Conclusions

In this work we have demonstrated that there are clear parallels between the heterogeneous and homogeneous chemistry of phosphomolybdate heteropolyanion systems. Surface intermediates that occur during a heterogeneous redox cycle in which methanol is oxidized have been isolated and compared to their stoichiometric counterparts by direct spectroscopic means. It has been established that the crucial intermediate is a methoxy group occupying a bridging site on the heteropolyanion framework. Because of the similarity of this chemistry to bulk metal oxide oxidations of alcohols, we expect further work on these systems to be a very fruitful strategy for clarifying the atomic scale picture of heterogeneous selective oxidation reactions.

Acknowledgment. The authors are grateful for the technical assistance of Willis Dolinger, Robert Carver, George Watunya, and James D. Simmons. Samples of the alkylated heteropolyanions were graciously provided by Walter Knoth. Solid-State ^{1}H NMR spectra were taken by A. J. Vega, to whom we are also grateful. W. E. Farneth would particularly like to thank J. B. Goodenough, E. M. Serwicka, and R. G. Finke for providing preprint copies of their manuscripts.

Cyanocarbon Acids: Direct Evidence That Their Ionization Is Not an Encounter-Controlled Process and Rationalization of the Unusual Solvent Isotope Effects

M. Hojatti, A. J. Kresge,* and W.-H. Wang

Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1, Canada. *Received December 10, 1986*

Abstract: The rate of exchange of the acidic hydrogen of *tert*-butylmalononitrile was examined by using tritium as a tracer, and the process was found not to be inhibited by hydronium ions in dilute aqueous hydrochloric acid solutions. This rules out the Swain–Grunwald mechanism for this reaction under these conditions. The bromination of malononitrile was investigated under conditions where reprotonation of the dicyanomethyl carbanion and its reaction with bromine occur at comparable rates, and the bromination reaction was found to have a specific rate twice that for reprotonation. Reprotonation therefore cannot be a diffusion-controlled process, and malononitrile is not a "normal" acid. The unusually large solvent kinetic isotope effects found for these cyanocarbon acid ionization reactions are explained by postulating that the transferring hydrogen and its positive charge are becoming associated with a solvent cluster rather than with a single water molecule. The thermodynamic acidity constant of malononitrile was determined to be 11.41 in aqueous solution at 25 °C.

Cyanocarbons such as malononitrile (**1**) and *tert*-butylmalononitrile (**2**) constitute an important class of organic acids inasmuch as their proton-transfer reactions are almost "normal"

$$\underset{\mathbf{1}}{(CN)_2CH_2} \qquad \underset{\mathbf{2}}{(CN)_2CH(t\text{-}Bu)}$$

in the Eigen sense.[1,2] Normal acids and bases are species whose proton-transfer reactions are almost completely diffusion-controlled; only in a small region near $\Delta pK = 0$ is the proton-transfer step of the overall proton-transfer process even partly rate-determining, and when ΔpK deviates from zero by as little as 2–3 pK units, encounter of the reactants or separation of the products becomes fully rate-determining.[1,3,4] Most carbon acids are not "normal" in this sense: the proton-transfer steps of their acid–base reactions are wholly rate-determining over a wide range of ΔpK.

Although much of the acid–base chemistry of cyanocarbons is well-understood, some aspects remain puzzling. In particular, solvent isotope effects on the rate of ionization of these acids in aqueous solution are unexpectedly large. For example, isotope effects measured by monitoring the rate of loss of tritium from labeled substrates to water are $k_{H_2O}/k_{D_2O} = 3.7$ for malononitrile and $k_{H_2O}/k_{D_2O} = 3.5$ for *tert*-butylmalononitrile.[5] On the assumption that proton transfer is rate-determining but nearly complete at the transition states of these reactions, eq 1, these solvent isotope effects would be attributed to the conversion of

$$RT + L_2O \rightarrow [R\overset{\delta-}{\cdots}T\overset{\delta+}{\cdots}OL_2]^{\ddagger} \rightarrow R^-{\cdot}TOL_2^+ \qquad (1)$$

two neutral hydrogen–oxygen bonds (L–O) to two positively charged ones (L–O$^+$), and they could be estimated by using fractionation factor theory[6] as $k_{H_2O}/k_{D_2O} = 1/l^2 = 2.1$. This difference between expected and observed values is made all the more remarkable by the fact that the isotope effect measured for detritiation of *tert*-butylmalononitrile when acetate ion rather than water is the proton acceptor, $k_{H_2O}/k_{D_2O} = 1.1$,[5] is not at all unusual.

These unexpectedly large isotope effects might be rationalized in terms of the Swain–Grunwald mechanism for diffusion-controlled isotope exchange reactions.[7] Although the evidence in-

(1) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–19.
(2) For a review of cyanocarbon acid–base behavior, see: Hibbert, F. In *Comprehensive Chemical Kinetics*, Vol. 8, Bamford, C. H., Tipper, C.F.H., Eds.; Elsevier: New York, 1977; Vol. 8, Chapt 2. See also Kreevoy et al. (Kreevoy, M. M.; Dolmar, J.; Langland, J. T. *Abstracts of Papers*, 166th National Meeting of the American Chemical Society; American Chemical Society: Washington, DC, 1973; PHYS 148) for the effect of viscosity on cyanocarbon ionization rate and Albery (Albery, W. J. In *Proton Transfer Reactions*; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; pp 294–296) for a discussion of isotope effects.
(3) Bell, R. P. *The Proton in Chemistry*; Cornell University Press: Ithaca, NY, 1973; (a) p 130, (b) p 22.
(4) Bergman, N.-Å; Chiang, Y.; Kresge, A. J. *J. Am. Chem. Soc.* **1978**, *100*, 5954–5956. Cox, M. M.; Jencks, W. P. *J. M. Chem. Soc.* **1978**, *100*, 5956–5957; **1981**, *103*, 572–580. Fischer, H.; De Candis, F. X.; Ogden, S. D.; Jencks, W. P. *J. Am. Soc.* **1980**, *102*, 1340–1347.
(5) Hibbert, F.; Long, F. A. *J. Am. Chem. Soc.* **1971**, *93*, 2836–2840.
(6) Kresge, A. J. *Pure Appl. Chem.* **1965**, *8*, 243–258. Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275–332. Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: New York, 1987; Vol. 7, Chapter 4.
(7) (a) Swain, C. G.; Labes, M. M. *J. Am. Chem. Soc.* **1957**, *79*, 1084–1088. Swain, C. G.; McKnight, J. T.; Kreiter, V. P. *J. Am. Chem. Soc.* **1957**, *79*, 1088–1093. Emerson, M. T.; Grunwald, E.; Kaplan, M. L.; Kromhout, R. A. *J. Am. Chem. Soc.* **1960**, *82*, 6307–6314. (b) Grunwald, E.; Ralph, E. K. *Acc. Chem. Res.* **1971**, *4*, 107–113. (c) Perrin, C. L.; Schiraldi, D. A.; Arrhenius, G. M. L. *J. Am. Chem. Soc.* **1982**, *104*, 196–201.

0002-7863/87/1509-4023$01.50/0

dicates that cyanocarbon acids are not quite normal and their acid–base reactions are therefore not diffusion-controlled in the region near $\Delta pK = 0$, the situation will be different when ΔpK is sufficiently far from zero. Even intrinsically very slow proton transfers from regular, "pseudo" carbon acids will become increasingly faster in the forward direction as the process becomes more strongly downhill and increasingly faster in the reverse direction as the process becomes more strongly uphill, and eventually, far enough away from $\Delta pK = 0$, they will become diffusion-controlled processes.[1,4,8] Neither of the cyanocarbon acids under discussion here is especially strong, $pK_a = 11.4$ (vide infra) for malononitrile and $pK_a = 13.2$ for *tert*-butylmalononitrile,[9] and proton transfer from these acids to water will be uphill by sizable amounts. This may be enough to make these reactions diffusion-controlled.

The Swain–Grunwald mechanism was proposed to account for the observation that hydrogen isotope exchange between some ammonium ions and hydroxylic solvents is inhibited by hydronium ions. This was explained by postulating that ionization of these ammonium ions occurs through proton transfer to a solvent molecule, e.g., water, which remains hydrogen bonded to the amine while giving up a different proton to another solvent molecule, eq 2. The immediate products of this ionization step are thus a

$$R_3N\text{-}H^+ + 2L_2O \rightleftharpoons R_3N\cdot HOL + L_3O^+ \qquad (2)$$

$$\downarrow L_2O$$

$$R_3N\cdot LOL$$

hydronium ion and an amine hydrate, with the latter still possessing the original, as yet unexchanged, ammonium ion hydrogen. Exchange requires replacement of this hydrogen through a process which breaks the amine hydrate hydrogen bond, and if this can occur in competition with reaction of the hydrate with hydronium ion to reform unexchanged ammonium ion, exchange will be inhibited by hydronium ions.

The first step of this reaction mechanism converts three uncharged L–O bonds to three charged ones, and that will contribute a factor of $1/l^3$ to the solvent isotope effect. Because the process is diffusion-controlled, its rate will also be slowed by the difference in viscosity between H_2O and D_2O ($\eta_{D_2O}/\eta_{H_2O} = 1.23$).[10] Combination of these factors leads to $k_{H_2O}/k_{D_2O} = 3.7$, which is nicely consistent with the effects observed for detritiation of malononitrile and *tert*-butylmalononitrile. Isotope effects of this magnitude have also been found for hydrogen exchange of some ammonium ions.[7b,11]

In order to obtain evidence bearing upon this explanation, we examined the detritiation of *tert*-butylmalononitrile for inhibition by hydronium ion. Unfortunately, we found none. We then studied the ionization of malononitrile using bromine to scavenge the dicyanomethyl carbanion as it formed, and we were able to obtain direct evidence showing that the rate of reprotonation of this carbanion is an order of magnitude slower than its reaction with bromine. This invalidates our rationalization of solvent isotope effects on the basis of the Swain–Grunwald mechanism, but we present another, somewhat related explanation to account for these unusual isotope effects.

In order to analyze our results, we needed to know the acid ionization constant of malononitrile. There are several reports of the determination of this constant in the literature,[12] but it is not clear whether the values cited are thermodynamic ionization constants referred to a standard state of zero electrolyte concentration or whether they are concentration quotients at some (unspecified) ionic strength. We have therefore measured this acidity constant ourselves.

Experimental Section

Materials. *tert*-Butylmalononitrile was prepared by adding methylmagnesium bromide to isopropylidenemalononitrile, which in turn was made by condensing malononitrile with acetone.[13] A sample of this material was tritiated by exchange with tritiated water in aqueous tetrahydrofuran (60:40) solution; the labeled substrate was purified to a constant melting point (78–79 °C) by repeated vacuum sublimation.

Malononitrile was purchased from Aldrich and was purified by vacuum distillation. All other substances were best available commercial grades and were used as received. Solutions were prepared with deionized water which had been purified further by distillation.

Acidity Constant Determination. The acid dissociation constant of malononitrile was determined spectroscopically by measuring the strong absorbance of its conjugate base at $\lambda_{max} = 225$ nm in solutions of known hydroxide ion concentration. The absorbance measurements were made on an HP Model 8451A spectrometer with cell compartment thermostated at 25.0 ± 0.05 °C. Two-milliliter portions of sodium hydroxide solutions were first allowed to come to temperature equilibrium with the cell compartment; 30-μL aliquots of a 3×10^{-3} M aqueous stock solution of malononitrile were then added and the absorbance readings were made. The ionic strength of the sodium hydroxide solutions was held constant at 0.100 M by adding sodium chloride as required; the hydroxide ion concentrations of these solutions were evaluated by measuring pH's (Beckman Model 1019 Research Meter operating with an Orion Model 810200 Ross Combination Electrode) and converting these to concentrations with use of the hydroxide ion activity coefficient recommended by Bates, $y = 0.76$.[14]

Kinetics, Tritium Exchange. Reactions were conducted in a constant temperature bath operating at 25.0 ± 0.02 °C. Fifty-milliliter portions of aqueous acids of appropriate concentration were first allowed to come to temperature equilibrium with this bath, and then 0.3-mL amounts of a stock solution of tritiated substrate dissolved in dioxane or tetrahydrofuran were added to initiate exchange. At appropriate time intervals, 3-mL samples of these reaction mixtures were withdrawn and were rapidly extracted with 15-mL portions of toluene. The toluene extracts were then dried over calcium chloride, and 10-mL aliquots were combined with 10-mL portions of toluene-based counting solution (4.0 g of PPO and 0.05 g of POPOP per liter of toluene) and were subjected to radiochemical assay with an LKB Model 1217 RACKBETA liquid scintillation counter. Sampling was continued for at least 6 half-lifes and "infinite-time" aliquots were taken after 10 half-lives. The data so obtained conformed to the first-order rate law well, and observed first-order rate constants were obtained by least-squares fitting to a linear expression.

Kinetics, Bromination. Rates of bromination were measured spectroscopically with a Cary Model 118 spectrometer with cell compartment thermostated at 25.0 ± 0.05 °C. Reactions were performed under first-order conditions with initial stoichiometric bromine concentrations ca. 5×10^{-2} M and initial malononitrile concentrations ca. 8×10^{-4} M. Reactions were initiated by adding 5-μL samples of malononitrile stock solution to 3-mL portions of acid and bromine solution, which had previously been allowed to come to temperature equilibrium with the spectrometer cell compartment. The decrease in bromine optical density was monitored at $\lambda = 509$ or 520 nm (the latter was used for initially bromide-free solutions). Reactions were followed to completion. The data fit the first-order rate law well, and observed rate constants were calculated by least-squares fitting to an exponential function.[15] Bromine concentrations in the reaction mixtures were determined by iodometric titration; in the case of initially bromide-free solutions, this was done immediately upon completion of the kinetic measurements in order to minimize bromine loss by evaporation.

Results

Acidity Constant of Malononitrile. The acid ionization constant of malononitrile was determined spectroscopically by measuring the change in absorbance produced by the ionization reaction at different sodium hydroxide concentrations. The data so obtained are summarized in Table I and are displayed as a titration curve

(8) Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354–360.
(9) Hibbert, F.; Long, F. A.; Walters, E. A. *J. Am. Chem. Soc.* **1971**, *93*, 2829–2835.
(10) Millero, F. J.; Dexter, R.; Hoff, E. *J. Chem. Eng. Data* **1971**, *16*, 85–87.
(11) Grunwald, E.; Eustace, D. In *Proton Transfer Reactions*; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; Chapt 4.
(12) (a) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439–2443. (b) Hashimoto, F.; Tanaka, J.; Nakakura, S. *J. Mol. Spectrosc.* **1963**, *10*, 401–417. (c) Boyd, R. H.; Wang, C.-H. *J. Am. Chem. Soc.* **1965**, *87*, 430–436. (d) Bowden, K.; Stewart, R. *Tetrahedron* **1965**, *21*, 261–266.
(13) Wheland, R. C.; Martin, E. L. *J. Org. Chem.* **1975**, *40*, 3101–3109.
(14) Bates, R. G. *Determination of pH. Theory and Practice*; Wiley: New York, 1973; p 49.
(15) Swain, C. G.; Swain, M. S.; Berg, L. F. *J. Chem. Inf. Comput. Sci.* **1980**, *20*, 47–51.

Table I. Absorbance Measurements Made To Determine the Acidity Constant of Malononitrile in Aqueous Solution at 25 °C, Ionic Strength = 0.10 M

$[NaOH]/10^{-3}$ M	absorbance[a]	$[NaOH]/10^{-3}$ M	absorbance[a]
0.199	0.020	9.94	0.397
0.994	0.100	19.9	0.447
1.99	0.199	39.8	0.476
3.98	0.299	59.6	0.485
5.96	0.346	79.5	0.489
7.95	0.381	99.4	0.493

$$A = \{(3.91 \pm 1.07) \times 10^{-5} + (5.02 \pm 0.02)[HO^-]\}/\{(2.66 \pm 0.08) \times 10^{-3} + [HO^-]\}$$

[a] Measured at λ = 225 nm on samples with total substrate concentration 2.73×10^{-5} M, 1.00 cm path length.

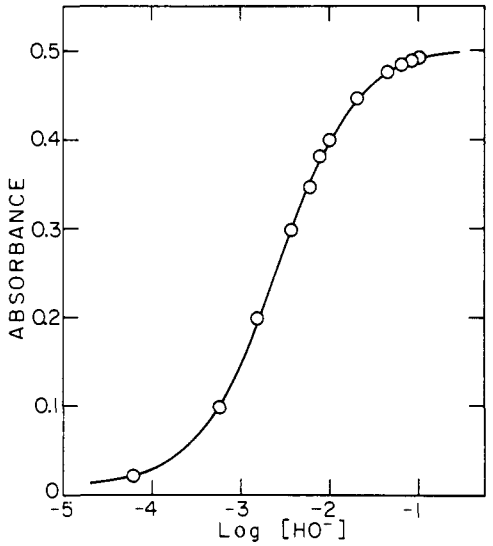


Figure 1. Spectrophotometric titration curve for the acid ionization of malononitrile in aqueous solution at 25 °C and ionic strength 0.10 M; the line shown was drawn with parameters obtained by least-squares fit to eq 3.

in Figure 1. They were fitted to the expression given in eq 3, where A is the absorbance of a solution with hydroxide ion con-

$$A = \frac{A_{AH}Q_B + A_{A^-}[HO^-]}{Q_B + [HO^-]} \quad (3)$$

centration $[HO^-]$, A_{AH} and A_{A^-} are the limiting absorbances of the acidic (AH) and basic (A^-) forms of the substrate, and Q_B ($=[AH][HO^-]/[A^-]$) is the basicity concentration quotient for this system at the ionic strength employed (0.10 M). Best values of the three parameters Q_B, A_{AH}, and A_{A^-} were obtained by nonlinear least-squares analysis. The results are $Q_B = (2.66 \pm 0.08) \times 10^{-3}$ M, $A_{AH} = (1.47 \pm 0.40) \times 10^{-2}$ cm^{-1}, and $A_{A^-} = (5.02 \pm 0.02) \times 10^{-1}$ cm^{-1}. These values were used to draw the line shown in Figure 1.

The constant Q_B may be converted to an acidity concentration quotient, $Q_a = (5.95 \pm 0.19) \times 10^{-12}$ M, by using the relationship $Q_aQ_B = 1.59 \times 10^{-14}$ M^2, in which 1.59×10^{-14} is the ion concentration product of water at ionic strength 0.10 M, obtained by using the thermodynamic ion activity product and activity coefficients for the hydrogen ion (y = 0.83) and hydroxyl ion (y = 0.76) recommended by Bates.[14] The concentration quotient Q_a may in turn be transformed into an estimate of the thermodynamic acid ionization constant, $K_a = (3.85 \pm 0.12) \times 10^{-12}$ M, $pK_a = 11.41 \pm 0.01$, using $y_{H^+} = 0.83$ and $y_{A^-} = 0.78$.

This pK_a is significantly greater than all previously reported values: 11.19,[12a] 11.16,[12b] 11.20,[12c] and 11.14.[12d] These earlier values, however, are much closer to the negative logarithm of the presently determined acidity concentration quotient, $pQ_a = 11.23$, and that suggests that the previous values were not corrected for the effect of ionic strength. The presently determined value of

Table II. Rates of Loss of Tritium from Labeled *tert*-Butylmalononitrile in Aqueous Solution at 25 °C

$[HCl]/10^{-2}$ M	$k_{obsd}/10^{-4}$ s^{-1}	$[HCl]/10^{-2}$ M	$k_{obsd}/10^{-4}$ s^{-1}
Ionic Strength = 0.10 M (NaCl)			
1.00	3.27	6.01	3.28
2.00	3.30	7.01	3.29
3.01	3.27	8.02	3.26
4.01	3.30	9.02	3.24
5.01	3.29	10.0	3.29
$k_{obsd}/s^{-1} = (3.29 \pm 0.01) \times 10^{-4} - (2.01 \pm 2.11) \times 10^{-5}$[HCl] Ionic Strength = [HCl]			
1.00	3.02	50.0	2.39
10.0	2.96	70.0	2.16
20.0	2.85	90.0	1.89
30.0	2.63		

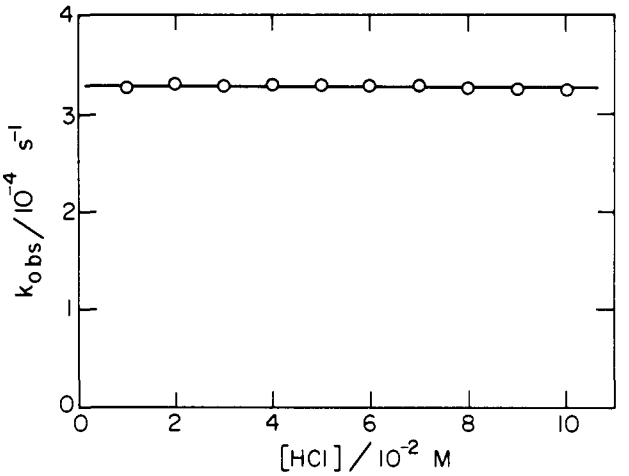


Figure 2. Relationship between acid concentration and specific rate of detritiation of *tert*-butylmalononitrile in aqueous HCl solutions at 25 °C.

A_{A^-} divided by the concentration of substrate used in our experiments gives $\epsilon_{A^-} = 18\,400 \pm 100$ M^{-1} cm^{-1} as the molar extinction coefficient of the conjugate base of malononitrile, in good agreement with earlier values $\epsilon_{A^-} = 18\,000$ M^{-1} cm^{-1} [12b] and $\epsilon_{A^-} = 18\,600$ M^{-1} cm^{-1}.[12d] The much smaller molar extinction coefficient of the acidic form determined here, $\epsilon_{AH} = 540 \pm 150$ M^{-1} cm^{-1}, is also consistent with the zero value for this quantity reported before.[12b,d]

Tritium Exchange. Two series of determinations of the rate of loss of tritium from labeled *tert*-butylmalononitrile in acid solutions were carried out, one at constant ionic strength (0.10 M) with [HCl] = 0.01–0.10 M and another at variable ionic strength equal to [HCl] with [HCl] in the range 0.01–0.9 M. These data are summarized in Table II.

As Figure 2 indicates, the rate constants measured in dilute acid solutions show no dependence of reaction rate upon hydronium ion concentration. Least-squares analysis gives a slope, $-(2.01 \pm 2.11) \times 10^{-5}$ M^{-1} s^{-1}, which is zero within the experimental uncertainty, and an intercept, $k = (3.29 \pm 0.01) \times 10^{-4}$ s^{-1}, which agrees very well with a previous determination, $k = (3.27 \pm 0.02) \times 10^{-4}$ s^{-1}.[9]

Rate constants measured in more concentrated acids, on the other hand, do show a modest drop with increasing acid concentration. The situation here is complicated, however, by the fact that the solutions employed are sufficiently concentrated to require the use of acidity functions as a measure of medium acid strength. It has been pointed out[7c,16] that in this circumstance a decrease in reaction rate with increasing acidity is not diagnostic of the Swain–Grunwald mechanism, for in such solutions even a process in which proton transfer is fully rate-determining, and the conditions required for the Swain–Grunwald mechanism are

(16) Rosenthal, D.; Grunwald, E. *J. Am. Chem. Soc.* **1972**, *94*, 5956–5961.

Table III. Rates of Bromination of Malononitrile in Aqueous Solution at 25 °C[a]

$[H^+]/10^{-2}$ M	$k_{obsd}/10^{-2}$ s^{-1}	$[H^+]/10^{-2}$ M	$k_{obsd}/10^{-2}$ s^{-1}
No Initial Bromide Ion:[b]			
1.00	2.65	6.00	1.62[c]
2.00	2.32	8.00	1.53
4.00	1.93	10.0	1.40
$(k_{obsd}/s^{-1})^{-1} = (3.58 \pm 0.17) \times 10^1 + (2.03 \pm 0.16) \times 10^1 [H^+]/[Br_2]$			
$[Br^-] = 0.10$ M[d]			
1.00	2.55	6.00	1.49
2.00	2.13	8.00	1.28
4.00	1.87	10.0	1.16
$(k_{obsd}/s^{-1}) = (3.47 \pm 0.14) \times 10^1 + (2.88 \pm 0.12) \times 10^1 [H^+]/[Br_2]$			

[a] Initial substrate concentration = 8.2×10^{-4} M. [b] Initial stoichiometric bromine concentration = 5.43×10^{-2} M unless otherwise indicated; H^+ supplied as $HClO_4$ and ionic strength held constant at 0.100 M with $KClO_4$. [c] Initial stoichiometric bromine concentration = 5.29×10^{-2} M. [d] Initial stoichiometric bromine concentration = 5.48×10^{-2} M; H^+ supplied as HBr and ionic strength held constant at 0.100 M with KBr.

Table IV. Summary of Rate Constants[a]

reaction	rate constant
$(CN)_2CH_2 \rightarrow (CN)_2CH^- + H^+$	2.85×10^{-2} s^{-1}
t-Bu$(CN)_2CT \rightarrow t$-Bu$(CN)_2C^- + T^+$	3.27×10^{-4} s^1
$(CN)_2CH^- + H^+ \rightarrow (CN)_2CH_2$	4.78×10^9 M^{-1} s^{-1}
$(CN)_2CH^- + Br_2 \rightarrow (CN)_2CHBr + Br^-$	8.27×10^9 M^{-1} s^{-1}
$(CN)_2CH^- + Br_3^- \rightarrow (CN)_2CHBr + 2Br^-$	3.8×10^9 M^{-1} s^{-1}

[a] Aqueous solution, 25 °C, ionic strength = 0.10 M.

therefore not fulfilled, is expected to show an inverse dependence on acidity. This expectation is substantiated by our bromination experiments (vide infra) which indicate that proton transfer is in fact rate-determining in the ionization of malononitrile and, by analogy, presumably also so in the ionization of *tert*-butylmalononitrile.

Bromination. The bromination of malononitrile was conducted under conditions where reprotonation of the dicyanomethyl carbanion and its reaction with bromine occur at comparable rates, i.e., $k_{-1}[H^+] \cong k_2[Br_2]$ (eq 4). The rate law for this situation, eq 5, leads to simple first-order kinetics if hydrogen ion and

$$RH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^- + H^+ \qquad (4)$$

$$\overset{k_2 \downarrow Br_2}{RBr}$$

$$\frac{-d[RH]}{[RH]\,dt} = k_{obsd} = \frac{k_1 k_2 [Br]}{k_{-1}[H^+] + k_2[Br_2]} \qquad (5)$$

bromine are supplied in large excess over malononitrile. This was achieved by using $[RH] = 8 \times 10^{-4}$ M, $[Br_2] = 5 \times 10^{-2}$ M, and $[H^+] = 0.01$–0.1 M. Reactions were monitored by measuring bromine concentrations spectroscopically; the absorbance changes were small, inasmuch as only 3% of the bromine was consumed, but these changes could be measured accurately with the spectrometer employed (Cary 118). Two sets of rate determinations were performed, one with no bromide ion added initially to the reaction mixture and another with initial bromide ion concentration = 0.10 M. These data are summarized in Table III.

Figure 3 shows that observed rate constants decrease with increasing acid concentration, as expected on the basis of the rate law of eq 5. This rate law requires $(k_{obsd})^{-1}$ to be a linear function of $[H^+]/[Br_2]$, eq 6, and Figure 4 shows that this is indeed the

$$(k_{obsd})^{-1} = \frac{1}{k_1} + \frac{k_{-1}}{k_1 k_2} \frac{[H^+]}{[Br_2]} \qquad (6)$$

case. Linear least-squares analysis gave the slope and intercept parameters listed in Table III.

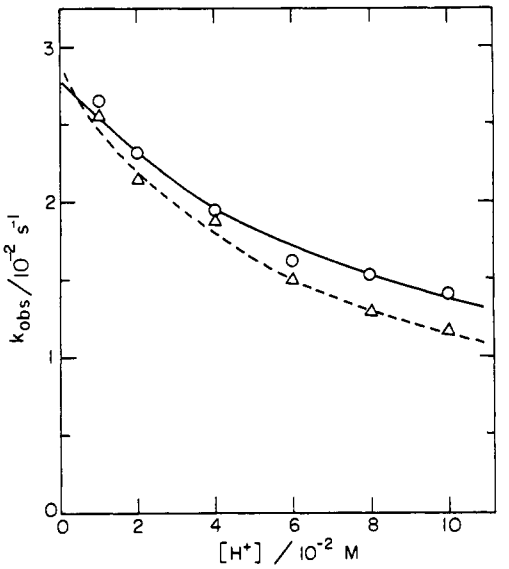


Figure 3. Inhibition by acid of the rate of bromination of malononitrile in aqueous solution at 25 °C; (○) no initial bromide ion; (△) $[Br^-] = 0.10$ M.

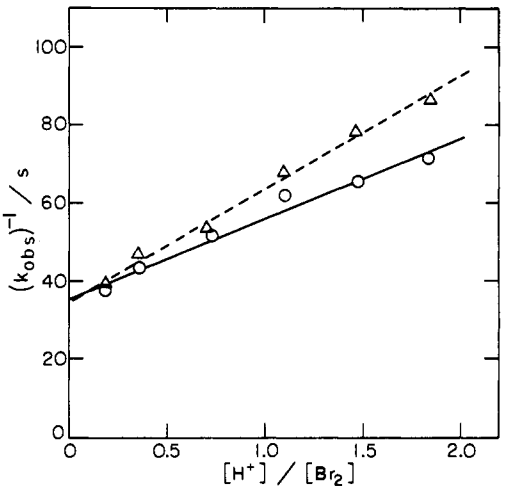


Figure 4. Data of Figure 3 plotted according to eq 5.

The intercepts give $k_1 = (2.79 \pm 0.14) \times 10^{-2}$ s^{-1} for the series with no initial bromide ion and $k_1 = (2.88 \pm 0.11) \times 10^{-2}$ s^{-1} for the series with $[Br^-] = 0.10$ M. These results are in good agreement with one another, and their weighted average, $k_1 = (2.85 \pm 0.09) \times 10^{-2}$ s^{-1}, also agrees well with a previous determination, $k_1 = (2.86 \pm 0.06) \times 10^{-2}$ s^{-1}.[9] Combination of this rate constant with the acidity concentration quotient of malononitrile determined here, $Q_a = 5.95 \times 10^{-12}$ M, leads to $k_{-1} = (4.78 \pm 0.21) \times 10^9$ M^{-1} s^{-1}.

The slopes of these linear relationships, when combined with the ratio k_1/k_{-1} ($=Q_a$), give $k_2 = (8.27 \pm 0.68) \times 10^9$ M^{-1} s^{-1} for the determinations made with no initially added bromide ion and $k_2 = (5.84 \pm 0.31) \times 10^9$ M^{-1} s^{-1} for those with $[Br^-] = 0.10$ M. The difference between these two values may be ascribed to the conversion of some bromine to the less reactive tribromide ion in the solutions containing initially added bromide ion. Bromide ion is of course a product of the bromination reaction, and the reaction mixtures with no initially added bromide ion are therefore not completely bromide ion free. The amount of bromide ion so produced, however, is negligibly small, and the rate constant measured in these solutions, $k_2 = 8.27 \times 10^9$ M^{-1} s^{-1}, may safely be attributed wholly to reaction of the dicyanomethyl carbanion with molecular bromine. Use of $K = 16.7$[17] for the $Br_2 + Br^-$

(17) (a) Griffith, R. O.; McKeown, A.; Winn, A. G. *Trans. Faraday Soc.* **1932**, *28*, 101–107. (b) Keeffe, J. R.; Kresge, A. J.; Toullec, J. *Can. J. Chem.* **1986**, *64*, 1224–1227.

= Br_3^- equilibrium then leads to a $[Br_2]/[Br_3^-]$ ratio for the bromide-added solutions from which $k_2 = 3.8 \times 10^9$ M^{-1} s^{-1} may be calculated for reaction of the dicyanomethyl carbanion with tribromide ion. This analysis makes bromine 2.2 times more reactive than tribromide ion, which is similar to the factors found for these two species in the acid-catalyzed bromination of a number of ketones.[18]

Discussion

Normal Acid or Pseudo Acid Behavior? We have found that the specific rate of reprotonation of the dicyanomethyl carbanion, eq 7, is half of that for reaction of this carbanion with bromine,

$$(CN)_2CH^- + H^+ \rightarrow (CN)_2CH_2 \quad (7)$$

eq 8. This indicates that the reprotonation reaction is *not* a

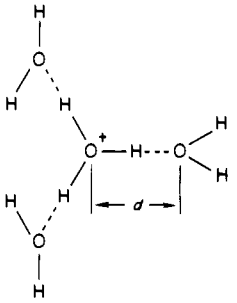
$$(CN)_2CH^- + Br_2 \rightarrow (CN)_2CHBr + Br^- \quad (8)$$

diffusion-controlled process, for, if it were, its rate constant would have to be *greater* than that of the bromination reaction. This follows from the fact that the diffusion coefficient of the proton in aqueous solution is unusually large, and that plus other factors make diffusion-controlled reactions of H^+ faster than diffusion-controlled reactions of other molecules or ions.

A quantitative estimate of the difference in specific rate of diffusion together of $(CN)_2CH^-$ with H^+ and with Br_2 may be made with use of the Debye–Smoluchowski equation.[19a] This equation (eq 9) expresses the rate constant, k_d, for diffusional encounter of two molecules, A and B, in terms of their diffusion coefficients (D_A, D_B) and reaction radii (r_A, r_B), plus an electrostatic term $\delta/(e^\delta - 1)$ which operates only if both A and B are ions. In the present case, all three of these factors favor the reprotonation reaction.

$$k_d = 4\pi N(D_A + D_B)(r_A + r_B)\delta/(e^\delta - 1) \quad (9)$$

The electrostatic term will contribute a factor of about 2 to reprotonation[19b] and nothing to bromination. The diffusion coefficient of H^+ in aqueous solution at 25 °C is 9.3×10^{-5} cm^2 s^{-1},[20] while that of Br_2 is six times less, 1.5×10^{-5} cm^2 s^{-1}.[22] The kinetically effective form of H^+ is generally taken to be the hydronium ion trihydrate $H_9O_4^+$ (**3**),[1,3b] for which the oxygen–oxygen



3

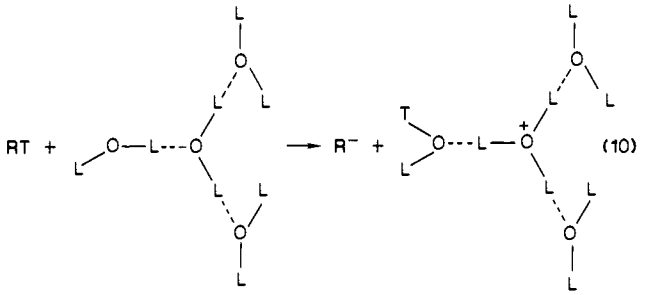
distance d has been determined to be 2.5 Å;[23] combination of that with the known geometry of the water molecule[24a] and the van der Waals radius of hydrogen[24b] leads to a reaction radius of 4.3 Å for this species.[25] A reaction radius of 3 Å for Br_2 may be estimated from the Br–Br bond length[24c] and the van der Waals radius of Br.[24b] These parameters, coupled with an estimated diffusion coefficient of 1×10^{-5} cm^2 s^{-1} and reaction radius of 5 Å for $(CN)_2CH^-$, make the specific rate of diffusion together of this carbanion with H^+ ten times that of the carbanion with Br_2.

Thus, if both reprotonation and bromination were diffusion-controlled processes, the specific rate of reprotonation would have to be ten times that for bromination. If bromination were not diffusion-controlled, the rate difference would have to be greater. Since the rate difference actually observed is a factor of 2 in the opposite direction, reprotonation cannot be diffusion-controlled and malononitrile is not quite—though almost—a normal acid.

It seems likely, on the other hand, that reaction of the dicyanomethyl carbanion with bromine is diffusion-controlled. Its rate constant, $k = 8.3 \times 10^9$ M^{-1} s^{-1}, is even greater than $k = 3.2 \times 10^9$ M^{-1} s^{-1} for the reaction of bromine with the enol of acetophenone[17b] and $k = 3.1 \times 10^9$ M^{-1} s^{-1} for the reaction of bromine with the enol of acetone,[27] both of which are believed to be diffusion-controlled processes.[18] The difference between $k = 8.3 \times 10^9$ M^{-1} s^{-1} for the reaction of $(CN)_2CH^-$ with Br_2 and $k = 3.8 \times 10^9$ M^{-1} s^{-1} for its reaction with Br_3^-, moreover, is just about that expected from the electrostatic term of the Debye–Smoluchowsky equation,[29] and this suggests that the tribromide ion reaction is diffusion-controlled as well.

Solvent Isotope Effects. These arguments lead to the conclusion that the acid-ionization of malononitrile misses being a diffusion-controlled process by a rate factor of at least 20. Proton transfer must therefore be the rate-controlling event in this process, and that invalidates our use of the Swain–Grunwald mechanism to explain the unusually large solvent isotope effects on this reaction.

The essential feature of that explanation was the hypothesis that three, rather than only two, L–O bonds share the positive charge transferred to the solvent in this reaction. This feature might still be retained by postulating that the proton being transferred is recieved not by a single water molecule but by a hydrogen-bonded solvent cluster. Such a mechanism involving a cluster of four water molecules and producing the $H_9O_4^+$ unit (**3**) directly has in fact been suggested on the basis of recent picosecond studies of excited state proton transfer.[30] This scheme, applied to the detritiation of cyanocarbon acids in H_2O and D_2O, eq 10, would give a hydronium ion trihydrate, $TL_8O_4^+$, with a



tritium on the outside and a positive charge associated with three L–O bonds in the center. The result is a rate-controlling event

(18) Dubois, J.-E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* **1981**, *103*, 5393–5401.
(19) Caldin, E. F. *Fast Reactions in Solution*; Blackwell: Oxford, 1964; (a) p 10–13, (b) p 293.
(20) Calculated from the limiting equivalent conductivity of H^+ [21a] by using the Nernst expression.[21b]
(21) Robinson, R. A.; Stokes, R. H. *Electrolyte Solutions*; Butterworths: London, 1959; (a) p 465, (b) p 317.
(22) Albery, W. J.; Greenwood, A. R.; Kibble, R. F. *Trans. Faraday Soc.* **1967**, *63*, 360–368.
(23) Triolo, R.; Narten, A. H. *J. Chem. Phys.* **1975**, *63*, 3624–3631.
(24) Pauling, L. *Nature of the Chemical Bond*; Cornell University Press: Ithaca, NY., 1948; (a) p 78, 302, (b) p 189, (c) p 165.
(25) This estimate may be too low, for there is some recent evidence that the kinetically effective unit is larger than $H_9O_4^+$.[26]
(26) Kresge, A. J.; Holzwarth, J. F., unpublished work reported in summary in the following: Kresge, A. J. *Proceedings First Conference on Physical Organic Chemistry*; Humeres, E., Ed.; University of Santa Caterina Press: Florianopolis, Brazil, 1982; pp 15–41.
(27) Estimated in the same way as for acetophenone enol[17b] with $K_E = 6.0 \times 10^{-9}$ as the keto–enol equilibrium constant for acetone.[28]
(28) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460–462.
(29) A minor contribution to the difference in specific rate between the Br_2 and Br_3^- reactions will be made by the 12% lower diffusion coefficient of Br_3^-.[22]
(30) Lee, J.; Robinson, G. W.; Webb, S. P.; Phillips, L. A.; Clark, J. H. *J. Am. Chem. Soc.* **1986**, *108*, 6538–6542. Robinson, G. W.; Thistlewaite, P. J.; Lee, J. *J. Phys. Chem.* **1986**, *90*, 4224–4233.

which transfers positive charge to three rather than two L-O bonds.

It is instructive to apply this idea to an analysis of the isotope effect on the ionization of *tert*-butylmalononitrile determined by measuring rates of tritium exchange,[5] represented schematically by eq 11. Application of fractionation factor theory gives

$$RT + (L_2O)_4 \rightarrow [\overset{\delta-}{R}\cdots\overset{\delta+}{T}-(OL_2)_4]^{\ddagger} \quad (11)$$

$k_{H_2O}/k_{D_2O} = 1/\Phi_{R^-}{}^{\ddagger} l^{3\beta_i}$, in which $\Phi_{R^-}{}^{\ddagger}$ refers to isotopic fractionation in the solvation shell of the developing cyanocarbanion and β_i is an isotopic exponent that measures the portion of a full positive charge transferred to the hydron-receiving water cluster at the transition state. A value of $\Phi_{R^-}{}^{\ddagger}$ may be estimated from the isotope effect determined for the analogous reaction of *tert*-butylmalononitrile with acetate ion, eq 12; for that system $k_{H_2O}/k_{D_2O} = \Phi_{OAc^-}/\Phi_{R^-}{}^{\ddagger}$, and, with $k_{H_2O}/k_{D_2O} = 1.12$[5] and $\Phi_{OAc^-} = 0.90$,[31] $\Phi_{R^-}{}^{\ddagger} = 0.80$. This result, coupled with $k_{H_2O}/k_{D_2O} = 3.5$ for the process of eq 11[5] and $l = 0.69$, leads to $\beta_i = 0.92$; this is a reasonable value for a process in which proton transfer is almost but not quite complete at the rate-determining transition state.

$$RT + OAc^- \rightarrow [\overset{\delta-}{R}\cdots\overset{\delta-}{T}-OAc]^{\ddagger} \quad (12)$$

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Registry No. H_2, 1333-74-0; $(CN)_2CH^-$, 41470-37-5; Br_3^-, 14522-80-6; Br_2, 7726-95-6; T_2, 10028-17-8; *tert*-butylmalononitrile, 4210-60-0; malononitrile, 109-77-3.

(31) Gold, V.; Lowe, B. M. *J. Chem. Soc. A.* **1968**, 1923-1932. Albery, W. J. In *Proton Transfer Reactions*; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; p 283.

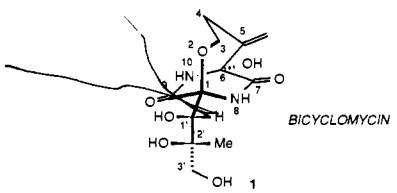
Mechanism, Biological Relevance, and Structural Requirements for Thiolate Additions to Bicyclomycin and Analogues: A Unique Latent Michael Acceptor System

Robert M. Williams,*‡ Kohtaro Tomizawa, Robert W. Armstrong, and Jen-Sen Dung

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received December 18, 1986*

Abstract: Several bicyclomycin analogues based on the 8,10-diaza-5-methylene-2-oxabicyclo[4.2.2]decane-7,9-dione ring system have been synthesized and examined for thiolate addition to the C-5 *exo*-methylene group. The results indicate that the minimum structural requirements for thiolate addition at pH 12.5 include the following: (1) obligate partnership of the C-5 *exo*-methylene and C-6-bridgehead hydroxyl groups; (2) secondary or unsubstituted (-NH-) amide at N-10; and (3) a C-1′-OH to activate the C-9 carbonyl for tautomeric ring opening to a reactive α,β-unsaturated ketone. Kinetics for conversion of **18** → **19a,b** indicate that a proton transfer from solvent is involved in the rate-limiting step: $K_{H_2O}/K_{D_2O} = 2.4$; $\Delta G^{\ddagger} = 19$ kcal/mol; $\Delta H^{\ddagger} = 17.5$ kcal/mol; $\Delta S^{\ddagger} = -5$ eu. The reaction of **18** with NaSMe to form sulfide adducts **19a,b** is irreversible as evidenced by ^{18}O incorporation and H/D exchange experiments. The results are discussed in the context of a recently proposed mechanism of action for bicyclomycin. It is shown that there is not a simple correlation between the capacity for structures to react with NaSMe and a capacity for antimicrobial activity.

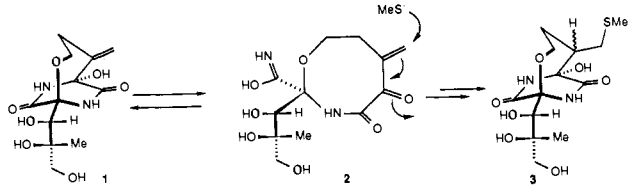
Bicyclomycin (**1**) is a commercially important antibiotic that is being produced from the fermentation harvest of *Streptomyces sapporonensis* at the Fujisawa Pharmaceutical Co. (Japan) where the natural product was originally isolated and identified.[1,2] This structurally unique bicyclic dipeptide is biosynthetically derived[3] from the amino acids leucine and isoleucine and constitutes both a mechanistically and a structurally new class of antibiotics. The low toxicity of bicyclomycin[1] coupled with the efficiency of the fermentation process has resulted in the introduction of bicyclomycin[4] on both the European and Japanese markets as an effective agent against nonspecific diarrhea in humans and bacterial diarrhea in livestock, respectively.[5]



1

Bicyclomycin is a weak antibiotic displaying activity[1] against Gram-negative organisms such as *Escherichia coli*, *Klebsiella*, *Shigella*, *Salmonella*, *Citrobacter*, *Enterobacter cloacae*, and *Neisseria* but is inactive toward *Proteus*, *Pseudomonas aeruginosa*, and Gram-positive bacteria. The mechanism of action of bi-

Scheme I



‡Fellow of the Alfred P. Sloan Foundation 1986-1988. NIH Research Career Development Awardee 1984-1989. Eli Lilly Grantee 1986-1988.

(1) (a) Miyoshi, T.; Miyari, N.; Aoki, H.; Kohsaka, M.; Sakai, H.; Imanaka, H. *J. Antibiot.* **1972**, *25*, 569. (b) Kamiya, T.; Maeno, S.; Hashimoto, M.; Mine, Y. *Ibid.* **1972**, *25*, 576. (c) Nishida, M.; Mine, Y.; Matsubara, T. *Ibid.* **1972**, *25*, 582. (d) Nishida, M.; Mine, Y.; Matsubara, T.; Goto, S.; Kuwahara, S. *Ibid.* **1972**, *25*, 594.

(2) Bicyclomycin (Aizumycin) was simultaneously isolated from *Streptomyces aizunensis*: (a) Miyamura, S.; Ogasawara, N.; Otsuka, N.; Niwayama, S.; Tanaka, H.; Take, T.; Uchiyama, T.; Ochiai, H.; Abe, K.; Koizumi, K.; Asao; Matsuki, K.; Hoshino, T. *J. Antibiot.* **1972**, *25*, 610. (b) Miyamura, S.; Ogasawara, N.; Otsuka, H.; Niwayama, S.; Tanaka, H.; Take, T.; Uchiyama, T.; Ochiai, H. *Ibid.* **1973**, *26*, 479.

(3) Miyoshi, T.; Iseki, M.; Konomi, T.; Imanaka, H. *J. Antibiot.* **1980**, *33*, 480, 488.

(4) The commercial synonym "bicozamycin" is the name liscensed to Fujisawa Pharmaceutical Co., Ltd., Japan, see: Merck Index, 10th ed.; Merck: Rahway, NJ, 1984; No. 1213.

0002-7863/87/1509-4028$01.50/0