Nucleophilic Addition to Olefins. 12.[1] Solvent-Induced Change in the Rate-Limiting Step of the Hydrolysis of Benzylidenemalononitrile in Acidic Me_2SO–Water Solution

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Abstract: A kinetic study of the reversible, four-step hydrolysis of benzylidenemalononitrile (BMN) to form benzaldehyde and malononitrile in water and Me_2SO–water mixtures (50%, 60%, and 70% Me_2SO (v/v)) is reported. At pH ≤2 the breakdown of the neutral tetrahedral intermediate, $PhCH(OH)CH(CN)_2$ (T°_{OH}, Scheme I, $k_{34}^{H_2O}$), is rate limiting in all solvents. Above pH 2 the breakdown of the anionic intermediate, $PhCH(O^-)CH(CN)_2$ (T^-_O, Scheme I, k_4), is rate limiting in water, while in the presence of Me_2SO oxygen deprotonation of T°_{OH} (k_3^B) becomes partially rate limiting at low buffer concentrations. A detailed kinetic analysis, coupled with a few assumptions about rates of diffusion-controlled proton transfers, allows one to estimate the rate and equilibrium constants of all kinetically important steps. This analysis shows that the solvent-induced change in the rate-limiting step is caused by an enhanced rate of breakdown of $T^-_O(k_4)$ in the Me_2SO-containing solvents. This rate enhancement can be understood in terms of an increased "push" by the less solvated anionic oxygen of T^-_O. This increased "push" is somewhat attenuated by a reduced "pull" which arises from the slight destabilization of $CH(CN)_2^-$ in the Me_2SO-containing solvents. On a more quantitative level the equilibrium constant, K_4, for the breakdown of T^-_O into benzaldehyde and $CH(CN)_2^-$ correlates remarkably well with the estimated solvent activity coefficients of T^-_O (${}^W\gamma^D{}_{T^-_O}$) and $CH(CN)_2^-$ (${}^W\gamma^D{}_{CH(CN)_2^-}$). A correlation of the solvent effect on the *rate* constant, k_4, of the breakdown of T^-_O with the same solvent activity coefficients suggests that the sensitivity of k_4 to ${}^W\gamma^D{}_{CH(CN)_2^-}$ ($\beta_{lg,sol} \approx 0.78 \pm 0.10$) is greater than its sensitivity to ${}^W\gamma^D{}_{T^-_O}$ ($\beta_{N,sol} \approx 0.57 \pm 0.05$). This "imbalance" is attributed to a rate-retarding effect which arises from early desolvation *of the oxyanion in the transition state, an effect which is magnified in the less aqueous solvents. The direct breakdown of* T°_{OH} into benzaldehyde and malononitrile ($k_{34}^{H_2O}$) probably occurs by a mechanism in which C–C bond cleavage is concerted with the removal of the OH proton by the solvent. Suggestive, though inconclusive, evidence is presented in favor of a transition state (**2**) in which oxygen deprotonation is coupled with protonation of the departing carbanion.

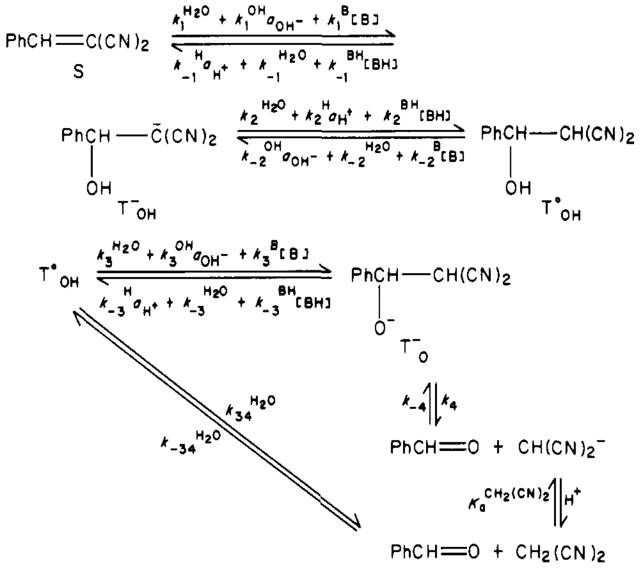
The reversible hydrolysis of benzylidenemalononitrile (BMN) proceeds by the mechanism shown in Scheme I,[1] a mechanism which is typical for the hydrolysis of activated olefins in general.[2-6] In aqueous solution at 25 °C the following steps are rate limiting in various pH ranges:[1] $k_{34}^{H_2O}$ at pH ≤0.3; k_4 at pH 0.3–5.0; $k_1^{H_2O}$ at pH 5.0–8.0; k_1^{OH} at pH 8.0–12.8.

In this and a subsequent paper[7] we wish to examine the effect of adding increasing amounts of dimethyl sulfoxide to the solvent on the rate constants of the various steps shown in Scheme I. The present paper deals with the reaction in acidic solution and the subsequent paper with the reaction in basic solution.

The addition of dimethyl sulfoxide to the solvent leads to a significant destabilization of T^-_O because of reduced hydrogen-bonding solvation.[8] This effect will increase the thermodynamic driving force of the breakdown of T^-_O into benzaldehyde and $CH(CN)_2^-$ and should increase k_4. This raises the question as to whether the increase in k_4 (4.66×10^4 s^{-1} in water at 25 °C)[1] is sufficient to produce a change in rate-limiting step from rate-limiting k_4 ($k_4 \ll k_{-3}^{H_2O} + k_{-3}^{H}a_{H^+} + k_{-3}^{BH}[BH]$) in water to (partially) rate-limiting oxygen deprotonation of T°_{OH} ($k_4 > (\gg) k_{-3}^{H_2O} + k_{-3}^{H}a_{H^+} + k_{-3}^{BH}[BH]$) in Me_2SO–water.

We now report that in 50%, 60%, and 70% aqueous dimethyl sulfoxide oxygen deprotonation of T°_{OH} indeed becomes (partially) rate limiting. We also show how insights about the transition-state structure for step k_4 can be obtained from the solvent dependence of k_4 compared to that of K_4.

Scheme I



Results

In general the same experimental problems were encountered and the same procedures were used as those reported for our study in water,[1] except for the following three minor differences. (1) Because of strong solvent absorption at 250 nm (λ_{max} of benzaldehyde) the kinetics were only monitored at or near λ_{max} of BMN (309 nm).

(2) The reaction temperature was 20 °C rather than 25 °C. This is because of the availability of pH calibration scales at 20 °C[9] but not at 25 °C. For better comparison with the results in water we have therefore performed a few experiments in water at 20 °C.

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(1) Part 11: Bernasconi, C. F.; Howard, K. A.; Kanavarioti, A. *J. Am. Chem. Soc.* **1984**, *106*, 6827.

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Table I. Initial Slopes, Intercepts, and Plateau Values in the Buffer Catalysis of the Hydrolysis of BMN in 50% Me_2SO–50% Water (v/v) at 20 °C[a]

buffer	pH	initial slope,[b] $M^{-1}\ s^{-1}$	intercept,[c] s^{-1}	plateau,[c] s^{-1}	plateau/intercept
$ClCH_2CH_2COO^-$	5.17	3.41×10^{-3}	1.32×10^{-4}	1.81×10^{-4}	1.36 ± 0.08
$ClCH_2COO^-$	4.78	4.23×10^{-5}	6.88×10^{-5}		
CH_3COO^-	4.72			7.40×10^{-5}[d]	
$CH_3OCH_2COO^-$	4.70	5.60×10^{-4}	5.11×10^{-5}	6.81×10^{-5}	1.33 ± 0.08
$ClCH_2COO^-$	4.55	*e*	3.68×10^{-5}	4.50×10^{-5}	1.22 ± 0.07
$ClCH_2COO^-$	3.71	5.86×10^{-5}	6.41×10^{-6}	7.47×10^{-5}	1.16 ± 0.07
Cl_2CHCOO^-	3.40	*e*	2.20×10^{-6}	2.46×10^{-6}	1.11 ± 0.06

[a] $\mu = 0.5$ M (KCl). [b] Estimated error ±10%. [c] Estimated error ±3%. [d] See text. [e] Uncertain.

Table II. Initial Slopes, Intercept, and Plateau Values in the Buffer Catalysis of the Hydrolysis of BMN in 60% Me_2SO–40% Water at 20 °C[a]

buffer	pH	initial slope,[b] $M^{-1}\ s^{-1}$	intercept,[c] s^{-1}	plateau,[c] s^{-1}	plateau/intercept
$ClCH_2CH_2COO^-$	5.60	5.36×10^{-3}	8.68×10^{-6}	1.36×10^{-5}	1.72
$ClCH_2COO^-$	4.70	2.45×10^{-4}	3.11×10^{-5}	5.44×10^{-5}	1.75
$ClCH_2COO^-$	4.10	$\approx 2.05 \times 10^{-4}$	1.52×10^{-4}	2.61×10^{-4}	1.57

[a] $\mu = 0.5$ M (KCl). [b] Estimated error ±8%. [c] Estimated error ±3%.

(3) The ionic strength was maintained at 0.5 M with KCl, just as in water, except in 70% Me_2SO–30% water where an ionic strength of 0.25 M was mandated because of the reduced solubility of KCl.

As before[1] we use the following symbols for the rate and equilibrium constants ($K_h = k_h/k_c$) for eq 1.

$$PhCH{=}C(CN)_2 + H_2O \underset{k_c}{\overset{k_h}{\rightleftharpoons}} PhCH{=}O + CH_2(CN)_2 \qquad (1)$$

Rates in 50% Me_2SO–50% Water (v/v). The reaction was studied at pH 5.17 in β-chloropropionate, at pH 4.70 in methoxyacetate, at pH 4.78, 4.55, and 3.71 in chloroacetate, and at pH 3.40 in dichloroacetate buffers. At the three highest pH values the rates were measured in the hydrolysis direction (k_h) while at the other pH values they were measured in the condensation direction. The latter approach was used because of extreme slowness of the hydrolysis in strongly acidic solution.

The condensation experiments were conducted under pseudo-first-order conditions with malononitrile as the excess component. The data were treated according to

$$k_{obsd} = k_h + k_c[CH_2(CN)_2]_0 \approx k_c[CH_2(CN)_2]_0 \qquad (2)$$

and k_h was calculated from

$$k_h = k_{obsd}\frac{K_h}{K_h + [CH_2(CN)_2]_0} \qquad (3)$$

with $K_h = 1.06 \times 10^{-3}$ M obtained from experiments described below.

The results of all buffer experiments are summarized in Tables S1 (pH 5.17, 4.70, 4.78, 32 rate constants) and S2 (pH 4.55, 3.71, 3.40, 15 rate constants) of the supplementary materials.[10] Figure 1 shows two representative plots of k_h vs. buffer base concentration. Both plots are characterized by a steep initial increase in k_h which is followed by a plateau. The plateaus appear to have slightly negative slopes.

Initial slopes, intercepts, and plateau values (obtained by extrapolation of the dashed lines in Figure 1) for all buffers are summarized in Table I. The initial slopes are based on the assumption that it is only the buffer base which is catalytic. The table also includes a "plateau" value for an acetate buffer at pH 4.72 which was obtained at a single (high) acetate ion concentration.

A second series of experiments was performed in HCl solutions (pH 0.29–3.73), again with the rates measured in the condensation direction. In some runs benzaldehyde rather than malononitrile was used as the excess component, with excellent agreement between the two methods. The results are in Table S3[10] (14 rate constants) while Figure 2 shows a pH–rate profile (○). Included in the figure are the buffer intercepts (△) and plateau values (●) from Table I.

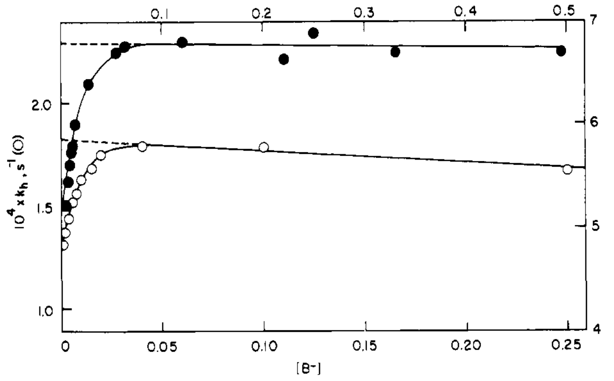

Figure 1. Methoxyacetate catalysis (pH 4.69, ●, right and top axes) and β-chloropropionate catalysis (pH 5.17, ○, left and bottom axes) in 50% Me_2SO–50% water.

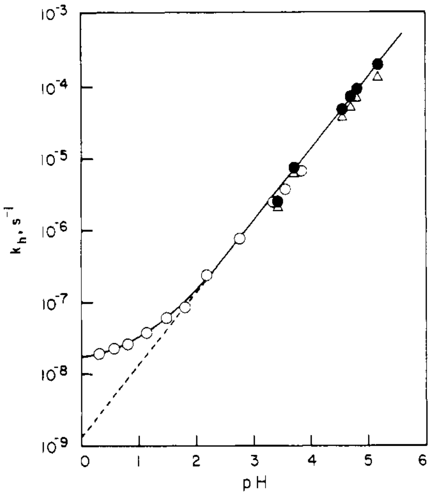

Figure 2. pH–rate profile in 50% Me_2SO–50% water: (○) experiments in HCl solution; (△) buffer intercepts (from Table I); (●) buffer plateaus (from Table I).

Rates in 60% Me_2SO–40% Water (v/v). In this solvent we studied the dependence on buffer concentration in β-chloropropionate (pH 5.60) and chloroacetate buffers (pH 4.70, 4.10). In the former the rates were measured in the hydrolysis direction, in the latter in the condensation direction. $K_h = 1.00 \times 10^{-3}$ M (see below) was used to calculate k_h according to eq 3.

The results are summarized in Table S4[10] (10 rate constants) and S5[10] (16 rate constants), while Figure 3 shows a representative plot of k_h vs. base concentration. The plot shows again a curvilinear dependence as in 50% Me_2SO–50% water, but the extent

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(10) See paragraph at the end of this paper regarding supplementary material.

Table III. Initial Slopes, Intercept, and Plateau Values in the Buffer Catalysis of the Hydrolysis of BMN in 70% Me_2SO–30% Water at 20 °C[a]

buffer	pH	initial slope,[b] $M^{-1}\ s^{-1}$	intercept,[c] s^{-1}	plateau,[c] s^{-1}	plateau/intercept
CH_3COO^-	6.42	4.90×10^{-2}	1.30×10^{-4}	7.68×10^{-4}	5.91
$ClCH_2CH_2COO^-$	6.22	1.36×10^{-2}	8.70×10^{-5}	4.34×10^{-4}	4.99
$CH_3OCH_2COO^-$	5.72	4.67×10^{-3}	3.25×10^{-5}	2.19×10^{-4}	6.57
$ClCH_2COO^-$	5.00			4.55×10^{-5}	
$ClCH_2COO^-$	4.90	5.20×10^{-4}	6.10×10^{-6}		
$ClCH_2COO^-$	4.70			2.00×10^{-5}	
Cl_2CHCOO^-	3.23	9.12×10^{-6}	2.88×10^{-7}	8.00×10^{-7}	2.78
Cl_2CHCOO^-	2.90	4.40×10^{-6}	2.35×10^{-7}	4.48×10^{-7}	1.91

[a] μ = 0.25 M (KCl). [b] Estimated error ±5%. [c] Estimated error ±3%.

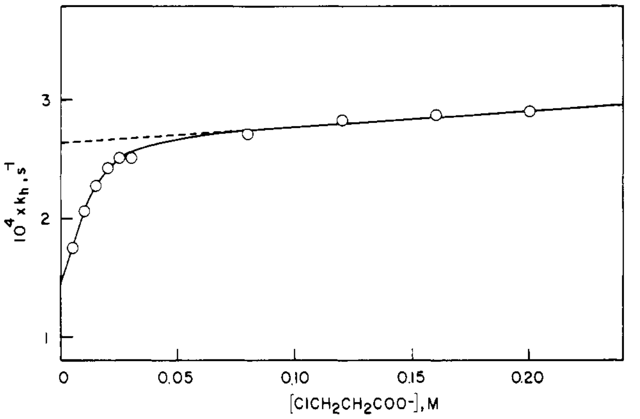

Figure 3. β-Chloropropionate catalysis in 60% Me_2SO–40% water at pH 5.60.

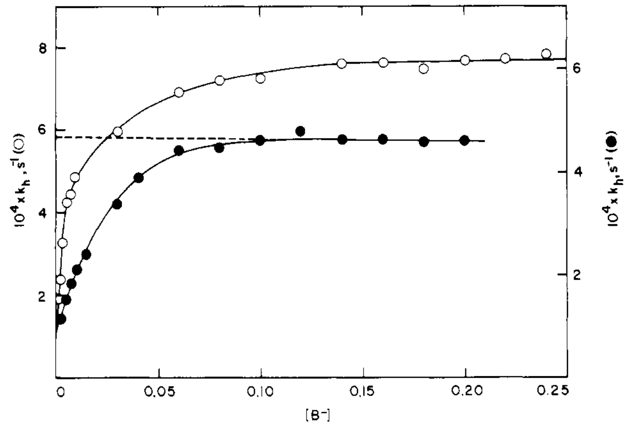

Figure 4. Acetate catalysis (pH 6.42, ○, left axis) and β-chloropropionate catalysis (pH 6.22, ●, right axis) in 70% Me_2SO–30% water.

of the catalysis, as measured by the ratio of plateau/intercept, is significantly larger. The plot also suggests that the plateau is again not strictly horizontal; however, in contrast to the situation in the more aqueous solvent, it is mildly *increasing* with increasing buffer concentration.

Table II summarizes the values for initial slopes, intercepts, and plateaus of the buffer plots.

Rates in 70% Me_2SO–30% Water (v/v). Rates were measured at pH 6.42 in acetate, at pH 6.22 in β-chloropropionate, at pH 5.72 in methoxyacetate, at pH 5.00 in chloroacetate, and at pH 3.23 and 2.90 in dichloroacetate buffers. All buffer data reported here are from experiments conducted in the hydrolysis direction, even in the most acidic buffers where the reaction is very slow. This is because in the strongly acidic chloro- and dichloroacetate buffers the reproducibility of the runs conducted in the condensation direction was not as good as those in the hydrolysis direction. It appears that in 70% Me_2SO there is a reaction between malononitrile and the buffer (or with an impurity in the buffer) which at the high concentrations leads to the slow development of a red color and which interferes with the condensation of malononitrile with benzaldehyde. The nature of this side reaction was not investigated further.

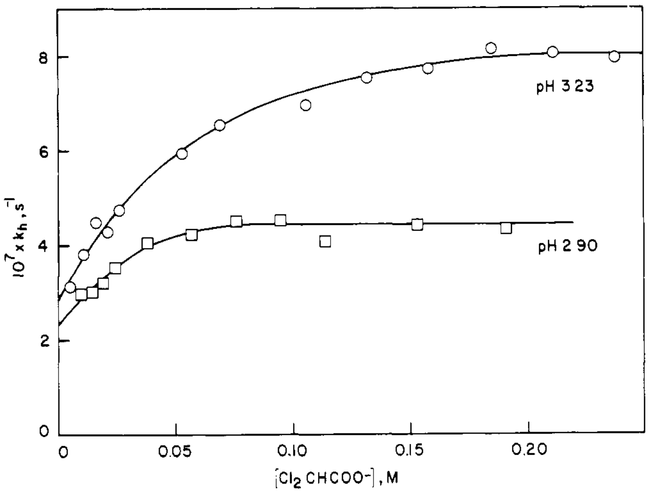

Figure 5. Dichloroacetate catalysis in 70% Me_2SO–30% water at pH 3.23 and 2.90.

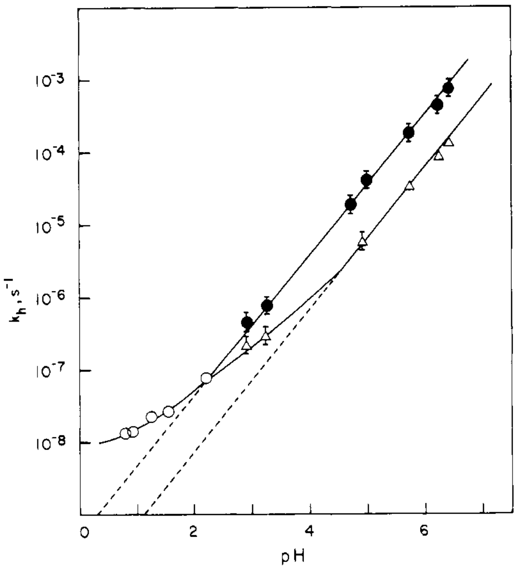

Figure 6. pH-rate profile in 70% Me_2SO–30% water: (○) experiments in HCl solution (from Table S8[10]); (△) buffer intercepts (from Table III); (●) buffer plateaus (from Table III).

Because of the extreme slowness of the hydrolysis below pH 3.5 k_h was determined by the method of initial rates as described in the Experimental Section.

The results of the buffer experiments are summarized in Tables S6[10] (63 rate constants) and S7[10] (24 rate constants) while Figures 4 and 5 show representative buffer plots. The plots are again curvilinear, but the extent of the catalysis is much greater than in the other two solvents. This is reflected in plateau/intercept ratios in the order of 5–6 in the more basic buffers (Table III); in the two most acidic buffers this ratio is significantly reduced.

As in 50% Me_2SO–50% water some determinations were also made in HCl solutions. Since no problems were encountered in measuring the rates in the condensation direction, this was the method of choice for these extremely slow reactions. The results are in Table S8[10] (5 rate constants) while Figure 6 shows a logarithmic plot of k_h vs. pH (○); the figure also includes the intercepts (△) and plateau values (●) of the buffer plots taken from Table III.

A few experiments were conducted aimed at examining the potential role played by specific salt effects. To this end KCl was replaced by potassium chloroacetate as the compensating electrolyte in some runs conducted in β-chloropropionate buffer. In one series of experiments pairs of runs at a given buffer concentration were compared where in one of the runs the compensating electrolyte was KCl, in the other $KOOCCH_2Cl$. The results are summarized in Table S9[10] (part A). k_h was observed to be between 2% and 6% higher with $KOOCCH_2Cl$ as the compensating electrolyte. This increase is barely outside the experimental error and is considered insignificant. This conclusion is supported by the results of a second series of experiments (Table S9, part B) in which the effect of gradually replacing KCl with $KOOCCH_2Cl$ at constant buffer concentration was investigated. Slight variations (±3%) were observed, but they were essentially random.

Rates in Water at 20 °C. The rate of hydrolysis of BMN was measured at five different pH values from pH 3.11 to 3.96 in methoxyacetate buffers at a single buffer concentration.[11] The results are in Table S10.[10] A plot (not shown) of k_h vs. $a_{H^+}{}^{-1}$ is linear with a slope = 2.15×10^{-9} M^{-1} s^{-1}.

Equilibrium Constants at 50%, 60%, and 70% Me_2SO and in Water. The equilibrium constant, K_h, of reaction 1 was determined kinetically. The rates were measured in the condensation direction, usually with malononitrile as the excess component but in some cases with benzaldehyde in excess. k_{obsd} was measured at various concentrations of the excess component and is given by

$$k_{obsd} = k_h + k_c[\mathrm{E.C.}]_0 \tag{4}$$

with $[\mathrm{E.C.}]_0$ being the concentration of the excess component.

The range of concentrations was chosen as to provide good values for both k_h (intercept) and k_c (slope). The results are summarized in Tables S11–S14.[10] The following K_h values were obtained: 1.06×10^{-3} M in 50% Me_2SO, 1.00×10^{-3} M in 60% Me_2SO, 8.21×10^{-4} M in 70% Me_2SO, and 3.22×10^{-3} M in water.

Discussion

Mechanism of Buffer Catalysis. In all three Me_2SO-containing solvents there is a curvilinear dependence of k_h on buffer concentration (Figures 1 and 3–5). We attribute this buffer dependence to general base catalysis as detailed below. In 50% Me_2SO the catalytic effect is quite small, though, with a total increase in k_h ranging from ~11% at the lowest pH to ~36% at the highest pH (plateau/intercept ratios in Table I). Such small increases raise the question whether we might be witnessing a specific salt or medium effect rather than authentic base catalysis; some reactions measured in mixed solvents are known to be particularly prone to such effects.[12,13]

In view of the fact that the catalytic effects occur at very low base concentration (0.01 to 0.02 M) this seems an unattractive interpretation.[13b] On the other hand, specific salt effects, or medium effects caused by the buffer acid, may play a role at *high* buffer concentration. The slightly sloping plateaus in 50% and 60% Me_2SO (Figures 1 and 3) are probably caused by such effects although it is not clear why the sign of the slopes changes from 50% to 60% Me_2SO and why no such effects are observed in 70% Me_2SO. Irrespective of the detailed interpretation of the sloping plateau, the effects are very small and barely outside the error limits, as is also confirmed by our limited investigation of salt effects (Table S9[10]).

The curvilinear dependence of k_h on base concentration indicates a change in rate-controlling step. In any given solvent the change always occurs at about the same buffer *acid* concentration. This behavior is easily understood in terms of a change from rate-limiting (or co-limiting) oxygen deprotonation of T°_{OH} at low buffer concentration to rate-limiting breakdown of T^-_O at high concentration, as previously observed in the hydrolysis of *p*-nitrobenzylidene Meldrum's acid.[2]

The expression for k_h, derived by means of the steady-state approximation for T^-_O and by assuming that the first two steps in Scheme I are rapid equilibria,[1] is given by

$$k_h = \frac{K_1^{H_2O}}{K_a^{CH}}\left\{\frac{(k_3^{H_2O} + k_3^{B}[\mathrm{B}] + k_3^{OH}a_{OH^-})k_4}{k_{-3}^{H}a_{H^+} + k_{-3}^{BH}[\mathrm{BH}] + k_{-3}^{H_2O} + k_4} + k_{34}^{H_2O}\right\} \tag{5}$$

$K_1^{H_2O}$ is the equilibrium constant for water addition to BMN (to form $T^-_{OH} + H^+$) while K_a^{CH} is the C–H acid dissociation constant of T°_{OH}. Note that eq 5 contains a $k_{34}^{H_2O}$ term for the direct conversion of T°_{OH} to malononitrile and benzaldehyde which becomes dominant in strongly acidic solution, as discussed below.

According to eq 5 the initial slopes of the buffer plots are given by

$$\text{slope} = \frac{K_1^{H_2O}}{K_a^{CH}}\,\frac{k_3^{B}k_4}{k_{-3}^{H}a_{H^+} + k_{-3}^{H_2O} + k_4} \tag{6}$$

Equation 5 also shows that it is indeed the buffer *acid* concentration (and/or a_{H^+}) which determines the change in rate-limiting step: at high [BH] ($k_{-3}^{BH}[\mathrm{BH}] \gg k_4$) and/or high a_{H^+} ($k_{-3}^{H}a_{H^+} \gg k_4$) eq 1 simplifies to

$$k_h = \frac{K_1^{H_2O}}{K_a^{CH}}\left\{\frac{K_a^{OH}}{a_{H^+}}k_4 + k_{34}^{H_2O}\right\} \tag{7}$$

with K_a^{OH} being the O–H acid dissociation constant of T°_{OH}.

It is the k_h values determined in HCl solution (○ in Figures 2 and 6) and the plateau values of the buffer plots (● in Figures 2 and 6) which obey eq 7. The pH–rate profiles in Figures 2 and 6 show that the pH-independent $k_{34}^{H_2O}$ term starts to become important below pH 2.

At zero buffer concentration eq 5 becomes

$$k_h = \frac{K_1^{H_2O}}{K_a^{CH}}\left\{\frac{(k_3^{H_2O} + k_3^{OH}a_{OH^-})k_4}{k_{-3}^{H}a_{H^+} + k_{-3}^{H_2O} + k_4} + k_{34}^{H_2O}\right\} \tag{8}$$

This corresponds to the intercepts of the buffer plots (△ in Figures 2 and 6). At pH values such that $k_{-3}^{H}a_{H^+} \ll k_{-3}^{H_2O}$ and $k_3^{H_2O} \ll k_3^{OH}a_{OH^-}$ eq 8 further simplifies to[14]

$$k_h = \frac{K_1^{H_2O}}{K_a^{CH}}\,\frac{k_4k_3^{OH}a_{OH^-}}{k_{-3}^{H_2O} + k_4} \tag{9}$$

Hence, in the pH range where eq 9 is valid the pH–rate profiles for plateaus (eq 7) and intercepts (eq 9) should be parallel as is clearly visible in Figure 6 at pH ~4.5 to 6.5. At lower pH where the $k_3^{H_2O}$ and $k_{-3}^{H}a_{H^+}$ terms (eq 8) are no longer negligible the two lines are no longer parallel.

These observations are best treated quantitatively by focusing on the ratios of plateau/intercept. These ratios are summarized in Tables I–III. At pH >2 where the $k_{34}^{H_2O}$ term can be neglected both in eq 7 and 8 we have

$$\begin{aligned}\frac{\text{plateau}}{\text{intercept}} &= \frac{K_a^{OH}}{a_{H^+}}\,\frac{k_{-3}^{H_2O} + k_{-3}^{H}a_{H^+} + k_4}{k_3^{OH}a_{OH^-} + k_3^{H_2O}}\\ &= \frac{k_{-3}^{H_2O} + k_{-3}^{H}a_{H^+} + k_4}{k_{-3}^{H_2O} + k_{-3}^{H}a_{H^+}} = 1 + \frac{k_4}{k_{-3}^{H_2O} + k_{-3}^{H}a_{H^+}}\end{aligned} \tag{10}$$

After rearranging and inverting eq 10 one obtains

$$\left\{\frac{\text{plateau}}{\text{intercept}} - 1\right\}^{-1} = \frac{k_{-3}^{H_2O}}{k_4} + \frac{k_{-3}^{H}a_{H^+}}{k_4} \tag{11}$$

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[11] No buffer dependence is expected since there is none at 25 °C.[1]

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[14] At these pH values the $k_{34}^{H_2O}$ term is negligible.

Table IV. Summary of Rate and Equilibrium Constants at 20 °C[a]

no.	parameter	water	50% Me_2SO	60% Me_2SO	70% Me_2SO
1	k_{-3}^{H}/k_4, M^{-1}		$\sim 1.7 \times 10^4$	$\sim 4.8 \times 10^3$	$6.8 \pm 1.5 \times 10^2$
2	$k_{-3}^{H_2O}/k_4$		3.0 ± 0.4	1.3 ± 0.1	0.21 ± 0.03
3	k_{-3}^{H}, $M^{-1}\ s^{-1}$	$\sim 4.0 \times 10^{10}$	$\sim 1.0 \times 10^{10}$	$\sim 0.75 \times 10^{10}$	$\sim 0.40 \times 10^{10}$
4	k_4, s^{-1}	$\sim 3.3 \times 10^4$	$\sim 5.9 \times 10^5$	$\sim 1.6 \times 10^6$	$\sim 5.9 \times 10^6$
5	k_{-4}, $M^{-1}\ s^{-1}$	$\sim 1.5 \times 10^5$	$\sim 1.4 \times 10^4$	$\sim 7.9 \times 10^3$	$\sim 3.0 \times 10^3$
6	K_4, M	$\sim 2.1 \times 10^{-1}$	$\sim 4.3 \times 10^1$	$\sim 2.0 \times 10^2$	$\sim 2.0 \times 10^3$
7	$k_{-3}^{H_2O}$, s^{-1}		$\sim 2.0 \times 10^6$	$\sim 2.0 \times 10^6$	$\sim 1.2 \times 10^6$
8	k_3^{OH}, $M^{-1}\ s^{-1}$		$\sim 1.5 \times 10^9$	$\sim 1.5 \times 10^9$	$\sim 1.5 \times 10^9$
9	pK_w	14.00	15.90	16.67	17.79
10	pK_a^{OH}	~ 11.2	~ 13.0	~ 13.8	~ 14.7
11	$K_1^{H_2O}/K_a^{CH}$	$\sim 1.0 \times 10^{-2}$	$\sim 1.5 \times 10^{-2}$	$\sim 2.8 \times 10^{-2}$	$\sim 2.5 \times 10^{-2}$
12	K_h, M	3.22×10^{-2}	1.06×10^{-3}	1.00×10^{-3}	8.21×10^{-4}
13	$pK_a^{CH_2(CN)_2}$	11.39	10.21	10.05	9.92
14	$(K_1^{H_2O}/K_a^{CH})k_{34}^{H_2O}$		1.60×10^{-8}		1.20×10^{-8}
15	$k_{34}^{H_2O}$, s^{-1}	$\sim 1.0 \times 10^{-6}$	1.05×10^{-6}		4.76×10^{-7}
16	$k_{34}^{H_2O}/[H_2O]$, $M^{-1}\ s^{-1}$	$\sim 1.8 \times 10^{-8}$	3.78×10^{-8}		2.85×10^{-8}
17	$K_{34}^{H_2O}$	~ 0.33	$\sim 6.9 \times 10^{-2}$		$\sim 3.25 \times 10^{-2}$

[a] $\mu = 0.5$ M except in 70% Me_2SO where $\mu = 0.25$ M.

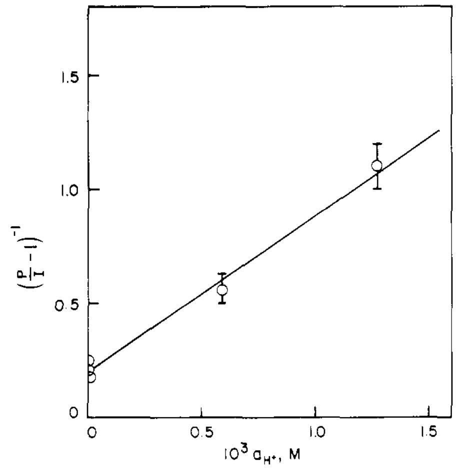

Figure 7. Plot according to eq 11 in 70% Me_2SO–30% water.

A plot according to eq 11 is shown in Figure 7 for 70% Me_2SO. It affords $k_{-3}^{H_2O}/k_4 = 0.21 \pm 0.03$ and $k_{-3}^{H}/k_4 = 6.8 \pm 1.5 \times 10^2$ M^{-1}. A similar analysis of the data in the other solvents leads to $k_{-3}^{H_2O}/k_4 = 3.0 \pm 0.3$ in 50% Me_2SO and 1.3 ± 0.1 in 60% Me_2SO while for k_{-3}^{H}/k_4 only crude estimates can be obtained ($\sim 1.7 \times 10^4$ M^{-1} in 50%, $\sim 4.8 \times 10^3$ M^{-1} in 60% Me_2SO).

Dissection of Individual Rate and Equilibrium Constants. Table IV provides a summary of various rate and equilibrium constants in water and in 50%, 60%, and 70% aqueous Me_2SO, all at 20 °C. This section details how they were obtained on the basis of our results, coupled with a few assumptions about diffusion or nearly diffusion-controlled proton transfers.

k_{-3}^{H}, $k_{-3}^{H_2O}$, and k_4. Our estimates for k_{-3}^{H} in the four solvents are listed under no. 3 in Table IV. They are based on rate constants of $3\text{–}5 \times 10^{10}$ $M^{-1}\ s^{-1}$ for the diffusion-controlled protonation of strongly basic oxyanions by H_3O^+ in water[15] and the following two corrections in the Me_2SO containing solvents. (1) The $\sim$3.5- to 4.4-fold higher viscosity of our Me_2SO–water mixtures[16] should reduce k_{-3}^{H} by corresponding factors.[19] If we take a value of 4×10^{10} $M^{-1}\ s^{-1}$ in water, k_{-3}^{H} in 50%, 60%, and 70% Me_2SO would be 1.16×10^{10}, 0.95×10^{10}, and 0.91×10^{10} $M^{-1}\ s^{-1}$, respectively.[16]

(2) An additional small downward adjustment has been applied because the smaller water concentration in the mixed solvents[20] is expected to reduce the effectiveness of the proton-jump mechanism.[15,19] In estimating the amount of this additional reduction we were guided by its effect on the value of pK_a^{OH} calculated from it, as discussed below.

A third factor which might reduce k_{-3}^{H} in all solvents about equally is the possibility of steric hindrance in the approach to the relatively bulky T^-_O. However, because of the small size of H_3O^+ and the availability of the proton-jump mechanism[15,19] such steric effects generally become significant only when the base is extremely crowded.[21] This is hardly the case for T^-_O and thus a significant steric retardation seems unlikely.

Coupled with the experimental k_{-3}^{H}/k_4 ratios (no. 1), our estimates for k_{-3}^{H} allow us now to estimate k_4 (no. 4) and from the experimental $k_{-3}^{H_2O}/k_4$ ratios (no. 2) we also obtain $k_{-3}^{H_2O}$ (no. 7) in the mixed solvents. It should be noted that k_4 and $k_{-3}^{H_2O}$ obtained in this manner are probably fairly reliable in 70% Me_2SO but less so in 50% and 60% Me_2SO because of the large uncertainty in k_{-3}^{H}/k_4. However, independent estimates discussed below show that our values in 50% and 60% Me_2SO are quite reasonable.

In water k_4 was obtained from k_h measured between pH 3.11 and 3.96 (Table S10);[10] in this range k_h obeys eq 7,[1] and $K_1^{H_2O}/K_a^{CH}$ and K_a^{OH} were estimated as discussed below.

k_3^{OH} and pK_a^{OH}. For k_3^{OH} we have assumed a value of 1.5 × 10^9 $M^{-1}\ s^{-1}$ in all solvents (no. 8). This value is an average based on direct experimental determination of k_3^{OH} in various similar systems, both in water and in 50% Me_2SO.[23] Together with $k_{-3}^{H_2O}$ and the ionic product of the solvent (no. 9) we now obtain pK_a^{OH} in the Me_2SO–water mixtures (no. 10).

A different method for estimating pK_a^{OH} is based on a Taft correlation[24] which leads to $pK_a^{OH} = 11.1$ in water at 25 °C.[1] Since pK_w is slightly higher at 20 °C than at 25 °C,[25] pK_a^{OH} is likely to be slightly higher, too. We shall assume $pK_a^{OH} = 11.2$ in water at 20 °C. Upon addition of Me_2SO the pK_a of an alcohol is expected to increase nearly as much as pK_w.[9] The pK_a^{OH} values listed in Table IV which were estimated on the basis of k_3^{OH} and $k_{-3}^{H_2O}$ are seen to reflect this expectation quite well: For the change from water to 50% Me_2SO we have $\Delta pK_a^{OH} = 1.8$, $\Delta pK_w = 1.90$; for the change from 50% to 60% Me_2SO $\Delta pK_a^{OH} = 0.8$, $\Delta pK_w = 0.77$; for the change from 60% to 70% Me_2SO $\Delta pK_a^{OH} = 0.9$, $\Delta pK_w = 1.13$. This consistency indicates that our estimates of pK_a^{OH} cannot be far off the mark.

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(15) (a) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1. (b) Eigen, M.; Kruse, W.; Maass, G.; DeMaeyer, L. *Prog. React. Kinet.* **1964**, *2*, 287.

(16) The viscosities in water and 50%, 60%, and 70% Me_2SO are 1.002,[17] 3.455,[18] ~4.2,[18] and ~4.4[18] cP, respectively.

(17) Weast, R. C., Ed. "Handbook of Chemistry and Physics", The Chemical Rubber Co.: Cleveland, Ohio, 1971; p F-36.

(18) Janz, G. J.; Tompkins, R. P. T. "Nonaqueous Electrolyte Handbook;" Academic Press: New York, 1972; Vol. 1, p 1043.

(19) Crooks, J. E. *Compr. Chem. Kinet.* **1977**, *8*, 197.

(20) $[H_2O]$ = 55.5, 27.8, 22.2, and 16.7 M, respectively.

(21) Bernasconi, C. F.; Carré, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 2698, 2707.

(22) Weller, A. *Prog. React. Kinet.* **1961**, *1*, 189.

(23) For example, in the hydrolysis of *p*-nitrobenzylidene Meldrum's acid $k_3^{OH} = 1.8 \times 10^9$ $M^{-1}\ s^{-1}$ in water,[3a] and in the hydrolysis of 1,1-dinitro-2,2-diphenylethylene $k_3^{OH} = 1.3 \times 10^9$ $M^{-1}\ s^{-1}$ in 50% Me_2SO–50% water.[4]

(24) Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205.

(25) Reference 17, p D-122.

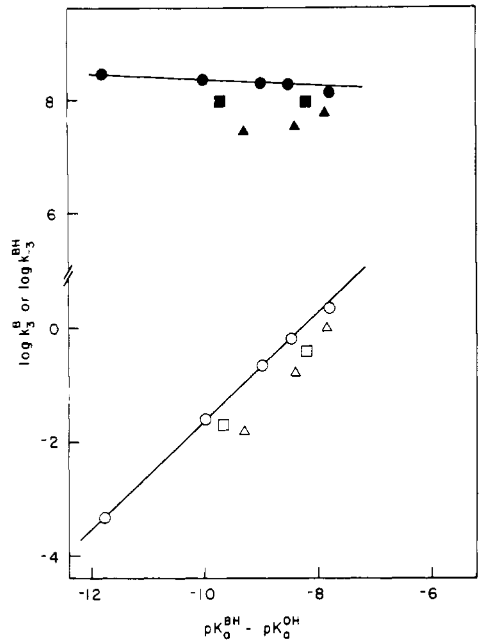


Figure 8. Eigen plot for the proton transfer $T^\circ_{OH} + B^- \rightleftharpoons T^-_O + BH$. Open symbols, k_3^B; filled symbols, k_{-3}^{BH} Circles, 70% Me_2SO; squares, 60% Me_2SO; triangles, 50% Me_2SO.

$\boldsymbol{K_1^{H_2O}/K_a^{CH}}$**,** $\boldsymbol{K_4}$**,** $\boldsymbol{k_{34}^{H_2O}}$**, and** $\boldsymbol{K_{34}^{H_2O}}$**.** The $K_1^{H_2O}/K_a^{CH}$ ratios (no. 11) in the Me_2SO–water mixtures can be obtained from

$$\frac{K_1^{H_2O}}{K_a^{CH}} = \frac{\text{intercept}}{k_3^{OH}a_{OH^-}}\left(\frac{k_{-3}^{H_2O}}{k_4} + 1\right) \qquad (12)$$

which is derived from eq 9. It should be noted that eq 12 contains the more reliable $k_{-3}^{H_2O}/k_4$ ratio rather than the less certain k_{-3}^{H}/k_4 ratio and hence our $K_1^{H_2O}/K_a^{CH}$ values are as good as our estimate for k_3^{OH} which is considered quite reliable.

In water we have assumed that $K_1^{H_2O}/K_a^{CH}$ is $^2/_3$ of its value in 50% Me_2SO, based on the slight increase in this ratio observed when the medium becomes richer in Me_2SO.

We now obtain the equilibrium constants for the breakdown of T^-_O into benzaldehyde and $CH(CN)_2^-$ (K_4, no. 6), and for the breakdown of T°_{OH} into benzaldehyde and $CH_2(CN)_2$ ($K_{34}^{H_2O}$, no. 17), via

$$K_4 = K_h \frac{K_a^{CH}}{K_1^{H_2O}} \frac{K_a^{CH_2(CN)_2}}{K_a^{OH}} \qquad (13)$$

$$K_{34}^{H_2O} = K_a^{OH}K_4/K_a^{CH_2(CN)_2} \qquad (14)$$

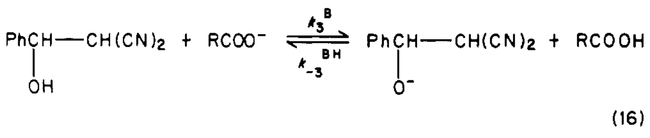
Finally, from the plateaus of the pH–rate profiles in 50% (Figure 2) and 70% Me_2SO (Figure 6) $k_{34}^{H_2O}$ (no. 15) is found via eq 7. In water $k_{34}^{H_2O}$ was estimated on the basis of the value found at 25 °C and assuming the same temperature dependence as for k_4.

$\boldsymbol{k_3^B}$ **and** $\boldsymbol{k_{-3}^{BH}}$**.** With $K_1^{H_2O}/K_a^{CH}$ being known we now evaluate the rate constants for oxygen deprotonation of T°_{OH} by buffer bases from the initial slopes of the buffer plots. Rearranging eq 6 provides

$$k_3^B = \text{slope}\frac{K_a^{CH}}{K_1^{H_2O}}\left(\frac{k_{-3}^{H_2O}}{k_4} + \frac{k_{-3}^{H}a_{H^+}}{k_4} + 1\right) \qquad (15)$$

k_{-3}^{BH} is obtained as $k_3^BK_a^{BH}/K_a^{OH}$ with K_a^{BH} being the acid dissociation constant of the buffer. The k_3^B and k_{-3}^{BH} values are summarized in Table V.

Rates of Proton Transfer. Figure 8 shows Eigen plots[15a] for the reaction



$$PhCH(OH)\text{—}CH(CN)_2 + RCOO^- \underset{k_{-3}^{BH}}{\overset{k_3^B}{\rightleftharpoons}} PhCH(O^-)\text{—}CH(CN)_2 + RCOOH \qquad (16)$$

Table V. Rate Constants for the Proton Transfer, $T^\circ_{OH} \rightleftharpoons T^-_O$[a]

	50% Me_2SO (pK_a^{OH} ~13.0)	60% Me_2SO (pK_a^{OH} ~13.8)	70% Me_2SO (pK_a^{OH} ~14.7)
$AcO^-/AcOH$			
k_3^B			2.3
k_{-3}^{BH}			1.4×10^8
pK_a^{BH}			6.90
$pK_a^{BH} - pK_a^{OH}$			−7.8
$ClCH_2CH_2COO^-/ClCH_2CH_2COOH$			
k_3^B	9.1×10^{-1}	4.4×10^{-1}	6.5×10^{-1}
k_{-3}^{BH}	6.2×10^7	7.4×10^7	1.9×10^8
pK_a^{BH}	5.17	5.60	6.22
$pK_a^{BH} - pK_a^{OH}$	−7.83	−8.20	−8.48
$MeOCH_2COO^-/MeOCH_2COOH$			
k_3^B	1.6×10^{-1}		2.2×10^{-1}
k_{-3}^{BH}	3.9×10^7		2.0×10^8
pK_a^{BH}	4.60		5.72
$pK_a^{BH} - pK_a^{OH}$	−8.40		−8.98
$ClCH_2COO^-/ClCH_2COOH$			
k_3^B	1.9×10^{-2}	1.9×10^{-2}	2.5×10^{-2}
k_{-3}^{BH}	3.7×10^7	9.8×10^7	2.4×10^8
pK_a^{BH}	3.71	4.10	4.70
$pK_a^{BH} - pK_a^{OH}$	−9.29	−9.70	−10.00
$Cl_2CHCOO^-/Cl_2CHCOOH$			
k_3^B			4.7×10^{-4}
k_{-3}^{BH}			2.7×10^8
pK_a^{BH}			2.92
$pK_a^{BH} - pK_a^{OH}$			−11.78

[a] In units of $M^{-1}\ s^{-1}$.

It should be noted that even though the absolute values of k_3^B and k_{-3}^{BH} depend on our estimates of $K_1^{H_2O}/K_a^{CH}$ and pK_a^{OH}, their *relative* values in a given solvent which determine the shape of the Eigen plots do not depend on these estimates.

In 70% Me_2SO buffer catalysis is quite strong and thus the initial slopes from which k_3^B is calculated are undoubtedly the most accurate. This is also the solvent in which the largest number of buffers was studied. The five points in this solvent (○ and ● in Figure 8) define two excellent straight lines whose slopes are $\beta = 0.96 \pm 0.05$ (k_3^B) and $\alpha = 0.05 \pm 0.05$ (k_{-3}^{BH}). These slopes which are indinstinguishable from 1.0 and 0.0, respectively, are typical for diffusion-controlled proton transfers.[15]

The results in 50% and 60% Me_2SO, even though more scattered, obey the same pattern as in 70% Me_2SO. A $\beta = 1.0$ was also found for the k_3^B step in the hydrolysis of *p*-nitrobenzylidene Meldrum's acid in water.[2]

It is noteworthy that the values for k_{-3}^{BH} are all significantly below the diffusion-controlled limit. On the basis of the work by Eigen[15] and his school[26] one expects the diffusion-controlled limit to be ~10^{10} $M^{-1}\ s^{-1}$ in water and between ~2.3 and 2.9×10^9 $M^{-1}\ s^{-1}$ in the more viscous Me_2SO–water mixtures.[16,19] Our values vary between 3.7×10^7 ($ClCH_2COOH$ in 50% Me_2SO) and 2.7×10^8 $M^{-1}\ s^{-1}$ ($ClCH_2CH_2COOH$ in 70% Me_2SO), i.e., they are from ~10- to ~70-fold lower than expected. This indicates the presence of a steric effect. Such steric effects on proton transfers between normal acids and bases which still show the typical limiting $\beta = 1.0$ and $\alpha = 0.0$ Brønsted coefficients for diffusion-controlled proton transfer are not uncommon.[21,22,27-29]

Molecular models suggest, though, that the steric crowding in the encounter complex is only moderate and does not prevent the reactants from coming into close proximity, particularly if one allows for the proton transfer to proceed through a water bridge.[15] The steric retardation can, however, be understood in terms of Weller's[22] model in which the rate constant may be expressed as

$$k_{-3}^{BH} = k_D\sigma_{BH}\sigma_{T^-_O} \qquad (17)$$

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(26) Ahrens, M.-L.; Maass, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 818.

(27) (a) Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147. (b) Bernasconi, C. F.; Muller, M. C.; Schmid, P. *J. Org. Chem.* **1979**, *44*, 3189.

(28) Bernasconi, C. F.; Murray, C. J.; Fox, J. P.; Carré, D. J. *J. Am. Chem. Soc.* **1983**, *105*, 4349.

(29) Barnett, G. H.; Hibbert, F. *J. Am. Chem. Soc.* **1984**, *106*, 2080.

Table VI. Solvent Activity Coefficients for the Transfer from Water to Me_2SO–Water Mixtures

	50% Me_2SO	60% Me_2SO	70% Me_2SO
$\log {}^{W}\gamma^{D}_{T^-_0}$ [a]	≈ 3.25	≈ 4.25	≈ 5.54
$\log {}^{W}\gamma^{D}_{PhCHO}$ [b]	≈ 0	≈ 0	≈ 0
$\log {}^{W}\gamma^{D}_{CH(CN)_2^-}$ [c]	≈ 0.75	≈ 0.93	≈ 1.13
$\log {}^{W}\gamma^{D}_{CH_2(CN)_2}$ [b]	≈ 0	≈ 0	≈ 0
$\log {}^{W}\gamma^{D}_{H^+}$ [d]	-1.93	-2.27	≈ -2.60
$\delta \log {}^{W}K_4^{D}$ (eq 18)	≈ 2.50	≈ 3.32	≈ 4.41
$\delta \log {}^{W}K_4^{D}$ (obsd)	2.31	2.98	3.98

[a] Assumed to be equal to $\log {}^{W}\gamma^{D}_{OH^-}$, from ref 30. [b] Assumed values. [c] Calculated via eq 19, see text. [d] From ref 30.

k_D is the diffusional rate constant given by the Smoluchowski equation[19] while σ_{BH} and $\sigma_{T^-_O}$ are the steric factors of the two reactants. These steric factors can be visualized as the spatial angles into which the proton can be donated ($\sigma_{T^-_O}$), or from which it can be removed (σ_{BH}), respectively. The molecular models suggest that $\sigma_{T^-_O}$ is indeed quite small which makes the relatively small values of k_{-3}^{BH} plausible.

Whether our finding that the k_{-3}^{BH} values in 70% Me_2SO are somewhat higher than in the other two solvents represents a real phenomenon (it is unlikely that the lower ionic strength in 70% Me_2SO is responsible for the higher rates) or whether it is an artifact caused by an accumulation of errors mainly in the more aqueous solvents is difficult to tell. The low k_{-3}^{BH} for $ClCH_2COOH$ and $MeOCH_2COOH$ in 50% Me_2SO is almost certainly the result of our difficulty in measuring accurate slopes for the very weak catalysis. If these two values are ignored the discrepancies between the k_{-3}^{BH} values in the different solvents are less than a factor of 3.

Our present findings suggest that our earlier estimate of $k_{-3}^{BH} \approx 10^{10}$ M^{-1} s^{-1} for the protonation of T^-_O derived from benzylidene Meldrum's acid[3a] by carboxylic acids in water needs to be revised downward. A value of $\sim 2 \times 10^8$ M^{-1} s^{-1}, reflecting the fact that T^-_O derived from Meldrum's acid is sterically somewhat bulkier than T^-_O derived from BMN (smaller $\sigma_{T^-_O}$ in eq 17), seems reasonable. This new estimate requires a corresponding adjustment in the pK_a^{OH} from 14.45[3] to 12.8 for benzylidene Meldrum's acid.

Solvent Effects on k_4 and K_4. Both k_4 and K_4 increase quite strongly with added dimethyl sulfoxide. The total increase from water to 70% Me_2SO amounts to a factor of ≈ 180 for k_4 (no. 4 in Table IV) and of nearly 10^4 for K_4 (no. 6). These increases are best understood in terms of a destabilization of the anionic oxygen in T^-_O which leads to an increased push on the departing $CH(CN)_2^-$. This destabilization is partly but not entirely (see below) reflected in the higher pK_a^{OH} values in the Me_2SO-containing solvents (no. 10).

Even though the decreased solvation of the anionic oxygen is the main factor which determines the solvent effect on the breakdown of T^-_O, changes in the solvation of the products are also expected to affect this solvent effect. Equation 18 expresses the solvent dependence of K_4 in terms of solvent activity coefficients[8] for the transfer from water to the Me_2SO-containing solvent of each species involved in the equilibrium.

$$\delta \log {}^{W}K_4^{D} = \log {}^{W}\gamma^{D}_{T^-_O} - \log {}^{W}\gamma^{D}_{PhCHO} - \log {}^{W}\gamma^{D}_{CH(CN)_2^-} \quad (18)$$

The solvent activity coefficients of these species are not known but can be estimated as follows. For T^-_O we assume that ${}^{W}\gamma^{D}_{T^-_O}$ is approximately the same as for OH^- (${}^{W}\gamma^{D}_{OH^-}$ is known[30]) while $\log {}^{W}\gamma^{D}_{PhCHO}$ is assumed to be ≈ 0 as is, e.g., the case for acetylacetone.[31] $\log {}^{W}\gamma^{D}_{CH(CN)_2^-}$ is estimated from

$$\Delta p^{W}K^{D}_{CH_2(CN)_2} = \log {}^{W}\gamma^{D}_{CH(CN)_2^-} + \log {}^{W}\gamma^{D}_{H^+} - \log {}^{W}\gamma^{D}_{CH_2(CN)_2} \quad (19)$$

with $\Delta p^{W}K^{D}_{CH_2(CN)_2}$ being the solvent effect on the pK_a of malononitrile (no. 13 in Table IV), $\log {}^{W}\gamma^{D}_{H^+}$ being known,[30] and $\log {}^{W}\gamma^{D}_{CH_2(CN)_2}$ assumed to be ≈ 0.

Our estimates are summarized in Table VI; the table also includes the experimental $\delta \log {}^{W}K_4^{D}$ values as well as $\delta \log {}^{W}K_4^{D}$ calculated according to eq 18. The agreement between the calculated and observed $\delta \log {}^{W}K^{D}_4$ values is quite good and indicates that our approach is basically sound.[32]

The most interesting conclusion to be drawn is that the increase in K_4 in the Me_2SO-containing solvents is entirely due to the destabilization of T^-_O, and that its effect on K_4 would be even larger if it were not attenuated by the destabilization of $CH(CN)_2^-$ ($\log {}^{W}\gamma^{D}_{CH(CN)_2^-} > 0$).[33]

Since $\delta \log {}^{W}K_4^{D}$ obeys eq 18 (with $\log {}^{W}\gamma^{D}_{PhCHO} \approx 0$) quite well one may expect that the solvent effect on k_4 may be expressed by an equation of the form

$$\delta \log {}^{W}k_4^{D} = \beta_{N,sol} \log {}^{W}\gamma^{D}_{T^-_O} - \beta_{lg,sol} \log {}^{W}\gamma^{D}_{CH(CN)_2^-} \quad (20)$$

The equation bears a formal resemblance to

$$\delta \log k = \beta\delta(pK_a^{BH}) - \alpha\delta(pK_a^{AH}) \quad (21)$$

which expresses the change in the rate constant of a proton transfer, $AH + B^- \rightarrow A^- + BH$, when the pK_a values of both AH and BH are changing simultaneously. Note that in eq 20 we use the subscript "sol" to indicate that the changes in the equilibrium are induced by changes in the solvent rather than in the substituents (eq 21).

If one assumes that $\beta_{N,sol}$ and $\beta_{lg,sol}$ are solvent independent one may estimate $\beta_{N,sol}$ and $\beta_{lg,sol}$ by solving pairs of simultaneous equations of the type of eq 20. For example, for the change from water to 50% and from 50% to 70% Me_2SO the pair of simultaneous equations takes on the form

$$0 \rightarrow 50\% \qquad 1.25 = 3.25\beta_{N,sol} - 0.75\beta_{lg,sol} \quad (22)$$

$$50\% \rightarrow 70\% \qquad 1.00 = 2.29\beta_{N,sol} - 0.38\beta_{lg,sol} \quad (23)$$

from which we obtain $\beta_{N,sol} = 0.57$ and $\beta_{lg,sol} = 0.80$. Choosing a different set, for example, the change from water to 50% Me_2SO, combined with that from 50% to 60% Me_2SO, leads to $\beta_{N,sol} = 0.59$, $\beta_{lg,sol} = 0.89$; for the change from water to 50% Me_2SO, combined with the change from 60% to 70% Me_2SO, we obtain $\beta_{N,sol} = 0.56$, $\beta_{lg,sol} = 0.76$.

It is important to realize that the reason why solving the pairs of simultaneous equations allows us to determine the $\beta_{N,sol}$ and $\beta_{lg,sol}$ parameters is that the ratio $\log {}^{W}\gamma^{D}_{T^-_O}/\log {}^{W}\gamma^{D}_{CH(CN)_2^-}$ for one solvent change (e.g., for water to 50% Me_2SO, 3.25/0.75 = 4.53) is different from the ratio $\log {}^{W}\gamma^{D}_{T^-_O}/\log {}^{W}\gamma^{D}_{CH(CN)_2^-}$ for the other solvent change (e.g., for 50% to 70% Me_2SO, 2.29/0.38 = 6.03). In other words, it is because the dependence of the free energy of solvation of the oxyanion not only shows a different *sensitivity* (slope) to the solvent composition from that of the malononitrile anion but because this dependence has a different *shape*.

The fact that the sets of $\beta_{lg,sol}$ and $\beta_{N,sol}$ are quite consistent with each other, regardless of which combination of solvent changes (i.e., which set of simultaneous equations) is used, suggests that the assumption that these parameters are solvent independent is a reasonable approximation. The slight variations from one set to another is probably the result of several factors: (a) the solvent activity coefficients are only approximate; (b) there is some experimental uncertainty in the k_4 values;[34] (c) the assumption

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(30) Wells, C. F. In "Thermodynamic Behavior of Electrolytes in Mixed Solvents-II;" Furter, W. F., Ed.; *Adv. Chem. Ser.* **1979**, *177*, 53.

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(32) The consistently somewhat higher $\delta \log {}^{W}K_4^{D}$ (eq 18) values compared to $\delta \log {}^{W}K_4^{D}$ (obsd) may indicate that $\log {}^{W}\gamma^{D}_{OH^-}$ slightly overestimates $\log {}^{W}\gamma^{D}_{T^-_O}$ because of a somewhat stronger hydrogen bonding solvation of the hydroxide ion. There may also be a slight contribution to the discrepancy from slightly positive $\log {}^{W}\gamma^{D}_{PhCHO}$ values and/or from slightly negative $\log {}^{W}\gamma^{D}_{CH_2(CN)_2}$ values; these latter would reduce $\log {}^{W}\gamma^{D}_{CH(CN)_2^-}$ (eq 19) thereby increasing $\delta \log {}^{W}K_4^{D}$ (eq 18).

(33) Note that the lower pK_a of malononitrile in the Me_2SO-containing solvents is not due to a stabilization of $CH(CN)_2^-$, but to a stabilization of the hydrogen ion ($\log {}^{W}\gamma^{D}_{H^+} < 0$), which overcompensates the destabilization of $CH(CN)_2^-$. By the same token, the increase in pK_a^{OH} is not as large as $\log {}^{W}\gamma^{D}_{T^-_O}$ because it is counteracted by the increased stability of the hydrogen ion.

of solvent independence of $\beta_{\mathrm{lg,sol}}$ and $\beta_{\mathrm{N,sol}}$ is only an approximation.

For these reasons we cannot attach great significance to the precise numerical values which are in the order of 0.78 ± 0.10 for $\beta_{\mathrm{lg,sol}}$ and of 0.57 ± 0.05 for $\beta_{\mathrm{N,sol}}$. We believe, however, that the inequality, $\beta_{\mathrm{lg,sol}} > \beta_{\mathrm{N,sol}}$, is authentic.[35] This inequality indicates that k_4 responds more strongly to the decreased solvation of $\mathrm{CH(CN)_2^-}$ (rate retarding) than to the decreased solvation of $\mathrm{T^-_O}$ (rate enhancing). The reason why the combination of the two effects nevertheless leads to a rate *enhancement* is that the decrease in the solvation of $\mathrm{T^-_O}$ ($\log {}^{\mathrm{W}}\gamma^{\mathrm{D}}{}_{\mathrm{T^-_O}}$) is much larger than the decrease in the solvation of $\mathrm{CH(CN)_2^-}$ ($\log {}^{\mathrm{W}}\gamma^{\mathrm{D}}{}_{\mathrm{CH(CN)_2^-}}$).

Some insight into the meaning of this inequality or "imbalance"[36] may be gained by comparing our reaction with the deprotonation of malononitriles by oxyanions

$$\mathrm{RCH(CN)_2 + B^- \rightleftharpoons RC(CN)_2^- + BH} \qquad (24)$$

Such a comparison suggests an analogy between $\beta_{\mathrm{lg,sol}}$ and the Brønsted α obtained by varying R, and between $\beta_{\mathrm{N,sol}}$ and the Brønsted β value determined by varying $\mathrm{B^-}$. With carboxylate ions as bases, α and β were found to be virtually identical and close to unity,[37] i.e., no imbalance was observed.[38]

On the basis of the results for reaction 24 one might have expected that $\beta_{\mathrm{lg,sol}}$ and $\beta_{\mathrm{N,sol}}$ should also be approximately equal to each other. However, $\beta_{\mathrm{N,sol}}$ is significantly smaller than $\beta_{\mathrm{lg,sol}}$. We attribute this to a reduction in $\beta_{\mathrm{N,sol}}$ which is caused by the stronger solvation of the highly basic $\mathrm{T^-_O}$ oxyanion than that of a carboxylate ion.

Before attempting to explain how this stronger solvation may lead to a reduced $\beta_{\mathrm{N,sol}}$ we would like to point out the similarity of this result with recent observations in the deprotonation of acetylacetone by hydroxide ion and carboxylate ions.[41] In that system all rate constants for the deprotonation of acetylacetone were found to increase with increasing $\mathrm{Me_2SO}$ content of the solvent. However, this increase is relatively less for $\mathrm{OH^-}$ (e.g., 4.33-fold for the change from water to 50% $\mathrm{Me_2SO}$) than with the carboxylate ions (e.g., 8.66-fold with acetate ion for the same solvent change), even though $\log {}^{\mathrm{W}}\gamma^{\mathrm{D}}{}_{\mathrm{OH^-}} > \log {}^{\mathrm{W}}\gamma^{\mathrm{D}}{}_{\mathrm{AcO^-}}$.[30] These observations are tantamount to a smaller β_{sol} for $\mathrm{OH^-}$ compared to acetate ion.

An alternative, but equivalent, way of looking at these proton-transfer data is to compare the Brønsted plots defined by the carboxylate ions in the two solvents and focus on the negative deviation of the hydroxide ion point from the Brønsted line. In water this deviation amounts to 2.79 log units, in 50% $\mathrm{Me_2SO}$ to more than 4.0 log units,[41] again showing the stronger solvation effect for the hydroxide ion.

The reduced reactivity of hydroxide ion and of other strongly basic oxyanions *relative to their pK_a* is a common observation.[42] It has been attributed to the strong solvation of these ions, *coupled with the requirement that the partial desolvation which accompanies the reaction is ahead of bond formation in the transition state.*[43] The small $\beta_{\mathrm{N,sol}}$ for the breakdown reaction of $\mathrm{T^-_O}$ as well as the small β_{sol} in the deprotonation of acetylacetone by $\mathrm{OH^-}$ (or the stronger negative deviation of the $\mathrm{OH^-}$ point from the Brønsted plot in $\mathrm{Me_2SO}$–water)[41] indicate that *this effect is magnified in the $\mathit{Me_2SO}$-containing solvents.* In other words, the energy required for the partial desolvation of the strongly basic alkoxide ions seems to be even larger in $\mathrm{Me_2SO}$–water than in water.

This conclusion may seem paradoxical since in the $\mathrm{Me_2SO}$–water mixtures solvation of the oxyanion is *weaker* than in water.[8] In view of our still very incomplete understanding of the molecular mechanism of solvation, particularly in mixed solvents,[44] any attempts to explain this apparent paradox must remain crude and tentative at best. Nevertheless, it is helpful to examine a number of simple solvation models which might provide a qualitative insight.

The crudest solvation model would be one where all solvation effects are accounted for by the inner solvation shell. In such a model there may be *n* water molecules around the anion in water, while in $\mathrm{Me_2SO}$–water one (or more) of the water molecules may be replaced by a $\mathrm{Me_2SO}$ molecule. Partial desolvation of the anion in $\mathrm{Me_2SO}$–water should then be *easier* than in water since it would presumably involve the removal of a $\mathrm{Me_2SO}$ molecule which is a weaker solvator than water.[8] This model can therefore *not* account for the experimental observations.

From the above discussion it appears that a successful model would have to include effects from the secondary solvation shell. In one version of such a model it is assumed that even in $\mathrm{Me_2SO}$–water mixtures the inner solvation shell of the ion contains only water molecules because of the presumably greater affinity of the hydrogen-bonding water molecules to the anion.[8] The reduced overall solvation of the ion would then mainly be a consequence of weaker solvation *beyond* the inner sphere.

A perhaps more realistic version of this model is the one suggested by Kebarle et al.[45] According to results in the gas phase it appears that the reason why liquid $\mathrm{Me_2SO}$ is a poorer solvator of anions (at least of halide ions) than liquid water is not so much because the solvation energy of a $\mathrm{Me_2SO}$ molecule interacting with the ion is smaller than that of a water molecule (it is in fact larger in the gas phase![45]) but because of the large size of the inner solvation cluster $\mathrm{B^-(Me_2SO)}_n$. This large size prevents solvation beyond the inner sphere of $\mathrm{B^-(Me_2SO)}_n$ while such solvation is quite effective with the smaller $\mathrm{B^-(H_2O)}_n$.[46]

Regardless of which version of this model is preferred, it is relatively easy to visualize why the removal of a solvent molecule from the inner solvation shell would be more difficult in $\mathrm{Me_2SO}$–water than in water. It may simply be a matter of the ion being less able to shed a solvent molecule when it is already inherently less stable by virtue of being placed in a less-solvating medium. In other words, the weaker the solvation of the ion, the more energy it takes to remove a solvent molecule.[47] This situation is similar to observations in the gas phase where the sequential removal of solvent molecules from the solvation shell of an ion becomes increasingly more difficult the fewer solvent molecules are left behind,[45,48] i.e., $\mathrm{B^-(sol)}_{n-1} \rightarrow \mathrm{B^-(sol)}_{n-2} + \mathrm{sol}$ is more difficult than $\mathrm{B^-(sol)}_n \rightarrow \mathrm{B^-(sol)}_{n-1} + \mathrm{sol}$, even though $\mathrm{B^-(sol)}_{n-1}$ is of higher energy than $\mathrm{B^-(sol)}_n$.

Mechanism of the $k_{34}^{\mathrm{H_2O}}$ Step. The direct breakdown of $\mathrm{T^\circ_{OH}}$ into benzaldehyde and malononitrile becomes dominant in strongly acidic solution. A similar direct breakdown has been observed in the hydrolysis of 1,1-dinitro-2,2-diphenylethylene[4] and arylidene Meldrum's acids.[2] In past discussions[1,2,4] we have favored a

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(34) The uncertainty in the *absolute* values of k_4 may well amount to factors of two or three. However, most of these uncertainties tend to cancel in $\delta \log {}^{\mathrm{W}}k_4{}^{\mathrm{D}}$ because the systematic errors in our estimates should be largely the same in all solvents.

(35) The inequality $\beta_{\mathrm{lg,sol}} > \beta_{\mathrm{N,sol}}$ also remains if somewhat lower $\log {}^{\mathrm{W}}\gamma^{\mathrm{D}}{}_{\mathrm{T^-_O}}$ values are assumed which may be justified since $\delta \log {}^{\mathrm{W}}K_4{}^{\mathrm{D}}$ (obsd) < $\delta \log {}^{\mathrm{W}}K_4{}^{\mathrm{D}}$ (eq 18).

(36) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948.

(37) Bell, R. P.; Grainger, S. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1367.

(38) This contrasts with the deprotonation of nitroalkanes,[39] ketoesters,[37] and arylacetonitriles[40] where strong imbalances have been observed.

(39) (a) Fukyama, M.; Flanagan, P. W. K.; Williams, F. T., Jr.; Frainer, L.; Miller, S. A.; Schechter, H. *J. Am. Chem. Soc.* **1970**, *92*, 4689. (b) Bordwell, F. G.; Boyle, W. J., Jr. *Ibid.* **1972**, *94*, 3907. (c) Bordwell, F. G.; Bartmess, J. E.; Hautala, J. A. *J. Org. Chem.* **1978**, *43*, 3107. (d) Kresge, A. J. *Can. J. Chem.* **1975**, *52*, 1897.

(40) Bernasconi, C. F.; Hibdon, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 4343.

(41) Bernasconi, C. F.; Bunnell, R. D. *Isr. J. Chem.*, in press.

(42) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475.

(43) Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, G.; Nakamura, C. *J. Am. Chem. Soc.* **1982**, *104*, 7045 and references cited therein.

(44) Reichhardt, C. "Solvent Effects in Organic Chemistry"; Verlag Chemie: New York, 1979.

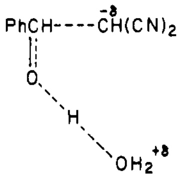
(45) Magnera, T. F.; Caldwell, G.; Sunner, J.; Ikuta, S.; Kebarle, P. *J. Am. Chem. Soc.* **1984**, *106*, 6140.

(46) Other authors, based on different kinds of evidence, have also concluded that the superior solvation of anions in liquid water is due as much to cooperative effects beyond the inner shell as to specific coordination effects: (a) Cogley, D. R.; Butler, J. N.; Grunwald, E. *J. Phys. Chem.* **1971**, *75*, 1477. (b) Arnett, E. M.; Chawla, B.; Hornung, N. J. *J. Sol. Chem.* **1977**, *6*, 781.

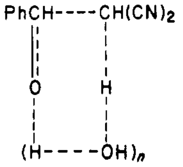
(47) Note that this model still allows for the ion to be more reactive in the mixed solvent because the extra activation energy required for its desolvation is *over*compensated by its greater destabilization brought about by the transfer from water to $\mathrm{Me_2SO}$–water.

(48) (a) Kebarle, P. *Annu. Rev. Phys. Chem.* **1977**, *28*, 445. (b) Lan, Y. K.; Ikuta, S.; Kebarle, P. *J. Am. Chem. Soc.* **1982**, *104*, 1462.

mechanism in which C–C bond cleavage is concerted with removal of the OH proton as shown in **1** for the present example; an attractive variation of this mechanism involves bifunctional catalysis by water as shown in **2**.



1



2

In support of this latter possibility we cite a recent observation of what appears to be bifunctional catalysis of the breakdown of T°_{OH} by the monoanion of malonic acid.[49] The fact that $k_{34}^{H_2O}/[H_2O]$ is virtually solvent independent (see no. 16 in Table IV) is also consistent with a transition state in which there is little charge development as in **2**. An interpretation of this solvent independence in terms of transition-state **1** cannot be ruled out, though, but is more contrived because it requires an almost perfect cancellation of the stabilizing effect of the positive charge by Me_2SO and its destabilizing effect on the negative charge.

Conclusions. (1) Oxygen protonation of T^-_O by carboxylic acids is somewhat slower than for unencumbered thermodynamically favorable proton transfers between oxygen atoms, but it shows the characteristic $\alpha \approx 0$ ($\beta \approx 1.0$ in the reverse direction) for diffusion-controlled proton transfers. This kind of steric reduction of diffusion-controlled proton transfers has now been observed in numerous systems.[21,22,27-29]

(2) The increase in K_4 for the breakdown of T^-_O into benzaldehyde and $CH(CN)_2^-$ in the Me_2SO-containing solvents is due to the destabilization of T^-_O although the effect is somewhat attenuated by a small destabilization of $CH(CN)_2^-$. The solvent effect on k_4 can be attributed to the interplay of the same factors which affect K_4, but the sensitivity of k_4 to the rate-enhancing reduced solvation of T^-_O ($\beta_{N,sol} \approx 0.57 \pm 0.05$) is lower than the sensitivity to the rate-retarding destabilization of $CH(CN)_2^-$ ($\beta_{lg,sol} \approx 0.78 \pm 0.10$). That k_4 nevertheless *increases* with the addition of Me_2SO is due to the much greater destabilization of T^-_O than of $CH(CN)_2^-$, as reflected in the larger solvent transfer activity coefficient for T^-_O compared to $CH(CN)_2^-$.

(3) The inequality $\beta_{N,sol} < \beta_{lg,sol}$ is an example of an imbalance. This imbalance appears to be a consequence of the need for early desolvation of the oxyanion in the transition state and a greater energy requirement for this desolvation in the Me_2SO–water mixtures than in water. This greater energy requirement for desolvation in the less-solvating solvent is somewhat analogous to the increased endothermicity in the sequential removal of solvent molecules from an ion in the gas phase.

(4) The mechanism for the direct breakdown of T°_{OH} into benzaldehyde and malononitrile probably involves concerted C–C bond cleavage and oxygen deprotonation by water. However, the intriguing but unprecedented possibility of bifunctional catalysis by water (**2**) merits further investigation; the absence of a significant solvent effect on $k_{34}^{H_2O}$ and a recent observation of what appears to be bifunctional catalysis by the monoanion of malonic acid support this possibility.

Experimental Section

Materials. Benzylidenemalononitrile (Aldrich) was recrystallized from ethanol, mp 83–84 °C (lit.[6] 84 °C). Dichloroacetic and chloroacetic acid (Aldrich) were recrystallized from petroleum ether. Methoxyacetic (Aldrich, 99%) and acetic acid (Mallinckrodt, reagent grade) were used without further purification. Benzaldehyde (Fluka) was purified according to literature procedures.[50] Malononitrile (Aldrich) was distilled and then recrystallized from benzene. Reagent grade dimethyl sulfoxide (Mallinckrodt) was stored over 4 Å molecular sieves prior to use.

Reaction Solutions and pH Determinations. Solutions were prepared by adding appropriate amounts of aqueous stock solutions to a measured amount of Me_2SO that would correspond to 50%, 60%, or 70% (v/v) of the final solution volume. The ionic strength was maintained at 0.5 M with KCl for all solutions except those in 70% Me_2SO–30% water where an ionic strength of 0.25 M was maintained because of the reduced solubility of KCl. All pH measurements were performed on an Orion Research 611 digital pH meter (water and 50% Me_2SO) and on a Metrohm/Brinkman 104 pH meter (60% and 70% Me_2SO). Both meters were equipped with a Corning No. 476022 glass electrode and a Beckman No. 39400 calomel reference electrode. The pH meters were calibrated for Me_2SO–water mixture with buffers described by Hallé et al.[9] Mallinckrodt standard buffer solutions were used to calibrate the pH meters for aqueous solutions.

Kinetic Experiments. The reactions were monitored spectrophotometrically at 320 nm (λ_{max} = 309 nm for BMN) in a Perkin-Elmer 559A UV/vis spectrophotometer. Hydrolysis reactions were initiated by adding microliter amounts of a stock BMN solution in methanol to a cuvette containing 3 mL of buffer solution pre-equilibrated at 20 °C. Condensation reactions were initiated by adding microliter amounts of either a stock solution of malononitrile in water or a stock solution of benzaldehyde in ethanol to a cuvette containing 3 mL of buffer solution at 20 °C. Linear plots of log ($OD - OD_\infty$) vs. time were observed for at least 3 half-lives for those reactions which could be followed to completion within a reasonable amount of time.

The slower hydrolysis rates observed in 70% Me_2SO–30% water below pH 3.5 were determined by the method of initial rates at 320 nm. The hydrolysis products do not absorb at this wavelength. Hence, hydrolysis rate constants were calculated from the initial slope of OD vs. time ($\Delta OD/\Delta t$) and the initial absorbance (OD_0) according to

$$k_{obsd} = \frac{\Delta OD}{\Delta t}\frac{1}{OD_0}$$

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Registry No. BMN, 2700-22-3; malononitrile, 109-77-3; benzaldehyde, 100-52-7.

Supplementary Material Available: Kinetic data, Tables S1–S14 (17 pages). Ordering information is given on any current masthead page.

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