phi_{CN^-} = 0.65$. The equilibrium constant of 0.75–0.80 for the reaction HCN + CH₃D ⇌ DCN + CH₄ in the gas phase (Hout, R. F., Jr.; Wolfsberg, M.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 3296–3298) and the value (calculated from $\phi_{CH_4}/\phi_{C_2H_2} = 1.246$ and $\phi_{C_2H_2} = 0.63$)[69] of $\phi_{CH_4} = 0.78$ give $\phi_{LCN} = 0.60$. This gives $\phi_{CN^-} = 0.79$ from eq 23.

(71) Gold, V.; Grist, S. *J. Chem. Soc. B* **1971**, 1665–1670. Jencks, W. P.; Salvesen, K. *J. Am. Chem. Soc.* **1971**, *93*, 4433–4436.
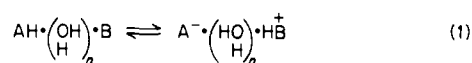

Direct Proton Transfer between HCN and Nitrogen and Oxygen Bases[1]

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Abstract: Selective saturation of the proton NMR signal of aqueous HCN results in transfer of saturation to methoxyethylammonium ion and trimethylammonium ion. This demonstrates that the removal of a proton from HCN by these amines occurs directly and is not mediated by an intervening water molecule. Apparent second-order rate constants (k_{obsd}) for the exchange of HCN protons catalyzed by amine and alcohol buffers were determined from the broadening of the HCN resonance. A leveling or fall-off of k_{obsd} is observed with amines (pK 3.8–9.9) and alcohols (pK 7.9–9.9) as the pH is increased above 4. A larger decrease in k_{obsd} occurs at higher concentrations of HCN. The decrease of k_{obsd} is caused by rapid return of the proton, which was transferred from HCN to the base, back to CN⁻ before it exchanges with solvent or loses the transverse magnetization of the HCN protons. At high pH, the chemical shift of the HCN resonance moves downfield, toward the ammonium ion, as the concentration of the amine is increased. These results require that the exchange occurs by direct transfer between HCN and the amine and not by transfer through a water molecule(s). Minimum estimates of the fraction of direct proton transfer between HCN and semicarbazide (>0.72), methoxyamine (>0.92), trifluoroethylamine (>0.94), glycinamide (>0.97), chloroethylamine (>0.96), tris(hydroxyethyl)amine (>0.99), hexafluoro-2-propanol (>0.93), *p*-nitrophenol (>0.96), *m*-nitrophenol (>0.97), and phenol (>0.98) were obtained by neglecting the exchange of >NH⁺ or –OH protons with water and broadening of the HCN resonance resulting from direct proton transfer. Accounting for these processes demonstrates that >99% of the proton transfer between HCN and these amines or alcohols occurs directly for reactions with ΔpK up to at least 5 units. It is suggested that hydrogen bonding of electronegative acids and bases to intermediate H₂O, H₃O⁺, and HO⁻ molecules decreases the rate constants for desolvation and increases the rate constant for proton transfer through water; the weaker hydrogen bonding of carbon favors the direct transfer mechanism even for the relatively normal HCN molecule.

Many proton-transfer reactions of oxygen and nitrogen acids and bases proceed with participation of one or more solvent molecules in hydroxylic solvents.[2] The solvent molecule acts as a bifunctional catalyst, that is, both as a proton acceptor and a proton donor (eq 1).

$$AH \cdot \left(\underset{H}{OH}\right)_n \cdot B \rightleftharpoons A^- \cdot \left(\underset{H}{HO}\right)_n \cdot H\overset{+}{B} \qquad (1)$$

For carbon acids and bases it is generally believed that proton transfer occurs directly ($n = 0$, eq 1).[3] This conclusion is based mainly on the failure to detect the primary and secondary solvent deuterium isotope effects that might be expected if proton transfer

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(2) Grunwald, E.; Eustace, D. In "Proton-Transfer Reactions"; Caldin, E., Gold, V., Eds.; Chapman and Hall: London, 1975; pp 103–120.

(3) Hibbert, F. In "Comprehensive Chemical Kinetics"; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1977; Vol. 8, pp 97–196.

occurred through water.[4,5] Optimal intramolecular catalysis by diamines of enamine formation through an 8-membered ring suggests direct proton transfer,[6] and the rate constants for protonation of ethyl vinyl ether by H_3O^+ in H_2O–Me_2SO mixtures suggest that direct proton transfer from H_2O to carbon is possible.[7] However, it has also been suggested that proton transfer to or from carbon can occur through a solvent molecule when there is intramolecular facilitation of proton transfer by an appropriately located acidic or basic group,[8,9] when the rate constant for protonation of a carbanion approaches the diffusion-controlled limit[2] or when there is steric hindrance to direct proton transfer and assistance by a metal ion.[10]

We describe here a search for solvent participation in proton transfers involving HCN. The results reported in the previous paper show that the protonation of CN^- by H_3O^+ is diffusion controlled and that proton transfers to or from electronegative atoms follow Eigen curves very similar to those for "normal" acids and bases.[11] It appears that HCN is the most normal carbon acid yet described, so that if proton transfer to or from carbon does occur through water, it should be observed with HCN. The results show no evidence for proton transfer through water and set small upper limits for the fraction of proton transfer that can occur through water. It has already been shown that the proton transfer from HCN to water does not occur through water by the Swain–Grunwald mechanism.[11]

The very rapid proton-transfer reactions of HCN may be attributed to the virtual absence of the changes in electron delocalization, hydridization, bond lengths and angles, and solvation upon ionization that are believed to be responsible for the slow rates of proton transfer from most carbon acids. The direct proton-transfer reactions of HCN, even with large values of ΔpK, suggest that the relatively poor hydrogen-bonding ability of carbon is maintained in HCN. This allows rapid desolvation to permit direct proton transfer and does not provide the stabilization of the transition state and intermediates by hydrogen bonding that makes proton transfer through water possible for reactions of more electronegative atoms.

Experimental Section

Materials and methods are described in the previous paper.[11] Proton NMR data were obtained at 270 mHz with an instrument designed by Redfield.[12]

Saturation Transfer. A solution containing HCN (~1 M) and the ammonium ion (0.025–0.10 M, pH 4.4–5.0) in 10% D_2O at ionic strength 1.0 M (KCl) at 20 °C was preirradiated at the HCN resonance frequency for 0.1 s at a power of 50–60 db. This was followed by a variable delay τ, a 4-ms homospoil pulse (to eliminate any signal induced by the preirradiation pulse), and a 7-ms recovery time before application of a roughly 60° "214" observation pulse.[11,13] To observe the HCN signal, the observation pulse was centered 250 Hz downfield from solvent and the spectrometer was set to a spectral band width of 400 Hz. To observe the ammonium ion signal, the observation pulse was centered 1000 Hz downfield from solvent and the spectral band width was 2000 Hz. A recycle time of 10 s elapsed before repeating the sequence. After each

4 transients a Fourier transformation was performed and a new τ was selected. Up to 8 τ values were selected before repeating the entire sequence.

In parallel experiments the recovery of the HCN and ammonium ion signals was monitored as τ was selectively varied from 0 to 10 s.

The degree of saturation was determined by comparison of the peak height and/or area for a given τ with spectra obtained with no preirradiation. Due to base line uncertainty, the area was calculated by integrating between the same two fixed points for all spectra in a series. The effect of varying these limits was investigated and average areas were used.

To determine if the saturation of the NH signal is due to "spillover" during preirradiation of the HCN, the preirradiation pulse was applied at a frequency symmetrically related to the ammonium ion resonance (i.e., the same "distance" from the NH signal but on the downfield side). Analogous controls were used to test for spillover into HCN under the conditions used to transfer saturation from the ammonium ion to HCN.

The exchange of protons between H_2O and HCN or $MeOEtNH_3^+$ (0.3 M) is about 150 times faster than the magnetic relaxation of water protons. Water protons were selectively saturated and the magnetic relaxation of the water protons was monitored by observing the $MeOEtNH_3^+$ peak. A half-time for recovery of 2.3 s (k_{mag} = 0.3 s⁻¹) was observed. The amount of water saturation in the saturation transfer experiments was estimated from the amount of saturation of the HCN and ammonium ion remaining after 200–500 ms, which is sufficient time for the system to equilibrate.

Proton Exchange between Ammonium Ions and Water. Rate constants for the exchange of protons of ammonium ions with water were obtained in order to make a correction for small changes in pH between the control and the sample in the saturation transfer experiments. The pseudo-first-order rate constant k_3, for the exchange of an ammonium ion with solvent (see Scheme II), was calculated from k_{HOH}, k_{OH}, and k_B at the desired pH, the concentration of amine, and appropriate statistical factors.

The exchange of $MeOEtNH_3^+$ (0.025–1.0 M) with water was studied in the pH range 1.5–5.2 by the saturation recovery method.[11] The data (Table S1) were analyzed according to the rate law in eq 2. The factor of 3 is due to the presence of three protons on the protonated primary

$$\text{rate}/[RNH_3^+] = 3k_{obsd} = k_{HOH} + k_{OH}a_{OH^-} + k_B[MeOEtNH_2] \quad (2)$$

amine (rate = $k_{obsd}[NH] = 3k_{obsd}[RNH_3^+]$). The three rate constants on the right-hand side of eq 2 refer to the removal of a proton from $MeOEtNH_3^+$ by H_2O, OH^-, and the conjugate base (through one or more water molecules). At low pH, k_{obsd} was found to be independent of pH and amine concentration, and the value of k_{HOH} was taken as $3k_{obsd}$. A plot of $(3k_{obsd} - k_{HOH})/[MeOEtNH_2]$ against $a_{OH^-}/[MeOEtNH_2]$ gave k_B as the y intercept and k_{OH} as the slope. The value of a_{OH^-} was calculated directly from the pH meter reading at 22 ± 2 °C by using pK_w = 14.08. The rate constants obtained at 20 °C are the following: k_{HOH} = 9.0 s⁻¹, k_{OH} = (2.9 ± 2.0) × 10¹⁰ M⁻¹ s⁻¹, and k_B = (8.1 ± 2) × 10⁷ M⁻¹ s⁻¹.

Proton exchange of 0.05–0.10 M trimethylammonium ion with water was measured by the same method at pH 4.3–4.5 (Table S1). A value of k_B = 1.2 × 10⁸ M⁻¹ s⁻¹ [14,15] was calculated according to eq 2, omitting the factor of 3, using k_{HOH} = 1.7 s⁻¹ [16,17] and k_{OH} = 2.1 × 10¹⁰ M⁻¹ s⁻¹.[18]

Simulation of a Three Exchanging System. The changes in the level of saturation of the proton NMR signals of HCN, ammonium ion, and water were simulated by the following method (see Scheme II). A differential equation was written for each of the three exchanging species to describe the change in saturation level with time. The first-order rate constants k_1, k_2, k_3, and k_{mag} were obtained as described above and in the Discussion section. Since the NMR experiments are carried out at dynamic equilibrium, the rates of the forward and reverse reactions are equal. The reverse first-order rate constants were calculated from the forward rate constant and the concentration of NH protons on the protonated catalyst (i.e., $k_{-2} = k_2[HCN]/[NH]$). The level of saturation of the preirradiated species caused by the preirradiation pulse was estimated from an extrapolation on a semilogarithmic plot of early data (variable delay τ = 0–16 ms) back to the end of the preirradiation pulse.

The concentration of saturated protons in the preirradiated species was set equal to the estimate obtained above and kept constant for the first

(4) Goodall, D. M.; Long, F. A. *J. Am. Chem. Soc.* **1968**, *90*, 238–243. Williams, J. M., Jr.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* **1968**, *6*, 63–101. Hibbert, F.; Long, F. A. *J. Am. Chem. Soc.* **1971**, *93*, 2836–2840. Albery, W. J.; Campbell-Crawford, A. N. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2190–2197. Kreevoy, M. M.; Eliason, R.; Landholm, R. A.; Straub, T. S.; Melquist, J. L. *J. Phys. Chem.* **1972**, *76*, 2951–2953.

(5) Albery, W. J. In "Proton-Transfer Reactions"; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; pp 285–294.

(6) Hine, J. *Acc. Chem. Res.* **1978**, *11*, 1–7.

(7) Kreevoy, M. M.; Williams, J. M., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 6809–6813.

(8) Kirby, A. J.; Lloyd, G. J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1762–1768.

(9) Bernasconi, C. F.; Carre, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 2698–2707. Bernasconi, C. F.; Hibdon, S. A.; McMurry, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3459–3471.

(10) Kluger, R.; Wong, M. K.; Dodds, A. K. *J. Am. Chem. Soc.* **1984**, *106*, 1113–1117.

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

(12) Redfield, A. G. In "NMR, Basic Principles and Progress"; Pintar, M. M., Ed.; Springer-Verlag: West Berlin, 1976; Vol. 13, pp 137–152.

(13) Redfield, A. G.; Kunz, S. D.; Ralph, E. K. *J. Magn. Reson.* **1975**, *19*, 114–117.

(14) This can be compared with a value of 3.7 × 10⁸ M⁻¹ s⁻¹ reported by Grunwald and Ku at 30 °C.[15]

(15) Grunwald, E.; Ku, A. Y. *J. Am. Chem. Soc.* **1968**, *90*, 29–31.

(16) Calculated from a value of 2.5 × 10¹⁰ M⁻¹ s⁻¹ for the diffusion-controlled protonation of trimethylamine by H_3O^+ at ionic strength zero and 20 °C,[17] and pK_a = 10.16[15] for the trimethylammonium ion.

(17) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–19.

(18) Determined at 20 °C and ionic strength zero.[17]

100 ms of the computer simulation. The concentration of saturated protons on the other two species was initially set to zero. The change in the concentration of each species was calculated sequentially from the differential equations, assuming that the concentration of the other species did not change significantly over a short time interval (0.1 ms). The change during this short time interval was added to the previous concentration, and the process was repeated. After the preirradiation period of 100 ms the concentration of the saturated protons was allowed to decrease in the manner defined by the differential equations.

Calculation of α. The parameter α is a measure of the insensitivity of broadening of a dominant resonance line to the direct return of a proton from a minor line. This parameter is used in calculating k_{obsd}/k_{TX}, as explained in the Discussion section (eq 10). We define $(1 - \alpha)$ in eq 3 as the ratio of the apparent rate of proton exchange, obtained from the

$$1 - \alpha = \frac{\Delta[HCN]}{\beta k_{-a}[CN^-][BH^+]} \quad (3)$$

observed line broadening of the dominant HCN peak and the concentration of HCN, to the rate of direct proton transfer from BH^+ to CN^-, where $\Delta = k_{obsd}([B] + [BH^+])$ is the broadening of the dominant line (i.e., $\pi \times$ increase in width, in Hz, at half-height), k_{-a} is the rate constant for proton transfer from BH^+ to CN^-, and β is the fraction of the proton transfer that occurs directly. Equation 4 describes the broadening of a dominant line in slow, intermediate, and fast exchange conditions.[19,20] This equation was used to calculate the values of α that are reported in Table S1 of the previous paper.[11] The values of δ used in the calculation are also given in Table S1. A value of 330 rad/s was used for J.[21] For phenols, and other catalysts that contain only one proton, $J = 0$ in eq 4.

$$1 - \alpha = \frac{t^2}{3} \frac{(\delta - J_{eff})^2}{1 + (\delta - J_{eff})^2 t^2} + \frac{\delta^2}{(1 + \delta^2 t^2)} + \frac{(\delta + J_{eff})^2}{1 + (\delta + J_{eff})^2 t^2} \quad (4)$$

where

$$t = \frac{p}{\beta k_{-a}[CN^-]} \left[\frac{[HCN]}{[NH] + [HCN]} \right]$$

$$J_{eff} = J \frac{T^1}{T^1 + t}$$

δ = the difference in resonance frequency of HCN and the ammonium ion resonance in units of rad/s

β = the fraction of proton transfer that occurs directly

p = the number of protons on the protonated catalyst

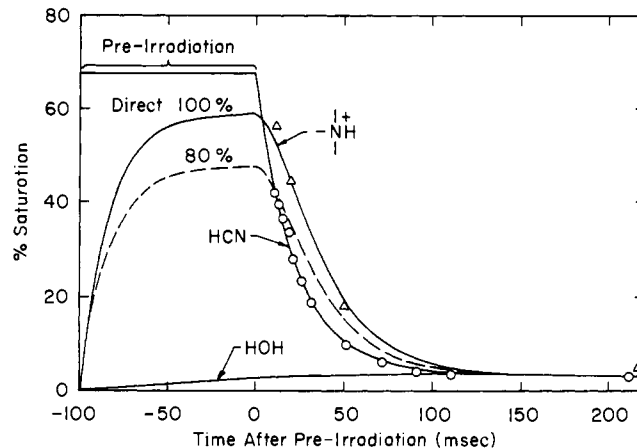J = the N–H coupling constant (rad/s)

T^1 = the quadrupole relaxation time for the ^{14}N nucleus

$[NH]$ = the concentration of protons on the protonated catalyst

Calculation of γ. The partitioning of BH^+ between return of a proton to CN^- and exchange with solvent is described by the coefficient γ, which is calculated from eq 5 where $k_{solv} = k_{HOH} + k_{OH}a_{OH^-} + k_B[B]$ (see Scheme I and eq 2).

$$\gamma = \frac{k_{-a}[CN^-]}{k_{-a}[CN^-] + k_{solv}} \quad (5)$$

The value of k_{HOH} was calculated from the pK_a of the ammonium ion (BH^+) and a diffusion-controlled recombination rate constant for B and H_3O^+ $(2 \times 10^{10}\ M^{-1}\ s^{-1})$.[17] A value of $2 \times 10^{10}\ M^{-1}\ s^{-1}$ was used for the rate constant for proton removal from the ammonium ion by OH^- (k_{OH});[17] this value is not critical because the k_{OH} term rarely makes a significant contribution to k_{solv} in the pH range used in this study. A value of $k_B = 10^8\ M^{-1}\ s^{-1}$ was used for the removal of a proton from an ammonium ion by its conjugate base through a water molecule(s).[22] In

(19) Modified from eq 2 of ref 20.
(20) Grunwald, E.; Price, E. *J. Am. Chem. Soc.* **1964**, *86*, 2970–2977.
(21) This is the value adopted by Grunwald and Price.[20] The choice of J does not significantly affect the result of this paper. A value of 0.0025 s was used in the calculation for T^1, which is the value reported for $(CH_3)_3NHCl$ in acetic acid at 25 °C.[20] Any error in the value of T^1 will have little or no effect on the calculated value of α, since usually $\tau \ll T^1$ and therefore J_{eff} is equal to J. An error in T^1 will have the most significant effect when τ is large. This will only be true when α is close to zero. All the calculations given in Table II are based on values of $\alpha \sim 1$. Smaller values of α were used only for calculating the dashed lines in Figures 2, 3, and 4.

Figure 1. Transfer of saturation from 0.98 M HCN to 0.025 M MeOEtNH$_3^+$, at pH 4.40, 20 °C, ionic strength 1.0 M (KCl) and 10% D$_2$O. The percent saturation of the HCN proton signal (O) and the NH signal (△) was measured after a 100 ms selective preirradiation pulse of the HCN signal. The lines are from a computer simulation described in the Experimental and Discussion sections. The solid lines show the calculated percent saturation of HCN, NH, and OH (water) protons if only direct proton transfer occurs between HCN and MeOEtNH$_2$ (k_1 = 48 s^{-1}, k_2 = 4.1 s^{-1}, k_3 = 7 s^{-1}, k_{mag} = 0.3 s^{-1} in Scheme II). The dashed line shows the expected amount of NH saturation if 20% of the amine-catalyzed exchange of HCN protons occurred through a water molecule(s)[23] (k_1 = 48.7 s^{-1}, k_2 = 3.3 s^{-1}, k_3 = 17.7 s^{-1} in Scheme II).

calculating the contribution of the k_B term to k_{solv}, the average [B] in the experiment was used. The effect of this approximation on the calculated value of k_{obsd}/k_{TX} (cf. eq 5 and 10 and supplementary Table S1[11]) is either negligible or within experimental error for all reactions, unless indicated otherwise.

Results

Saturation Transfer. Transfer of saturation of the proton NMR signal between HCN and protonated amines was measured at 20 °C. The results obtained with methoxyethylammonium ion at pH 4.4 are shown in Figure 1. The HCN protons were detected as a single peak 157 Hz downfield from solvent, and the NH protons of MeOEtNH$_3^+$ were seen as a broad triplet 812 Hz downfield from solvent. The HCN protons were selectively preirradiated for 0.1 s. The percent saturation of the HCN proton signal at selected times after the preirradiation pulse is indicated by the circles in Figure 1. A large amount of saturation of the NH proton signal was also seen, as indicated by the triangles.

The saturation of the NH signal is not due to off-resonance saturation (or "spillover") because preirradiation at a frequency symmetrically related to the MeOEtNH$_3^+$ resonance was shown to have no effect on the NH signal. The saturation of the NH signal is also not due to saturation of water protons because only ~3% of the water protons were saturated during this experiment. The lines in Figure 1 were obtained by a simulation, as described in the Experimental and Discussion sections. These results show that saturation is transferred from HCN to MeOEtNH$_3^+$.

The results of experiments carried out at other pH values and concentrations of HCN and MeOEtNH$_3^+$ are summarized in Table I. The value of the percent saturation of the preirradiated species at $t = 0$ was obtained by extrapolation. The percent saturation of CH, NH, and OH protons and the ratio of the percent saturation of NH to CH at 11 ms are given. Transfer of saturation in the reverse direction, from MeOEtNH$_3^+$ to HCN, was observed when the NH signal of MeOEtNH$_3^+$ was selectively saturated. Transfer of saturation from HCN to trimethylammonium ion was also demonstrated (Table I).
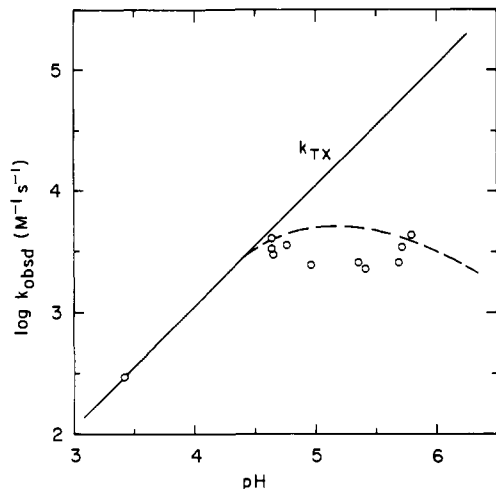
Rate Constants for Proton Transfer and Exchange. The observed rate constant for buffer catalysis of proton exchange, k_{obsd}, was determined from the broadening of the HCN resonance, as

(22) Reference 2, p 106. Grunwald, E.; Ralph, E. K. In "Dynamic Nuclear Magnetic Resonance Spectroscopy"; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; p 639.

Figure 2. The dependence on pH of log k_{obsd}, determined from broadening of the HCN resonance catalyzed by glycinamide, at 20 °C, ionic strength 1.0 (KCl), 1.0 M [HCN], and 10% D_2O. The values of k_{TX} and k_{obsd} are expressed in terms of the total buffer concentration, [B] + [BH$^+$]. The solid line (k_{TX}) shows the pH-dependent rate constant for removal of a proton from HCN (eq 9). The dashed line was calculated from eq 10, for the direct proton transfer between HCN and the amine with β = 1; values of α (eq 4) and γ (eq 5) were calculated by using k_{HOH} = 110 s^{-1}, k_{OH} = 2 × 10^{10} M^{-1} s^{-1}, k_B = 10^8 M^{-1} s^{-1}, T^1 = 0.0025 s, J = 330 rad/s, and δ = 3100 rad/s.
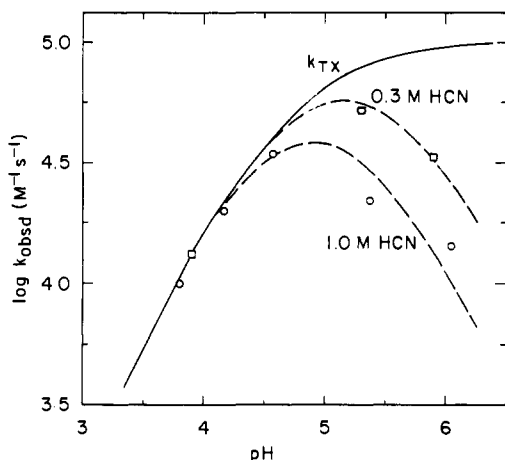
Figure 3. Effect of the concentration of HCN on the pH dependence of log k_{obsd} for the methoxyamine-catalyzed reaction at 20 °C, ionic strength 1.0 M (KCl), and 10% D_2O. See the legend of Figure 2 for explanation. The dashed lines were calculated from eq 4, 5, and 10 by using k_{HOH} = 2.4 × 10^5 s^{-1}, k_{OH} = 2 × 10^{10} M^{-1} s^{-1}, k_B = 10^8 M^{-1} s^{-1}, T^1 = 0.0025 s, J = 330 rad/s, and δ = 4000 rad/s.

described in the previous paper.[11] Figure 2 shows the dependence on pH of log k_{obsd} for broadening of the HCN resonance catalyzed by glycinamide. The second-order rate constant, k_{obsd}, is expressed in terms of total buffer concentration and is defined in eq 6, in

$$k_{obsd} = \frac{\Delta f_{1/2} \cdot \pi}{[B] + [BH^+]}$$ (6)

which $\Delta f_{1/2}$ is the increase in width (in Hz) of the HCN peak at half-height. At high pH values, the value of k_{obsd} is less than expected from the rate of amine-catalyzed proton transfer at lower pH values (solid line, Figure 2).

Figure 3 shows the effect of the concentration of HCN on the broadening of the HCN resonance catalyzed by methoxyamine. At high concentrations of HCN there is a larger decrease in the value of k_{obsd} at high pH values. Figure 4 illustrates similar behavior for catalysis by *m*-nitrophenoxide ion.

Rate constants for the base-catalyzed removal of a proton from HCN (k_a) and a minimum estimate (β_{min}) and calculated value (β_{calcd}) for the fraction of direct proton transfer were obtained
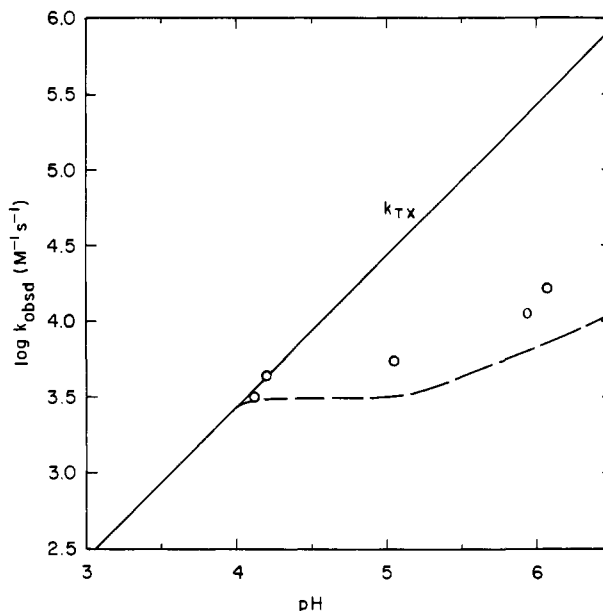
Figure 4. The dependence on pH of log k_{obsd} for broadening of the HCN resonance catalyzed by *m*-nitrophenoxide ion at 20 °C, ionic strength 1.0 M (KCl), 1.0 M [HCN], and 10% D_2O. See legend of Figure 2 for explanation. The dashed line was calculated from eq 4, 5, and 10 by using δ = 7100 rad/s, k_B = 10$^{8.75}$ M^{-1} s^{-1}, and a rate constant for acid-catalyzed proton exchange from PhOH (which contributes to k_{solv}, cf. eq 5) of 1.5 × 10^7 M^{-1} s^{-1}.[27]
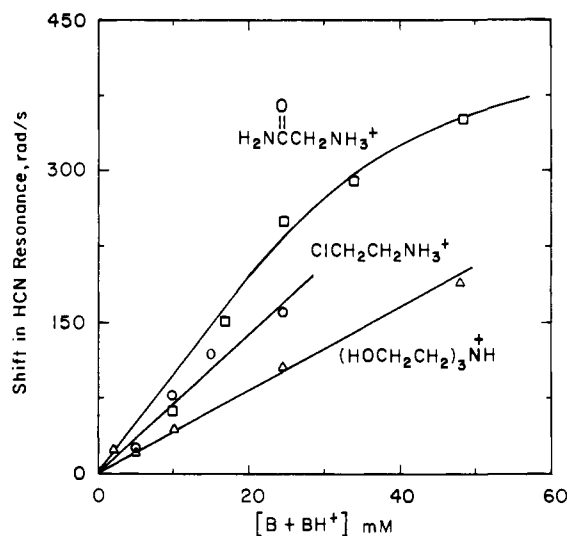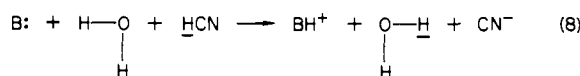

Figure 5. Downfield shift of the HCN resonance as a function of the concentration of added catalyst at 20 °C, ionic strength 1.0 M (KCl), and 10% D_2O. Catalysts: glycinamide at pH 5.77 (□), 2-chloroethylamine at pH 5.90 (O), and tris(hydroxyethyl)amine at pH 5.87 (△).

as described in the Discussion section and are summarized in Table II. Table S1 of the previous paper[11] contains the primary data for the series of catalysts listed in Table II.

The shift in the HCN resonance frequency as the concentration of amine catalyst is increased is shown in Figure 5.

Discussion

Catalysis of proton removal from HCN by a base in aqueous solution can occur by two possible mechanisms. Equation 7 illustrates a direct-transfer mechanism while eq 8 illustrates a mechanism in which proton transfer is mediated by one or more solvent molecules. Two approaches were used to distinguish these mechanisms.

$$B: + \underline{H}CN \longrightarrow B\underline{H}^+ + CN^-$$ (7)

$$B: + H\!-\!\underset{\underset{H}{|}}{O} + \underline{H}CN \longrightarrow BH^+ + \underset{\underset{H}{|}}{O}\!-\!\underline{H} + CN^-$$ (8)
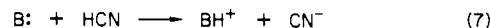
Table I. Transfer of Saturation between HCN and Ammonium Ions[a]

	percent saturation				(NH/CH)$_{obsd}$	(NH/CH)$_{calcd}$
pH[b]	HCN 0 ms[c]	HCN 11 ms	NH 11 ms	OH 11 ms[d]	11 ms[e]	11 ms[f]
MeOEtNH$_3^+$ (Transfer *from* HCN)						
4.44[g]	68	42	58	~2	1.4	1.3
4.39[g]	66	42	55	~3	1.3	1.3
4.81[g]	49–64	39	49	≤2	1.3[h]	1.1
4.81[g]	76	56	67	8–10[i]	1.2[j]	1.1
4.98[g]	60	36	42	~2	1.2	1.1
4.87[k]	>64	36	53	2–6	1.5[l,m]	1.1
4.81[h]	>37	17[n]	25[n]	1–13	1.5[m,o]	1.0
MeOEtNH$_3^+$ (Transfer *to* HCN)						
4.58[n]		34				
4.86[k]		26	24–35	~0	0.9–1.4	1.4
4.81[n]		31	35	4–5	1.1	1.1
4.81[n]		20[o]	27[o]		1.40[o]	1.1[o]
Me$_3$NH$^+$ (Transfer *from* HCN)						
4.57[k]	42	27	28	1–3	1.0	1.0

[a] At 20 °C and ionic strength 1.0 M (KCl), 10% D$_2$O. [b] Observed with pH electrode. [c] Estimated by extrapolation to the end of the preirradiation. [d] Determined from the saturation of HCN and NH as described in the Experimental Section. [e] Ratio at 11 ms unless indicated otherwise. [f] Calculated from the simulation described in the Experimental Section for 100% direct proton transfer. If the transfer occurred via water the ratio would be 0. [g] [RNH$_3^+$] = 0.025 M; [HCN] = 0.98 M. [h] Average value of 4 time points between 11 and 17 ms with a standard deviation of 2%. [i] The larger amount of saturation of H$_2$O is due to spillover during saturation of HCN. [j] Average value of 7 time points between 5 and 17 ms is 1.33 with a standard deviation of 8%. [k] [RNH$_3^+$] = 0.05 M; [HCN] = 0.90 M. [l] Average of data at 11 and 15 ms. [m] The reason for the large values observed may be related to the relatively large amount of saturation transferred to water under the experimental conditions. [n] [RNH$_3^+$] = 0.10 M; [HCN] = 0.90 M. [o] At 15 ms.

Table II. Rate Constants for the Base-Catalyzed Removal of a Proton from HCN (k_a) and a Minimum Estimate (β_{min}) and Calculated Value (β_{calcd}) for the Fraction of Direct Proton Transfer[a]

catalyst	pK_{BH^+}[b]	k_a,[c] M^{-1} s^{-1}	β_{min}[d]	β_{calcd}[e]
H$_2$NCONHNH$_2$	3.86[f]	$10^{4.26}$	>0.72	1.6[g]
CH$_3$ONH$_2$	4.72[h]	$10^{5.00}$	>0.92	1.1[g]
CF$_3$CH$_2$NH$_2$	5.81[i]	$10^{5.71}$	>0.94	1.0
H$_2$NCOCH$_2$NH$_2$	8.25[j]	$10^{7.30}$	>0.97	1.0
ClCH$_2$CH$_2$NH$_2$	8.81[k]	$10^{7.51}$	>0.96	1.0
CH$_3$OCH$_2$CH$_2$NH$_2$	9.72[f]	$10^{7.58}$		1.0[l]
(HOCH$_2$CH$_2$)$_3$N	7.99[m]	$10^{6.96}$	>0.99	1.0
(CH$_3$)$_3$N	10.16[n]	$10^{7.38}$		1.0[l]
p-NO$_2$PhO$^-$	7.14[f]	$10^{6.75}$	>0.96	1.0
m-NO$_2$PhO$^-$	8.35[f]	$10^{7.78}$	>0.97	0.98, 0.99
PhO$^-$	9.86[f]	$10^{8.68}$	>0.98	1.0
(CF$_3$)$_2$CHO$^-$	9.3[h]	$10^{7.97}$	>0.93	0.98

[a] At 20 °C and ionic strength 1.0 M (KCl) in 10% D$_2$O. [b] At 25 °C and ionic strength 1.0 M (KCl). [c] Obtained from the broadening of the HCN line as described previously.[11] [d] Minimum estimate of the fraction of direct proton transfer, assuming α and γ in eq 10 are equal to 1. [e] Calculated fraction of direct proton transfer using eq 10. Values of α and γ were calculated as described in the Experimental Section and are given in Table S1 of the previous paper.[11] In calculating γ (eq 5), $k_{HOH} = 10^{10.3-pK_{BH^+}}$ s^{-1}; $k_{OH} = 10^{10.3}$ M^{-1} s^{-1}; $k_B = 10^8$ M^{-1} s^{-1}, except $k_B = 10^{6.3}$ M^{-1} s^{-1} for (HOCH$_2$CH$_2$)$_3$N. [f] Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622–2637. [g] These values are unrealistically large (see text). [h] Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436–1449. [i] St. Pierre, T.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 3817–3827. [j] Estimated from the observed pH on partial neutralization. [k] Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 572–580. [l] By the saturation transfer technique (Table I). [m] Smith, R. M.; Martell, A. E. "Critical Stability Constants"; Plenum Press: New York, 1976; Vol. 2, p 118. [n] Reference 15.

Saturation Transfer. The logic of the first approach is to label the HCN protons and to determine if this label is transferred to the ammonium ion protons (BH$^+$). The labeling is achieved by selective radio frequency irradiation, which results in the loss of the NMR signal from the saturated protons. The direct proton-transfer mechanism (eq 7) will result in transfer of saturation to BH$^+$. However, solvent-mediated proton transfer (eq 8) will result in loss of the saturated proton to the large sink of solvent protons and no transfer of saturation to BH$^+$.

The evidence presented in Figure 1 and Table I demonstrates that saturation is transferred from HCN to MeOEtNH$_3^+$ and to Me$_3$NH$^+$. Transfer of saturation in the reverse direction, from

Scheme I

$$HCN + B \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} BH^+ + CN^-$$

$$\downarrow\uparrow k_{solv}$$

$$B + H_{sol}^+$$
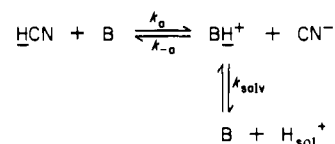
MeOEtNH$_3^+$ to HCN, was also demonstrated (Table I). This transfer of saturation is clear qualitative evidence for direct proton transfer between HCN and an amine (MeOEtNH$_2$ and Me$_3$N).

In order to interpret these results quantitatively it is necessary to determine how much transfer of saturation is expected if the removal of HCN protons catalyzed by the amine B, occurs exclusively by direct transfer. Scheme I shows that in the steady state the concentration of labeled ammonium ion, BH$^+$, depends on the partitioning of BH$^+$ between reaction with CN$^-$ (k_{-a}[CN$^-$]) or with solvent (k_{solv}). This partitioning is described by the coefficient γ (eq 5). The rate constant k_{solv} was determined by measuring the rate of exchange of the ammonium ion with solvent by the saturation recovery method, as described in the Experimental Section. The rate constant k_{-a}, for the removal of a proton from the ammonium ion by CN$^-$, was calculated from k_a and the equilibrium constant for proton transfer.[11] Under the conditions of the experiment shown in Figure 1, $k_{solv} = 7$ s^{-1} and k_{-a}[CN$^-$] = 54 s^{-1}; therefore, $\gamma = 0.89$ and the saturation of the NH signal at the steady state should be 89% of the saturation of the HCN signal if proton transfer occurs directly. The larger saturation of the NH signal than that of the HCN signal at 11 ms is caused by a more rapid decay of the HCN saturation than of the NH saturation.

It is possible to place a limit on the amount of saturation present during the steady state. An estimate of the percent saturation of the HCN proton signal caused by the preirradiation pulse was obtained by extrapolation of the early data back to $t = 0$ (see Experimental Section). This extrapolation indicates that 67% of the HCN signal is saturated during the steady state. The saturation of the ammonium ion signal must be at least 56%, which is the observed value at 11 ms. This estimate shows directly that at least 84% of the HCN saturation was transferred to the ammonium ion (BH$^+$). Since the partition coefficient γ predicts only 89% transfer of saturation, we can conclude that at least 94% of the transfer reaction between HCN and MeOEtNH$_2$ occurs directly.

Scheme II
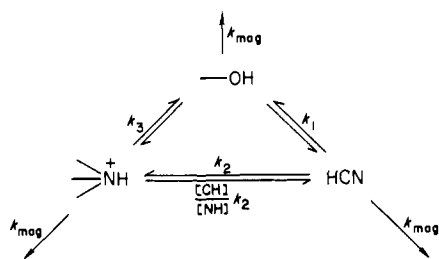
A more exact treatment of the data requires consideration of all types of chemical exchange. Scheme II illustrates the three types of chemical exchange that can occur. It also includes pathways for magnetic relaxation of CH, OH, and NH protons, k_{mag}. At a particular pH value the chemical exchange can be described by three independent rate constants, k_1, k_2, and k_3. The rate constant k_1 was obtained from the loss of saturation from HCN in the absence of amine. This loss of saturation is dominated by chemical exchange with solvent.[11] The rate constant k_2 was calculated from the concentration of free base amine and the second-order rate constant for the reaction of HCN with MeOEtNH$_2$. This rate constant was determined from the broadening of the HCN resonance resulting from addition of amine.[11] The rate constant k_3 was obtained from a measurement of the loss of saturation from MeOEtNH$_3^+$ in the absence of HCN (see Experimental Section). The value of k_{mag} (0.3 s^{-1}) was determined from the loss of saturation from solvent protons. The same value was assumed for relaxation of protons on HCN and MeOEtNH$_3^+$. An error in this assumption is unlikely to have a significant effect because the magnetic relaxation processes are slow compared with chemical exchange and the rate of magnetic relaxation is dominated by the large concentration of solvent protons.

The time-dependent changes of the saturation of CH, NH, and OH protons were simulated as described in the Experimental Section. The solid lines in Figure 1 are the predicted levels of saturation if all of the exchange of HCN protons that is catalyzed by MeOEtNH$_2$ occurs by direct proton transfer, while the dashed line indicates the expected amount of saturation of the NH signal if 20% of the exchange occurred through water-mediated proton transfer.[23] The observed transfer of saturation from HCN to MeOEtNH$_3^+$ is in quantitative agreement with direct transfer of essentially all protons during the exchange of HCN protons catalyzed by MeOEtNH$_2$ (eq 7), without any significant contribution from a pathway involving transfer through an intervening water molecule(s) (eq 8).

Table I summarizes the results of experiments demonstrating transfer of saturation: (1) from HCN to MeOEtNH$_3^+$ under a variety of experimental conditions, (2) from MeOEtNH$_3^+$ to HCN, and (3) from HCN to Me$_3$NH$^+$. There is significant transfer of saturation and in all cases the ratio of the observed percent saturation of the NH to CH signal at 11 ms (NH/CH)$_{obsd}$ compares well with the calculated ratio for 100% direct proton transfer, (NH/CH)$_{calcd}$. There is no transfer through water between HCN and MeOEtNH$_2$ or Me$_3$N, within the experimental error of the measurements.

Rate Constants for Proton Transfer and Proton Exchange. The second approach used to distinguish between proton transfer directly or through water is a comparison of the rate constant for *proton transfer* with the rate constant for *proton exchange*. If proton transfer occurs directly (eq 7), there will be no exchange with solvent when the proton that is removed from HCN by B is returned to form HCN, by reaction of BH$^+$ with CN$^-$, before it has time to exchange with the solvent. There will then be two proton transfers without any proton exchange with the solvent and the observed rate constant for proton exchange of HCN is

likely to be less than the rate constant for proton transfer. However, if the proton transfer occurs through an intervening water molecule(s) (eq 8), every transfer of a proton from HCN will result in exchange with the solvent and the rate constant for proton transfer will be equal to the rate constant for proton exchange.[24]

The broadening of the HCN resonance line caused by addition of a base catalyst was used to determine observed rate constants for proton exchange, k_{obsd}, as described previously.[11] Figure 2 illustrates the dependence on pH of log k_{obsd}, for the exchange of HCN protons catalyzed by glycinamide buffers. At pH values well below the pK_a of glycinamide there is a 10-fold increase in the free base concentration for each unit increase in pH and a corresponding 10-fold increase in the rate constant for proton transfer, k_{TX}, which is defined by the rate law of eq 9. This rate constant is indicated by the straight line labeled k_{TX} in Figure

$$rate = k_{TX}[HCN]([BH^+] + [B]) \qquad (9)$$

2.[25] However, the data fall below this line at pH $\geq$4.5. At pH 5.7 the observed rate constant for proton exchange, k_{obsd}, is only 6% of the rate constant for proton transfer, k_{TX}. The fact that the observed rate constant for proton exchange is less than that for proton transfer demonstrates qualitatively that a proton that is transferred from HCN to glycinamide is transferred back to HCN, so that proton transfer occurs by the direct mechanism (eq 7).

Is it possible that some fraction of the amine-catalyzed proton transfer occurs through water? In order to analyze the data quantitatively, we define the parameter β as the fraction of the proton transfers between HCN and the base that occurs directly; $1 - \beta$ is the fraction that occurs through water. If all of the observed line broadening from proton exchange were due to proton transfer through water (eq 8), then $k_{obsd} = k_{TX}(1 - \beta^2)$. The β term is squared because two proton transfers are required for removal and return of the same proton, but only one needs to be through water in order to give proton exchange. Applying this model to the data at pH 5.7 in Figure 2 indicates that at least 97% of the proton transfers occur directly, i.e., β is >0.97. Table II gives a minimum estimate for β, β_{min}, for several other amines. This method of calculating β yields only a minimum estimate of β because it does not consider contributions to k_{obsd} that result from the direct proton transfer mechanism (eq 7).

The observed line broadening also depends on the partitioning of the proton on the ammonium ion, BH$^+$, between return to CN$^-$ and exchange with solvent (Scheme I), as defined by the partition coefficient γ (eq 5). The fraction of protons that contribute fully to line broadening because they exchange with solvent before they return to CN$^-$ is $1 - \gamma$. This contributes $\beta^2(1 - \gamma)$ to k_{obsd}/k_{TX} because β^2 is the fraction of these reactions that involves two direct proton transfers and $(1 - \gamma)$ is the fraction of the reactions in which the same proton is not returned (i.e., it is exchanged with solvent while it is on the ammonium ion).

Finally, the line broadening depends on how long the proton remains on BH$^+$ before it returns to CN$^-$. In the limit of slow exchange on the NMR time scale, the broadening of the HCN line is sensitive to all exchange processes, even those that involve return of the same proton to the HCN pool. Slow exchange occurs when the lifetime of the proton on the ammonium ion $(k_{-a}[CN^-])^{-1}$ is long compared with the difference in the resonance frequencies of HCN and the ammonium ion (δ, in units of rad/s).[26] The parameter α, defined in eq 3, is a measure of the sensitivity of k_{obsd} to return of the same proton. In the slow exchange limit ($\alpha = 0$) k_{obsd} is fully sensitive to all exchange processes and in the fast exchange limit ($\alpha = 1$) k_{obsd} is not sensitive to return of the

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(23) In this case the amount of CH to NH exchange is decreased by 20% ($k_2' = 0.80k_2$, $k_{-2}' = 0.80k_{-2}$) and there is a corresponding increase in CH to OH exchange ($k_1' = k_1 + 0.20k_2$) and NH to OH exchange ($k_3' = k_3 + 0.20k_{-2}$).

(24) The water molecule that contains the proton transferred from HCN exchanges with solvent much faster than HOH·CN$^-$ is protonated by acid.[11]

(25) These rate constants were determined[11] by NMR line broadening in a pH range where the broadening is fully sensitive to all proton transfers. This occurs under conditions where $\alpha\beta^2\gamma$ in eq 10 equals zero.

(26) Actually. the sum of the lifetimes for exchange defined by $\tau^{-1} = (t_{NH})^{-1} + (t_{HCN})^{-1}$ should be compared. However, since [HCN] $\gg$ [NH], the proton spends little time on NH and therefore $(t_{NH})^{-1}$ dominates τ^{-1}.

"same proton". Thus, the directly returned protons contribute $\beta^2\gamma(1 - \alpha)$ to k_{obsd}/k_{TX} because β^2 is the fraction of the reactions occurring through two direct transfers, in γ of the reactions the proton is returned directly without exchanging with solvent, and the contribution of returned protons to the line broadening is $(1 - \alpha)$.

Equation 10 is obtained by adding these contributions to k_{obsd}/k_{TX}, which result from the contributions of (1) the sensitivity of line broadening to return of the same proton (α), (2) the fraction of direct proton transfer between HCN and B (β), and (3) the fraction of BH$^+$ that partitions to return rather than exchange with solvent (γ).

$$k_{obsd}/k_{TX} = (1 - \beta^2) + \beta^2(1 - \gamma) + \beta^2\gamma(1 - \alpha) = 1 - \alpha\beta^2\gamma \tag{10}$$

The values of α and γ were calculated as described in the Experimental Section and are given in Table S1 of the supplementary material of the previous paper.[11] At low pH values the line broadening (k_{obsd}) is sensitive to all proton transfers ($\alpha \sim 0$) and k_{obsd} is equivalent to k_{TX} (Figure 2). At high pH the line broadening is insensitive to the immediate return of a proton derived from HCN back to CN$^-$ ($\alpha \sim 1$) and the observed proton exchange (k_{obsd}) is less than the proton transfer (k_{TX}), demonstrating that the proton transfer must be direct ($\beta > 0$). The dashed line in Figure 2 shows the values of k_{obsd} calculated from eq 10, assuming that all proton transfers occur directly (i.e., $\beta = 1$). The observation that the values of k_{obsd} do not fall above this line demonstrates quantitatively that proton transfer between HCN and glycinamide occurs directly (eq 7) and not through water (eq 8).

Figure 4 demonstrates that oxygen bases show the same kind of behavior as amine bases. Rate constants for proton exchange from HCN catalyzed by *m*-nitrophenolate anion, k_{obsd}, fall below the rate constants for proton transfer, k_{TX}, at pH $\geqslant$5. The dashed line shows the calculated values of k_{obsd} if 100% of the proton transfers between HCN and the phenolate ion occur by the direct proton-transfer mechanism (eq 7) based on data for proton exchange of phenol.[27] The experimental points fall somewhat above this line, corresponding to 98–99% direct proton transfer, but the difference is less than the uncertainty of the calculation for this reaction.

The results obtained from measurements of the broadening of the HCN resonance line by a series of primary amines, tertiary amines, and phenolate bases are tabulated in Table II. The parameter β_{min} is an absolute lower limit on the fraction of direct transfer. It assumes that all of the observed catalysis of proton exchange occurs by proton transfer through water. The values of β_{calcd} were obtained from eq 10, which takes into account the amount of broadening expected for direct proton transfer. The values of $\beta_{calcd} = 1.0$ for basic amines indicate that >99% of the proton transfers between HCN and these base catalysts occur directly (eq 7). The values of $\beta_{calcd} > 1$ for semicarbazide and methoxyamine probably arise from experimental error in the NMR data because only a small drop-off in k_{obsd}/k_{TX} is observed with these weakly basic amines.

Figure 3 illustrates the effect of the concentration of HCN on the value of k_{obsd} obtained from the broadening of the HCN resonance by methoxyamine. The observed rate constants at low pH values are equal to k_{TX}, for removal of a proton from HCN, and are independent of the concentration of HCN. However, the data indicate that k_{obsd} is a function of CN$^-$ concentration at higher pH values. As the concentration of CN$^-$ is increased, either by increasing [HCN] or by increasing the pH, the observed rate constant for proton exchange (k_{obsd}) decreases. Increasing the concentration of CN$^-$ increases the first-order rate constant of the reverse reaction (k_{-a}[CN$^-$], Scheme I) and the fraction of the protons on the ammonium ion derived from HCN that are returned to CN$^-$ before they exchange with solvent; i.e., it increases the partition coefficient γ (eq 5). Additionally, the faster return of the protons will result in a smaller contribution to the broad-

ening because α is closer to 1 (eq 10). The dependence of k_{obsd} on the HCN concentration is predicted by the direct transfer mechanism (eq 7) but is inconsistent with proton transfer through water (eq 8). The dashed lines in Figure 3 show the calculated values of k_{obsd} if 100% of the proton transfers between HCN and methoxyamine occur directly ($\beta = 1$).

The shift in the position of the HCN resonance toward the ammonium ion resonance (and away from the water resonance), as shown in Figure 5, provides additional evidence that amines catalyze direct exchange between CH and NH sites rather than exchange between CH and OH sites by transfer through water. The resonances of species undergoing proton exchange tend to approach one another as the rate of exchange increases.[28]

It is possible to calculate a value of k_B, for proton transfer from tris(hydroxyethyl)ammonium ion to tris(hydroxyethyl)amine through an intermediate water molecule, from the value of $k_{obsd}/k_{TX} = 0.014$ for tris(hydroxyethyl)amine at pH 5.87. Under these conditions the observed line broadening of HCN is caused by exchange of the proton of BH$^+$ with solvent, k_{solv}, which occurs predominantly through the k_B term (Scheme I, eq 5). A value of $k_B = 10^{6.3}$ M^{-1} s^{-1} (20 °C) was calculated from eq 4, 5, and 10, taking $\alpha = \beta = 1.0$.[29] This agrees satisfactorily with a literature value of $10^{6.56}$ M^{-1} s^{-1} obtained at 30 °C[30] and offers a check on the method employed here.

Tertiary amines have a greater preference for transfer via water than do primary and secondary amines and ammonia in symmetrical proton-transfer reactions.[2] For ammonia, 96% of the symmetrical exchange occurs directly, while <8% of the symmetrical exchange for trimethylamine occurs directly. Less than 14% of the exchange between trimethylamine and ammonium ion occurs directly. On this basis one might expect that proton transfer via water is a property mainly associated with tertiary amines. However, there is no detectable transfer via water between HCN and the tertiary amines trimethylamine and tris(hydroxyethyl)-amine ($\beta = 1.0$, Table II).

The following constraints must be met in order to use the methods described in this paper to evaluate the role of solvent in proton-transfer reactions. The saturation transfer method requires that proton exchange with solvent be slow compared with the exchange between acid and base ($k_2 > k_1$, $k_{-2} > k_3$ in Scheme II). Additionally, it is necessary that both the acid and the base be in slow exchange on the NMR time scale so that separate peaks are observed for the acid, the protonated base, and water. In the present study this required the following: (1) an ammonium ion with a high pK (p$K \geqslant 9$), which exchanges slowly with water (both chemically and on the NMR time scale); (2) a pH of <6 in order to prevent broadening of the HCN peak by OH$^-$ catalyzed exchange; (3) a low concentration of amine in order to minimize intermolecular catalysis by the amine of proton removal from the ammonium ion through water (which contributes to k_3); and (4) a concentration of amine that is high enough to catalyze detectable removal of the HCN protons ($k_2 > k_1$).

The line-broadening method is not limited by the need to observe the ammonium ion or phenol protons directly; the conjugate acid of the base catalyst can be in fast exchange with water on the NMR time scale. In order to observe a drop-off in k_{obsd} (proton exchange less than proton transfer), the return of a proton from BH$^+$ to CN$^-$ (k_{-a}[CN$^-$]) must be faster than its exchange with solvent. It also must occur before the proton "forgets" that it is an HCN proton ($\alpha > 0$); i.e., the CH and NH (or ArOH) sites must be in fast exchange on the NMR time scale. The maximum drop-off will be observed at high pH and a high concentration of HCN. The pH must be less than ~6 in order that HCN is in slow exchange with water on the NMR time scale. In this study the line-broadening method is optimal for catalysts with pK_a

(27) Grunwald, E.; Puar, M. S. *J. Phys. Chem.* **1967**, *71*, 1842–1845.
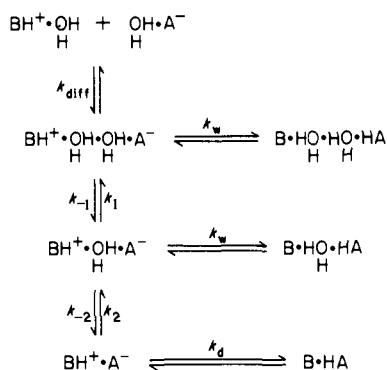
(28) Sandström, J. "Dynamic NMR Spectroscopy"; Academic Press: London, 1982; p 79.
(29) Calculated from: $k_{obsd}/k_{TX} = 0.014$ at pH 5.87 (Table S1),[11] $\alpha = 1$, $\beta = 1$, $k_a = 10^{6.96}$ M^{-1} s^{-1}, p$K_{BH^+} = 7.99$, [HCN] = 1 M, $k_{HOH} = 10^{(10.3-pK_{BH^+})}$s^{-1}, and $k_{OH} = 2 \times 10^{10}$ M^{-1} s^{-1}.
(30) Grunwald, E.; Fong, D.-W.; Ralph, E. K. *Israel J. Chem.* **1971**, *9*, 287–292. Reference 2, p 106.

Scheme III

$$BH^+ \cdot OH + OH \cdot A^-$$
$$H H$$

$$\Big\updownarrow k_{diff}$$

$$BH^+ \cdot OH \cdot OH \cdot A^- \xrightleftharpoons{k_w} B \cdot HO \cdot HO \cdot HA$$
$$H H H H$$

$$k_{-1} \Big\updownarrow k_1$$

$$BH^+ \cdot OH \cdot A^- \xrightleftharpoons{k_w} B \cdot HO \cdot HA$$
$$H H$$

$$k_{-2} \Big\updownarrow k_2$$

$$BH^+ \cdot A^- \xrightleftharpoons{k_d} B \cdot HA$$

between 5 and 9. The line-broadening method is difficult to use with strong bases ($pK_a > 9$) because of the decrease of k_{-a} with increasing pK_a of the base.[11] With basic amines it is not possible to avoid the slow exchange limit for CH and NH exchange in the experimentally accessible range of pH; i.e., α is always ~ 0. The value of k_{-a} is independent of pK for catalysts with pK_a less than that of HCN (pK 9.0).[11] However, the line-broadening method also becomes difficult for weakly basic amines ($pK_a \lesssim 5$) because of the rapid exchange with water of ammonium ions with a low pK_a.

Why Is Proton Transfer Direct? We would like to know why proton transfer occurs directly between an acid and a base in some reactions and indirectly, through one or several water molecules, in others.[2] The pathways for proton transfer from an acid BH^+ to a base A^- that are initially hydrogen bonded to water are shown in Scheme III. For thermodynamically favorable proton transfer between electronegative atoms the diffusion together of the solvated reactants, k_{diff}, is at least partially rate limiting; one or two desolvation steps, k_{-1} and k_{-2}, may also contribute to the observed rate constants. Proton transfer can then occur through water, k_w' and k_w, or directly, k_d. For thermodynamically unfavorable transfer the corresponding diffusional separation and solvation steps in the reverse direction are rate limiting. The first question is whether the preferred pathway depends on (1) the relative barriers for proton transfer directly or through water (k_d and $k_w + k_w'$, Scheme III) or (2) the relative barriers for proton transfer through water ($k_w + k_w'$) and for one or more diffusion-separation steps (k_{-1} and k_{-2}).

Proton transfer through water requires at least two proton transfers and may be either concerted or stepwise. At least one of the proton-transfer steps is thermodynamically unfavorable for the reactions considered here. It is unlikely that the barrier for two such proton transfers is smaller than that for a single, thermodynamically favorable direct transfer. It is probable, therefore, that the preferred mechanism for fast proton transfers depends on the relative barriers for proton transfer through water and for diffusion-separation steps, $k_w + k_w'$ and k_{-1} or k_{-2}. When proton transfer becomes slower ($k_d < k_2$), direct proton transfer will be rate limiting.

The observed direct proton transfer from HCN and to CN^- means that the barriers for loss of hydrogen-bonded water from BH^+ and A^-, including HCN and CN^-, and for proton transfer are smaller than the barrier for proton transfer through water, even when the proton transfer is strongly favorable. It is remarkable that there is no detectable proton transfer through water for reactions of RNH_3^+ and CN^- that are thermodynamically favorable by factors of up to 10^5 and for reactions of Me_3N and PhO^- with HCN that are favorable by a factor of ~ 10. There is no evidence for proton transfer through water by the Swain–Grunwald mechanism for proton exchange between HCN and H_2O,[11] even though the reaction of H_3O^+ and CN^- in the reprotonation direction occurs with a ΔpK between the proton donor and acceptor of 10.7 units and a diffusion-controlled rate constant of 4×10^{10} M^{-1} s^{-1}. These results require that a significant barrier for the proton-transfer step through water must be maintained for all of the proton donors and acceptors examined in this work,

with the possible exception of H_3O^+, even though HCN behaves very nearly like a normal acid and gives a typical "Eigen curve" for proton transfer to strong and weak bases.[11] We do not know if a very small, but significant, barrier is maintained for thermodynamically favorable direct proton transfer.

There are three reasons why proton transfer through water is more likely to occur with electronegative atoms than with carbon as proton donors and acceptors.

(1) Although the rate constants for proton transfer from HCN follow an Eigen curve which is very similar to that for normal acids, proton transfer from HCN to nitrogen bases at $\Delta pK \sim 0$ is significantly slower than is observed for normal acids. There is an even larger barrier for transfer to RS^- and CN^-.[11] This means that the barrier for the proton-transfer step itself is significantly smaller for the more electronegative proton donors.

(2) Electronegative atoms form relatively strong hydrogen bonds, so that extrusion of hydrogen-bonded water (k_{-1} and k_{-2}) is likely to be slower from these atoms than from CN^- and HCN. This desolvation may be the rate-limiting step for direct proton transfer between electronegative atoms[15] and with highly reactive carbanions.[31] It may also account for the relatively slow reaction of HCN with basic amines;[11] Me_3N is known to lose solvating water with a relatively slow rate constant of 10^{10} s^{-1}.[15,32] A slow desolvation step has been suggested previously to account for the tenfold smaller limiting rate constants of basic oxygen anions compared with azide ion and a mercaptan for reaction with unstable 1-phenylethyl carbocations.[33]

(3) Intermediates such as $A^- \cdot H^+(OH_2)_n \cdot B$ or $AH \cdot HO^- \cdot HB^+$ that may be formed along the reaction path and the rate-limiting transition state for proton transfer through water will be stabilized by hydrogen bonding to electronegative atoms. Therefore, proton transfer by this pathway is expected to be faster for normal acids and bases with electronegative atoms that can provide such hydrogen bonding[34] than for carbon acids.

The structure of hydrogen cyanide should make hydrogen bonding of CN^- and HCN unusually favorable, compared with other carbon acids that ionize to more delocalized anions. The conclusion that weak hydrogen bonding plays a significant role in proton-transfer reactions of HCN suggests that it plays an even more important role in other carbon acids and contributes significantly to their slow rates of proton transfer.

The absence of any detectable transfer through water with HCN, even for strongly favorable proton transfer and for reaction with Me_3N, suggests that stabilization of the transition state for proton transfer through water by hydrogen bonding must play an important role in making this pathway possible for proton transfer between electronegative atoms. Since proton transfer is direct with HCN, it is reasonable to conclude that it is direct with other carbon acids and their carbanions that are less normal and have larger intrinsic barriers for proton transfer, compared with HCN. It also provides a rationale for the direct mechanism in enzyme-catalyzed proton transfers to or from carbon.

Three possible exceptions to this conclusion that cannot be rigorously excluded at this time are (1) proton transfers to strongly basic and relatively normal carbanions that have an even larger ΔpK than the reactions described here, (2) protonation of carbanions when there is steric hindrance to direct proton transfer, and (3) protonation of carbanions with intramolecular assistance by groups that are not close enough to permit direct proton transfer. The same mechanism must, of course, hold for the reverse deprotonation reaction in which the carbanion is formed.

If a carbanion is sufficiently basic the barrier for proton transfer through water, k_w in Scheme III, may become smaller than the barrier for extrusion of water, k_{-2}, so that the pathway through water is followed. The same pathway must be followed in both directions, so that the lowest energy pathway for proton removal

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would also occur through water. Even though the reaction of H_3O^+ and CN^- does not occur through water by the Swain–Grunwald mechanism, the possibility has not been excluded that it occurs through water in a diffusion-controlled reaction of a hydrogen-bonded $H_2O \cdot H_3O^+$ kinetic unit.[11]

It is probable that catalysis of the enolization of methyl acetonylphosphonate by 2,6-lutidine and Mn^{2+} ion involves an intermediate water molecule, because direct transfer is sterically unfavorable.[10] However, it is possible that the reaction is stepwise, with proton removal by HO^- that is stabilized by Mn^{2+} and by hydrogen bonding to the protonated catalyst (**1**). This mechanism is consistent with the observed Brønsted slope of $\beta = 0.82$, which is larger than the value of $\beta = 0.69$ for the reaction with unhindered pyridines in the absence of Mn^{2+} and suggests a large amount of proton transfer to the pyridine in the transition state. The large inhibition of this and related reactions by steric hindrance in the absence of a metal ion shows that the pathway through water is not normally followed.[10,35]

1
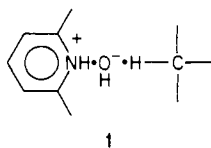
Intramolecular assistance of proton transfer to carbon through an intervening water molecule has been proposed to account for the rapid ionization of the monoanion of monoethyl malonate,[8] facilitation of the protonation of carbanions by neighboring amines,[9,36] and protonation of the enolate ion of acetone by H_3O^+ (with assistance by the oxygen anion).[37] The neighboring group assistance in these reactions could involve direct intramolecular protonation in a concerted reaction (k_c, eq 11),[9] protonation by H_3O^+ that is stabilized by hydrogen bonding to the basic group A^- (k_h),[37] or protonation by water, to give a hydroxide ion that is stabilized by hydrogen bonding to AH (k_h').[37] The H_3O^+ or HO^- could come from the solvent or could be generated at the site of reaction; however, these species will be at equilibrium with

the bulk solvent in most cases. Electrostatic interactions with the catalyzing group can also stabilize the transition state and increase the observed rate constant.[38]   The absence of detectable proton transfer to CN^- through water supports the stepwise, direct

(11)
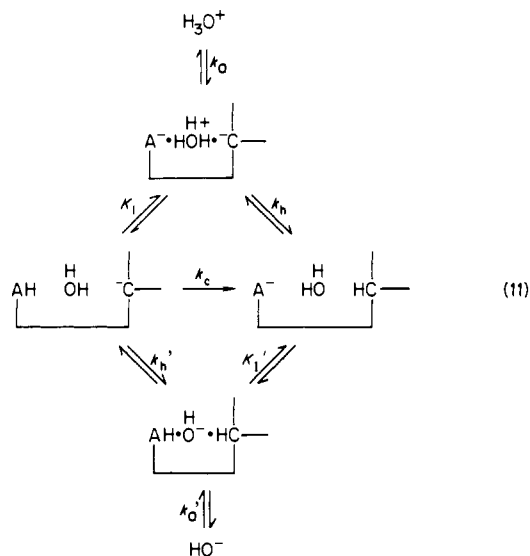
mechanism of proton transfer (k_h and k_h', eq 11). The large Brønsted coefficient of $\alpha \sim 1.0$ for intramolecular proton transfer in piperidine and morpholine adducts of α-cyano-4-nitrostilbene is also consistent with the stepwise hydrogen-bonding mechanism through the H_3O^+ intermediate in eq 11.[36]

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