Is HCN a Normal Acid? Proton Transfer from HCN to Bases and Small Inhibition of Proton Exchange by Acid[1]

Rodney A. Bednar[†] and William P. Jencks*

Contribution No. 1569 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254. Received February 19, 1985

Abstract: Rate constants for the exchange of HCN protons in aqueous solution were determined by NMR line broadening and saturation recovery. The rate constant for the pH-independent exchange with water is 40 s^{-1} at 20 °C and ionic strength 1.0 M. This corresponds to a rate constant of 4×10^{10} M^{-1} s^{-1} for the protonation of CN^- by H_3O^+, from $pK_a = 9.0$ for HCN, and suggests that the exchange reaction is diffusion controlled. Thermodynamically favorable proton transfer from carboxylic acids and protonated amines to CN^-, and from HCN to phenolates, occurs with rate constants of $\sim 10^9$ M^{-1} s^{-1}. The rate constants for proton transfer at $\Delta pK = 0$ decrease in the following order: phenols, 1×10^8 M^{-1} s^{-1}; amines, 3×10^7 M^{-1} s^{-1}; thiols, $\leq 5 \times 10^5$ M^{-1} s^{-1}; and cyanide, $<10^5$ M^{-1} s^{-1}. A solvent isotope effect of $k_{H_2O}/k_{D_2O} = 4.5$ was observed at pH 2 for the pH-independent exchange reaction of HCN protons. No significant inhibition by acid of the rate of HCN proton exchange was observed at low acid concentration (<1 M). This result is inconsistent with proton transfer through water to give a hydrogen-bonded water–CN^- intermediate according to the Swain–Grunwald mechanism. Only slight inhibition of HCN proton exchange was observed in strong sulfuric, hydrochloric, perchloric, and phosphoric acid solutions. Salts (KCl, NaCl, NaClO₄) cause more inhibition than the corresponding acids. The observed rate constants for exchange of HCN protons were used to define an H_- acidity function for the ionization of HCN in acid solutions. The possibility of an acid-catalyzed isomerization mechanism for exchange in strong acid is discussed. It is concluded that HCN is an almost normal acid.

Proton transfer between the electronegative atoms of "normal" acids and bases is essentially diffusion controlled in the thermodynamically favorable direction and involves diffusion-controlled separation of the products in the unfavorable direction; near ΔpK = 0 there is a small region in which the proton transfer step itself is partially rate limiting. The Brønsted plots for such reactions follow "Eigen curves" with slopes of 0 and ± 1.0 in the favorable and unfavorable directions, respectively, and a small transition region near ΔpK = 0, in which the proton-transfer step gives rise to a small solvent deuterium isotope effect when it becomes partly rate limiting.[2-5] In hydroxylic solvents most proton transfers of this kind occur through one or more intermediate solvent molecules, as well as directly from the acid to the base. One example of such proton transfer through water is observed in the dissociation of protonated amines according to the Swain–Grunwald mechanism, in which proton exchange is inhibited by added acid when the proton that has been transferred to a water molecule is transferred back to the amine by reprotonation of the amine–water complex before it undergoes diffusional separation.[6-8]

Proton transfer to or from carbon differs from these normal proton transfers in that it is usually much slower and is generally believed to occur directly, rather than through a solvent molecule. This slow proton transfer has been variously attributed to changes in electron delocalization and hybridization accompanied by changes of the lengths and angles of bonds to heavy atoms, poor hydrogen bond donor–acceptor properties of carbon, and solvent reorganization in the rate-limiting transition state.[9-11] It is important to understand the reasons for this slow proton transfer because, among other things, it is responsible for the stability of many organic compounds that are required for living systems to function.

In this series of papers we describe an examination of proton transfers involving HCN, an especially simple carbon acid that requires little or no electron delocalization or changes in bond lengths and angles of heavy atoms upon ionization. It has the additional advantage that its pK_a value makes possible the measurement of rate constants for proton transfer near ΔpK_a = 0, at which the intrinsic barriers for the proton-transfer step are expected to be most significant compared with the barriers for diffusional combination and separation.

The results show that the behavior of HCN is similar, although not identical, to that of normal acids. The rate constants for proton

transfer follow an Eigen curve similar to that for normal acids and bases with electronegative atoms but show a larger barrier for proton transfer near ΔpK = 0. There is no indication of the inhibition by acid of proton transfer to water that is expected for the Swain–Grunwald mechanism. In fact, the observed inhibition by acid is much smaller than predicted by most known acidity functions. The relatively small inhibition is used to define an acidity function that reflects stabilization of the CN^- ion in acid solution. We conclude that HCN is the most normal carbon acid known but that it still maintains behavior that is characteristic of other carbon acids.

Experimental Section

Solution Preparation. Stock solutions of HCN, base catalysts, and KCl were prepared with glass-distilled water at ionic strength 1.0 M (KCl) containing 5–10% D₂O. A 1.0 M stock solution of HCN was prepared by neutralization of KCN (recrystallized from ethanol–water) with 5 M HCl or other acids. The aqueous KCN solution was cooled on ice and vortexed during the addition of the HCl solution. All open solutions of HCN were handled in a hood. Solutions of the amine catalysts were prepared by partial neutralization of the amine hydrochlorides with KOH, except that free methoxyethylamine was used to neutralize a measured quantity of HCl. The carboxylic acid catalysts were prepared

---

[†] Present address: Department of Pharmacological Sciences, SUNY at Stony Brook, Stony Brook, New York 11794-8651.

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

(3) Schuster, P.; Wolschann, P.; Tortschanoff, K. In "Chemical Relaxation in Molecular Biology"; Pecht, I., Rigler, R., Eds.; Springer-Verlag: Berlin, 1977; pp 107–190. Crooks, J. E. In "Comprehensive Chemical Kinetics"; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1977; Vol. 8, pp 197–250.

(4) Bergman, N.-Å.; Chiang, Y.; Kresge, A. J. *J. Am. Chem. Soc.* **1978**, *100*, 5954–5956. Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5956–5957.

(5) Fischer, H.; DeCandis, F. X.; Ogden, S. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 1340–1347.

(6) Emerson, M. T.; Grunwald, E.; Kaplan, M. L.; Kromhout, R. A. *J. Am. Chem. Soc.* **1960**, *82*, 6307–6314.

(7) Grunwald, E. *J. Phys. Chem.* **1963**, *67*, 2211–2214. Grunwald, E.; Ralph, E. K. *Acc. Chem. Res.* **1971**, *4*, 107–113.

(8) Grunwald, E.; Eustace, D. In "Proton-Transfer Reactions"; Caldin, E., Gold, V., Eds.; Chapman and Hall: London, 1975; pp 103–120. See p 113.

(9) Bell, R. P. "The Proton in Chemistry", 2nd ed.; Cornell University Press: Ithaca, 1973; p 194. Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354–360. Hine, J. *Adv. Phys. Org. Chem.* **1977**, *15*, 1–61.

(10) Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335–2348.

(11) Vinogradov, S. N.; Linnell, R. H. "Hydrogen Bonding"; Van Nostrand-Reinhold: New York, 1971; pp 120–124.

7118 *J. Am. Chem. Soc., Vol. 107, No. 24, 1985*

Bednar and Jencks

by neutralization of the free acid with KOH to give stock solutions that were 1.0 M in the anion. The pH was measured with an Orion Research Model 701A pH meter with a Radiometer GK2321C combination electrode standardized at pH 7.0 and 4.0 or 10.0. Solutions of HCN, base catalysts, and KCl were adjusted to the same pH with KOH or HCl before mixing. In order to prevent a rise in the pH on transfer to an NMR tube, it was necessary to rinse the pasteur pipet and NMR tube with several aliquots of the solution until no change in pH was detected. The pH was measured at room temperature both before and after NMR measurements and generally agreed within 0.1 pH units. An average pH value was used without correction for the effect of 5–10% D_2O. This is unlikely to introduce a significant error since the small effects of 10% D_2O on pH and pK values tend to cancel and the necessary correction is less than the uncertainty of the pH measurement.[12]

Solutions in Strong Acids. A stock solution of 2 M $K^{13}C^{15}N$ (Prochem, 90.6 atom % ^{13}C, 99.4 atom % ^{15}N) was prepared in water and 25 μL was added to a 5-mm NMR tube. To this tube was added 25 μL of D_2O, $(450 - X)$ μL of H_2O, and finally X μL of concentrated acid solution. The tube was capped and the solution was mixed. The apparent volume percent (vol %) is defined as 100X/500. The weight percent (wt %) of strong acid was calculated from eq 1, in which (wt %)$_{stock}$ and

$$wt \% = \frac{(wt \%)_{stock}(d)_{stock}(vol \%)}{(d)_{stock}(vol \%) + (100 - (vol \%))(d)_{H_2O}} \quad (1)$$

$(d)_{stock}$ are the weight percent and density of the concentrated acid and $(d)_{H_2O}$ is the density of water. When small amounts of acid were added, a correction was made to vol % to account for the acid required to titrate the KCN.

The chemical shift of the HCN proton was determined by spiking the sample (after T_1 was measured) with CH_3CN and $(CH_3)_4N^+Cl^-$ to act as internal standards.

NMR Measurements. NMR data were obtained at 270 MHz on an instrument designed by Redfield.[13] In order to minimize the interference of solvent protons with the proton signal from HCN (about 170 Hz downfield from water), a "214" observation pulse[14] was employed. It has a power spectrum which can excite the resonance of interest but has a complete null at the water frequency and therefore does not cause significant excitation of the water protons. In order to eliminate interference from water spinning side bands, the spectra were recorded with a 5-mm nonspinning NMR tube.

All reactions were carried out at 20 ± 1 °C. The temperature was measured by a thermocouple inserted into the probe. The probe temperature was calibrated with the chemical shift difference of the methyl and hydroxyl protons of methanol (containing 0.03% (v/v) concentrated HCl) by using the equation of Van Geet.[15]

Determination of the Rate Constant for Exchange of HCN Protons with Solvent. The exchange of HCN protons with solvent (in the range 10–100 s^{-1}) was determined from the T_1 of the HCN proton signal, which was measured by the technique of saturation recovery.[16] The HCN proton resonance was partially saturated by a long (0.1 s), weak preirradiation pulse at the resonance frequency of the HCN. This was followed by a variable delay, τ, a 4-ms homospoil pulse[13] (to destroy any signals induced by the preirradiation pulse), and a 7-ms recovery time, before application of a roughly 60° "214" observation pulse at a frequency 250 Hz downfield from solvent and a spectral band width of 400 Hz. The free induction decay was stored followed by a delay of 1–10 s before repeating the cycle 4 times. After 4 cycles a Fourier transformation was performed. This procedure was repeated for each of 8 τ values. The end point was determined by using a τ approximately 5–10 times the expected half-time. The other 7 delays (τ) were chosen in the range 0 to ~3 half-times. The entire sequence was repeated 20–500 times in order to improve the signal-to-noise ratio.

Pseudo-first-order rate constants were obtained from semilog plots of height(∞) – height(t) against time. The plots were linear for ≥2–3 half-lives.

(12) The correction to the pH meter reading for 10% D_2O of 0.1 × 0.4 = 0.04 units (Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188–190) is close to the correction of 0.05 to 0.06 for the pK of the acid in 10% D_2O (Laughton, P. M.; Robertson, R. E. In "Solute–Solvent Interactions"; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; Vol. 1, pp 399–538).

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

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

(15) Van Geet, A. L. *Anal. Chem.* **1970**, *42*, 679–680.

(16) Johnston, P. D.; Redfield, A. G. *Nucleic Acids Res.* **1977**, *4*, 3599–3615. Johnston, P. D.; Redfield, A. G. In "Transfer RNA: Structure, Properties, and Recognition"; Schimmel, P. R., Söll, D., Abelson, J. N., Eds.; Cold Spring Harbor Laboratory, 1979; pp 191–206.
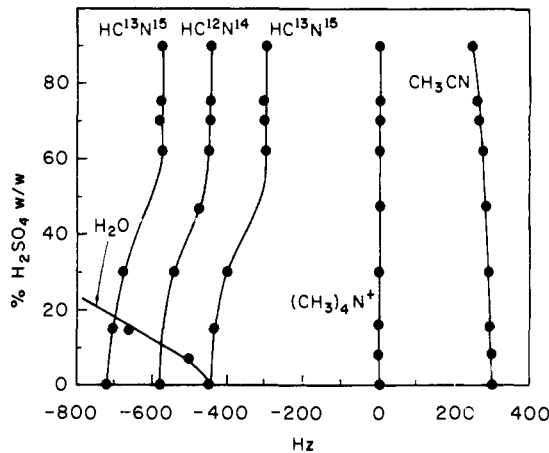
Figure 1. Dependence on sulfuric acid concentration of the shift in the resonance frequencies of the proton signals of HCN and CH_3CN. Tetramethylammonium ion $((CH_3)_4N^+)$ was used as an internal standard. Measurements were made at 270 MHz in 5% D_2O and 20 °C with use of a Redfield 214 observation pulse.

A correction for the contribution of magnetic relaxation processes was made when T_1 of the HCN protons was <10 s^{-1}. The fraction of the recovery rate constant that is attributable to chemical exchange was determined by measurement of saturation transfer from water.[17] The water protons were completely saturated by a preirradiation pulse of 1–10 s, which is long compared with T_1 of the HCN protons, in order to set up a steady state. The HCN resonance was observed with a zero variable delay, τ. The reduction in the observed height of the HCN signal is indicative of chemical exchange of the solvent protons with HCN. It was verified that this reduction was not due to direct off-resonance saturation (or "spillover") by showing that a similar preirradiation at a frequency symmetrically related to the HCN had no effect on the HCN protons. The inability to decrease the HCN signal further by increasing the power of the water preirradiation pulse provides evidence for complete saturation of water. The fraction of saturation transfer, $f_{sat\ tx}$, is defined by eq 2, in which h_{wo} and h_w are the heights of the HCN signal without and

$$f_{sat\ tx} = \frac{h_{wo} - h_w}{h_{wo}} = \frac{k_{ex}}{(k_{ex} + k_{mag})} \quad (2)$$

with water preirradiation, respectively.[17] The rate constant for chemical exchange, k_{ex}, is the product of this fraction and the observed rate constant for saturation-recovery, $k_{ex} + k_{mag}$.[17] Typically, k_{mag} is 0.3–0.5 s^{-1}.

It is unlikely that dipolar cross-relaxation contributes significantly to k_{ex} or transfer of saturation because there is no indication of a leveling of the values of k_{ex} with increasing acidity down to values of $k_{ex} = 2$ s^{-1} (see Figure 3). It was shown directly that chemical exchange occurs in 90% sulfuric acid because DCN is completely converted to HCN at the earliest observed time of 1 min; in contrast, the exchange of NH_4^+ has a half-time of 15 h in 70% sulfuric acid.[6]

Determination of Rate Constants for the Removal of HCN Protons by Bases. An apparent second-order rate constant for buffer-catalyzed proton exchange from HCN, based on total buffer concentration, was determined by plotting the width of the HCN peak at half-height (in units of Hz) against the concentration of total buffer. The slope of this plot multiplied by π yields k_{obsd} as defined in eq 3, in which $\Delta f_{1/2}$ is the increase in the width of the HCN peak at half-height. The broadening

$$k_{obsd} \equiv \pi \Delta f_{1/2}/[buffer] \quad (3)$$

of the HCN line is sensitive to all base-catalyzed proton transfers if the first-order rate constant for return of the proton to CN$^-$ is small compared to the reciprocal of the frequency difference between HCN and the species which is returning the proton to CN$^-$.[18] The experimental criteria used to determine that this condition holds are given in the following paper.[19] A second-order rate constant, k_a, for catalysis of

(17) (a) Redfield, A. G.; Waelder, S. *J. Am. Chem. Soc.* **1979**, *101*, 6151–6162. (b) Lambert, J. B.; Nienhuis, R. J.; Keepers, J. W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 496–500. (c) Sandström, J. "Dynamic NMR Spectroscopy"; Academic Press: London, 1982; p 53ff. (d) Forsen, S.; Hoffman, R. A. *J. Chem. Phys.* **1963**, *39*, 2892–2901.

(18) For a discussion of line broadening see ref 17c, p 14 ff.

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

Is HCN a Normal Acid?

J. Am. Chem. Soc., Vol. 107, No. 24, 1985 7119
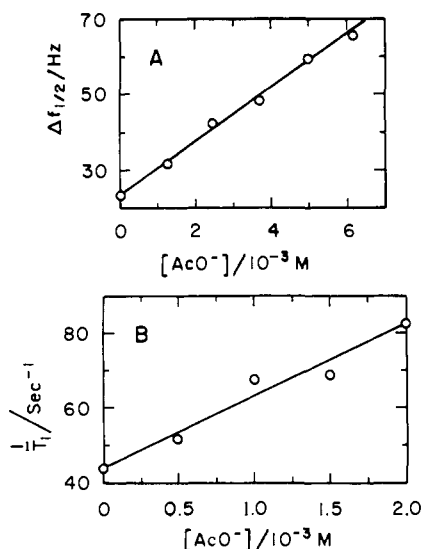
Figure 2. (A) The width of the HCN peak at one-half height ($\Delta f_{1/2}$) is plotted against the concentration of acetate ion at pH 4.55, $I = 1.0$ M (KCl), 10% D_2O, and 20 °C. (B) The reciprocal of the longitudinal relaxation time of the HCN proton resonance is plotted against the concentration of acetate ion at pH 4.65, $I = 1.0$ M (KCl), 10% D_2O, and 20 °C.

proton transfer by the free base was obtained by dividing k_{obsd} by the fraction of free base present at the experimental pH.

Results

The rate constants for base-catalyzed removal of a proton from HCN (eq 4) were determined by use of the proton NMR techniques of line broadening, saturation recovery, and transfer of

$$HCN + B \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} CN^- + BH^+ \qquad (4)$$
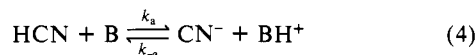
saturation from water.[20] A Redfield 214 observation pulse,[14] which avoids significant excitation of water protons, was used in order to detect the HCN proton signal in solutions containing 90–95% H_2O.

The chemical shifts of the proton NMR signals relative to $(CH_3)_4N^+$ are shown in Figure 1. The HCN signal is 0.6 ppm downfield from that of H_2O in a weakly acidic solution. The use of $^{13}C^{15}N$-enriched HCN gives two additional proton signals from HCN ($J = 267$ Hz)[21] and provides a signal that is easier to detect because it is further away from the water signal. As the solution is made more acidic, the water signal moves downfield through the HCN signal. HCN shows an upfield shift while CH_3CN shows a downfield shift as the percent H_2SO_4 is increased. The small shift in the CH_3CN resonance signal could reflect hydrogen bonding to the nitrogen atom[22] in the acid solutions. The upfield shift in the resonance signal of HCN could result from the loss of a hydrogen bond between water and the proton of HCN[23] as the activity of water decreases in the strong acid solutions.

The results of a typical line-broadening experiment are shown in Figure 2A. These experiments were carried out in aqueous solution with 1 M HCN, of normal isotopic abundance, which gives a satisfactory signal-to-noise ratio. The line width of the HCN peak at half-height is plotted against the concentration of acetate ion at pH 4.55 in 10% D_2O. The slope of this plot
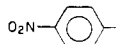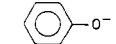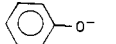
(20) See, for example: Waelder, S. F.; Redfield, A. G. *Biopolymers* **1977**, *16*, 623–629.

(21) This value is in good agreement with previous values (Friesen, K. J.; Wasylishen, R. E. *J. Magn. Reson.* **1980**, *41*, 189–191 and references therein).

(22) (a) Allerhand, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1963**, *85*, 866–870. (b) There is evidence that isocyanides form stronger hydrogen bonds than nitriles: Grundnes, J.; Klaboe, P. In "The Chemistry of the Cyano Group"; Rappoport, Z., Ed.; Wiley-Interscience: New York, 1970; pp 136–142. (c) Mautner, M. *J. Am. Chem. Soc.* **1984**, *106*, 1257–1264.

(23) Green, R. D. "Hydrogen Bonding by C–H Groups"; John Wiley & Sons: New York, 1974, pp 119–123.

**Table I.** Rate Constants for General-Base Catalysis of HCN Proton Exchange[a]

catalyst	pK_a[b]	log k_a, M^{-1} s^{-1}	log k_{-a}, M^{-1} s^{-1}
H_2O	−1.74	−0.14	10.6
OH^-	15.74	9.9	3.2
$CNCH_2COO^-$	2.23[c]	2.34	9.11
$ClCH_2COO^-$	2.65[c]	2.67	9.02
$CH_3OCH_2COO^-$	3.33[c]	3.32	8.99
CH_3COO^-	4.65[c]	4.32	8.67
$H_2NC(O)NHNH_2$	3.86[c]	4.26	9.40
CH_3ONH_2	4.72[c]	5.00	9.28
$CF_3CH_2NH_2$	5.81[e]	5.71	8.90
$(CH_3)_3N^+CH_2CH_2NH_2$	7.32[f]	7.13	8.81
$H_3N^+CH_2CH_2NH_2$	7.5[g]	7.17	8.67
$H_2NCOCH_2NH_2$	8.25[f]	7.30	8.05
$ClCH_2CH_2NH_2$	8.81[g]	7.51	7.70
$CH_3OCH_2CH_2NH_2$	9.72[d]	7.58	6.86
$HOCH_2CH_2NH_2$	9.87[g]	7.81	6.94
$CH_3CH_2NH_2$	10.97[d]	7.7	5.73
(structure, piperazinium)	3.47[d]	4.22	9.75
(structure)	4.64[f]	5.15	9.51
(structure, H_2N ... NH)	6.01[d]	6.36	9.35
$Me_2NH^+(CH_2)_2NMe_2$	6.47[f]	6.87	9.40
(structure, HN ... N)	7.24[h]	6.78	8.54
$(HOCH_2CH_2)_3N$	7.99[i]	6.96	7.97
$Me_2N^+HCH_2CH(OH)CH_2NMe_2$	8.01[f]	7.72	8.71
$Me_2N^+H(CH_2)_3NMe_2$	8.39[f]	7.48	8.09
$Me_2N^+H(CH_2)_4NMe_2$	9.24[f]	7.46	7.22
$(CH_3)_3N$	10.16[j]	7.38	6.22
O_2N—⬡—O^-	7.14[d]	6.75	8.61
⬡—O^- (NO_2)	8.35[d]	7.78	8.43
$(CF_3)_2CHO^-$	9.3[c]	7.97	7.67
⬡—O^-	9.86[d]	8.68	7.82
$CF_3C(O^-)(OH)CH_3$	10.5[k]	8.57	7.07
$CF_3CH_2O^-$	12.4[l]	9.28	5.88
$HOCH_2CH_2S^-$	9.61[m]	≤6.1	≤5.4
CN^-	9.0[n]	≤5.0	≤5

[a] 20 °C and ionic strength 1.0 M (KCl) in 10% D_2O. The rate constants k_a and k_{-a} are defined in eq 4. [b] pK_a is for 25 °C at ionic strength 1.0 M (KCl). [c] Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436–1449. [d] Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622–2637. [e] St. Pierre, T.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 3817–3827. [f] This work. [g] Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 572–580. [h] Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6353–6361. [i] Smith, R. M.; Martell, A. E. "Critical Stability Constants"; Plenum Press: New York, 1976; Vol. 2, p 118. [j] Grunwald, E.; Ku, A. Y. *J. Am. Chem. Soc.* **1968**, *90*, 29–31. $I = 0.5$. [k] Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7031–7044. [l] Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795–798. Low ionic strength. [m] Jencks, W. P.; Salvesen, K. *J. Am. Chem. Soc.* **1971**, *93*, 4433–4436. [n] References 28 and 29.

multiplied by π gives a second-order rate constant of $k_a = 2.2 \times 10^4$ M^{-1} s^{-1}.[24]

Table I shows a compilation of k_a values for a variety of catalysts. The value of k_a reported for each buffer catalyst was determined at two or more pH values, as described in supple-

(24) This procedure is valid when the first-order rate constant for return of the proton to CN^- is small compared to the reciprocal of the frequency difference between HCN and the species which is returning the proton to CN^-, as described in the accompanying paper.[19]
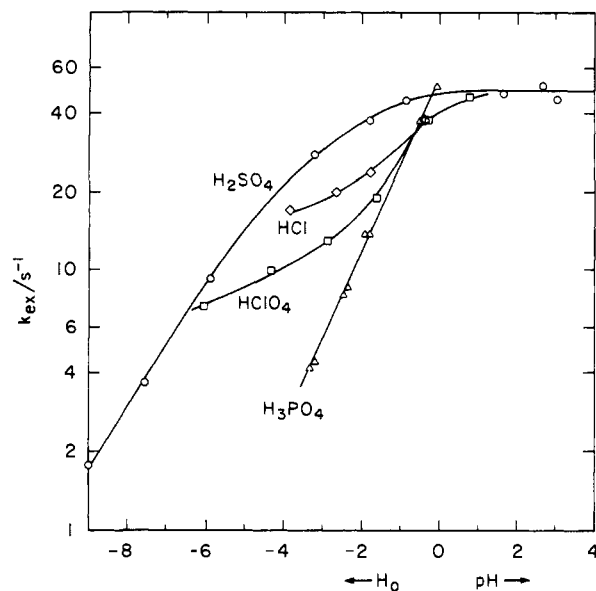
Figure 3. Dependence of the rate constants for exchange of HCN protons in solutions of strong acids on the Hammett H_0 acidity function.[26] These experiments were carried out in 5% D_2O at 20 °C.

mentary Table S1. For the carboxylate catalysts the value of k_a was determined at 0.5 and 0.8 or 0.9 fraction base. The value of k_a is independent of pH with an average deviation of $\sim$14%. Broadening of the HCN resonance catalyzed by amines and phenolate ions was measured at 3–12 pH values between pH 2 and 6. For some of the amine and phenolate catalysts the value of k_a is independent of pH at low pH values but shows a negative deviation at higher pH values. The maximum k_a value observed at low pH was taken as the correct k_a; the negative deviation observed at higher pH values is discussed in the accompanying paper.[19] The k_a values reported here could, in principle, refer to removal of a proton by the base either directly or through one or more intermediate water molecules; in fact, they refer to direct proton removal.[19] The rate constant of $k_a = (8 \pm 3) \times 10^9$ M^{-1} s^{-1} for hydroxide ion, based on a_{OH^-}, was obtained from the intercepts of the buffer plots, the measured pH at 22 $\pm$ 2 °C, and a value of $pK_w = 14.08$. A value of $k_a = 3.7 \times 10^9$ M^{-1} s^{-1}, based on hydroxide ion concentration, has been obtained from ultrasonic absorption measurements at 25 °C and ionic strength 0.01–0.05 M.[25]

The rate constants for the reverse reaction, k_{-a}, were obtained from the experimentally determined forward rate constant, k_a, and the equilibrium constant for proton transfer (eq 5).

$$K_{eq} = \frac{[CN^-][BH^+]}{[HCN][B]} = \frac{k_a}{k_{-a}} \qquad (5)$$

The saturation recovery method involves labeling the HCN proton by a selective preirradiation pulse that saturates the HCN proton signal. The time-dependent recovery of this signal is then monitored in a series of experiments to determine the relaxation rate constant of the HCN proton, $1/T_1$. For $1/T_1 > 10$ s^{-1}, the recovery of the HCN proton signal is the result of chemical exchange of a saturated HCN proton for a nonsaturated proton; for $1/T_1 < 10$ s^{-1}, the recovery results from a combination of chemical exchange and magnetic relaxation processes with $k_{mag} \sim 0.4$ s^{-1}.

The contribution of chemical exchange was determined by saturation transfer from water. The steady-state level of saturation of the HCN signal when the H_2O signal is saturated provides a measure of the relative rates of chemical exchange and magnetic relaxation; for example, 75% transfer of the H_2O saturation to HCN indicates that 75% of the observed relaxation of the HCN
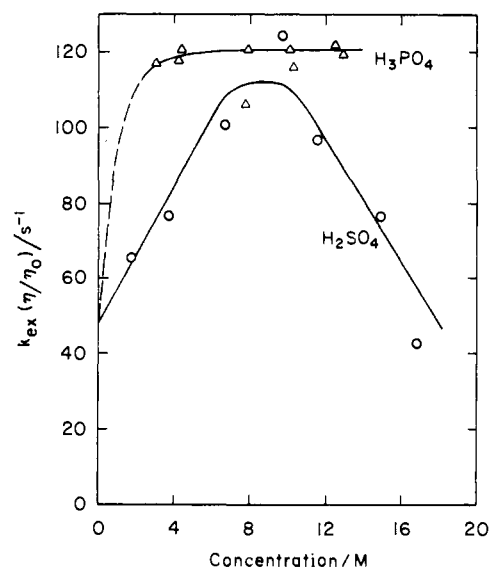
Figure 4. Dependence of the rate constant for proton exchange corrected for viscosity on the concentration of H_2SO_4 (O) and H_3PO_4 ($\triangle$). The solid line drawn through the H_2SO_4 data is based on a rate constant for catalysis by sulfate of $k_{SO_4^{2-}} = 35$ M^{-1} s^{-1} and the concentration of SO_4^{2-} in sulfuric acid solution, determined from Raman spectroscopy.[48b]
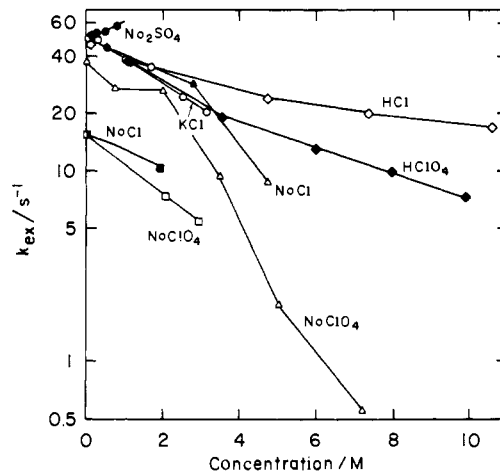
Figure 5. A comparison of the effects of salts and acids on the exchange of HCN protons with solvent (k_{ex}) at pH $\sim$2 and 20 °C in 10% (v/v) D_2O. The degree of inhibition caused by NaCl and NaClO$_4$ in 4.8 M HClO$_4$ is shown by the squares. The NaClO$_4$ solutions also contained NaCl, which decreased from 0.8 to 0.1 M with increasing [NaClO$_4$].

proton signal is due to chemical exchange and 25% is due to magnetic relaxation processes.[17]

Figure 2B illustrates data for the acetate-catalyzed removal of a proton from HCN, determined by the saturation recovery method. The T_1 of the HCN proton signal is dominated by the chemical exchange term. The slope of this plot yields a rate constant of $k_a = 1.9 \times 10^4$ M^{-1} s^{-1}, which agrees with the value of 2.2×10^4 M^{-1} s^{-1} obtained by the line-broadening technique. This agreement supports the assignment of the observed line broadening to chemical exchange.

A combination of the saturation-recovery and saturation-transfer methods was used to determine rate constants for the water-catalyzed exchange of HCN protons. Figure 3 shows the dependence of the rate constants for exchange of HCN on pH and on the Hammett acidity function H_0.[26] Figure 4 shows the rate constant for proton exchange, after correction for viscosity,[27]

(25) Stuehr, J.; Yeager, E.; Sachs, T.; Hovorka, F. *J. Chem. Phys.* **1963**, *38*, 587–593.

(26) (a) Paul, M. A.; Long, F. A. *Chem. Rev.* **1957**, *57*, 1–45. (b) Johnson, C. D.; Katritzky, A. R.; Shapiro, S. A. *J. Am. Chem. Soc.* **1969**, *91*, 6654–6662. See p 6660. (c) O'Connor, C. J. *J. Chem. Educ.* **1969**, *46*, 686–689. (d) Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley-Interscience: New York, 1972; pp 65–66.
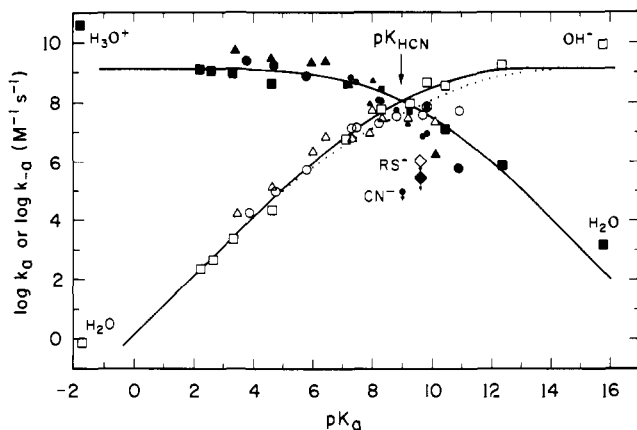
Figure 6. Brønsted plot for general acid–base catalysis of proton exchange from HCN at 20 °C and ionic strength 1.0 M (KCl) in 10% (v/v) D_2O. Open symbols are for the removal of a proton from HCN by a general base and the solid symbols are for the protonation of CN^- by a general acid. The squares are for oxygen-containing catalysts (pK 2–5 are RCOOH, and pK 7–15 are ROH), circles are for primary amines, and triangles are for tertiary amines (including diamine monocations) or a secondary amine (pK 6.01). Upper limits for the catalysis by β-mercaptoethanol and CN^- are indicated. The lines are theoretical Eigen curves (see text) using $k_d = 1.3 \times 10^9$ M^{-1} s^{-1} and $k_d/k_{-d} = 0.1$ M^{-1}. The solid line was calculated by using $k_p(\Delta pK = 0) = 10^{9.1}$ s^{-1}. The dotted line was calculated by using $k_p(\Delta pK = 0) = 10^{8.6}$ s^{-1}.

as a function of the concentration of sulfuric and phosphoric acids. These results are tabulated in supplementary Table S2.

Figure 5 shows the effect of added salts on the rate of exchange of HCN protons with solvent. The increase of the rate constant for exchange with increasing concentration of Na_2SO_4 corresponds to a value of $k_a = 19$ M^{-1} s^{-1} for catalysis by the SO_4^{2-} ion.

The solvent isotope effect on the exchange of HCN protons with the solvent (L_2O) was determined by measuring the T_1 of HCN in a pH-independent region near pH 2, at ionic strength 1.0 M (KCl) and 20 °C. In separate experiments, the observed rate constants for the loss of a proton from HCN in 99% D_2O were found to be 9.2 and 9.6 s^{-1}, while the observed rate constants were 38 and 44 s^{-1} in 10% D_2O. Extrapolation of the average rate constants to 100% D_2O and 0% D_2O yields $k_{D_2O} = 9.9$ s^{-1} and $k_{H_2O} = 45$ s^{-1}. The solvent isotope effect, k_{H_2O}/k_{D_2O}, is 4.5 with an uncertainty of 0.5 based on the extremes of the observed data.
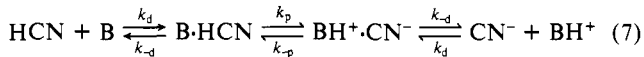
Discussion

The reaction of HCN with water appears to be a diffusion-controlled process. The rate constant of $k_a = 40$ s^{-1} for the exchange of HCN protons with solvent (at 20 °C, ionic strength 1.0 M, 10% D_2O) is independent of pH in the region of pH 1–3. If the mechanism of this exchange reaction involves the ionization of HCN to CN^- and H_3O^+, then a rate constant for the protonation of CN^- by H_3O^+ of $k_{-a} = 4 \times 10^{10}$ M^{-1} s^{-1} can be calculated from the observed rate constant and $pK_a = 9.0$ for HCN at ionic strength 1.0 M.[28,29] This rate constant is of the magnitude that has been observed[2] for diffusion-controlled reactions of "normal" bases with H_3O^+ and suggests that the rate-limiting step is the diffusion together of CN^- and H_3O^+, k_d in eq 6. By microscopic

$$H_2O + HCN \rightleftharpoons H_3O^+\cdot CN^- \underset{k_d}{\overset{k_{-d}}{\rightleftharpoons}} H_3O^+ + CN^- \quad (6)$$
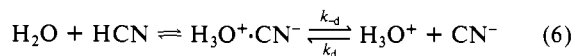
reversibility, the rate-limiting step for the reaction of HCN and

H_2O is the diffusional separation of CN^- and H_3O^+, k_{-d} in eq 6. The rate constant for protonation of CN^- by H_3O^+ is the largest rate constant for the protonation of a carbanion that has been reported, although it is approached by the rate constants for protonation of disulfone anions.[30] It suggests that HCN may be a normal carbon acid.

Brønsted plots for buffer catalysis of the exchange of HCN protons are shown in Figure 6. The open symbols are for the removal of a proton from HCN by a general base, the forward reaction in eq 7, and the solid symbols are for the protonation of

$$HCN + B \underset{k_{-d}}{\overset{k_d}{\rightleftharpoons}} B\cdot HCN \underset{k_{-p}}{\overset{k_p}{\rightleftharpoons}} BH^+\cdot CN^- \underset{k_d}{\overset{k_{-d}}{\rightleftharpoons}} CN^- + BH^+ \quad (7)$$

CN^- by a general acid in the reverse direction. The Brønsted plots follow Eigen curves that are typical of those for proton transfer between electronegative atoms;[2,3] they differ from the linear or gently curved Brønsted plots that are generally observed for carbon acids.[9] The data can be interpreted in terms of the simple three-step model for proton transfer shown in eq 7.[2] For thermodynamically favorable proton transfers diffusion together, k_d, is the rate-limiting step, and for thermodynamically unfavorable proton transfers diffusion apart, k_{-d}, is rate limiting. For proton transfers to or from catalysts that are within 4 units of the pK_a of HCN, diffusion together (k_d), the actual proton transfer within the encounter complex (k_p), and diffusion apart (k_{-d}) are all partially rate limiting.

The limiting rate constants for the thermodynamically favorable proton transfers are $\sim 10^9$ M^{-1} s^{-1}. This is a typical value for normal acids and bases.[2] The positive deviations of the reactions involving water probably result from the ability of H_3O^+ and OH^- to undergo facilitated diffusion; a positive deviation of 20–40-fold is often observed for protonation by H_3O^+ compared with buffer acids.[2]

Theoretical Eigen curves were calculated[5] from eq 8, which is the steady-state solution to eq 7. The value of k_p is defined by eq 9, which assumes that α for the proton-transfer step is 0.5 at $\Delta pK = 0$ and in the adjacent region in which it contributes to k_a.

$$k_a = \frac{k_d k_p k_{-d}}{(k_p k_{-d} + k_{-d} k_{-d} + k_{-d} k_{-p})} \quad (8)$$

$$k_p = k_{p(\Delta pK=0)} 10^{0.5(\Delta pK)} \quad (9)$$

The solid lines in Figure 6 were calculated from eq 8 by using $k_d = 1.3 \times 10^9$ M^{-1} s^{-1}, $k_{-d} = 1.3 \times 10^{10}$ s^{-1}, and $k_p = 10^{9.1}$ s^{-1} at $\Delta pK = 0$. This line provides a reasonable fit to the data for oxygen catalysts (squares, RCOOH and ROH). The dotted line was calculated in the same way with $k_p = 10^{8.6}$ s^{-1} at $\Delta pK = 0$. This line provides a reasonable fit to the data for primary amines (circles), except for the negative deviation of ethylamine.

These results show that the rate constants for proton transfer from HCN are close to or identical with those observed for normal acids and bases with electronegative atoms. They support the conclusion that slow proton transfers in other carbon acids involve a larger intrinsic barrier for reaction that arises from electron delocalization, rehybridization, changes in bond lengths and angles of heavy atoms, and changes in solvation.[9–11] Although some of these changes must take place during the ionization of HCN, they are small and cause little or no decrease in rate. We conclude that proton transfer to and from carbon is not intrinsically much slower than that of more electronegative atoms.

The relatively small rate constants near $\Delta pK = 0$ for amines correspond to an intrinsic rate constant for proton transfer that is slower for nitrogen-containing catalysts than for oxygen-containing catalysts by a factor of ~ 3. A similar difference has been

(27) (a) For viscosity of H_2SO_4 and HCl solutions at 20 °C, see: Bates, S. J.; Baxter, W. P. In "International Critical Tables"; Washburn, E. W., Ed.; McGraw-Hill: New York, 1929; Vol. 5, pp 12–19. (b) For viscosity of $HClO_4$ solutions at 25 °C, see: Kresge, A. J.; Capen, G. L. *J. Am. Chem. Soc.* **1975**, *97*, 1795–1797. (c) For viscosity of H_3PO_4 solutions, see: Edwards, O. W.; Huffman, E. O. *Chem. Eng. Data Ser.* **1958**, *3*, 145–146.

(28) Smith, R. M.; Martell, A. E. "Critical Stability Constants"; Plenum Press: New York, 1976; Vol. 4, p 26.

(29) Reenstra, W. W.; Abeles, R. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 1016–1024.

(30) (a) Bell, R. P.; Cox, B. G. *J. Chem. Soc. B.* **1971**, 652–656. (b) Hibbert, F.; Long, F. A.; Walters, E. A. *J. Am. Chem. Soc.* **1971**, *93*, 2829–2835. (c) Hibbert, F.; Long, F. A. *J. Am. Chem. Soc.* **1972**, *94*, 2647–2651. (d) Hibbert, F. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1289–1292. (e) Kresge, A. J.; Lin, A. C. *J. Chem. Soc., Chem. Commun.* **1973**, 761–762. (f) Dahlberg, D. B.; Kresge, A. J.; Lin, A. C. *J. Chem. Soc., Chem. Commun.* **1976**, 35–36. (g) Lin, A. C.; Chiang, Y.; Dahlberg, D. B.; Kresge, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 5380–5386.

Scheme I

$$AH \cdot OH \cdot OH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A^- \cdot HO + H_3O^+$$
$$ H H H H$$

$$HOH \dashv \downarrow k_H$$

$$A^- \cdot HO + HO$$
$$ H {}^-H$$

observed previously for the ionization of acetylacetone[31] and for proton transfer between two nitrogen atoms compared with two oxygen atoms.[2,32] However, the intrinsic rate constants are the same for proton transfer between imidazole and other amines and between carboxylic acids and their anions.[33]

The rate constants for proton removal from HCN by a sulfur and carbon base (CN⁻) are over 200- and 1000-fold slower, respectively, and correspond to still larger intrinsic barriers for proton transfer. The order of decreasing reactivity at $\Delta pK = 0$, O > N > S and C, parallels the decreasing electronegativity and hydrogen-bonding ability of these atoms.[11] This suggests that hydrogen bonding stabilizes the transition state, so that loss of this hydrogen-bonding ability increases the intrinsic barrier for proton transfer.[33] The decrease in electronegativity has little or no effect on proton transfers with HCN if only a single atom of low electronegativity is involved, so that one effective hydrogen bond is maintained, but the slow proton transfers from HCN to RS⁻ and CN⁻ suggest that there is a large decrease in rate if both the donor and acceptor atoms have low electronegativity. Proton transfers between two sulfur atoms and between sulfur and nitrogen are slower than those between more electronegative atoms near $\Delta pK = 0$,[33] but the differences are smaller than for HCN. Both CN⁻ and RS⁻ ions have been shown to be less effective than oxygen anions of similar pK_a for the ionization of a ketone.[34] Thiol anions are less effective than oxygen anions, but are similar to nitrogen bases, for the ionization of acetylacetone.[31]

Several diamine dications show positive deviations in their reactions with CN⁻ (Table I, Figure 6), presumably because of a favorable electrostatic effect on the diffusional step of thermodynamically favorable proton transfers.[2,35] There is a corresponding deviation for the thermodynamically unfavorable reactions in the reverse direction, of the monocations with HCN, that may reflect electrostatic stabilization of the ion pair intermediate.

The limiting rate constants for thermodynamically favorable proton transfer to basic amines are significantly smaller than those for transfer to oxygen anions of $pK_a > 9$. There are indications of similar behavior for reactions of thiols with amines.[2] One possible reason for this behavior is that loss of a solvating water molecule that is hydrogen bonded to the amine[8] provides an additional kinetic barrier to proton transfer,[30c] as it does for nucleophilic attack by amines.[33a]

Several carbon acids that require little electron delocalization and desolvation upon ionization, such as acetylenic, sulfonyl, halogen, and cyano activated acids, show behavior close to that expected for normal acids when the proton-transfer step is strongly favorable in one direction.[30,36] However, the rate constants for reaction with buffers of $\sim 10^8$ M⁻¹ s⁻¹ in the thermodynamically favorable direction for disulfones and malononitriles and of $\sim 10^7$ M⁻¹ s⁻¹ at $\Delta pK = 0$ for bromomalononitrile are significantly smaller than those for the corresponding reactions of HCN.[30a–d]

---

(31) Ahrens, V. M.-L.; Eigen, M.; Kruse, W.; Maass, G. *Ber. Bunsenges. Phys. Chem.* **1970**, *74*, 380–385. Bernasconi, C. F.; Bunnell, R. D. *Israel J. Chem.*, in press.

(32) Kresge, A. J.; Powell, M. F. *J. Am. Chem. Soc.* **1981**, *103*, 972–973.

(33) (a) Ahrens, M.-L.; Maass, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 818–819. (b) Jencks, W. P.; Haber, M. T.; Herschlag, D.; Nazaretian, K. L. *J. Am. Chem. Soc.*, in press.

(34) Pohl, E. R.; Hupe, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 8130–8133.

(35) Walters, E. A.; Long, F. A. *J. Am. Chem. Soc.* **1969**, *91*, 3733–3739. Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* **1973**, *95*, 803–806. Chwang, W. K.; Eliason, R.; Kresge, A. J. *J. Am. Chem. Soc.* **1977**, *99*, 805–808.

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

Table II. Comparison of the Observed Rate Constants for Exchange of HCN Protons with Those Calculated Based on the Swain–Grunwald Mechanism

[HClO₄], M	k_{ex},[a] s⁻¹	k_{calcd},[b] s⁻¹
0.14	47	50[c]
1.05	38	7.9
3.58	19	0.23
6.0	13	0.0048
8.0	10	0.000094
9.92	7.2	0.000002

[a] 20 °C. [b] Based on Boyd's H_- acidity function[38] using eq 11 with $k_H = 1 \times 10^{11}$ s⁻¹; $k_{-1}^0 = 4 \times 10^{10}$ M⁻¹ s⁻¹; $K_a^0 = 10^{-9.36}$;[42] viscosity values at 25 °C were obtained from ref 27b. [c] Experiment done at ionic strength 0.24 M. The pK of HCN between ionic strength 0.1 and 1.0 is ~9.0 (ref 28). This value was used here.

Role of the Swain–Grunwald Mechanism. Proton transfer from a number of protonated amines to water occurs through a hydrogen-bonded water molecule according to the Swain–Grunwald mechanism, as shown in Scheme I.[6–8] The experimental evidence for this conclusion is that acids greatly retard the rate of proton exchange between the nitrogen acid and water. For example, the half-time for exchange of a proton between trimethylammonium ion and water increases from 170 ms at pH 2 to 74 h in 54% sulfuric acid;[6] a 6-fold inhibition is seen in 1 M hydrochloric acid.[7] According to the Swain–Grunwald mechanism, the initial products of proton transfer through water are the base, A⁻, which is hydrogen bonded to a water molecule through the proton that has just been transferred, and H_3O^+. When the acid concentration is high enough to reprotonate the amine through the same water molecule $(k_{-1}[H_3O^+])$ before the hydrogen bond to the water molecule is broken (k_H), the original proton is returned to the base and proton exchange with the solvent is inhibited.

Figure 3 shows that there is no significant inhibition of the exchange of HCN protons in the presence of dilute acids and only a small inhibition in the presence of concentrated acids. The observed rate constants for exchange are plotted against the Hammett acidity function H_0. There is only a 20-fold decrease in k_{ex} over a 9-unit change in H_0 and no inhibition of exchange is seen at the concentrations of acid that cause inhibition of reactions that occur through the Swain–Grunwald mechanism.[6,7,37]

The rate equation that describes Scheme I for HCN is given in eq 10. The observed inhibition by acid is less than that calculated for a rate constant for hydrogen bond breaking of $k_H = 10^{12}$ s⁻¹; this value is larger than the rate constant for the dielectric relaxation of water.

$$\frac{rate}{[HCN]} = \frac{k_1 k_H}{k_H + k_{-1}[H^+]} \tag{10}$$

Consideration of the effect of strong acid media on k_1 (cf. eq 14 below; $k_1 = k_a$) and the effect of viscosity on the diffusion-controlled rate constants k_H and k_{-1} yields eq 11, in which K_a is the thermodynamic equilibrium constant for ionization of HCN,

$$\frac{rate}{[HCN]} = \frac{K_a k_{-1}^0 \dfrac{\eta_0}{\eta} \dfrac{[H^+]}{h_-} k_H \dfrac{\eta_0}{\eta}}{k_H \dfrac{\eta_0}{\eta} + k_{-1}^0 \dfrac{\eta_0}{\eta}[H^+]} \tag{11}$$

η/η_0 is the viscosity relative to the viscosity in dilute aqueous solution, k_{-1}^0 is the reverse rate constant in dilute aqueous solution, and h_- is an acidity function for the ionization of a neutral acid.

Table II compares the observed rate constants for the exchange of HCN protons in HClO₄ with those calculated from eq 11 for the Swain–Grunwald mechanism, using the Boyd H_- acidity

---

(37) Acid inhibition could be decreased if protonation of CN⁻ on nitrogen were thermodynamically favorable and diffusion controlled. Such protonation could facilitate exchange by decreasing the rate of reprotonation and return of the original proton to carbon. However, competition between diffusion-controlled N-protonation and C-protonation through k_{-1} (Scheme I) would still give 50% inhibition of exchange, which is not observed.

function for the ionization of carbon acids.[38] There is no indication of the inhibition expected for the Swain–Grunwald mechanism. Indeed, the observed inhibition is *less* than predicted from any known acidity function for a carbon acid. If the observed inhibition were attributed to an unusual acidity function for HCN (see below), an even more unusual acidity function would be required if the Swain–Grunwald mechanism were operative. These results suggest that the ionization of HCN does not occur by proton transfer through water according to the Swain–Grunwald mechanism.

Exchange of HCN Protons in Strong Acid Media. An H_-^{HCN} Acidity Function. Grunwald, Perrin, and their co-workers[39] have pointed out that inhibition of the rate of ionization of an acid is expected in strong acid media because of acidity function effects. If the mechanism of proton exchange from HCN involves the simple ionization of HCN to produce CN^- and H_3O^+ (eq 12), then the large increase in the activity of H_3O^+ in strong acid will

$$HCN \ (+ \ H_2O) \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} CN^- + H_3O^+ \qquad (12)$$

tend to shift the equilibrium to the left. This inhibition of ionization results in a decrease in the concentration quotient Q_a (eq 13). Since k_{-a} is diffusion limited, the decrease in Q_a results in

$$Q_a = \frac{[CN^-][H_3O^+]}{[HCN]} = K_a \frac{[H_3O^+]}{a_{H_3O^+}} \frac{f_{HCN}}{f_{CN^-}} = \frac{k_a}{k_{-a}} \qquad (13)$$

a decrease of k_a.[40] Rearrangement of eq 13, using the definition[26a] of $h_- \equiv a_{H_3O^+}(f_{CN^-}/f_{HCN})$, shows that k_a is expected to decrease in direct proportion to the ratio $[H_3O^+]/h_-$, as shown in eq 14.

$$k_a = k_{-a}K_a \frac{[H_3O^+]}{h_-} \qquad (14)$$

The observed half-time for proton exchange in 10 M $HClO_4$ is 100 ms (Figure 3), which is smaller than the half-time of 2.6 h predicted by eq 14 and the Boyd H_- acidity function for carbon acids by a factor of 10^5. The absence of strong inhibition of the exchange of HCN protons in strong acid solution indicates that some component of proton donation must stabilize the transition state for exchange and offset the inhibition that is expected from the increase in $a_{H_3O^+}$. This proton donation may be partial (hydrogen bonding) or complete (protonation) and it may occur on either the carbon or the nitrogen atom of CN^-.

The simplest explanation for the absence of this strong inhibition by acid is that the ionization of HCN, a weak acid, follows an acidity function that is very different from the Boyd H_- acidity function. Stabilization of CN^- by hydrogen bonding is a molecular description of this acidity function effect. An alternative, but less likely, possibility is that a pathway for acid-catalyzed proton exchange becomes significant in acidic solutions, which compensates for the inhibition and causes little or no net increase in the rate because of activity coefficient effects.

If the first explanation is correct, the observed decrease in the rate constant for proton exchange, $k_a = k_{ex}$, can be used to calculate an H_- acidity function for HCN. Equation 15, in which k_{-a}^0 is the value of k_{-a} in dilute acid solution, shows that the

$$I = \frac{[CN^-]}{[HCN]} = \frac{Q_A}{[H_3O^+]} = \frac{k_a}{k_{-a}[H_3O^+]} = \frac{k_a}{k_{-a}^0 \dfrac{\eta_0}{\eta}[H_3O^+]} \qquad (15)$$

ionization ratio, I, can be calculated from the observed rate constant for exchange. This ionization ratio was used to define

Figure 7. The H_- acidity function for HCN in $HClO_4$ (□), HCl (◇), H_2SO_4 (○), and H_3PO_4 (△). The values were calculated from the rate constant for exchange of HCN protons by using eq 16 and 15. The Hammett H_0 acidity function[26] is shown for comparison.
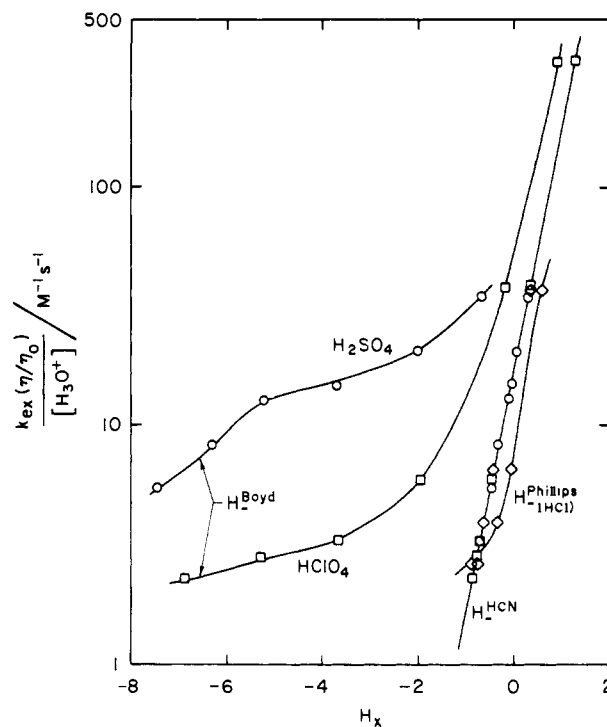
Figure 8. A logarithmic plot of $k_{ex}(\eta/\eta_0)/[H_3O^+]$ against several H_- acidity functions.

the H_- acidity function for HCN according to eq 16, in which pK_a^0 is the thermodynamic pK_a of HCN (9.36 at 20 °C).[41] The

$$H_- = pK_a^0 + \log I \qquad (16)$$

values of the H_- acidity function for HCN in HCl, $HClO_4$, H_2SO_4, and H_3PO_4 are shown graphically in Figure 7 and in tabular form in supplementary Table S2. The value of the Hammett H_0 acidity function is shown for comparison.

(38) Boyd, R. H. *J. Am. Chem. Soc.* **1961**, *83*, 4288–4290. Boyd, R. H. *J. Phys. Chem.* **1963**, *67*, 737–744. Boyd, R. H. *J. Am. Chem. Soc.* **1963**, *85*, 1555–1561.

(39) Perrin, C. L.; Schiraldi, D. A.; Arrhenius, G. M. L. *J. Am. Chem. Soc.* **1982**, *104*, 196–201. Rosenthal, D.; Grunwald, E. *J. Am. Chem. Soc.* **1972**, *94*, 5956–5961.

(40) The value of the diffusion-controlled rate constant k_{-a} is also expected to decrease by the factor η/η_0 because of the increased viscosity of strong acid media.

(41) Perrin, D. D. "Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution", 2nd ed.; Pergamon Press: Oxford, 1982.

Figure 8 shows a logarithmic plot of $k_{ex}(\eta/\eta_0)/[H_3O^+]$ against several H_- acidity functions. The H_-^{HCN} acidity function, by definition, falls on a straight line with slope 1.0. The data are also plotted against Boyd's H_- acidity function[38] based on cyanocarbon acids and the Phillips' H_- acidity function.[42]

The H_- acidity function for HCN is much weaker than Boyd's acidity function[38] based on highly charge-delocalized cyanocarbon acids. It is similar to the H_- acidity function reported by Phillips[42] for the first ionization of a series of phosphorus-containing acid indicators. The rate constant for the addition of cyanide ion to aquocobalamine and cyanocobalamine in the pH range 0–1 is faster than expected from the concentration of H^+.[43,44] This is consistent with an acidity function for HCN similar to H_-^{HCN} or the Phillips H_- function.

The H_- acidity function for HCN and Phillips' H_- acidity function differ greatly from the H_- acidity functions for the 1,3,5-trinitrobenzene phenoxide σ complex[45] (a nitronate ion), picrate,[46] and formate,[47] as well as H_- for cyanocarbon acids.[38] These differences might be explained by localization of charge in the CN^- ion and in the phosphate and phosphonate oxyanions compared with the highly delocalized cyanocarbon, nitronate, and picrate ions.[45] However, the difference between formate and phosphate oxyanions is difficult to explain. These differences indicate that the activity coefficient ratio, f_{A^-}/f_{HA}, cannot be assumed to be invariant at a given solvent composition for the protonation of anions with even slightly different structures.[45]

The weak acidity functions observed for HCN and for phosphates and phosphonates indicate that there is a large stabilization of the anion in strong acid media (a decrease in f_{CN^-}) that counterbalances the large destabilization of H_3O^+ (an increase in $f_{H_3O^+}$). The stabilization of sulfate ion in sulfuric acid solutions provides a precedent for the stabilization of anions in strong acid media. There is approximately 20% sulfate ion present in sulfuric acid solutions ($[SO_4^{2-}]/[H_2SO_4]_t \sim 0.2$) over the range 1–11 M H_2SO_4.[48] Since the activity of H_3O^+ increases by $>10^8$ over this range,[49] SO_4^{2-} must be stabilized relative to HSO_4^- by a similar amount in order to maintain the approximately constant fraction of ionized sulfate. This stabilization may result from the formation of an ion pair, $SO_4^{2-} \cdot H_3O^+$.[48] Similarly, the stabilization of CN^- could result from a $CN^- \cdot H_3O^+$ ion pair. The CN^- ion is $\sim 10^8$ more basic than SO_4^{2-}, but carbanions generally form comparatively weak hydrogen bonds. However, the CN^- ion is believed to have a dipole moment with negative charge on the electronegative nitrogen atom[50] and the ion pair with H_3O^+ may represent attachment to the nitrogen rather than the carbon atom of CN^-.

The CN^- ion has a high charge density because its charge is localized on only two atoms. This is consistent with a strong interaction of CN^- with H_3O^+ and with the hydroxyl group of water, as indicated by the following: (a) The enthalpy of hydration of CN^- is large,[50] -78.1 kcal mol^{-1}. (b) The solvent effect on $\Delta G°$ for proton removal from toluene by CN^-, $\Delta G°(g) - \Delta G°(aq)$, is similar to that for oxyanions of similar basicity, such as phenolate

ion.[51]   (c) The pK_a of HCN is 3.7 units larger in Me_2SO than in water;[52] in contrast, the pK_a of malononitrile is 0.3 units smaller in Me_2SO.[53]   (d) The rate constant for nucleophilic attack of CN^- on a disulfide is increased 100-fold in Me_2SO compared with water, whereas the rate constant for attack of the anion of malononitrile is increased only 3-fold.[54]   (e) The solvent deuterium isotope effect on the ionization of HCN suggests that there is a solvent isotope effect on the stability of CN^-, similar to that on the stability of RO^- and HO^-, which arises from strong solvation of the anion (see below).

Effects of Concentrated Salts. The inhibition of proton exchange by several concentrated salt solutions is *larger* than inhibition by the corresponding acids (Figure 5); similar inhibition is observed at pH 2 and in 4.8 M $HClO_4$. This is also consistent with the hypothesis that acids facilitate proton exchange by stabilizing the CN^- ion.

We do not understand the mechanism of this inhibition by salts. It is generally similar to the decrease in the rate of proton transfer between water molecules in concentrated salt solutions, as measured by ^{17}O NMR,[55] although the effect of 8 M $NaClO_4$ is somewhat larger. A similar proton-transfer step may be required for proton exchange from HCN (eq 6). This inhibition has been discussed in terms of salt-induced changes in "water structure". Roberts has observed a different shape of the curves with increasing salt concentration for inhibition of proton conductance, determined by a polarographic method, and has suggested that ions suppress proton transfer through the Grotthuss mechanism by polarizing hydrogen bonds.[56]   Huppert et al. have observed a larger inhibition of the rate of proton transfer to water from an acid in the excited state by concentrated salt solutions and have suggested that this arises from a decreased availability of the several water molecules that accept the proton; there is a linear correlation of log k with log a_{H_2O} for three salt solutions.[57]   The slope of such a correlation for the inhibition of HCN exchange by $NaClO_4$ is ca. -9.[58]   The much larger inhibition by salts compared with acids is apparent from a comparison of the amount of inhibition at the same value of $a_{H_2O} = 0.8$:[58] the rate constant for exchange, k_{ex}, in $NaClO_4$ is 20% of that in $HClO_4$ and in NaCl it is 32% of that in HCl.

Sodium sulfate causes a significant *increase* in the rate of proton exchange from HCN (Figure 5) and the inhibition of exchange by sulfuric acid is smaller than that with other acids (Figure 3); the viscosity-corrected rate constants actually show an increase with increasing H_2SO_4 concentration up to 8 M (Figure 4). These results may be explained by base catalysis by the SO_4^{2-} ion. The Brønsted plot for general base catalysis (Figure 6) predicts a value of $k_a = 16$ M^{-1} s^{-1} for SO_4^{2-}, based on a pK_a of 1.1 for HSO_4^-.[59] This is similar to the observed value of $k_a = 19$ M^{-1} s^{-1} for Na_2SO_4; correction for viscosity[60] gives $k_a = 51$ M^{-1} s^{-1}.

The solid line through the H_2SO_4 data in Figure 4 shows the amount of catalysis predicted from the concentration of SO_4^{2-} in sulfuric acid solution determined by Raman spectroscopy[48] and a rate constant for catalysis by sulfate, $k_{SO_4^{2-}}$, of 35 M^{-1} s^{-1}. It is possible that the increase in the viscosity-corrected rate constants for exchange of HCN protons in phosphoric acid solutions (Figure 4) arises from analogous catalysis by phosphate; however, we have

(42) Phillips, J. N. *Aus. J. Chem.* **1961**, *14*, 183–189.

(43) Reenstra, W. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 5780–5791.

(44) However, the inhibition of the CN^- mediated cleavage of carbon–cobalt bonds at acid concentrations from 1 to 4 M HCl[29] does not follow the Phillips H_- acidity function. The reason for this behavior is not known. The inhibition may be caused by a difference in the acidity function for specific acid catalysis of carbon–cobalt cleavage and for the loss of a proton from HCN, or by protonation of $MCMB_{12}H^+$ that gives little or no change in its spectrum.[29]

(45) Buncel, E.; Eggimann, W. *Can. J. Chem.* **1976**, *54*, 2436–2444.

(46) Buncel, E.; Jonczyk, A.; Webb, J. G. K. *Can. J. Chem.* **1975**, *53*, 3761–3767.

(47) Cox, B. G.; McTigue, P. T. *J. Chem. Soc.* **1964**, 3893–3896.

(48) (a) Young, T. F.; Maranville, L. F.; Smith, H. M. In "The Structure of Electrolytic Solutions"; Hamer, W. J., Ed.; John Wiley and Sons: New York, 1959; pp 35–63. (b) Chen, H.; Irish, D. E. *J. Phys. Chem.* **1971**, *75*, 2672–2681. (c) See also: Malinowski, E. R.; Cox, R. A.; Haldna, U. L. *Anal. Chem.* **1984**, *56*, 778–781.

(49) Yates, K.; McClelland, R. A. *Prog. Phys. Org. Chem.* **1974**, *11*, 323–420. See p 370.

(50) Payzant, J. D.; Yamdagni, R.; Kebarle, P. *Can. J. Chem.* **1971**, *49*, 3308–3314.

(51) Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247–350.

(52) Ritchie, C. D.; VanVerth, J. E.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1982**, *104*, 3491–3497.

(53) Bordwell, F. G.; Bartmess, J. E.; Hautala, J. A. *J. Org. Chem.* **1978**, *43*, 3095–3101.

(54) Gilbert, H. F. *J. Am. Chem. Soc.* **1980**, *102*, 7059–7065.

(55) Hertz, H. G.; Versmold, H.; Yoon, C. *Ber. Bunsenges. Phys. Chem.* **1983**, *87*, 577–582.

(56) Roberts, N. K.; Northey, H. L. *J. Chem. Soc., Faraday Trans. 1* **1974**, *70*, 253–262. Roberts, N. K. *J. Phys. Chem.* **1976**, *80*, 1117–1120.

(57) Huppert, D.; Kolodney, E.; Gutman, M.; Nachliel, E. *J. Am. Chem. Soc.* **1982**, *104*, 6949–6953.

(58) Robinson, R. A.; Stokes, R. H. "Electrolyte Solutions"; Academic Press: New York, 1955; pp 28, 461, 468.

(59) This pK_a is for ionic strength 1.0 M. Reference 28, p 79.

(60) For viscosity at 25 °C, see: Stokes, R. H.; Mills, R. "Viscosity of Electrolytes and Related Properties"; Pergamon Press: New York, 1965; p 123.

Is HCN a Normal Acid?

*J. Am. Chem. Soc., Vol. 107, No. 24, 1985* 7125

no information on the concentration of different phosphate species in phosphoric acid solutions.

Acid-Catalyzed Exchange. Alternatively, the absence of strong inhibition of the exchange of HCN protons in acid could be accounted for by a direct role of acid in the chemistry of proton exchange, rather than by a stabilization of CN^-. The absence of an increase in the rate of exchange in acid would then arise from incomplete cancellation of activity coefficient effects, rather than from a large decrease in the activity coefficient of CN^- in strong acid.

One such mechanism for acid-catalyzed exchange involves electrophilic displacement at carbon with a transition state in which the leaving and entering protons interact weakly with CN^-, as shown in **1**. However, the strong inhibition by acid of exchange

1
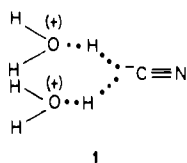
of protonated amines[6,7] suggests that this mechanism is unlikely. A second possibility is an isomerization mechanism with protonation on nitrogen, as shown in eq 17. Both mechanisms require a fortuitous matching of the rate constants for the pH-independent

(17)
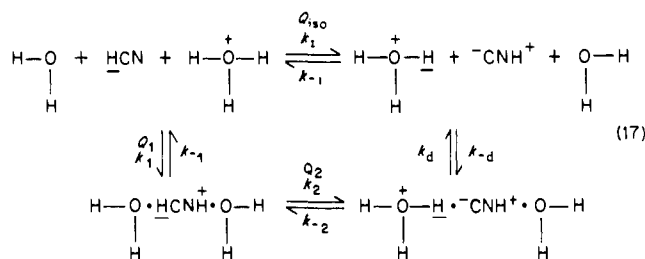
and acid-catalyzed pathways such that there is little change in the observed rate constants with increasing acidity. The rate and equilibrium constants that are required for the isomerization mechanism are close to the limits of expected values but do not exclude it.

One set of equilibrium constants for the scheme of eq 17 that will account for a value of $k_{ex}' = 10 \text{ s}^{-1}$ in the presence of 1 M acid is $Q_{iso} = 10^{-7}$, $pK_{NH} = \log Q_1 = -9$, and $pK_{CH} = -\log (Q_2 k_d/k_{-d}) = -2$. The value of Q_{iso} is larger than calculated and experimental values of $Q_{iso} = 10^{-8}$–10^{-13} in the gas phase,[61] but more favorable values would be expected in aqueous solution.[62] The value of pK_{NH} is higher than an estimated value of $pK_a \sim -10.2$ for protonated acetonitrile, based on the observation of half-protonation in 99.6% H_2SO_4 and an acidity function for protonated nitrobenzenes.[63] However, $HCNH^+$ is likely to follow a different acidity function and the protonation of HCN by H_3O^+ is thermodynamically favorable in the gas phase.[64] These equilibrium constants give rate constants of 10^2, 10, and 10^3 s^{-1} for the three steps of the reaction, k_1, $k_2 Q_1$, and $Q_1 Q_2 k_d$, respectively, assuming values of $k_{-1} = 10^{11} \text{ s}^{-1}$, $k_2 = 10^{10} \text{ s}^{-1}$, and $k_{-d} = 10^{10} \text{ M}^{-1} \text{ s}^{-1}$. The increase in k_{ex}' could compensate for the decrease in k_{ex} (for proton transfer to water) with increasing acid concentration.

As the acid concentration increases further the solvated proton becomes a stronger acid and k_{-2} may exceed k_d. The diffusional separation step, k_d, then becomes rate limiting and the rate law

(61) Pau, C.-F.; Hehre, W. J. *J. Phys. Chem.* **1982**, *86*, 321–322 and references therein.

(62) Isocyanides form stronger hydrogen bonds than nitriles[22] and the acidic proton of $^-CNH^+$ would be expected to hydrogen bond strongly in water.

(63) Hantzsch, A. *Z. Phys. Chem.* **1909**, *65*, 41–60. Liler, M.; Kosanović, D. *J. Chem. Soc.* **1958**, 1084–1090. Deno, N. C.; Gaugler, R. W.; Wisotsky, M. J. *J. Org. Chem.* **1966**, *31*, 1967–1968. Reference 22b, p 126.

(64) Tanaka, K.; Mackay, G. I.; Bohme, D. K. *Can. J. Chem.* **1978**, *56*, 193–204.

Scheme II

$$\underline{AH} \cdot OH \cdot OH \rightleftharpoons A^- + \underline{HO} \cdot H_3O^+$$

for the acid-catalyzed isomerization is given by eq 18, in which Q_{iso} is the concentration ratio $[^-CNH^+]/[HCN]$ and K_{iso} is the

$$k_{ex}' = \frac{\text{rate}}{[HCN]} = k_d Q_1 Q_2 \frac{k_{-d}}{k_{-d}} [H_3O^+] = k_{-d} Q_{iso} [H_3O^+] =$$

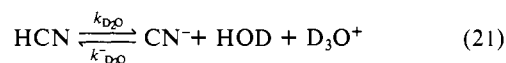$$k_{-d} K_{iso} \frac{f_{HCN}}{f_{-CNH^+}} [H_3O^+] \quad (18)$$

corresponding thermodynamic equilibrium constant for isomerization. This rate law shows that the observed rate constant for exchange is proportional only to the concentration of acid, $[H_3O^+]$, and an activity coefficient ratio. The rate constant would not increase if the increased concentration of acid were offset by a comparatively small decrease in the activity coefficient ratio f_{HCN}/f_{-CNH^+}. This could occur if there is an increase in f_{-CNH^+} relative to f_{HCN}, because destabilization of the $^-CNH^+ \cdot OH_2$ hydrogen bond is more important than stabilization of the $H_2OH^+ \cdot ^-CNH^+$ hydrogen bond[22] with increasing acid concentration.

Solvent Isotope Effects. It is important to distinguish carefully between the Swain–Grunwald mechanism, which involves a hydrogen-bonded $NC^- \cdot HOH$ intermediate, and other mechanisms that involve proton transfer through water bridges. For the Swain–Grunwald mechanism, the rate-limiting step in dilute acid involves the diffusion together/apart of an $NC^- \cdot HOH$ kinetic unit and the protonating species (Scheme I). An alternative mechanism involves the rate-limiting diffusion together/apart of CN^- and an $H_3O^+(H_2O)_x$ kinetic unit (Scheme II). The faster protonation of CN^- by H_3O^+ than by buffer acids (Figure 6) may be explained by the ability of H_3O^+ to utilize facilitated diffusion. Even though diffusion is facilitated by proton transfer through water bridges, the protonation of CN^- may or may not occur "through a water molecule". If it does, this water molecule must be part of the kinetic unit of the protonating species $H_3O^+(H_2O)_x$ and not of the CN^- ion, because the absence of inhibition by dilute acids is inconsistent with any mechanism involving proton transfer through a water molecule that is part of the CN^- kinetic unit.

The solvent isotope effect for proton exchange can, in principle, determine if any water bridges are involved regardless of the kinetic unit to which the water belongs.[65] Unfortunately, the observed solvent isotope effect of $k_{H_2O}/k_{D_2O} = 4.5$ does not permit a decision as to which mechanism is correct for HCN exchange, because of uncertainty in the calculated values for the two mechanisms. Equations 19 and 21 describe the direct transfer mechanism in D_2O to give HOD_2^+ and transfer through solvent to give D_3O^+,

$$HCN \underset{k^-_{D_2O}}{\overset{k_{D_2O}}{\rightleftharpoons}} CN^- + HOD_2^+ \quad (19)$$
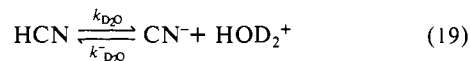
$$\frac{k_{H_2O}}{k_{D_2O}} = \frac{K_{H_2O} k^-_{H_2O}}{K_{D_2O} k^-_{D_2O}} = \frac{\phi_{HCN}}{\phi_{CN^-} l^2} \frac{\eta_{D_2O}}{\eta_{H_2O}} \quad (20)$$

$$HCN \underset{k^-_{D_2O}}{\overset{k_{D_2O}}{\rightleftharpoons}} CN^- + HOD + D_3O^+ \quad (21)$$

$$\frac{k_{H_2O}}{k_{D_2O}} = \frac{K_{H_2O} k^-_{H_2O}}{K_{D_2O} k^-_{D_2O}} = \frac{\phi_{HCN}}{\phi_{CN^-} l^3} \frac{\eta_{D_2O}}{\eta_{H_2O}} \quad (22)$$

respectively. Following Fong and Grunwald,[65] the solvent isotope effects for the two mechanisms are given by eq 20 and 22, in which ϕ_{HCN}, ϕ_{CN^-}, and $l = 0.69$ are the fractionation factors for HCN, CN^-, and H^+, respectively,[66] and $\eta_{D_2O}/\eta_{H_2O} = 1.3$ is the solvent isotope effect on viscosity.[67] We assume that there is no solvent

(65) Fong, D.-W.; Grunwald, E. *J. Am. Chem. Soc.* **1969**, *91*, 2413–2422.

(66) Albery, J. In "Proton-Transfer Reactions"; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; pp 263–315.

(67) Lankhorst, D.; Schriever, J.; Leyte, J. C. *Ber. Bunsenges. Phys. Chem.* **1982**, *86*, 215–221.

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.

---

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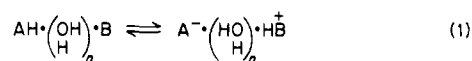
Direct Proton Transfer between HCN and Nitrogen and Oxygen Bases[1]

Rodney A. Bednar† and **William P. Jencks***

Contribution No. 1570 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254. Received February 19, 1985

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).

$$AH\cdot\left(\!\!\begin{array}{c}OH\\ \\ H\end{array}\!\!\right)_{\!n}\!\!\cdot B \;\rightleftharpoons\; A^-\cdot\left(\!\!\begin{array}{c}HO\\ \\ H\end{array}\!\!\right)_{\!n}\!\!\cdot \overset{+}{H}B \qquad (1)$$

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

---

† Present address: Department of Pharmacological Sciences, SUNY at Stony Brook, Stony Brook, New York 11794-8651.

(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) 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.