

Experimental and Computational Determination of the Effect of the Cyano Group on Carbon Acidity in Water

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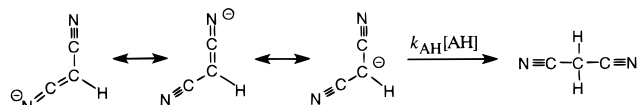
Abstract: Rate constants k_{DO} ($\text{M}^{-1} \text{s}^{-1}$) for the deprotonation of cyanoalkanes by deuterioxide ion in D_2O at 25 °C were determined by following the appearance of the deuterium-labeled cyanoalkanes by ^1H NMR. These data were evaluated to give the following $\text{p}K_{\text{a}}$'s in water: CH_3CN , 28.9; $\text{CH}_3\text{CH}_2\text{CN}$, 30.9; $\text{NCCH}_2\text{-CH}_2\text{CN}$, 26.6. High level ab initio calculations on cyanoalkanes and α -cyano carbanions and combined QM/Monte Carlo calculations of their free energies of solvation were carried out. The interaction between a carbanionic center and an α -cyano substituent is concluded to be largely polar. The 5.1-fold difference in α -cyano and β -cyano substituent effects on carbon acidity in water which, nominally, is consistent with significant resonance stabilization of α -cyano carbanions is attributed to the differential solvation of cyanoalkanes and cyanocarbanions. The free energy change for the highly unfavorable tautomerization of acetonitrile to ketenimine in water was computed as $\Delta G_{\text{T}} = 30.7$ kcal/mol. We propose that the large instability of the ketenimine cumulative double bond favors the valence bond resonance form of the α -cyanocarbanion in which there is a formal carbon–nitrogen triple bond and the negative charge is localized at the α -carbon.

Introduction

We would like to understand why there are chemical barriers for many strongly thermodynamically favorable reactions of unstable carbocations and carbanions in solution and how these activation barriers change with changing thermodynamic driving force for the reaction.¹ The observation of a relatively large Marcus intrinsic rate constant of $10^7 \text{ M}^{-1} \text{ s}^{-1}$ ^{2a} for thermoneutral protonation of the dicyanomethyl carbanion by secondary ammonium cations has been interpreted as reflecting only a small transfer of negative charge from the α -carbon to the cyano substituents (Scheme 1).^{3,4} This is reasonable because there is good evidence that the intrinsic barriers to the protonation of carbanions^{2,5} and to nucleophilic additions to carbocations^{1,2b} increase with increasing stabilization of charge resulting from its transfer to neighboring substituents. By contrast, a recent comparison of Hirshfeld atomic charges at acetonitrile and the cyanomethyl carbanion shows that deprotonation of acetonitrile results in a ca. 0.4 unit increase in negative charge at the cyano group⁶ and that there should be an even larger transfer of negative charge to the *two* cyano groups of the dicyanomethyl carbanion.

The results of these experiments and calculations raise interesting questions about the relationship between the extent of transfer of charge to the α -cyano substituents at α -cyano carbanions, the stabilization which results from this transfer of negative charge, and the activation barrier to the protonation

Scheme 1



of α -cyano carbanions. For example, the negative charge at acetate ion is delocalized over two oxygen atoms, but this delocalization provides only a small stabilization of the hypothetical charge-localized anion.⁷ By analogy, it is interesting to consider the possibility that the small Marcus intrinsic barrier for protonation of the delocalized dicyanomethyl carbanion reflects a relatively small resonance stabilization resulting from the transfer of negative charge to nitrogen, and the corresponding small barrier to the relocalization of this charge at carbon on moving to the transition state for proton transfer ($k_{\text{AH}}[\text{AH}]$, Scheme 1).^{8–10}

The development of models to rationalize the magnitude of the interaction between the cyano group and a neighboring carbanion requires accurate values of the $\text{p}K_{\text{a}}$'s for ionization of simple cyanoalkanes in water. The widely cited $\text{p}K_{\text{a}}$ of 25 for acetonitrile is based on a long extrapolation of a rate–equilibrium relationship for the ionization of relatively strong carbon acids.¹¹ This value is almost certainly too low, since a better documented value of $\text{p}K_{\text{a}} = 26.7$ has been estimated for $\text{PhSCH}_2\text{CH}_2\text{CN}$,¹² and there is good evidence that, in ethanol, the addition of a β -thiophenyl substituent results in an increase

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in cyanoalkane acidity.¹³ The results of ab initio calculations give $pK_a = 28.6$ for acetonitrile in water,^{14,15} and $pK_a = 31$ has been determined for acetonitrile in dimethyl sulfoxide.¹⁶

We have shown that ¹H NMR spectroscopy is an effective analytical method to monitor the base-catalyzed exchange for deuterium of the α -carbonyl protons of thiol and oxygen esters.^{17–19} We report here second-order rate constants for the lyoxide-ion-catalyzed exchange of the α -hydrogens of several simple cyanoalkanes, along with evidence that the protonation of simple α -cyano carbanions by solvent water is limited by the rate of rotation of a molecule of water into a reactive configuration. The pK_a 's for these α -cyano carbon acids have been calculated from the experimental rate constants for α -cyano carbanion formation and the estimated rate constant of 10^{11} s^{-1} for the reverse protonation of the carbanions, which is limited by reorganization of the solvent, with $k_{\text{reorg}} \approx 10^{11} \text{ s}^{-1}$.^{20–22} We also report the results of calculations of the following: (1) The proton affinities of simple cyanocarbanions in the gas phase.²³ (2) The relative free energies of transfer of simple cyanoalkanes and cyanocarbanions from the gas phase to water and their use in an analysis of solvent effects on the relative basicity of α -cyano and β -cyano carbanions. (3) The free energy of tautomerization of acetonitrile to ketenimine in water.

Experimental Section

Materials. Propanenitrile, succinonitrile, quinuclidine hydrochloride, 3-quinuclidinol, deuterium chloride (37 wt %, 99.5% D), and potassium deuterioxide (40 wt %, 98+% D) were purchased from Aldrich. D₂O (99.9% D) and CD₃CN (99.8% D) were purchased from Cambridge Isotope Laboratories. Acetonitrile and methanol (HPLC grade) and standard solutions of potassium hydroxide were purchased from Fisher. Quinuclidine hydrochloride was recrystallized from ethanol, and 3-quinuclidinol was recrystallized from acetone. All other chemicals were reagent grade and were used without further purification. [*d*₄]-Succinonitrile (NCCD₂CD₂CN) was prepared by the reaction of NCCH₂-CH₂CN (0.25 g) in 0.10 M KOD in D₂O (5 mL) for 4 h at room temperature. The product (0.1 g, 99% D) was isolated by extraction into chloroform.

¹H NMR Spectroscopy. ¹H NMR spectra at 400 and 500 MHz were recorded at 25 °C on Varian Unity Inova 400 and 500 NMR spectrometers, respectively. The relaxation times for all of the exchangeable protons of the cyanoalkanes studied in this work were determined to be in the range $T_1 = 4\text{--}6 \text{ s}$. In all cases the relaxation delay between pulses was at least 10-fold longer than the longest T_1 of the protons of the compound under examination. Chemical shifts were referenced to the solvents CHCl₃ and HOD at 7.24 and 4.67 ppm, respectively. In many cases, the baseline of the NMR spectrum was subjected to a first-order drift correction before integration. The methylene protons of CH₃CH₂CN and CH₃CHDCN were subject to

inverse gated homonuclear decoupling by irradiation of the methyl protons during data acquisition (5 s). There should be no nuclear Overhauser effect on the signal for the methylene protons when the methyl protons are irradiated only during the acquisition of spectral data.²⁴

Deuterium and Hydrogen Exchange Reactions. The methods used for preparation of solutions is described in the Supporting Information. The pDs of buffered solutions were determined by adding 0.40 to the reading of a pH meter standardized in H₂O.²⁵ The details of the procedures used to monitor the following isotope exchange reactions are given in the Supporting Information: exchange reactions of CH₃-CN in D₂O, exchange reactions of CD₃CN in H₂O, exchange reactions of CH₃CH₂CN in D₂O, exchange reactions of NCCCH₂CH₂CN in D₂O, exchange reactions of NCCD₂CD₂CN in H₂O.

Calculations. The procedures for ab initio calculations are described in the Supporting Information. Statistical mechanical Monte Carlo simulations were carried out to evaluate the differences in the free energies of solvation of the cyanoalkanes and of the cyanocarbanions in water. In these computations, we employ a combined quantum mechanical and molecular mechanical (QM/MM) potential that has been developed at Buffalo for the treatment of solute and solvent interactions.²⁶ Specifically, the solute molecules are represented by the semiempirical Austin model 1 (AM1)²⁷ method and the solvent molecules are described by the three-point charge potential (TIP3P) developed by Jorgensen.²⁸ The method has been shown to provide reliable calculations of the free energies of solvation of a wide range of organic molecules.^{29–32} The details of these simulations are described in the Supporting Information.

Results

The hydron exchange reactions of the simple cyanoalkanes examined in this work are much faster than hydrolysis of these nitriles to the corresponding carboxylate ions. For example, no hydrolysis products were detected by ¹H NMR spectroscopy during the course of quantitative exchange for deuterium of the α -hydrogens of succinonitrile in alkaline D₂O, followed by the quantitative re-exchange for hydrogen of the α -deuteriums of the product [*d*₄]-succinonitrile in alkaline H₂O. Similarly, there was no detectable hydrolysis of the nitrile groups of acetonitrile or propanenitrile during their base-catalyzed deuterium exchange reactions in D₂O.

The exchange for deuterium of the first α -hydrogen of CH₃-CN in D₂O (Scheme 2, X = H) was followed by monitoring the disappearance of the α -CH₃ group of the substrate and the appearance of the α -CH₂D group of the product by ¹H NMR spectroscopy at 400 MHz. Representative ¹H NMR spectra of recovered acetonitrile obtained during exchange of 24% of the first α -hydrogen for deuterium in the presence of deuterioxide ion in D₂O at 25 °C and $I = 1.0$ (KCl) are shown in Figure S1A of the Supporting Information. Exchange leads to the disappearance of the singlet at 1.983 ppm due to the α -CH₃ group of acetonitrile and the appearance of an upfield triplet at 1.972 ppm due to the α -CH₂D group of monodeuterated

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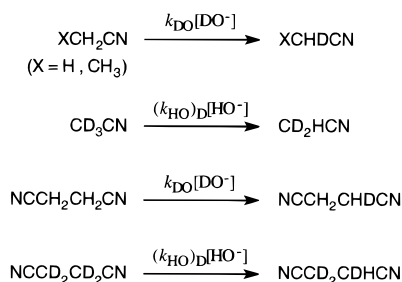
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Scheme 2



acetonitrile, in which the remaining α -protons are coupled to the α -deuterium ($J_{\text{HD}} = 2.4$ Hz). The progress, R , of deuterium exchange was determined from the integrated areas of the singlet due to the α -CH₃ group of CH₃CN (A_{CH_3}) and of the triplet due to the α -CH₂D group of the monodeuterio product ($A_{\text{CH}_2\text{D}}$), according to eq 1. It was only possible to obtain baseline

$$R = \frac{A_{\text{CH}_3}}{A_{\text{CH}_3} + \frac{A_{\text{CH}_2\text{D}}}{2}} \quad (1)$$

separation of the last of the three peaks for the triplet due to the α -CH₂D group of CH₂DCN. Therefore, the integrated area of this triplet ($A_{\text{CH}_2\text{D}}$) was calculated by multiplying the integrated area of only the most upfield of the three peaks by three, and the integrated area of the singlet due to the α -CH₃ group of CH₃CN (A_{CH_3}) was calculated as the difference between the total integrated area of all the signals and that calculated for the triplet.¹⁸ Semilogarithmic plots of reaction progress R against time were linear during exchange of up to 30% of the first α -hydrogen of CH₃CN (Figure S2 of the Supporting Information). The negative slope of these plots is $k_{\text{ex}} = k_{\text{obsd}}/3$, where k_{obsd} (s^{-1}) is the observed first-order rate constant for exchange of the first α -hydrogen of acetonitrile catalyzed by deuterioxide ion (Scheme 2).^{33,34}

Figure 1A (●) shows the dependence of k_{obsd} for exchange of the first α -hydrogen of acetonitrile on the concentration of deuterioxide ion in D₂O at 25 °C and $I = 1.0$ (KCl). The slope of this correlation is the second-order rate constant for exchange of the first α -hydrogen of CH₃CN catalyzed by deuterioxide ion, $k_{\text{DO}} = 2.7 \pm 0.4 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ (Table 1, error calculated at the 80% confidence limit).

Figure S9 of the Supporting Information shows that k_{obsd} for exchange of the first α -hydrogen of CH₃CN does not depend on the concentration of quinuclidine buffer (Figure S9A, $[\text{B}]/[\text{BD}^+] = 1.0$, pD = 12.2) or 3-quinuclidinol buffer (Figure S9B, $[\text{B}]/[\text{BD}^+] = 1.0$, pD = 10.8) in D₂O at 25 °C and $I = 1.0$ (KCl). The inset to Figure S9B is a logarithmic plot of k_{obsd} against $[\text{DO}]$, which includes the data from Figure 1A and those for the reaction in the presence of quinuclidine and 3-quinuclidinol buffers. The solid line of unit slope through the data was calculated from the rate law $k_{\text{obsd}} = k_{\text{DO}}[\text{DO}^-]$, using $k_{\text{DO}} = 2.7 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ (see above).

The exchange for hydrogen of the first α -deuterium of CD₃-CN in H₂O at 25 °C and $I = 1.0$ (KCl) (Scheme 2) was followed by monitoring the appearance of the α -CD₂H group of the product by ¹H NMR spectroscopy at 400 MHz, using CH₃CN as an internal standard. Exchange leads to appearance of a pentet at 1.960 ppm ($J_{\text{HD}} = 2.4$ Hz) due to the α -CD₂H group of the

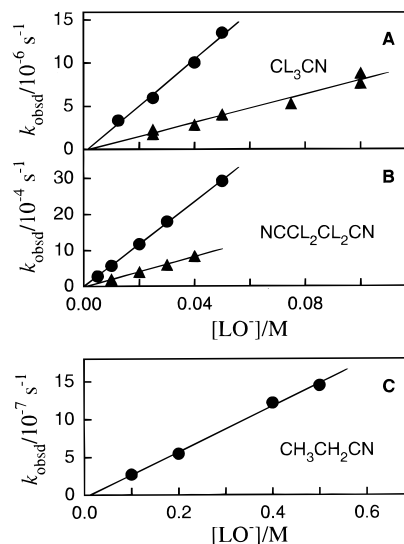


Figure 1. The dependence of k_{obsd} (s^{-1}) for exchange of the first α -hydrogen of simple cyanoalkanes on the concentration of lyoxide ion in water at 25 °C and $I = 1.0$ (KCl). (A) hydron exchange reactions of CL₃CN. Key: (●) reaction of CH₃CN in D₂O; (▲) reaction of CD₃CN in H₂O. (B) hydron exchange reactions of NCCL₂CL₂CN. Key: (●) reaction of NCCH₂CH₂CN in D₂O; (▲) reaction of NCCD₂CD₂CN in H₂O. (C) Hydron exchange reaction of CH₃CH₂CN in D₂O.

product, which is shifted upfield from the singlet at 1.983 ppm due to CH₃CN present as an internal standard (Figure S1B of the Supporting Information). The progress, f_{CD_3} , of hydrogen exchange was determined from the integrated areas of the signals due to the CH₃CN standard (A_{CH_3}) and the α -CD₂H group of the product ($A_{\text{CD}_2\text{H}}$) according to eq 2, where $[\text{CD}_3\text{CN}]/[\text{CH}_3$ -

$$f_{\text{CD}_3} = \frac{10.3A_{\text{CH}_3} - 3A_{\text{CD}_2\text{H}}}{10.3A_{\text{CH}_3}} \quad (2)$$

CN] = 10.3 is the ratio of the concentrations of the CD₃CN substrate and the CH₃CN standard present at zero time. Semilogarithmic plots of reaction progress f_{CD_3} against time were linear during exchange of up to 5% of the first α -deuterium of CD₃CN (Figure S3 of the Supporting Information). The negative slope of these plots is k_{obsd} (s^{-1}), the observed first-order rate constant for exchange of the first α -deuterium of CD₃CN catalyzed by hydroxide ion (Scheme 2). The values of k_{obsd} determined in different experiments at the same concentration of hydroxide ion were reproducible to $\pm 10\%$. Figure 1A (▲) shows the dependence of k_{obsd} for exchange of the first α -deuterium of CD₃CN on the concentration of hydroxide ion in H₂O at 25 °C and $I = 1.0$ (KCl). The slope of this correlation is the second-order rate constant for exchange of the first α -deuterium of CD₃CN catalyzed by hydroxide ion, $(k_{\text{HO}})_\text{D} = 8.2 \pm 1.0 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ (Table 1, error calculated at the 80% confidence limit).

Figure S4 of the Supporting Information shows representative ¹H NMR spectra at 500 MHz in the methylene region of recovered propanenitrile obtained during exchange of 16% of the first α -hydrogen for deuterium in the presence of deuterioxide ion in D₂O at 25 °C and $I = 1.0$ (KCl) (Scheme 2, X = CH₃). In these spectra, couplings between the methylene protons of CH₃CH₂CN and CH₃CHDCN and the protons of the methyl groups were eliminated using an inverse gated decoupling procedure (see Experimental Section). The deuterium-exchange reaction leads to disappearance of the singlet at 2.363 ppm due to the α -CH₂ group of propanenitrile and appearance of an

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Table 1. Rate and Equilibrium Constants for Ionization of Simple α -Cyano Carbon Acids (Cyanoalkanes) in Water at 25 °C and $I = 1.0$ (KCl)

carbon acid	k_{DO}^a ($\text{M}^{-1} \text{s}^{-1}$)	k_{HO}^b ($\text{M}^{-1} \text{s}^{-1}$)	k_{HOH}^c (s^{-1})	$\text{p}K_{\text{a}}^d$	$\text{p}K_{\text{a}} + \log p^e$
CH ₃ CN	$2.7 \pm 0.4 \times 10^{-4 f}$	$1.1 \times 10^{-4 h}$	1×10^{11}	28.9	29.4
CD ₃ CN		$8.2 \pm 1.0 \times 10^{-5 ij}$			
CH ₃ CH ₂ CN	$3.0 \pm 0.2 \times 10^{-6 f}$	$1.25 \times 10^{-6 h}$	1×10^{11}	30.9	31.2
NCCH ₂ CH ₂ CN	$6.0 \pm 0.2 \times 10^{-2 g}$	$2.5 \times 10^{-2 h}$	1×10^{11}	26.6	27.2
NCCD ₂ CD ₂ CN		$2.1 \pm 0.2 \times 10^{-2 ik}$			

^a Second-order rate constant deprotonation of the carbon acid by deuterioxide ion in D₂O determined as the slope of a plot of k_{obsd} (s^{-1}) for exchange of the first α -hydrogen for deuterium against the concentration of deuterioxide ion (Figure 1). The error was calculated at the 80% confidence limit. ^b Second-order rate constant for deprotonation of the carbon acid by hydroxide ion in H₂O. ^c First-order rate constant for protonation of the cyanocarbanion by solvent water, estimated as $k_{\text{HOH}} = k_{\text{reorg}} \approx 10^{11} \text{ s}^{-1}$, where k_{reorg} is the rate constant for reorganization of solvent by dielectric relaxation (see text). ^d Acidity of the carbon acid in water, calculated according to eq 6 of the text. ^e Acidity of the carbon acid statistically corrected for the number of acidic protons, p . ^f Determined by following exchange of up to 30% of the first α -hydrogen for deuterium catalyzed by deuterioxide ion in D₂O. ^g Determined by following exchange of up to 70% of all four α -hydrogens for deuterium catalyzed by deuterioxide ion in D₂O. ^h Calculated from the value of k_{DO} using the relationship $k_{\text{HO}} = k_{\text{DO}}/2.4$, where 2.4 is the maximum secondary solvent isotope effect on the reactivity of hydroxide ion (see text). ⁱ Determined as the slope of a plot of k_{obsd} (s^{-1}) for the exchange of the first α -deuterium for hydrogen against the concentration of hydroxide ion (Figure 1). The error was calculated at the 80% confidence limit. ^j Determined by following exchange of up to 5% of the first α -deuterium for hydrogen catalyzed by hydroxide ion in H₂O. ^k Determined by following exchange of 50–60% of all four α -deuteriums for hydrogen catalyzed by hydroxide ion in H₂O.

upfield triplet at 2.351 ppm ($J_{\text{HD}} = 2.5$ Hz) due to the α -CHD group of the product. The progress, R , of deuterium exchange was determined from the integrated areas of the singlet due to the α -CH₂ group of the substrate (A_{CH_2}) and the triplet due to the α -CHD group of the product (A_{CHD}), according to eq 3. It

$$R = \frac{A_{\text{CH}_2}}{A_{\text{CH}_2} + A_{\text{CHD}}} \quad (3)$$

was only possible to obtain baseline separation of the last of the three peaks for the triplet due to the α -CHD group, and the integrated area of this triplet (A_{CHD}) was calculated as described for CH₂DCN.¹⁸ Semilogarithmic plots of reaction progress R against time were linear during exchange of up to 30% of the first α -hydrogen of CH₃CH₂CN (Figure S5 of the Supporting Information). The negative slope of these plots is $k_{\text{ex}} = k_{\text{obsd}}/2$, where k_{obsd} (s^{-1}) is the observed first-order rate constant for exchange of the first α -hydrogen of propanenitrile catalyzed by deuterioxide ion (Scheme 2).^{33,34} Figure 1C shows the dependence of k_{obsd} for exchange of the first α -hydrogen of propanenitrile on the concentration of deuterioxide ion in D₂O at 25 °C and $I = 1.0$ (KCl). The slope of this correlation is the second-order rate constant for exchange of the first α -hydrogen of CH₃CH₂CN catalyzed by deuterioxide ion, $k_{\text{DO}} = 3.0 \pm 0.2 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$ (Table 1, error calculated at the 80% confidence limit).

The exchange for deuterium of the α -hydrogens of succinonitrile in D₂O at 25 °C and $I = 1.0$ (KCl) (Scheme 2) was followed by monitoring the complete disappearance of the α -hydrogens by ¹H NMR spectroscopy at 500 MHz, using methanol as an internal standard. Representative ¹H NMR spectra of succinonitrile obtained during exchange of 60% of the α -hydrogens for deuterium in the presence of deuterioxide ion in D₂O at 25 °C and $I = 1.0$ (KCl) are shown in Figure S6 of the Supporting Information. The progress, f_{H} , of deuterium exchange, calculated as the fraction of hydrogen remaining in succinonitrile, was determined from the integrated areas of the signals due to the CH₃OD standard ($A_{\text{CH}_3\text{OD}}$) and the protons of all the forms of succinonitrile (A_{suc}) according to eq 4

$$f_{\text{H}} = \frac{(A_{\text{suc}}/A_{\text{CH}_3\text{OD}})}{(A_{\text{suc}}/A_{\text{CH}_3\text{OD}})_0} \quad (4)$$

where $(A_{\text{suc}}/A_{\text{CH}_3\text{OD}})_0$ is the ratio of these areas at zero time. Semilogarithmic plots of reaction progress f_{H} against time were linear during exchange of up to 70% of all four α -hydrogens

of NCCH₂CH₂CN (Figure S7 of the Supporting Information). The negative slope of these plots is k_{ex} (s^{-1}), the first-order rate constant for exchange of *all four* α -hydrogens of succinonitrile catalyzed by deuterioxide ion. The observed first-order rate constant for exchange of the *first* α -hydrogen of succinonitrile catalyzed by deuterioxide ion is k_{obsd} (s^{-1}) = $4k_{\text{ex}}$ (Scheme 2). Figure 1B (●) shows the dependence of k_{obsd} for exchange of the first α -hydrogen of succinonitrile on the concentration of deuterioxide ion in D₂O at 25 °C and $I = 1.0$ (KCl). The slope of this correlation is the second-order rate constant for exchange of the first α -hydrogen of NCCH₂CH₂CN catalyzed by deuterioxide ion, $k_{\text{DO}} = 6.0 \pm 0.2 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ (Table 1, error calculated at the 80% confidence limit).

The exchange for hydrogen of the α -deuteriums of [d_4]-succinonitrile in the presence of hydroxide ion in H₂O at 25 °C and $I = 1.0$ (KCl) (Scheme 2) was followed by monitoring the appearance of the partially protonated forms of succinonitrile by ¹H NMR spectroscopy at 500 MHz, using methanol as an internal standard. The progress, f_{D} , of hydrogen exchange, calculated as the fraction of deuterium remaining in succinonitrile, was determined from the integrated areas of the signals due to the CH₃OH standard ($A_{\text{CH}_3\text{OH}}$) and the protons of the partially protonated forms of succinonitrile (A_{suc}) according to eq 5

$$f_{\text{D}} = \frac{(A_{\text{suc}}/A_{\text{CH}_3\text{OH}})_{\infty} - (A_{\text{suc}}/A_{\text{CH}_3\text{OH}})}{(A_{\text{suc}}/A_{\text{CH}_3\text{OH}})_{\infty}} \quad (5)$$

where $(A_{\text{suc}}/A_{\text{CH}_3\text{OH}})_{\infty}$ is the ratio of these areas when the reaction is complete. Semilogarithmic plots of reaction progress f_{D} against time were linear during exchange of 50–60% of all four α -deuteriums of NCCD₂CD₂CN (Figure S8 of the Supporting Information). The negative slope of these plots is $k_{\text{ex}} = k_{\text{obsd}}/4$, where k_{obsd} (s^{-1}) is the first-order rate constant for exchange of the first α -deuterium of NCCD₂CD₂CN catalyzed by hydroxide ion (Scheme 2). Figure 1B (▲) shows the dependence of k_{obsd} for exchange of the first α -deuterium of NCCD₂CD₂CN on the concentration of hydroxide ion in H₂O at 25 °C and $I = 1.0$ (KCl). The slope of this correlation is the second-order rate constant for exchange of the first α -deuterium of NCCD₂CD₂-CN catalyzed by hydroxide ion, $(k_{\text{HO}})_{\text{D}} = 2.1 \pm 0.2 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ (Table 1, error calculated at the 80% confidence limit).

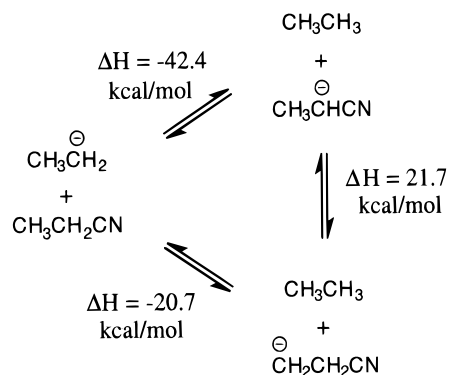
Calculations

Table 2 gives the values of ΔE° , ΔH^{298} (proton affinity), ΔS , and ΔG for the ionization of CH₃CH₃, the ionization of CH₃-

Table 2. Computed Thermodynamic Quantities from MP2/Aug-cc-PVDZ and HF/6-311+G(d,p) Calculations for the Reaction $AH \rightarrow A^- + H^+$ at 298 K

A^-	$\Delta E^{\circ a}$ (kcal/mol)	ΔH^{298} (PA) (kcal/mol)	ΔS (cal/ mol·K)	ΔG (kcal/mol)	PA (exp) ^b (kcal/mol)
$CH_3CH_2^-$ ^c	427.7	417.4	29.3	408.6	420
CH_3CH^-CN	383.2	375.0	26.9	367.0	375 ± 2
$^-CH_2CH_2CN$	405.4	396.7	25.8	389.0	391 ± 5
$NCCH_2CH^-CN$	366.0	357.9	26.8	349.9	

^a Since the 6-311+G(d,p) basis set is slightly larger than Dunning's double- ζ function, the electronic energy at 0 K is computed as follows: $\Delta E^{\circ} = \Delta E_{HF}(6-311+G(d,p)) + \Delta E_{MP2}(aug-cc-PVDZ) - \Delta E_{HF}(aug-cc-PVDZ)$. Total energies for CH_3CH_2CN are -171.00720 , -170.98323 , and -171.56303 hartree at the HF/6-311+G(d,p), HF/aug-cc-PVDZ//HF/6-311+G(d,p) and MP2/aug-cc-PVDZ levels, respectively. ^b Data from ref 23. ^c Energies calculated at the MP4(SDTQ)/aug-cc-PVDZ//HF/6-311+G(d,p) level.

Scheme 3

CH_2CN at C- α and at C- β , and the ionization of $NCCH_2CH_2CN$ that were calculated at the MP2/aug-cc-PVDZ//HF/6-311+G(d,p) level. Figure S10 of the Supporting Information shows selected geometrical parameters for propanenitrile (**1**) and the corresponding α - and β -cyano carbanions (**2** and **3**), and succinonitrile (**4**) and the corresponding α -cyano carbanion (**5**).

The proton affinities of the carbanions given in Table 2 (ΔH^{298}) were used to calculate the values of ΔH for the isodesmic reactions shown in Scheme 3. The calculated stabilization of the ethyl carbanion by the addition of an α -cyano group (42.4 kcal/mol) is in good agreement with the earlier reported value of 44 kcal/mol obtained from calculations at the G2+(MP2) level²³ and with the value from experiment of 45 kcal/mol.²³ Similarly, a value of 43 kcal/mol for stabilization of the methyl carbanion by the addition of a cyano group has been obtained from calculations at the G2+(MP2) level.⁶ The structure of the α -cyano carbanion CH_3CH^-CN (**2**, Figure S10) obtained from ab initio calculations at the HF/6-311+G(d,p) level shows that the C–CN bond (1.394 Å) is shortened by 0.077 Å and the CN bond (1.156 Å) is lengthened by 0.026 Å in comparison with the neutral carbon acid propanenitrile (**1**, Figure S10). A Mulliken population analysis indicates that the cyano group at **2** has a total net charge of -0.549 e, while the remaining charge densities are nearly equally distributed over the CH and CH_3 groups. These structural and electronic changes upon deprotonation of propanenitrile are consistent with the conclusion from a more detailed computational study of acetonitrile and the corresponding cyanomethyl carbanion that there is significant transfer of negative charge to the nitrile group of α -cyano carbanions.⁶

The large stabilization of the ethyl carbanion by the addition of a β -cyano group has been noted.²³ For example, the stabilization energy of 20.7 kcal/mol calculated here at the MP2/

Table 3. Relative Free Energies of Solvation of Cyanoalkanes and Cyanocarbanions by Water Determined from Monte Carlo QM/MM Simulations at 298 K

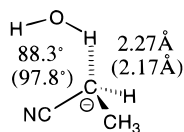
molecule	$\Delta G^{el a}$ (kcal/mol)	$\Delta G^{vdW}(A \rightarrow B)^a$ (kcal/mol)	$\Delta \Delta G_{hyd}(A \rightarrow B)^{a,b}$ (kcal/mol)
CH_3CH_2CN	-0.1 ± 0.1	0.0	0.0
$NCCH_2CH_2CN$	-0.5 ± 0.1	-0.2 ± 0.1	-0.6 ± 0.1
			-5.4 ± 0.2^c
			Average = -3 ± 2.4
CH_3CH^-CN	-45.6 ± 0.3	0.0	0.0
$NCCH_2CH^-CN$	-38.5 ± 0.2	0.2 ± 0.1	7.3 ± 0.4

^a Quantities from Scheme S1 and eq 3 of the Supporting Information. ^b Free energies of transfer of the cyanoalkanes and cyanocarbanions from the gas phase to water, relative to the arbitrary value of $\Delta G_{hyd} = 0$ for the cyanoalkane CH_3CH_2CN and the cyanocarbanion CH_3CH^-CN , computed according to eq 3 of the Supporting Information. Note that long-range electrostatic (Born) corrections beyond the cutoff distance for the anions are canceled out. ^c Computed using Jorgensen's OPLS parameters for acetonitrile with the assumption that $NCCH_2CH_2CN$ has the same parameters. In these calculations, the solute molecules are treated classically.

aug-cc-PVDZ level (Scheme 3) is in reasonable agreement with the value of 23 kcal/mol from the G2+(MP2) calculation;²³ however, it is 8 kcal/mol smaller than the experimental value of 29 ± 6 kcal/mol.²³ The value of $\Delta H = 21.7$ kcal/mol for isomerization of the α -cyanoethyl to the β -cyanoethyl carbanion (Scheme 3) is also in accord with the values of 16 ± 7 and 21.9 kcal/mol determined, respectively, by experiment and calculations at the G2+(MP2) level.²³

Table 3 gives the free energies for the transfer of cyanoalkanes and cyanocarbanions from the gas phase to solution, relative to the arbitrary value of $\Delta G_{hyd} = 0$ for the cyanoalkane CH_3CH_2CN and the cyanocarbanion CH_3CH^-CN that were determined by Monte Carlo QM/MM calculations. The difference in the free energies of solvation of two molecules **A** and **B**, $\Delta \Delta G_{hyd}(A \rightarrow B)$ was computed as described in the Supporting Information, where $\Delta G^{el}(A) - \Delta G^{el}(B)$ is the difference in the "electrostatic decoupling" for **A** and **B** and $\Delta G^{vdW}(A \rightarrow B)$ is the difference in the van der Waals interactions of **A** and **B** with solvent. The AM1/TIP3P model predicts that ΔG_{hyd} for succinonitrile is only 0.6 kcal/mol more negative than for propanenitrile (Table 3). However, this method probably underestimates the free energy of solvation of succinonitrile, because the same type of calculations predict a free energy of solvation of acetonitrile of 0.9 ± 0.3 kcal/mol, which is substantially more positive than the experimental value of -3.8 kcal/mol. This tendency of the AM1/TIP3P calculations to underestimate the free energy of solvation of acetonitrile is probably due to the failure of the method to fully account for the effect of polarization of charge at the cyano group on solvation. The OPLS parameters developed by Jorgensen to calculate ΔG_{hyd} for acetonitrile using classical Monte Carlo simulations gives a better agreement with experiment. The same OPLS parameters give a free energy of solvation for succinonitrile that is 5.4 kcal/mol more favorable than for propanenitrile, which is similar to the 5.7 kcal/mol difference in the experimental free energies of solvation of ethane and propanenitrile. We consider it unlikely that the addition of the first and second cyano groups to ethane to give succinonitrile should cause equally large changes in ΔG_{hyd} . Rather some attenuation of the effect of the cyano group is expected to result from interactions between individual solvent molecules which prevent optimal solvation of closely spaced cyano groups in a single molecule. Therefore, we regard the values of $\Delta \Delta G_{hyd}(A \rightarrow B)$ (Table 3) for succinonitrile obtained by these two computational methods

Scheme 4



$$\Delta E = -13.7 \text{ (-14.6)}$$

as upper and lower limits for the difference in the free energies of solvation of this compound and propanenitrile.

To ensure that the combined AM1/TIP3P potential provides an adequate description of the interactions between the cyano-carbanions and water, the bimolecular hydrogen-bonded complex between water and the α -cyanoethyl carbanion was examined at the HF/6-311+G(d,p) level, and the results were compared with those obtained using the combined AM1/TIP3P model (Scheme 4). It was found that if the value of σ for the carbon Lennard-Jones parameter is increased from the standard value of 3.5 Å for the neutral species to 3.75 Å for anionic carbon, then there is reasonable agreement (Scheme 4) between the hydrogen-bond energy (ΔE , kcal/mol) and length obtained from ab initio and combined AM1/TIP3P calculations (values in parentheses). This modification, along with the Lennard-Jones parameters determined in earlier work, were used in this study.³⁵

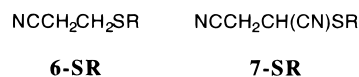
Thermodynamic data were determined for the nitrile and ketenimine tautomers of acetonitrile at the MP2/aug-cc-PVDZ//HF/6-311+G(d,p) level using Gaussian 92, as described in the Supporting Information. Vibrational frequency calculations confirmed that the C_{3v} and C_s geometries are energy minima for CH_3CN and $\text{CH}_2=\text{C}=\text{NH}$, respectively. The computed values of ΔE° , ΔH , ΔS , and ΔG for the tautomerization of CH_3CN to give $\text{CH}_2=\text{C}=\text{NH}$ are, respectively, 29.4 kcal/mol, 28.4 kcal/mol, 0.29 cal/mol·K, and 28.3 kcal/mol at 298 K. A somewhat larger value of $\Delta E^\circ = 34.3$ kcal/mol was reported in earlier work (MP2/6-31+G**/6-31+G*).³⁶ The difference in the free energies of solvation of CH_3CN and $\text{CH}_2=\text{C}=\text{NH}$ in water was determined by Monte Carlo free energy perturbation calculations using a three-site model, developed originally by Jorgensen for CH_3CN ,³⁷ and parameters developed in this work for $\text{CH}_2=\text{C}=\text{NH}$. The free energy of solvation was computed to be 2.4 kcal/mol more favorable for CH_3CN than for $\text{CH}_2=\text{C}=\text{NH}$, which gives $\Delta G^\circ = 28.3 + 2.4 = 30.7$ kcal/mol at 298 K for the tautomerization of acetonitrile to ketenimine in water.

Discussion

The second-order rate constant for exchange for deuterium of the first α -hydrogen of acetonitrile catalyzed by deuteroxide ion in D_2O at 25 °C determined in this work, $k_{\text{DO}} = 2.7 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, is in fair agreement with the early literature value of $k_{\text{DO}} = (3-5) \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ that was estimated by making a small temperature correction of the rate constant determined at 35 °C.³⁸ The difference in these rate constants is probably due to the improvement in analytical methods over the last sixty years.

Mechanism for Hydron-Exchange Reactions. There is good evidence for the formation of α -cyano carbanions as intermediates of the base-catalyzed elimination reactions of thiol adducts

of acrylonitrile (**6-SR**) and fumaronitrile (**7-SR**).^{12,39} The



formation of similar α -cyano carbanions as intermediates of base-catalyzed exchange of the α -hydrogens of simple cyanoalkanes will also be favored because there is no strong imperative for a concerted exchange mechanism that avoids the carbanion intermediate.⁴⁰

The data in this work give $(k_{\text{DO}})_{\text{H}}/(k_{\text{HO}})_{\text{D}} = 3.3$ and 2.9 for acetonitrile and succinonitrile, respectively, where $(k_{\text{DO}})_{\text{H}}$ is the second-order rate constant for exchange for deuterium of the first α -hydrogen of the carbon acid catalyzed by deuteroxide ion in D_2O , and $(k_{\text{HO}})_{\text{D}}$ is the second-order rate constant for exchange for hydrogen of the first α -deuterium of the perdeuterated carbon acid catalyzed by hydroxide ion in H_2O (Table 1). These rate constant ratios reflect the secondary solvent isotope effect resulting from the stronger hydrogen bonds between hydroxide ion and H_2O than between deuteroxide ion and D_2O , with a maximum equilibrium value of 2.4,^{41,42} together with any primary isotope effect on exchange. This analysis neglects α -secondary isotope effects on exchange, but these are expected to be very small.⁴³

Scheme 5 shows a detailed mechanism for stepwise hydron exchange at an α -cyano carbon, catalyzed by lyoxide ion, and Figure 2 shows the corresponding free-energy reaction coordinate profile for deuterium exchange at acetonitrile. In this mechanism, the carbanion formed by hydron abstraction by lyoxide ion (k_{p}) must undergo solvent reorganization (k_{reorg}) in order for incorporation of the isotopic label to occur ($k_{\text{L}^2\text{OL}^2}$). Both the primary isotope effect and the secondary solvent isotope effect will be expressed in the rate constant ratio $(k_{\text{DO}})_{\text{H}}/(k_{\text{HO}})_{\text{D}}$ when hydron exchange takes place by this stepwise mechanism in which the initial hydron abstraction is rate-determining ($k_{\text{L}^2\text{OL}^2} < k_{\text{reorg}}$). However, when the rate-determining step for hydron exchange becomes the reorganization of solvent that exchanges the hydron of substrate with the labeled hydron of solvent ($k_{\text{L}^2\text{OL}^2} > k_{\text{reorg}}$), then this ratio will reflect only the equilibrium secondary solvent isotope effect on the basicity of lyoxide ion of 2.4 (see above).^{42,43} The values of $(k_{\text{DO}})_{\text{H}}/(k_{\text{HO}})_{\text{D}}$ for the hydron-exchange reactions of acetonitrile and succinonitrile determined in this work are slightly larger than 2.4 (see above), a fact which shows that, in addition to the secondary solvent isotope effect, there are small primary isotope effects on exchange.

The conclusion that there is a small contribution of a primary isotope effect to the rate constant ratio $(k_{\text{DO}})_{\text{H}}/(k_{\text{HO}})_{\text{D}}$ is consistent with a stepwise mechanism in which hydron abstraction from the substrate is partly rate-determining for exchange. It is not easily rationalized by a concerted mechanism for exchange in which hydron abstraction by lyoxide ion and hydron transfer from labeled solvent occur in a single step, because the transition states for the hypothetical concerted hydron exchange at both

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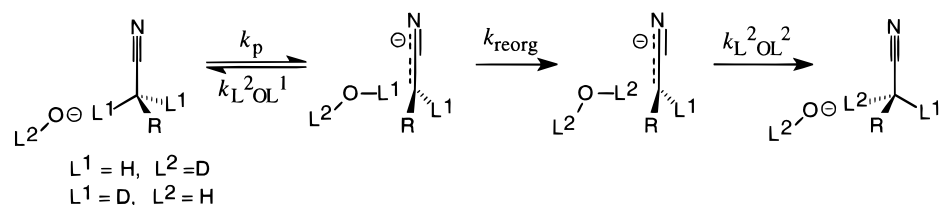
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Scheme 5



Scheme 6

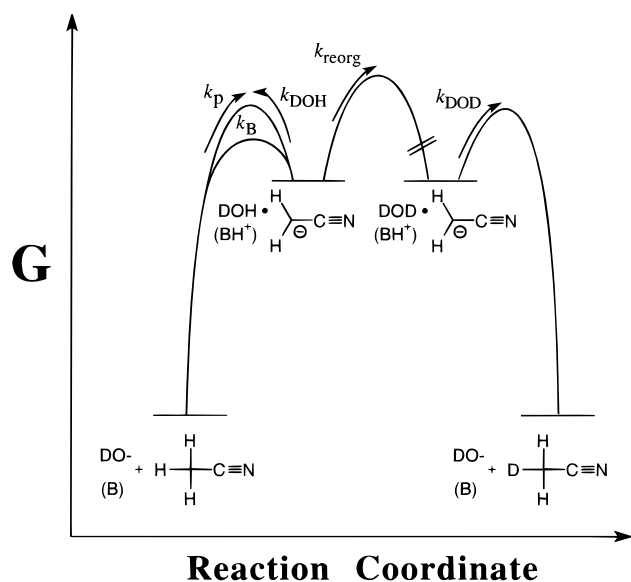
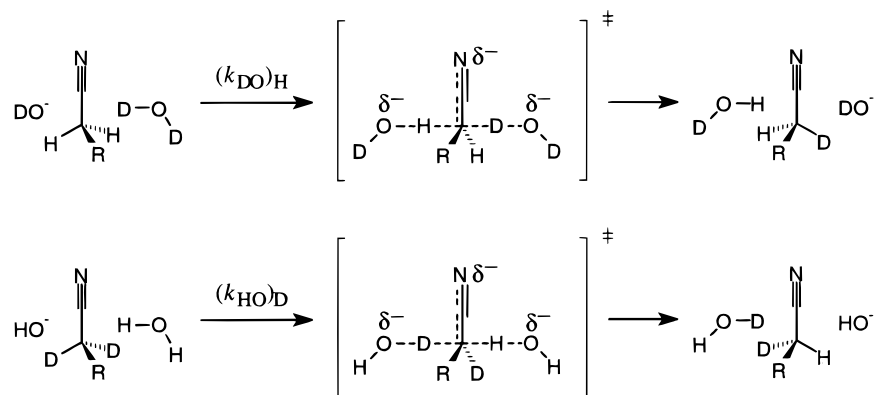


Figure 2. Free-energy reaction coordinate profile for exchange for deuterium of the first α -hydrogen of acetonitrile catalyzed by deuterioxide ion in D_2O . In this mechanism, the carbanion formed by hydron abstraction by deuterioxide ion (k_p) must undergo solvent reorganization (k_{reorg}) to place a molecule of D_2O in a position to react with the carbanion (k_{DOD}). The slashed lines indicate that solvent reorganization is irreversible, because the concentration of DOH in D_2O is negligible. When the rate of deuterium exchange is limited by solvent reorganization ($k_{DOH} > k_{reorg}$), proton abstraction by general bases (k_B) does not result in general base catalysis of exchange, because the barrier to diffusional separation of the ion pair $BH^+ \cdot CH_2CN$ (not shown) is larger than that for solvent reorganization ($k_{-d} < k_{reorg}$).¹⁸

protonated and deuterated substrates are symmetrical (Scheme 6). The fractionation factor for the α -C-L bond at cyanoalkanes is close to unity,¹² so that the net change in zero-point energy at the transferring hydrons on proceeding from reactants to the transition state must be similar for the two substrates, and any primary isotope effect on this concerted reaction should be small or negligible (Scheme 6). Thus, for the hypothetical concerted exchange mechanism, the ratio $(k_{DO})_H/(k_{HO})_D$ would be domi-

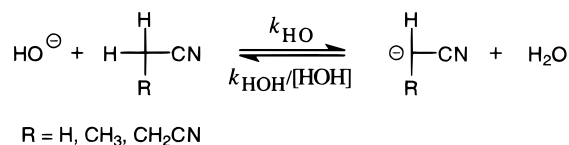
nated by the secondary solvent isotope effect on the reactivity of lyoxide ion, $k_{DO}/k_{HO} \leq 2.4$.

Rate-Determining Step for Hydron Exchange. The rate constant $(k_{DO})_H$ for exchange of the first α -hydrogen of simple cyanoalkanes in D_2O may be limited by either deprotonation of the substrate by deuterioxide ion (k_p , Figure 2), or if this step is reversible, by the rate constant for reorganization of solvent to place a molecule of D_2O in a position to deliver a labeled hydron to the α -cyano carbanion (k_{reorg} , Figure 2). The following observations provide strong evidence that hydron transfer to lyoxide ion is reversible and that the reorganization of solvent is largely rate-determining for the lyoxide-ion-catalyzed exchange of the α -hydrons of simple cyanoalkanes.

(1) The value of $(k_{DO})_H/(k_{HO})_D$ for hydron exchange at CL_3 -CN is expected to lie between (a) an upper limit of $(k_{DO})_H/(k_{HO})_D \approx (1.8)(4) = 7.2$ when proton transfer (k_p , Scheme 5) is rate-determining, where 1.8 is the secondary solvent isotope effect observed for the lyoxide-ion-catalyzed deprotonation of **6-SR** and **7-SR**,³⁹ and 4 is the primary isotope effect observed for the deprotonation of these carbon acids¹² and (b) a lower limit of $(k_{DO})_H/(k_{HO})_D = 2.4$ when reorganization of solvent (k_{reorg} , Scheme 5) is rate-determining, so that the full equilibrium difference in the basicities of deuterioxide and hydroxide ions is expressed in the transition state (see above).^{42,43} The observed ratios of $(k_{DO})_H/(k_{HO})_D = 3.3$ and 2.9 for the hydron-exchange reactions of acetonitrile and succinonitrile, respectively, are considerably smaller than those expected for rate-determining deprotonation of the substrate, and they are consistent with a pathway in which solvent reorganization is largely rate-determining for hydron exchange.

(2) General base catalysis by amines of the stepwise elimination reactions of **6-SR** and **7-SR** is observed when the leaving group RS^- is weakly basic so that formation of the α -cyano carbanion is rate-limiting for the elimination reaction.³⁹ By contrast, there is no catalysis by methylamine of exchange of the α -hydrogen of **7-SMe**¹² and no catalysis by quinuclidine or 3-quinuclidinol of deuterium exchange at CH_3CN (Figure S9 of the Supporting Information). These results are consistent with the reaction coordinate profile for deuterium exchange at simple cyanoalkanes shown in Figure 2, in which general bases

Scheme 7



decrease the barrier to proton abstraction from the substrate (k_{B}), but solvent reorganization (k_{reorg}) is rate-determining for deuterio-catalyzed exchange.¹² General base catalysis of the elimination reactions of **6-SR** and **7-SR** is observed when the barrier to reprotonation of the α -cyano carbanion by solvent to regenerate substrate (k_{DOH}) is larger than the barrier to expulsion of the thiol anion leaving group from the carbanion to give the alkene. However, proton abstraction from the substrate by general bases (k_{B}) does not result in general base catalysis of deuterium exchange because solvent reorganization is largely rate-determining for exchange ($k_{\text{DOH}} > k_{\text{reorg}}$, Scheme 5).¹²

The Acidity of Simple Cyanoalkanes. Table 1 gives the $\text{p}K_{\text{a}}$'s of the simple cyanoalkanes acetonitrile, propanenitrile, and succinonitrile in water determined in this work. These $\text{p}K_{\text{a}}$'s were calculated using eq 6 derived for Scheme 7

$$\text{p}K_{\text{a}} = \text{p}K_{\text{w}} + \log(k_{\text{HOH}}/k_{\text{HO}}) \quad (6)$$

where k_{HO} is the second-order rate constant for deprotonation of the carbon acid by hydroxide ion in H₂O (Table 1), $k_{\text{HOH}} = 10^{11} \text{ s}^{-1}$ is the first-order rate constant for protonation of the α -cyano carbanion by solvent water,¹² and $K_{\text{w}} = 10^{-14}$ is the ion product of water. The values of k_{HO} (Table 1) were calculated from the corresponding rate constants for deprotonation of the carbon acids by deuteroxide ion in D₂O (Table 1) using the relationship $k_{\text{HO}} = k_{\text{DO}}/2.4$, where 2.4 is the maximum secondary solvent isotope effect on the reactivity of lyoxide ion. This is appropriate because almost the entire difference in the basicities of deuteroxide and hydroxide ions will be expressed in the transition state for carbanion formation when solvent reorganization is rate-limiting for exchange (see above). The principle of microscopic reversibility requires that the reverse protonation of the α -cyano carbanions by solvent water also be limited mainly by solvent reorganization, with a rate constant on the order of that for the dielectric relaxation of water, $k_{\text{HOH}} = k_{\text{reorg}} \approx 10^{11} \text{ s}^{-1}$.²⁰⁻²²

The value of $k_{\text{HOH}} = 10^{11} \text{ s}^{-1}$ should not severely overestimate the limiting rate constant possible for the strongly thermodynamically favorable protonation of carbanions by solvent water, because there is good evidence that the rate constant for the reaction of solvent water with other highly unstable species can approach 10^{11} s^{-1} . For example, the reaction of solvent water with the 3,5-dinitrofluoromethylbenzyl carbocation is 5-fold faster than the reaction of 1.0 M azide ion⁴⁴ and $k_{\text{az}} \approx 6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ has been determined⁴⁵ for the diffusion-limited reaction of azide ion with unstable benzylic carbocations.⁴⁶ There is no

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(46) The average rate constant for the diffusion-limited reaction of azide ion with highly unstable carbocations is $k_{\text{az}} = 6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.⁴⁵ However, the 3,5-dinitrofluoromethylbenzyl carbocation is so short-lived that it cannot be trapped by azide ion so that essentially all of the observed azide ion adduct is formed by a preassociation mechanism with an apparent rate constant that is larger than $6 \times 10^9 \text{ s}^{-1}$ for the diffusion-limited reaction of 1 M azide ion.⁴⁴

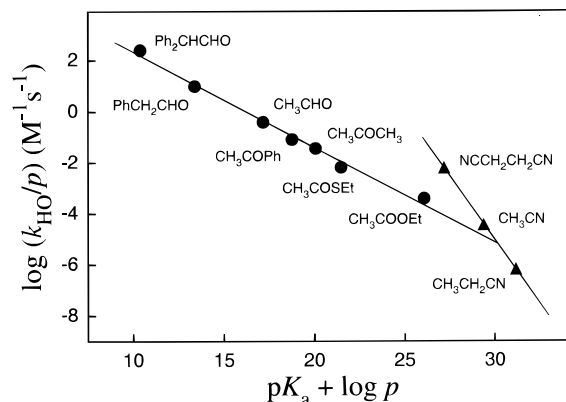


Figure 3. Rate-equilibrium correlations for the deprotonation of simple α -carbonyl carbon acids (\bullet , slope = -0.37) and simple α -cyano carbon acids (\blacktriangle , slope = -1.0) by hydroxide ion in H₂O at 25 °C. The rate constants, k_{HO} ($\text{M}^{-1} \text{ s}^{-1}$), and the carbon acidities, K_{a} , have been corrected for the number of acidic protons of the carbon acid, p . The data for the α -carbonyl carbon acids were compiled in an earlier publication,¹⁸ and the data for the α -cyano carbon acids (cyanoalkanes) were taken from Table 1.

chemical barrier to the reaction of this carbanion with solvent,⁴⁴ so that $k_{\text{reorg}} \approx k_{\text{s}} > 3 \times 10^{10} \text{ s}^{-1}$. The failure of tertiary amines to catalyze deuterium exchange into acetonitrile (see Results) requires that the lifetime of the $\text{BH}^+ \cdot \text{CH}_2\text{CN}$ ion pair complex of the buffer reaction be so short that its protonation by D₂O occurs before there is significant separation to free ions ($k_{\text{DOD}} > k_{\text{-d}} \approx 10^{10} \text{ s}^{-1}$).^{12,18,39,47} We conclude that k_{HOH} for the protonation of the cyanocarbanions in this work by solvent water lies between 10^{10} and 10^{11} s^{-1} . This introduces an uncertainty of at most ± 0.5 units in the $\text{p}K_{\text{a}}$'s reported in Table 1. There is less uncertainty in the relative values of the $\text{p}K_{\text{a}}$'s reported in Table 1, because in all cases k_{HOH} (Scheme 7 and eq 6) is largely limited by the rotation of a molecule of solvent into a reactive position, and this process should be nearly independent of the structure of the reacting carbanion.

The value of $\text{p}K_{\text{a}} = 28.9$ for acetonitrile reported here is higher than the widely cited estimate of $\text{p}K_{\text{a}} = 25$.¹¹ The earlier value was obtained by extrapolation of a linear rate-equilibrium relationship for relatively strongly acidic α -carbonyl and α -nitro carbon acids. Figure 3 shows the fit of the data for deprotonation of the simple α -cyano carbon acids (cyanoalkanes) determined in this work to a more extensive rate-equilibrium relationship for the deprotonation of simple α -carbonyl carbon acids by hydroxide ion.¹⁸ In this correlation, the values of k_{HO} and $\text{p}K_{\text{a}}$ have been statistically corrected for the number of acidic protons at the carbon acid, p . The point for succinonitrile exhibits a positive deviation from the correlation line for α -carbonyl acids, as a result of the relatively small intrinsic barrier to proton transfer at cyanoalkanes.² However, the point for acetonitrile lies close to the intersection of the correlation lines for the cyanoalkanes (\blacktriangle , slope = -1.0) and the α -carbonyl carbon acids (\bullet , slope = -0.37). This point of intersection *must* occur when $k_{\text{HOH}} = k_{\text{reorg}} \approx 10^{11} \text{ s}^{-1}$ for the reverse protonation of both enolates and α -cyano carbanions by solvent water, because this is the point at which both correlations must break to a slope of -1.0 (eq 6). The small 0.4 unit positive deviation of $\log k_{\text{HO}}$

(47) The small association constants for the formation of ion pairs in water, $K_{\text{as}} = k_{\text{a}}/k_{\text{-d}} \approx 0.1\text{--}0.2 \text{ M}^{-1}$ [Davies, C. S. *Ion Association*; Butterworth: London, 1962; pp 77–87; Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373–1383], and the large rate constants for ion pair formation in diffusion-limited reactions ($k_{\text{d}} = 6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$)⁴⁵ require $k_{\text{-d}} \approx 10^{10} \text{ s}^{-1}$ for the diffusional separation of ion pairs to free ions.

Scheme 8

	$\begin{array}{c} \text{H} \\ \\ \text{H}-\text{C}-\text{H} \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{H} \\ \\ \text{H}-\text{C}-\text{CN} \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{H} \\ \\ \text{H}-\text{C}-\text{CN} \\ \\ \text{CN} \end{array}$	$\begin{array}{c} \text{CN} \\ \\ \text{H}-\text{C}-\text{CN} \\ \\ \text{CN} \end{array}$
$\text{p}K_{\text{a}} + \log p$	49.6	29.4	11.7	-5.1
$\Delta(\text{p}K_{\text{a}} + \log p)$		20.2	17.7	16.8

($\text{M}^{-1} \text{s}^{-1}$) for the deprotonation of acetonitrile by hydroxide ion from the linear correlation for simple α -carbonyl carbon acids shows that any difference in the intrinsic barriers to proton transfer at α -cyano carbon acids and α -carbonyl carbon acids of $\text{p}K_{\text{a}} > 29$ is *not* reflected in the rate constant for deprotonation of the carbon acid to give the *free* carbanion, because solvent reorganization (k_{reorg}) rather than the chemical step (k_{p}) is then largely rate-determining for proton transfer (Scheme 5 and Figure 2).

The value of $k_{\text{DO}} = 1.7 \times 10^{-3} \text{M}^{-1} \text{s}^{-1}$ for the deuterioxide-ion-catalyzed exchange of the first α -hydrogen of ethyl acetate in D_2O is larger, and the $\text{p}K_{\text{a}}$ of 25.6 for this carbon acid is smaller,¹⁸ than the corresponding values of $k_{\text{DO}} = 2.7 \times 10^{-4} \text{M}^{-1} \text{s}^{-1}$ and $\text{p}K_{\text{a}} = 28.9$ for acetonitrile (Table 1). We conclude that an α -ester substituent has a larger effect than an α -cyano substituent on both the rate and the equilibrium constant for the deprotonation of methane. By contrast, $\text{p}K_{\text{a}} = 21.4$ for $\text{PhSCH}_2\text{CO}_2\text{Et}$ in DMSO is 0.6 units *higher* than $\text{p}K_{\text{a}} = 20.8$ for PhSCH_2CN in the same solvent,⁴⁸ and similar gas-phase acidities are observed for methyl acetate (PA = 371.0 kcal/mol) acetonitrile (PA = 372.2 kcal/mol).⁴⁹ The larger increase in the acidity of α -ester than of α -cyano carbon acids observed on moving from the gas phase to water is consistent with a greater stabilization by solvation of an enolate oxyanion, where the charge is mostly localized at oxygen, than of an α -cyano carbanion, where a greater fraction of the negative charge (0.6 units) lies at the α -carbon.⁶

Resonance and Polar Effects. There are two interactions between the α -cyano group and the carbanionic center that may be responsible for the greater stability of α -cyano carbanions than of alkyl carbanions: (a) a stabilizing polar interaction between the electron-deficient cyano carbon and the adjacent negative charge and (b) stabilization due to transfer of negative charge from the α -cyano carbon to the nitrile nitrogen, which we will refer to as a *resonance* effect.⁵⁰ We have used two methods to evaluate the relative contribution of these polar and resonance interactions to the overall effect of the α -cyano substituent on carbon acidity.

Saturation of the Resonance Effect.⁵⁰ The stabilization of α -cyano carbanions by the transfer of negative charge to the nitrile nitrogen should result in a decrease in the effect of an α -cyano substituent on carbon acidity as the number of α -cyano groups is increased. This is because each α -cyano substituent will lead to a decrease in the remaining negative charge at a carbon that is available to interact with an additional α -cyano substituent.⁵¹ Scheme 8 summarizes the effects of an α -cyano

substituent on carbon acidity as a function of the number of α -cyano groups attached to the acidic carbon. A $\text{p}K_{\text{a}}$ of 49.0 for methane was estimated from $\text{p}K_{\text{a}} = 50.6$ for ethane determined by ab initio calculation,¹⁴ with the assumption that there is the same 1.8 unit difference between the statistically corrected $\text{p}K_{\text{a}}$'s of propanenitrile (31.2, Table 1) and acetonitrile (29.4, Table 1), and ethane and methane. This $\text{p}K_{\text{a}}$ for ethane is viewed as reliable because the same calculations give $\text{p}K_{\text{a}} = 28.6$ for acetonitrile,^{14,15} which is in excellent agreement with the experimental value of $\text{p}K_{\text{a}} = 28.9$ determined here. The data for dicyanomethane ($\text{p}K_{\text{a}} = 11.4$)⁵² and tricyanomethane ($\text{p}K_{\text{a}} = -5.1$)⁵³ were taken from the literature. Scheme 8 shows that there is only a 3.4 unit decrease, from 20.2 to 16.8 pK units, in the effect of an individual α -cyano substituent on carbon acidity, as the number of α -cyano substituents is increased from none at methane to two at dicyanomethane. This 17% decrease in the α -cyano substituent effect is smaller than the 25% decrease reported in a similar analysis by Bordwell for the ionization of acetonitrile and malononitrile in DMSO, which utilized a larger estimated $\text{p}K_{\text{a}}$ of 56.2 for ethane.⁵⁴

By contrast, the addition of an acetyl group to methane results in a large ca. 30 unit decrease in carbon acidity from $\text{p}K_{\text{a}} = 49.0$ for methane (see above) to $\text{p}K_{\text{a}} = 19.3$ for acetone,⁵⁵ but the addition of a second acetyl group results in a much smaller ca. 10 unit decrease in carbon acidity to $\text{p}K_{\text{a}} = 8.9$ for acetyl acetone.⁵⁶ The marked absence of any large tendency toward "saturation" of the α -cyano substituent effect on carbon acidity as the number of α -cyano substituents is increased is consistent with the conclusion that the stabilization of cyanocarbanions by transfer of negative charge onto the α -cyano groups is relatively unimportant in comparison with their stabilization by the polar effect of cyano substituents.

Falloff Factors. The polar effect of the α -cyano substituent on acidity could be determined from the "pure" polar effect of a β -cyano substituent and the change in this polar interaction that occurs upon removal of the intervening methylene group between the cyano substituent and the acidic site. However, care must be exercised in the interpretation of these data, which show considerable variation depending upon whether the reactions occur in water or in the gas phase. A comparison of the effect of an α -cyano group on the statistically corrected $\text{p}K_{\text{a}}$ of ethane ($51.4 - 31.2 = 20.2$ units, Table 4) and of a β -cyano group on the $\text{p}K_{\text{a}}$ of propanenitrile ($31.2 - 27.2 = 4.0$ units) gives a factor of $20.2/4.0 = 5.1$ for the falloff in the effect of an α -cyano substituent on carbon acidity in water resulting from insertion of an intervening methylene group. A different result is obtained from the corresponding analysis of cyano substituent effects on carbon acidity in the gas phase. Here an α -cyano substituent results in a 42 kcal/mol stabilization of the ethyl carbanion, and the resulting $\text{CH}_3\text{CH}^-\text{CN}$ is stabilized by a further 17 kcal/mol by the addition of a β -cyano substituent to give $\text{NCCH}_2\text{CH}^-\text{CN}$ (Table 2). These data give a smaller falloff factor of $42/17 = 2.5$ for the effect of a cyano substituent on carbon acidity in the gas phase (Table 4).

A related analysis shows that α -cyano and β -cyano substituents stabilize the ethyl carbanion in the gas phase by 42 and 20 kcal/mol, respectively (Table 2),²³ which gives a falloff factor

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(50) The *resonance* effect is defined as the stabilization of a hypothetical localized α -cyano carbanion resulting from the transfer of negative charge from the α -carbon to the nitrile nitrogen. No attempt is made here to distinguish *resonance* stabilization resulting from the intrinsic stability of delocalized compared with localized charge from that resulting from the intrinsic stability of nitrogen-localized compared with carbon-localized negative charge at the α -cyanomethyl carbanion.

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(55) Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley and Sons: Chichester, 1990; pp 399–480.

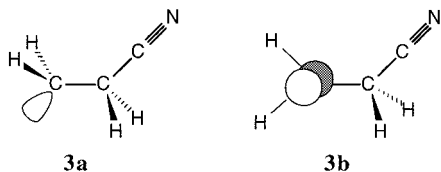
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Table 4. Comparison of the Effects of α -Cyano and β -Cyano Substituents on Carbon Acidity in the Gas Phase and in Water

carbon acid	gas phase				water			
	carbon acidity ΔG° (kcal/mol)	substituent effect ^a		falloff factor ^b C_α/C_β	carbon acidity $pK_a + \log p^f$	substituent effect ^e		falloff factor ^b C_α/C_β
		α -cyano (kcal/mol)	β -cyano (kcal/mol)			α -cyano (kcal/mol)	β -cyano (kcal/mol)	
CH ₃ CH ₃	409				51.4 ^g			
CH ₃ CH ₂ CN	367 (C_α) 389 (C_β)	42	20 (16.5) ^d	2.1 (2.5) ^d	31.2 (C_α)	27.5		
NCCH ₂ CH ₂ CN	350		17	2.5	27.2		5.4	5.1

^a Effect of removal of the cyano substituent on the free energy change for ionization of the carbon acid in the gas phase. ^b Ratio of α -cyano and β -cyano substituent effects, see text. ^c Free energy change for reaction $AH \rightarrow A^- + H^+$ in the gas phase at 298 K. Data taken from Table 2. ^d Values in parentheses are corrected for the stabilization of $^-CH_2CH_2CN$ by a p - σ^* interaction, see text. ^e Effect of removal of the cyano substituent on the free energy change for ionization of the carbon acid in water. ^f Acidity of carbon acid in water at 25 °C, statistically corrected for the number of acidic protons, p . Data taken from Table 1, unless noted otherwise. ^g Calculated from $pK_a = 50.6$ for ethane determined by ab initio calculation (ref 14).

of (42/20) = 2.1 in the gas phase (Table 4). However, the stabilization of the ethyl carbanion by a β -cyano substituent results in part from electron donation from the anionic carbon to the σ^* orbital of the C–CN bond at $^-CH_2CH_2CN$.²³ The importance of this effect was assessed by determining the difference in energies of the two conformers of the β -cyanoethyl carbanion: the lower energy configuration **3a** where the effect is a maximum, and **3b** where the p - σ^* interaction is minimized



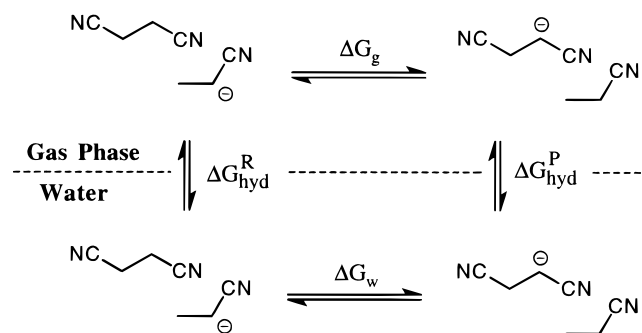
by the perpendicular arrangement of orbitals. At the HF/6-311+G(d,p) level, structure **3b** is 3.5 kcal/mol higher in energy than structure **3a** so that no more than (20 – 3.5) = 16.5 kcal/mol of the effect of a β -cyano substituent on carbanion stability can be polar in origin. This gives a slightly larger falloff factor of (42/16.5) = 2.5 for the effect of a cyano substituent on carbon acidity in the gas phase (Table 4).

The magnitude of polar effects on reaction equilibria ($\Delta \log K$) usually falls off by (2–3)-fold with insertion of a methylene group between interacting polar centers.⁵⁷ This decrease is similar to the ca. 2.5-fold falloff observed for the α -cyano substituent effect in the gas phase, but it is smaller than the 5.1-fold falloff observed for ionization of cyanoalkanes in water (Table 4).

Solvent Effects. The difference between the falloff factor of 2.5 obtained from comparison of the effect of an α -cyano group on the acidity of ethane and that of a β -cyano group on the acidity of propanenitrile in the gas phase (Table 4) and the much larger falloff factor of 5.1 obtained from comparison of the same cyano substituent effects on carbon acidity in water is the direct result of the 11.6 kcal/mol difference in the Gibbs free energy change for proton transfer between succinonitrile and CH_3CH^-CN to give propanenitrile and $NCCH_2CH^-CN$ of $\Delta G_g = -17$ kcal/mol in the gas phase and $\Delta G_w = -5.4$ kcal/mol for the same reaction in water (Scheme 9 and eq 7).

$$\Delta G_g - \Delta G_w = \Delta G_{\text{hyd}}^R - \Delta G_{\text{hyd}}^P = -11.6 \text{ kcal/mol} \quad (7)$$

To better understand this solvent effect, we have carried out Monte Carlo QM/MM calculations of the relative free energies of solvation of these cyanoalkanes and cyanocarbanions by water (Table 3). The 11.6 kcal/mol difference between ΔG_g and ΔG_w

Scheme 9

(Scheme 9 and eq 7) requires that the solvation of the reactants (succinonitrile and CH_3CH^-CN) be 11.6 kcal/mol *more favorable* than the solvation of the products (propanenitrile and $NCCH_2CH^-CN$). In other words, the addition of a β -cyano group to propanenitrile results in a relative increase in the stabilizing solvation of the neutral cyanoalkane and a relative decrease in the stabilizing solvation of the cyanocarbanion (eq 8 derived for Scheme 9). The Monte Carlo QM/MM calculations

$$\Delta G_{\text{hyd}}^R - \Delta G_{\text{hyd}}^P = [\Delta G_{\text{hyd}}(\text{NCCH}_2\text{CH}_2\text{CN}) - \Delta G_{\text{hyd}}(\text{CH}_3\text{CH}_2\text{CN})] + [\Delta G_{\text{hyd}}(\text{CH}_3\text{CN}^-) - \Delta G_{\text{hyd}}(\text{NCCH}_2\text{CH}^-)] \quad (8)$$

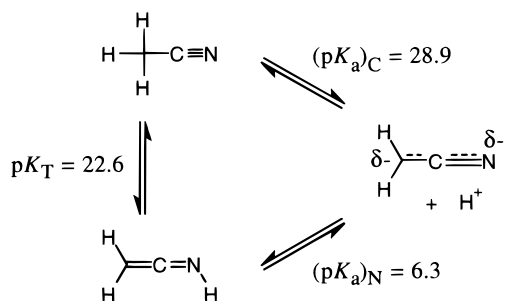
show that the addition of a β -cyano substituent results in an *increase* in the stabilizing solvation of the cyanoalkane of $\Delta G_{\text{hyd}}(\text{NCCH}_2\text{CH}_2\text{CN}) - \Delta G_{\text{hyd}}(\text{CH}_3\text{CH}_2\text{CN}) = -3 \pm 2.4$ kcal/mol (average value from Table 3), but a *decrease* in the stabilizing solvation of the cyanocarbanion of $\Delta G_{\text{hyd}}(\text{NCCH}_2\text{CH}^-) - \Delta G_{\text{hyd}}(\text{CH}_3\text{CH}^-) = 7.3$ kcal/mol (Table 3). The good agreement between the difference of these calculated β -cyano substituent effects on solvation, $-3 - 7.3 = -10.3$ kcal/mol (eq 8) and $\Delta G_g - \Delta G_w = -11.6$ kcal/mol (Scheme 9 and eq 7) shows that the experimental acidities of propanenitrile and succinonitrile determined in water are internally consistent with those determined from ab initio calculation (Table 2) and the relative free energies of solvation of these cyanoalkanes and the corresponding cyanocarbanions (Table 3).

We propose that there are two effects that contribute to make the free energy of solvation of $NCCH_2CH^-CN$ 7.3 kcal/mol less favorable than that of CH_3CH^-CN (Table 3).

(1) The difference is due, in part, to the additional polar interaction between the β -cyano group and the anionic carbon at $NCCH_2CH^-CN$ which will tend to cause this carbanion to prefer the gas phase where polar interactions are most strongly

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Scheme 10



stabilizing. This stabilizing polar interaction is largely responsible for the favorable free energy change for proton transfer from propanenitrile to this carbanion in the gas phase, $\Delta G_g = -17$ kcal/mol (Scheme 9). The magnitude of the attenuation of the gas-phase polar substituent effects on proton transfer at anionic carbon on moving to solution has not been determined. However, the change from reaction in the gas phase to reaction in solution results in a 30% reduction in the effect of aromatic ring substituents on the Gibbs free-energy change for proton transfer from α, α -dimethylbenzyl carbocations to α -methylstyrene to give the corresponding ring-substituted α -methylstyrenes and the unsubstituted cumyl carbocation.⁵⁸ A similar 30% attenuation of the 17 kcal/mol β -cyano substituent effect on the acidity of propanenitrile in the gas phase on moving to water would result in a ca. 5 kcal/mol decrease in the free energy change for proton transfer between succinonitrile and $\text{CH}_3\text{CH}^-\text{CN}$ to $\Delta G_w \approx 12$ kcal/mol in water, and hence a free energy of solvation of $\text{CH}_3\text{CH}^-\text{CN}$ ca. 5 kcal/mol more favorable than that of $\text{NCCH}_2\text{CH}^-\text{CN}$ (Scheme 9).

(2) The expected stabilizing interactions between the β -cyano group and solvent at $\text{NCCH}_2\text{CH}^-\text{CN}$ may not be fully realized because the solvent is "overloaded" with polar centers requiring stabilization by solvation. For example, the solvation of the carbanionic carbon of $\text{NCCH}_2\text{CH}^-\text{CN}$ may not be compatible with the arrangement of water molecules required for optimal dipole-dipole interactions between solvent and the two electron-withdrawing cyano groups, because of unfavorable steric and/or electrostatic interactions that develop as water molecules are moved into an alignment that provide optimal stabilization of these centers by hydrogen-bonding and electrostatic interactions.

In summary, the falloff factor of ca. 2.5 observed for α -cyano substituent effects in the gas phase is consistent with a largely polar substituent effect on carbanion stability.⁵⁷ Our computational study shows that the increase in the falloff factor to 5.1 for the α -cyano substituent effect in water is not due to a larger contribution of a resonance effect to carbanion stability in water but rather is the result of differential solvation of cyanoalkanes and α - and β -cyano stabilized carbanions (Scheme 9).

Tautomerization of Acetonitrile to Keteneimine. We have calculated the free energy change for the tautomerization of acetonitrile to give keteneimine in the gas phase as $\Delta G_T = 28.3$ kcal/mol (see Results). The free energy of solvation of acetonitrile determined by Monte Carlo simulations is 2.4 kcal/mol more favorable than that for the keteneimine tautomer, so that $\Delta G_T = 30.7$ kcal/mol for the tautomerization of acetonitrile to keteneimine in water, which corresponds to $pK_T = 22.6$ (Scheme 10).

The values of $pK_T = 22.6$ and $(pK_a)_C = 28.9$ (Table 1) for acetonitrile can be combined to give $(pK_a)_N = 6.3$ for deprotonation of the keteneimine tautomer at nitrogen (Scheme 10),

(58) Richard, J. P.; Jagannadham, V.; Amyes, T. L.; Mishima, M.; Tsuno, Y. *J. Am. Chem. Soc.* **1994**, *116*, 6706–6712.

so that this keteneimine is an unusually strong neutral nitrogen acid (cf. $pK_a \approx 41$ for ammonia).⁵⁹ The large unfavorable equilibrium constant for the tautomerization of acetonitrile provides insight into the following results.

(1) Ab initio calculations show that a substantial portion of the negative charge at the cyanomethyl carbanion (ca. 0.6 units) resides at the α -carbon, despite the greater electronegativity of nitrogen than carbon.⁶ The large value of $pK_T = 22.6$ for tautomerization of acetonitrile (Scheme 10) requires that a carbon–nitrogen triple bond at a nitrile be substantially more stable than the cumulative double bonds at a keteneimine. This favors the hypothetical cyanomethyl carbanion, in which there is carbon–nitrogen triple bond and the negative charge is localized at the α -carbon, and opposes the preference for negative charge to reside at the more electronegative nitrile nitrogen. The result is a ground-state carbanion with greater negative charge at the more weakly electronegative α -carbon (0.6 units) than at the nitrile nitrogen (0.4 units).⁶

(2) Only a small fraction of the stabilization of carbanions by an α -cyano substituent can be attributed to the transfer of negative charge from carbon to nitrogen (vide infra). The inherent greater stability of delocalized than of localized charge favors a structure of the cyanomethyl carbanion in which there is some transfer of negative charge from the α -carbon to the nitrile nitrogen, and this is reinforced by the greater electronegativity of nitrogen. However, there is also an opposing preference for a structure in which there is a carbon–nitrogen triple bond rather than cumulative double bonds, which favors localization of the negative charge at the α -carbon (see above). We suggest that these opposing effects largely cancel, so that the change in energy associated with the structural and electronic reorganization of the hypothetical cyanomethyl carbanions in which all of the negative charge is localized either at the α -carbon or at the nitrile nitrogen, to give the ground-state structure, is minimal.

We also suggest the following: (1) It is useful to distinguish between (a) the *strong* stabilization of carbanions that is observed when delocalization results in a large transfer of negative charge from a weakly electronegative carbon to a strongly electronegative atom, such as is observed for α -carbonyl carbanions (enolate ions), and (b) the *weak* resonance stabilization of anions in which the charge is shared equally between two atoms, such as is observed for carboxylate ions⁷ and α -cyano carbanions. In the case of carboxylate ions, the results of a computational study of the effect of the α -carbonyl group on the acidity of simple alcohols provide evidence that the greater acidity of acetic acid ($pK_a = 4.8$)⁵⁹ than of ethanol ($pK_a = 15.9$)⁶⁰ is due mainly to the polar effect of the α -carbonyl group and that the resonance stabilization of carboxylate anions is relatively small.⁷ (2) No large intrinsic barrier to proton-transfer arises from the requirement for the transfer of negative charge from nitrogen to carbon on moving to the transition state for protonation of α -cyano carbanions^{2a} because this transfer of negative charge, which shows no preference to lie at carbon or nitrogen, is a facile process.

Acknowledgment. We acknowledge the National Institutes of Health (GM 39754) and the National Science Foundation (CHE 9712709) for support of this work. We thank Dr. Tina L. Amyes for helpful discussion.

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Supporting Information Available: Descriptions of the experimental procedures to monitor the following hydron exchange reactions: CH_3CN in D_2O , CD_3CN in H_2O , $\text{CH}_3\text{CH}_2\text{CN}$ in D_2O , $\text{NCCH}_2\text{CH}_2\text{CN}$ in D_2O , $\text{NCCD}_2\text{CD}_2\text{CN}$ in H_2O , descriptions of the procedures for ab initio calculations; descriptions of the procedures for Monte Carlo free energy perturbation calculations to determine the difference in the free energies of solvation of cyanoalkanes and the corresponding cyanocarbanions and of CH_3CN and $\text{CH}_2=\text{C}=\text{NH}$; Figures S1–S8: representative ^1H NMR spectra obtained during hydron exchange at CL_3CN , $\text{CH}_3\text{CH}_2\text{CN}$, and $\text{NCCH}_2\text{CH}_2\text{CN}$; and semilogarithmic plots of reaction progress against time for the LO^- -catalyzed hydron exchange reactions of CL_3CN , $\text{CH}_3\text{CH}_2\text{CN}$, and $\text{NCCL}_2\text{-CL}_2\text{CN}$; Figure S9: dependence of k_{obsd} (s^{-1}) for exchange for deuterium of the first α -hydrogen of acetonitrile on the concentration of quinuclidine and 3-quinuclidinol buffers and

logarithmic plot of k_{obsd} against the concentration of deuterioxide ion; Figure S10: selected geometrical parameters for propanenitrile (**1**), the α -cyanoethyl and β -cyanoethyl carbanions (**2** and **3**), succinonitrile (**4**), and the corresponding α -cyano carbanion (**5**); Table S1: results of individual simulations of the free energy of solvation of the cyanoalkanes and cyanocarbanions in Table 3; Table S2: results of simulations of the free energy of solvation of acetonitrile and $\text{H}_2\text{C}=\text{C}=\text{NH}$; Table S3: Lennard–Jones parameters and partial charges of acetonitrile and $\text{H}_2\text{C}=\text{C}=\text{NH}$ used in these simulations; Table S4: comparison of the hydrogen-bonding interaction energies and geometries predicted by the empirical potentials and by ab initio HF/6-31G* calculations (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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