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Kinetics of Proton Transfer from 2-Nitro-4-X-phenylacetonitriles to Piperidine and Morpholine in Aqueous Me$_2$SO. Solvent and Substituent Effects on Intrinsic Rate Constants. Transition State Imbalances

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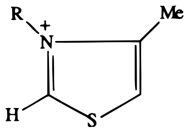
Abstract: Rate constants (k_1^{B}) for the deprotonation of 2-nitro-4-X-phenylacetonitrile, **2-X** (X = NO$_2$, SO$_2$CH$_3$, CN, CF$_3$, Br, and Cl) by piperidine and morpholine and for the reverse reaction (k_{-1}^{BH}) have been determined in 90% Me$_2$SO−10% water, 50% Me$_2$SO−50% water, and water (X = NO$_2$, SO$_2$CH$_3$, CN only). Brønsted β_B values (dlog k_1^{B}/dpK_a^{BH}), Brønsted α_{CH} values (dlog k_1^{B}/dlog K_a^{CH}), and intrinsic rate constants (log k_o = log(k_1/q) for pK_a^{BH} − pK_a^{CH} + log(p/q) = 0) were calculated from these data. α_{CH} is smaller than β_B, implying an imbalance which is consistent with a transition state in which delocalization of the negative charge into the 2-nitrophenyl moiety lags behind proton transfer. A consequence of this imbalance is that the intrinsic rate constant decreases with increasing electron withdrawing strength of X. For π-acceptor substituents (NO$_2$, SO$_2$CH$_3$, CN) there is a further decrease in k_o due to a lag in the delocalization of the charge into X. The intrinsic rate constants depend very little on the Me$_2$SO content of the solvent which is shown to be the result of compensation of mainly two competing factors. One is the stabilization of the polarizable transition state by the polarizable Me$_2$SO which increases k_o; the other is attributed to a lag in the solvation of the developing carbanion behind proton transfer at the transition state which leads to a decrease in k_o.

When dealing with chemical reactivity it is good practice to separate thermodynamic driving force from a purely kinetic factor commonly referred to as the intrinsic barrier ($\Delta G_0^{\ddagger} = \Delta G_1^{\ddagger} = \Delta G_{-1}^{\ddagger}$ when $\Delta G° = 0$) or the intrinsic rate constant ($k_o = k_1 = k_{-1}$ when $K_1 = 0$).[1] Indeed, many important insights regarding the factors that influence proton transfer from carbon acids to a variety of bases have been gained from the determination of the intrinsic rate constants of these reactions.[2] A major conclusion to be drawn from a recent compilation of some 40 examples[2b] is that k_o progressively decreases with increasing resonance stabilization of the resulting carbanion. This decrease in k_o has been attributed to a lag in charge delocalization behind proton transfer at the transition state. Another important factor that can substantially reduce k_o is a lack of synchronization, at the transition state, between the proton transfer and the solvation of the products or desolvation of the reactants, in particular the lag in the solvation of the developing carbanion behind the proton transfer.[2a,b]



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A dramatic illustration of these points comes from the comparison of phenylnitromethane with **1**. For **1**, log $k_o \sim 9.0$ for deprotonation by carboxylate ions in water[3] represents one extreme which suggests that **1** behaves essentially like a normal acid with no charge delocalization or resonance stabilization of its conjugate base, and solvation effects that are too small to significantly affect k_o. At the other extreme, log $k_o = -1.22$ and -2.10 for the deprotonation of phenylnitromethane in water by the piperidine/morpholine pair[4,5] and carboxylate ions,[5] respectively, show the very large k_o-depressing effect of nonsynchronous resonance development and solvation. That the lag in the *solvation* of the developing nitronate ion contributes substantially to the overall lowering of k_o can be seen from the much higher log k_o values in 90% or 100% Me$_2$SO (log k_o = 1.75 and 1.88 for deprotonation by R$_2$NH and RCOO$^-$, respectively, in 90% Me$_2$SO−10% water;[5] log k_o = 2.81 for deprotonation by ArCOO$^-$ in pure Me$_2$SO[6]) which are consistent with the much weaker solvation of the nitronate ion by Me$_2$SO than by water. Similar results have been reported for the deprotonation of nitromethane.[5]

Acetylacetone takes an intermediate position between **1** and phenylnitromethane, with log k_o = 3.14 for deprotonation by RCOO$^-$ and log k_o = 2.60 for deprotonation by piperidine/morpholine in aqueous solution, and log k_o = 5.27 (RCOO$^-$) and 3.64 (pip/mor) in 90% Me$_2$SO−10% water.[8] The intermediate values for log k_o are consistent with a smaller degree of resonance stabilization of the acetylacetonate ion compared to the phenylnitromethane anion; and the smaller solvent effect on log k_o is consistent with the smaller solvational stabilization

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(1) For a reaction with a forward rate constant k_1, a reverse rate constant k_{-1} and an equilibrium constant K_1.

(2) For recent reviews, see (a) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301. (b) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119. (c) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9.

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(6) Based on data in reference 7.

(7) Keeffe, J. R.; Morey, J.; Palmer, C. A.; Lee, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 1295.

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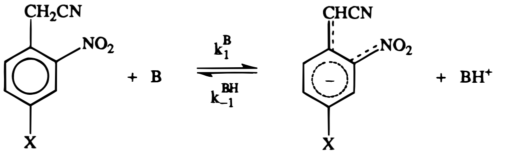
by water of the acetylacetonate compared to the phenylnitronate anion.[9] 1,3-Indandione shows very similar behavior as acetylacetone.[10]

A qualitatively different situation has been observed with 9-cyanofluorene,[11] 9-carbomethoxyfluorene[11] and (α-cyanodiphenylmethane)bis(tricarbonylchromium(0)).[12] For example, deprotonation of 9-cyanofluorene by primary amines in 10% Me_2SO−90% water is characterized by log $k_o = 3.62$ which is not much larger than for acetylacetone and again places it about midway between **1** and phenylnitromethane. Here, however, most of the reduction in k_o relative to that for **1** comes from the resonance effect of the fluorenyl ion while solvation is relatively unimportant. This can be seen from the fact that a change to 90% Me_2SO−10% water leaves k_o essentially unaffected. This finding is consistent with the 9-cyanofluorenyl anion being *less* solvated in the water-rich than in the Me_2SO-rich solvent,[9] which is a consequence of the negative charge not being concentrated on oxygen atoms that can be solvated by hydrogen bonding (nitronate and enolate ions), but being strongly dispersed over a large π-system.

An interesting but as yet unexplored case with respect to solvent effects on k_o is the deprotonation of 2-nitro-4-X-phenylacetonitrile (**2-X**). The only member of this series for which a few relevant kinetic data are available is 2,4-dinitrophenylacetonitrile (**2-NO₂**). In 50% Me_2SO−50% water log $k_o = 2.75$ with piperidine/morpholine[13] places it close to acetylacetone in terms of the combined effects of resonance and solvation. In the carbanion, **2-NO₂**$^-$, there is undoubtedly a significant amount of charge delocalization over the extended π-system which makes it similar to the 9-cyanofluorenyl anion. On the other hand, a good portion of this charge is likely to be concentrated on the two nitro groups of **2-NO₂**$^-$ which should allow for hydrogen bonding solvation in a water-rich solvent. Hence the solvent effect on k_o for deprotonation of **2-NO₂** may be somewhere between that for the deprotonation of acetylacetone and 9-cyanofluorene. A major objective of this paper is to test this prediction, to determine the relative solvation energies (solvent transfer coefficients)[9] for **2-NO₂**$^-$ in various Me_2SO-water mixtures, and analyze the solvent effect on k_o based on these solvation energies.



2-X **2-X⁻** (1)

A second objective is to examine how a change in the X-substituent of **2-X** affects the rate of proton transfer, thereby providing information about (a) possible transition state imbalance, (b) changes in transition state structure, (c) substituent effects on k_o, and (d) substituent dependence of the solvent effect on k_o.

Results

Rate and pK_a Determinations. Rate constants k_1^B and k_{-1}^{BH} for the reaction in eq 1 with B being piperidine and morpholine were determined in a stopped-flow spectrophotometer for X = NO_2, CN, CH_3SO_2, CF_3, Br and Cl and 90% Me_2SO−10% water (v/v) and 50% Me_2SO−50% water (v/v), and for X = NO_2, CN and CH_3SO_2 in water, at 20 °C. With X = CF_3, Br and Cl in water the acidity of **2-X** was too low for such measurements. All experiments were conducted under pseudo-first-order conditions in excess amine buffer.

The pseudo-first-order rate constants for equilibrium approach is given by eq 2 which includes terms for the water, H^+ and OH^- reactions. These latter terms were either negligible

$$k_{obsd} = k_1^{H_2O} + k_{-1}^{H} a_{H^+} + k_1^{OH} a_{OH^-} + k_{-1}^{H_2O} + k_1^{B}[B] + k_{-1}^{BH}[BH^+] \quad (2)$$

(especially in 90% Me_2SO) or resulted in a small intercept when k_{obsd} was plotted vs [B] or [BH^+]; k_1^B and k_{-1}^{BH} which are the focus of this study were determined from the slopes of these plots as follows.

When $pK_a^{BH} \gg pK_a^{CH}$ (CH refers to **2-X**), the slope of a plot of k_{obsd} vs [B] yielded k_1^B directly and k_{-1}^{BH} was calculated as $k_{-1}^{BH} = k_1^B K_a^{BH}/K_a^{CH}$. This was the case for the reactions of piperidine with **2-NO₂**, **2-SO₂CH₃**, **2-CN** and **2-CF₃** in 90% Me_2SO, the reaction of morpholine with **2-NO₂** and **2-SO₂CH₃** in 90% Me_2SO, the reactions of piperidine with **2-SO₂CH₃** and **2-CN** in 50% Me_2SO, and the reaction of piperidine with **2-NO₂** in water. When $pK_a^{BH} \ll pK_a^{CH}$ the slope of a plot of k_{obsd} vs [BH^+] afforded k_{-1}^{BH} directly and k_1^B was obtained as $k_1^B = k_{-1}^{BH} K_a^{CH}/K_a^{BH}$. The reactions of morpholine with **2-Br** and **2-Cl** in 90% Me_2SO, of morpholine with **2-CF₃**, **2-Br** and **2-Cl** in 50% Me_2SO, and of **2-SO₂CH₃** and **2-CN** with morpholine in water fall into this category. When $pK_a^{CH} \sim pK_a^{BH}$ the slope of a plot of k_{obsd} vs [B] is pH dependent and given by $k_1^B + k_{-1}^{BH} a_{H^+}/K_a^{BH}$. A plot of this slope vs a_{H^+} then yields k_1^B and k_{-1}^{BH}/K_a^{BH}, and k_{-1}^{BH} can be obtained from k_{-1}^{BH}/K_a^{BH} and the known K_a^{BH}. This situation prevailed in the reactions of morpholine with **2-CN** and **2-CF₃** in 90% Me_2SO, the reactions of piperidine with **2-Cl** and **2-Br** in 90% Me_2SO, the reactions of morpholine with **2-SO₂CH₃** and **2-CN** and of piperidine with **2-CF₃** in 50% Me_2SO, and the reactions of morpholine with **2-NO₂** and of piperidine with **2-SO₂CH₃** and **2-CN** in water. A representative example is shown in Figure 1S of the supporting information[14] where k_{obsd} for the reaction of **2-Cl** with piperidine is plotted versus piperidine concentrations at various pH values. The plot of the slopes for Figure 1S versus a_{H^+} is shown in Figure 2S.[14]

The various rate constants determined as described above are summarized in Table 1 while the raw data are reported elsewhere.[15]

The pK_a^{CH} values of the various **2-X** in the three solvents were measured spectrophotometrically. They are included in Table 1. In those cases where both k_1^B and k_{-1}^{BH} could be determined from the pH-dependence of the slopes of k_{obsd} vs [B] the agreement between the kinetically and spectrophotometrically obtained pK_a^{CH} values was very good.

Transfer Activity Coefficients. Activity coefficients for the transfer of **2-X** from water to 50% Me_2SO (${}^0\gamma_{CH}^{50}$), from water to 90% Me_2SO (${}^0\gamma_{CH}^{90}$), and from 50% to 90% Me_2SO (${}^{50}\gamma_{CH}^{90}$) were determined from partition experiments with p-xylene, as detailed in the Experimental Section. In conjunction

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(14) See paragraph concerning supporting information at the end of this paper.

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Table 1. Rate Constants[a] for Proton Transfer between **2-X** and Amines at 20 °C

		piperidine[b]		morpholine[c]	
2-X	pK_a^{CH}	k_1^B, $M^{-1}s^{-1}$	k_{-1}^{BH}, $M^{-1}s^{-1}$	k_1^B, $M^{-1}s^{-1}$	k_{-1}^{BH}, $M^{-1}s^{-1}$
		90% Me_2SO−10% Water[d]			
2-NO$_2$	6.00 ± 0.02	1.85×10^5	3.27×10^0	1.92×10^4	2.36×10^1
2-SO$_2$CH$_3$	7.85 ± 0.02	7.39×10^4	9.52×10^1	7.86×10^3	6.85×10^2
2-CN	8.14 ± 0.04	5.48×10^4	1.38×10^2	6.02×10^3	1.02×10^3
2-CF$_3$	9.24 ± 0.02	2.76×10^4	8.76×10^2	2.59×10^3	5.53×10^3
2-Br	11.03 ± 0.02	6.29×10^3	1.22×10^4	4.21×10^2	5.55×10^4
2-Cl	11.15 ± 0.05	5.52×10^3	1.42×10^4	3.60×10^2	6.26×10^4
		50% Me_2SO−50% Water[e]			
2-NO$_2$[f]	8.06	2.37×10^4	2.43×10^1	1.71×10^3	3.74×10^2
2-SO$_2$CH$_3$	9.40 ± 0.02	1.10×10^4	2.46×10^2	9.47×10^2	4.54×10^3
2-CN	9.53 ± 0.03	9.70×10^3	2.93×10^2	8.44×10^2	5.45×10^3
2-CF$_3$	10.71 ± 0.03	4.78×10^3	2.71×10^3	3.20×10^2	3.13×10^4
2-Br	12.02 ± 0.04	1.54×10^3	1.44×10^4	5.66×10^1	1.13×10^5
2-Cl	12.17 ± 0.02	1.26×10^3	1.66×10^4	4.33×10^1	1.22×10^5
		Water[e]			
2-NO$_2$	9.91 ± 0.03	3.94×10^3	9.45×10^1	3.69×10^2	3.78×10^3
2-SO$_2$CH$_3$	11.12 ± 0.05	2.65×10^3	1.02×10^3	2.31×10^2	3.83×10^4
2-CN	11.43 ± 0.02	2.39×10^3	1.90×10^3	1.62×10^2	5.41×10^4

[a] Error limits estimated at ±4% or better. [b] $pK_a^{BH} = 10.74$ (90% Me_2SO), 11.05 (50% Me_2SO), 11.53 (water). [c] $pK_a^{BH} = 8.91$ (90% Me_2SO), 8.72 (50% Me_2SO), 8.90 (water). [d] $\mu = 0.06$ M (KCl). [e] $\mu = 0.5$ M (KCl). [f] Reference 13.

Table 2. Transfer Activity Coefficients for the Transfer of **2-X** and Some Other Carbon Acids from Water to 50% and 90% Me_2SO and from 50% to 90% Me_2SO at 20 °C

CH	$\log {}^0\gamma_{CH}^{50}$	$\log {}^{50}\gamma_{CH}^{90}$	$\log {}^0\gamma_{CH}^{90}$
2-NO$_2$	−0.70	−0.99	−1.68
2-SO$_2$CH$_3$	−0.82	−1.26	−2.08
2-CN	−0.70	−0.55	−1.25
2-CF$_3$	−0.59	−2.09	−2.68
2-Br	−0.38	−1.95	−2.33
2-Cl		−1.77	
9-CN-Fl[a,b]	−1.64[d]	−2.24	−3.88[e]
$[(CO)_3C_6H_5]_2CHCN$[c]		<−2.53	
9-COOMe-Fl[a,b]	−1.90[d]	−2.24	−4.14[e]
1,3-indandione[b]	−0.39[d]	−1.21	−1.60[e]
$CH_2(COCH_3)_2$[b]	0.21	−0.43	−0.22
$PhCH_2NO_2$[b]	−1.11	−1.75	−2.86
CH_3NO_2[b]	−0.10	−0.77	−0.87

[a] Fl = fluorene. [b] Reference 9. [c] (α-Cyanodiphenylmethane)bis(tricarbonylchromium(0)), ref 12. [d] $\log^{10}\gamma_{CH}^{50}$. [e] $\log^{10}\gamma_{CH}^{90}$.

Table 3. Transfer Coefficients for the Transfer of **2-X**$^-$ and Some Other Carbanions from Water to 50% and 90% Me_2SO and from 50% to 90% Me_2SO

C^-	$\log {}^0\gamma_{C^-}^{50}$	$\log {}^{50}\gamma_{C^-}^{90}$	$lo {}^{50}\gamma_{C^-}^{90}$
2-NO$_2^-$	−0.62	−1.93	−2.54
2-SO$_2$CH$_3^-$	−0.61	−1.39	−2.00
2-CN$^-$	−0.67	−1.11	−1.78
2-CF$_3^-$		−2.44	
2-Br$^-$		−1.82	
2-Cl$^-$		−1.67	
9-CN-Fl$^-$ [a,b]	−1.37[d]	−2.65	−4.02[e]
$[(CO)_3C_6H_5]_2CCN^-$ [c]		<−2.56	
9-COOMe-Fl$^-$ [a,b]		−2.12	
1,3-indandione$^-$ [b]	0.41[d]	1.38	1.79[e]
$CH(COCH_3)_2^-$ [b]	2.36	2.67	5.03
$PhCH{=}NO_2^-$ [b]	1.99	2.10	4.09
$CH_2{=}NO_2^-$ [b]	2.87	3.83	6.70

[a] Fl = Fluorene. [b] Reference 9. [c] Reference 12. [d] $\log^{10}\gamma_{C^-}^{50}$. [e] $\log^{10}\gamma_{C^-}^{90}$.

with the transfer activity coefficient of the hydronium ion (γ_{H^+})[16] and the solvent dependence of pK_a^{CH}, the transfer activity coefficients for **2-X**$^-$ (${}^0\gamma_{C^-}^{50}$, ${}^0\gamma_{C^-}^{90}$, and ${}^{50}\gamma_{C^-}^{90}$) were then obtained from equations such as eq 3.

$$\log {}^0\gamma_{C^-}^{50} = {}^0\Delta^{50}pK_a^{CH} - \log {}^0\gamma_{H^+}^{50} + \log {}^0\gamma_{CH}^{50} \qquad (3)$$

The various log γ_{CH} values for **2-X** and some other carbon acids are summarized in Table 2, the log $\gamma_{C}-$ values for **2-X**$^-$ and other carbanions in Table 3. Note that we have adopted Parker's[17] definition of transfer coefficients as illustrated in eq 4 for ${}^0\gamma_{C^-}^{90}$, where ${}^0\Delta^{90}G_{tr}(C^-)$ is

$$\log {}^0\gamma_{C^-}^{90} = {}^0\Delta^{90}G_{tr}(C^-)/2.303RT \qquad (4)$$

the free energy of transfer of C^- from water to 90% Me_2SO. Thus a negative log ${}^0\gamma_{C^-}^{90}$ means that C^- is more strongly, a positive log ${}^0\gamma_{C^-}^{90}$ that C^- is less strongly solvated in 90% Me_2SO than in water.

Discussion

Solvent Dependence of pK_a^{CH}. The pK_a^{CH} values for all **2-X** decrease with increasing Me_2SO content of the solvent. This is because the stronger solvation of **2-X** by Me_2SO than by water is matched by an even somewhat larger increase in the solvation of the anion **2-X**$^-$ in the Me_2SO-containing solvents, i.e., $\log {}^0\gamma_{C^-}^{50}$, $\log {}^{50}\gamma_{C^-}^{90}$, etc. (Table 3) are somewhat more negative than $\log {}^0\gamma_{CH}^{50}$, $\log {}^{50}\gamma_{CH}^{90}$, etc. (Table 2). Coupled with the significantly stronger solvation of the hydronium ion by Me_2SO ($\log {}^0\gamma_{H^+}^{50} = -1.93$, $\log {}^{50}\gamma_{H^+}^{90} = -1.12$)[16] this leads to a significant decrease in pK_a^{CH} as seen, e.g., by solving eq 3 for ${}^0\Delta^{50}pK_a^{CH}$.

The stronger solvation of **2-X**$^-$ by Me_2SO is a reflection of the dispersion of the negative charge, as is also observed for the conjugate anions of 9-cyanofluorene, 9-carbomethoxyfluorene and (α-cyanodiphenylmethane)bis(tricarbonylchromium(0)) (Tables 2 and 3). This contrasts with the nitronate and enolate ions where the negative charge is more localized on oxygen which leads to stronger solvation by water than by Me_2SO (positive $\log {}^0\gamma_{C^-}^{50}$, $\log {}^{50}\gamma_{C^-}^{90}$, etc., Table 3) and hence to an increase in pK_a^{CH} in the Me_2SO-containing solvents.[18]

Substituent Effects on Acidities of 2-X. As one would expect, the acidity of **2-X** increases with increasing electron withdrawing strength of X. This increase is quite substantial and leads to a difference of about 4 pK units in 50% Me_2SO and about 5 pK_a units in 90% Me_2SO between the weakest (**2-Cl**) and strongest (**2-NO$_2$**) acid. Figure 1 shows Hammett plots of log K_a^{CH} versus σ^-.[19] They yield ρ values of 4.59 ± 0.41 in 90% Me_2SO and 3.77 ± 0.24 in 50% Me_2SO. The fact that correlation with σ^- is quite satisfactory and plots versus the standard σ-values show strong positive deviations for CN, SO_2CH_3 and especially NO_2 indicates that resonance effects in the stabilization of **2-X**$^-$ are quite strong.

The ratio ${}^{50}r^{90} = \rho^{90}/\rho^{50}$ of 1.22 ± 0.18 is a measure of relative sensitivity of pK_a^{CH} to X in the two solvents. An alternate source for ${}^{50}r^{90}$ is the slope of a plot of log $K_a^{CH}(90)$ versus log $K_a^{CH}(50)$ (Figure 4); it yields ${}^{50}r^{90} = 1.23 \pm 0.04$. Because it is not dependent on the choice of appropriate σ^- values, this second method is superior to the first, as reflected

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[16] Wells, C. F. In *Thermodynamic Behavior of Electrolytes in Mixed Solutions—II*; Furter, W. F., Ed.; American Chemical Society: Washington, D. C.; Advances in Chemistry 177, p 53.

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[18] For example, pK_a^{CH} of CH_3NO_2 is 10.28 in water, 11.32 in 50% DMSO and 14.80 in 90% DMSO.[5]

[19] σ^- = 1.25 (NO_2), 1.05 (SO_2CH_3), 0.99 (CN), 0.64 (CF_3), 0.26 (Br), 0.24 (Cl).[20a]

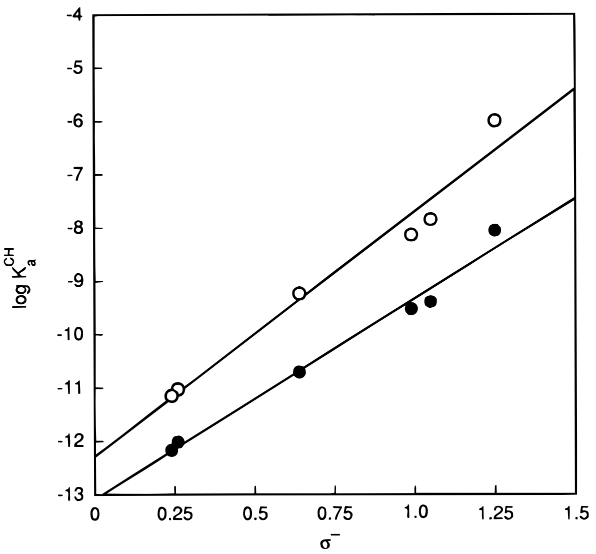

Figure 1. Hammett plots of log K_a^{CH} vs. σ^-. Open circles: 90% Me$_2$SO, filled circles: 50% Me$_2$SO.

in the much smaller standard deviation. A similar plot (not shown) of log $K_a^{CH}(50)$ versus log $K_a^{CH}(0)$ for X = NO$_2$, SO$_2$CH$_3$ and CN yields $^{50}r^{90} = 1.01 \pm 0.11$. The sensitivity of p$K_a^{CH}$ to the *para* substituent is therefore 1.00, 1.01 and 1.24 ($^{0}r^{50} \times {}^{50}r^{90}$) in water, 50% Me$_2$SO and 90% Me$_2$SO, respectively. The higher sensitivity to the substituent effect in the less aqueous, i.e., less polar solvent is a common phenomenon for ionization reactions,[20b] but the *r* values indicate that the solvent dependence is quite modest. This contrasts with $^{0}r^{100} = \rho(\mathrm{Me_2SO})/\rho(\mathrm{H_2O}) \approx 3$[7] for the p$K_a^{CH}$ of XC$_6$H$_4$CH$_2$NO$_2$ which implies a very strong solvent dependence. This contrast can be traced to the fact that the **2-X**$^-$ anions are, as indicated earlier, better solvated by Me$_2$SO than by water (negative $\log {}^{0}\gamma_{C^-}^{50}$, and $\log {}^{50}\gamma_{C^-}^{90}$, Table 3) while the opposite is true for PhCH=NO$_2^-$ (positive $\log {}^{0}\gamma_{C^-}^{50}$, and $\log {}^{50}\gamma_{C^-}^{90}$, Table 3).

Brønsted Parameters. From two-point Brønsted plots of $\log(k_1^B/q)$[21] vs $pK_a^{BH} + \log(p/q)$[21] (not shown) approximate Brønsted β_B and log k_o (log k_1^B/q when $pK_a^{BH} - pK_a^{CH} + \log(p/q) = 0$) values can be obtained. They are summarized in Table 4.

Table 4. Brønsted β_B (α_{BH}) and log k_o for the Reactions of **2-X** with Piperidine and Morpholine at 20 °C[a]

2-X	pK_a^{CH}	β_B	α_{BH^+}[b]	log k_o	$p_{xy} = \partial\beta_B/\partial pK_a^{CH}$
		90% Me$_2$SO−10% Water			
2-NO$_2$	6.00	0.54	0.46	2.54	
2-SO$_2$CH$_3$	7.85	0.53	0.47	3.18	
2-CN	8.15	0.52	0.48	3.24	
2-CF$_3$	9.24	0.56	0.44	3.43	0.046 ± 0.012
2-Br	11.03	0.64	0.36	3.79	
2-Cl	11.15	0.65	0.35	3.81	
		50% Me$_2$SO−10% Water			
2-NO$_2$	8.06	0.49	0.51	2.76	
2-SO$_2$CH$_3$	9.40	0.46	0.54	3.14	
2-CN	9.53	0.46	0.54	3.15	
2-CF$_3$	10.71	0.51	0.50	3.35	0.090 ± 0.012
2-Br	12.02	0.62	0.38	3.60	
2-Cl	12.17	0.63	0.37	3.62	
		Water			
2-NO$_2$	9.91	0.39	0.61	2.85	
2-SO$_2$CH$_3$	11.12	0.40	0.60	3.14	
2-CN	11.43	0.44	0.56	3.20	

[a] Estimated error in β_B and α_{BH^+} is ±0.02. [b] α_{BH^+} = dlog k_{-1}^{BH}/dlog K_a^{BH}.

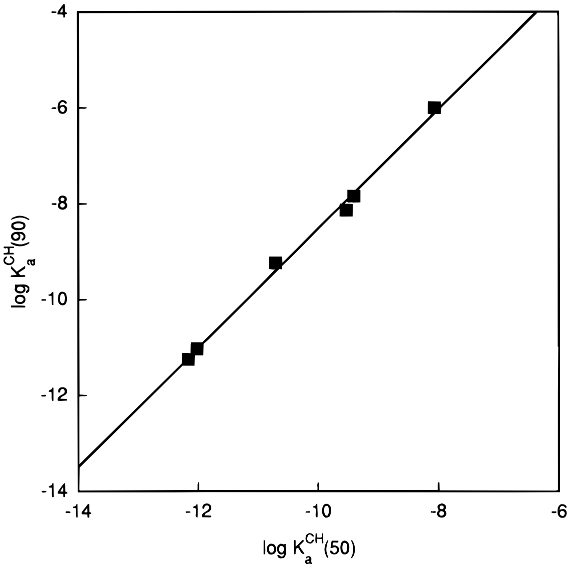

Figure 2. Plot of log $K_a^{CH}(90)$ versus log $K_a^{CH}(50)$.

By plotting log k_1^B vs log K_a^{CH} one may also evaluate Brønsted α_{CH} values. Such plots are displayed in Figures 3 and 4 for the reactions in 90% and 50% Me$_2$SO, respectively. These plots show downward curvature which, in principle, could be interpreted as “Marcus curvature.”[22,23] However, we prefer an interpretation according to which the points for the π-acceptor substituents CN, SO$_2$CH$_3$ and NO$_2$ are considered to deviate negatively from the Brønsted line defined by the other substituents (CF$_3$,[24] Br, Cl). This sort of negative deviation has been observed in other systems[25] and has been attributed to a lag in the development of the resonance effect of these substituents behind proton transfer at the transition state.[2a,b] This point will be further discussed under “Substituent Dependence of Intrinsic Rate Constants.” The α_{CH} values reported in Table 5 are therefore based on the three non-π-acceptor substituents only, and no α_{CH} is reported in water since rate constants for the deprotonation of **2-CF$_3$**, **2-Br**, and **2-Cl** could not be measured in this solvent.

Changes in Transition State Structure. α_{CH} decreases with increasing pK_a^{BH} while β_B for **2-CF$_3$**, **2-Cl** and **2-Br** increases with increasing pK_a^{CH}. These changes in the Brønsted coefficients are related by the interaction coefficient $p_{xy} = \partial\beta_B/\partial pK_a^{CH} = \partial\alpha_{CH}/-\partial pK_a^{BH}$.[23,26] Plots of β_B vs pK_a^{CH} (Figure 3S)[14] yield $\partial\beta_B/\partial pK_a^{CH} = 0.046 \pm 0.012$ in 90% Me$_2$SO and 0.090 ± 0.012 in 50% Me$_2$SO while $\partial\alpha_{CH}/-\partial pK_a^{BH}$ is 0.049 ± 0.011 in 90% Me$_2$SO and 0.086 ± 0.017 in 50% Me$_2$SO.

The positive p_{xy} values reflect changes in transition state structure with changing pK_a of carbon acid and amine, respec-

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(20) (a) Exner, O. In *Correlation Analysis in Chemistry*, Chapman, N. B.; Shorter, J., Eds.; Plenum: New York, 1978; p 439. (b) Exner, O. In *Advances in Linear Free Energy Relationships*, Chapman, N. B.; Shorter, J., Eds.; Plenum: New York, 1972; p 1.

(21) p = 2 and q = 1 are statistical factors referring to the number of equivalent protons on BH$^+$ and the number of basic sites on B, respectively.

(22) (a) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891. (b) Cohen, A. D.; Marcus, R. A. *Ibid.* **1968**, *72*, 4249.

(23) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.

(24) Strictly speaking CF$_3$ is also a π-acceptor but it is quite weak ($\sigma^- = 0.64$ vs $\sigma = 0.54$)[20a] and is, for the purposes of our discussion, included with the substituents that are not π-acceptors.

(25) (a) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1988**, *110*, 4008. (b) Stefanidis, D.; Bunting, J. W. *J. Am. Chem. Soc.* **1991**, *113*, 991.

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

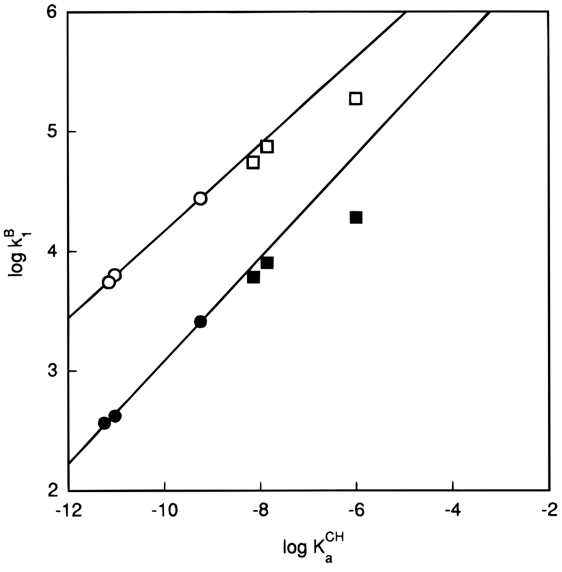


Figure 3. Brønsted plots of log k_1^B versus log K_a^{CH} in 90% Me_2SO. Open symbols: piperidine; filled symbols: morpholine; circles: **2-Cl**, **2-Br** and **2-CF$_3$**; squares: **2-CN**, **2-SO$_2$CH$_3$** and **2-NO$_2$**.

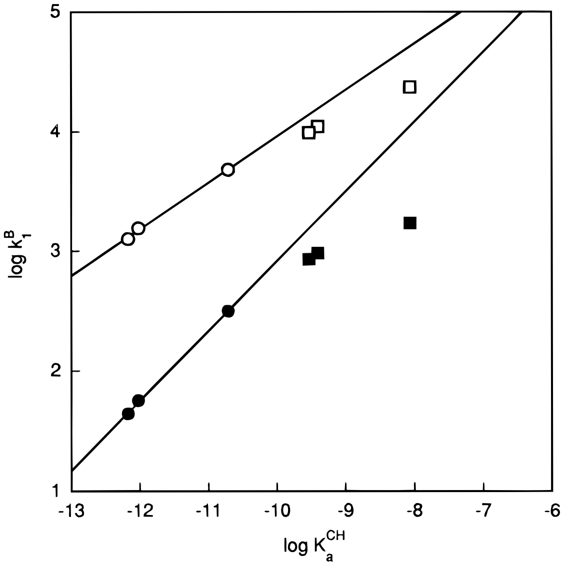
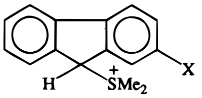
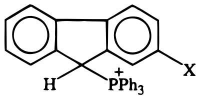


Figure 4. Brønsted plots of log k_1^B versus log K_a^{CH} in 50% Me_2SO. Open symbols: piperidine; filled symbols: morpholine; circles: **2-Cl**, **2-Br** and **2-CF$_3$**; squares: **2-CN**, **2-SO$_2$CH$_3$** and **2-NO$_2$**.

tively. Other systems for which positive p_{xy} values have been reported are the deprotonation of **3-X** by primary aliphatic amines (0.04) and carboxylate ions (0.07) in water,[27] and the deprotonation of **4-X** by primary aliphatic amines (0.03) and by the piperidine/morpholine pair (0.01) in 50% Me_2SO−50% water.[28] These changes can be understood on the basis of a reaction coordinate diagram as described by Murray and Jencks[27] and also discussed by Bernasconi and Fairchild;[28] these papers should be consulted for details.



3-X



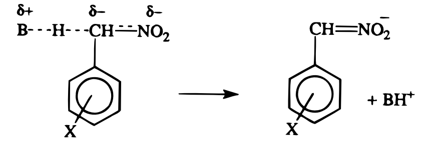
4-X

Table 5. Brønsted α_{CH} (β_{C^-}) for the Reactions of **2-X** (X = CF_3, Br, Cl) with Piperidine and Morpholine at 20 °C

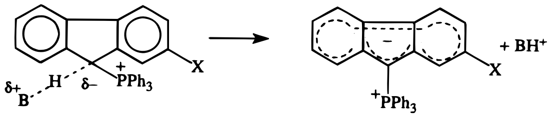
R_2NH	pK_a^{BH}	α_{CH}	β_{C^-}[a]	$p_{xy} = \partial\alpha_{CH}/-\partial pK_a^{BH}$
		90% Me_2SO−10% Water		
piperidine	10.74	0.36 ± 0.01	0.64 ± 0.01	0.049 ± 0.011
morpholine	8.91	0.45 ± 0.01	0.52 ± 0.01	
		50% Me_2SO−50% Water		
piperidine	11.05	0.38 ± 0.02	0.62 ± 0.02	0.086 ± 0.017
morpholine	8.72	0.58 ± 0.02	0.42 ± 0.02	

[a] β_{C^-} = dlog k_{-1}^{BH}/dpK_a^{CH}.

Imbalance. The deprotonation of carbon acids that lead to resonance stabilized carbanions is characterized by transition state imbalances which manifest themselves in α_{CH} not being equal to β_B.[2a,b] These imbalances are caused by a lag in the development of resonance and of the solvation of the developing carbanion behind proton transfer. This can lead to either $\alpha_{CH} > \beta_B$ or $\alpha_{CH} < \beta_B$. The former situation prevails when the transformation of the transition state into the carbanion leads to a shift of the negative charge away from the X-substituent (e.g., $XC_6H_4CH_2NO_2$ + R_2NH, eq 5, α_{CH} = 1.29,[4] β_B = 0.48[5] in water), while in the latter situation negative charge shifts toward the X-substituent (e.g., **4-X** + R_2NH, eq 6, α_{CH} = 0.28, β_B = 0.47 in 50% Me_2SO).[28] This interpretation of α_{CH} and β_B presumes that β_B can be viewed as at least an approximate measure of proton or charge transfer at the transition state,[29] while α_{CH} is clearly not such a measure because it is distorted by the lag in the resonance development or charge delocalization/solvation. Note that the magnitude of $|\alpha_{CH} - \beta_B|$ tends to be large when the carbanion is strongly stabilized by resonance and solvation ($|\alpha_{CH} - \beta_B|$ = 0.81 for $ArCH_2NO_2$ + R_2NH in water) and smaller for less strongly stabilized carbanions ($|\alpha_{CH} - \beta_B|$ = 0.19 for **4-X** + R_2NH in 50% Me_2SO).



(5)



(6)

The reaction of **2-X** with amines also shows an imbalance. Because of the dependence of α_{CH} on pK_a^{BH}, and of β_B on pK_a^{CH}, we shall use average Brønsted coefficients ($\bar{\alpha}_{CH}$, $\bar{\beta}_B$), as for the reactions of **4-X**.[28] Furthermore, since β_B is likely to be influenced by the resonance effect of the π-acceptors *p*-NO_2, *p*-SO_2CH_3 and *p*-CN, $\bar{\beta}_B$ is based on **2-CF$_3$**, **2-Br** and **2-Cl** only. In 90% Me_2SO, $\bar{\alpha}_{CH}$ = 0.40 and $\bar{\beta}_B$ = 0.62, for an imbalance $\bar{\alpha}_{CH} - \bar{\beta}_B = -0.22$; in 50% Me_2SO, $\bar{\alpha}_{CH}$ = 0.48 and $\bar{\beta}_B$ = 0.58, for an imbalance $\bar{\alpha}_{CH} - \bar{\beta}_B = -0.10$.

In view of the fact that averages of α_{CH} and β_{BH} are used, and that each Brønsted coefficient is associated with an uncertainty in the order of ±0.02, the numerical values of these imbalances should be regarded as crude estimates from which

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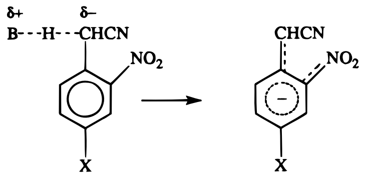
[27] Murray, C. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1990**, *112*, 1880.

[28] Bernasconi, C. F.; Fairchild, D. E. *J. Phys. Org. Chem.* **1992**, *5*, 409.

[29] This is the traditional view[23,30] although this view has been challenged.[31] The fact that one finds $\alpha_{CH} > \beta_B$ in cases where the charge in the carbanion presumably shifts away from the X-substituent whereas one observes $\alpha_{CH} < \beta_B$ in cases where the charge in the carbanion is presumably closer to the X-substituent than it is in the transition state may itself be taken as strong evidence in support of the traditional view.

only qualitative conclusions can be drawn. Nevertheless, an alternate method for estimating $\bar{\alpha}_{CH} - \bar{\beta}_B$ discussed below yields values that are consistent with the ones reported here.

The qualitative conclusions are (a) that $\bar{\alpha}_{CH} - \bar{\beta}_B$ is a negative number and (b) the absolute value of the imbalance is larger in 90% Me_2SO than in 50% Me_2SO. The negative sign is consistent with charge shifting closer to the X-substituent during the transformation of the transition state into the carbanion (eq 7), a situation which is similar to that for eq 6. The larger magnitude of the imbalance in the Me_2SO-rich solvent is mainly a consequence of the stronger solvation of **2-X**$^-$ by Me_2SO than by water, as seen in the negative $\log {}^{50}\gamma_{C^-}^{90}$ values (Table 3). This contrasts with a *smaller* imbalance in Me_2SO than in water for the reaction of $XC_4H_6CH_2NO_2$ with amines ($\alpha_{CH} - \beta_B = 0.90 - 0.55 = 0.35$ in Me_2SO;[6] $\alpha_{CH} - \beta_B = 1.29 - 0.48 = 0.81$ in water[32]), which is a consequence of the *weaker* solvation of $XC_6H_4CH{=}NO_2^-$ (positive $\log {}^{0}\gamma_{C^-}^{90}$, Table 3) by Me_2SO than by water.



(7)

Substituent Dependence of Intrinsic Rate Constants. The intrinsic rate constants are summarized as $\log k_o$ in Table 4. They show a decreasing trend with increasing electron withdrawing strength of the X-substituent. For the substituents that only exert an inductive effect (X = Cl, Br, CF_3) the dependence of $\log k_o$ on X is relatively small and is simply a consequence of the imbalanced transition state. It can be shown that the change in $\log k_o$ with changing pK_a^{CH} is given by eq 8[2a,b] (I = inductive effect) for the ideal case where $p_{xy} = 0$; for $p_{xy} \neq 0$ eq 8

$$\frac{\delta \log k_o^{I}}{-\delta pK_a^{CH}} = (\alpha_{CH} - \beta_B) \qquad (8)$$

should be a good approximation with α_{CH} replaced by $\bar{\alpha}_{CH}$, β_B by $\bar{\beta}_B$.[33]

Plots of $\log k_o$ vs pK_a^{CH} (not shown) afford $\bar{\alpha}_{CH} - \bar{\beta}_B = -0.20 \pm 0.01$ in 90% Me_2SO and -0.18 ± 0.02 in 50% Me_2SO; the value in 90% Me_2SO is close to $\bar{\alpha}_{CH} - \bar{\beta}_B = -0.22$ obtained directly from $\bar{\alpha}_{CH}$ and $\bar{\beta}_B$ (see previous section) but the value in 50% Me_2SO is not in close agreement with that calculated directly (−0.10). The relatively poor agreement between $\bar{\alpha}_{CH} - \bar{\beta}_B$ obtained via eq 8 and that calculated directly in 50% Me_2SO probably reflects the relatively large experimental uncertainties in $\bar{\alpha}_{CH}$ and $\bar{\beta}_B$ mentioned previously, the large difference between $\bar{\alpha}_{CH}$ and the actual α_{CH} values, and the likelihood that the standard deviations associated with $\bar{\alpha}_{CH} - \bar{\beta}_B$ obtained via eq 8 underestimate the true error.

For the π-acceptor substituents (CN, SO_2CH_3, NO_2) the k_o-reducing inductive effect is augmented by a k_o-lowering resonance effect which is a consequence of the lag in the delocalization of the negative charge into X behind proton transfer at the transition state.[34] This is the same effect that leads to the negative deviations from the Brønsted plots (Figures 3 and 4) discussed earlier. Hence, it is not surprising that with the strongest π-acceptor, NO_2, $\log k_o$ is particularly low.

Table 6. Solvent Effects on $\log k_o$ of the Reactions of Carbon Acids with the Piperidine/Morpholine Pair at 20 °C

CH	${}^{0}\delta^{50}\log k_o$	${}^{50}\delta^{90}\log k_o$	${}^{0}\delta^{90}\log k_o$
2-NO$_2$	−0.09	−0.22	−0.31
2-SO$_2$CH$_3$	0.00	0.04	0.04
2-CN	−0.05	0.09	0.04
2-CF$_3$		0.08	
2-Br		0.19	
2-Cl		0.19	
9-CN-Fl[a,b]	0.14[g,h]	−0.19[g]	−0.05[g,i]
$[(CO)_3C_6H_5]_2CHCN$[c]		−0.32	
9-COOMe-Fl[a,b]		0.25[g]	
1,3-indandione[d]	0.16[h]	0.72	0.88[i]
$CH_2(COCH_3)_2$[e]	0.15	0.89	1.04
$PhCH_2NO_2$[f]	0.97	2.00	2.97
CH_3NO_2[f]	1.32	2.33	3.65

[a] Fl = fluorene. [b] Reference 11. [c] (α-Cyanodiphenylmethane)bis(tricarboxylchromium(0)), ref 12. [d] Reference 10. [e] Reference 8. [f] Reference 5. [g] Reactions with primary aliphatic amines. [h] ${}^{10}\delta^{50}\log k_o$. [i] ${}^{10}\delta^{90}\log k_o$.

Solvent Effects on Intrinsic Rate Constants. Table 6 provides a summary of the solvent effects on $\log k_o$ for the deprotonation of **2-X** and several other carbon acids by the piperidine/morpholine pair. ${}^{0}\delta^{50} \log k_o$ is defined as $\log k_o$(50% Me_2SO) − $\log k_o$(water), ${}^{50}\delta^{90} \log k_o$ as $\log k_o$(90% Me_2SO) − $\log k_o$(50% Me_2SO), etc. These solvent effects fall into three distinct categories. The first comprises all the **2-X** as well as (α-cyanodiphenylmethane)bis(tricarbonylchromium(0)), 9-cyano- and 9-carbomethoxyfluorene. Their $\log k_o$ values show a small solvent dependence and, in some cases, tend to be slightly lower in the less aqueous solvent. The second group consists of the two β-diketones; their $\log k_o$ values increase by roughly one unit from water to 90% Me_2SO, or somewhat less than one unit from 50% to 90% Me_2SO. The third group, the nitroalkanes, show qualitatively similar behavior as the diketones but the solvent effects are much larger.

To a good approximation, these solvent effects can be explained by invoking two main factors. The first is the difference in the solvation of the carbanion in the different solvents, and the fact that, at the transition state, the solvation of the incipient carbanion lags behind proton transfer. When solvation of the carbanion is weaker in the Me_2SO-richer solvents ($\log {}^{0}\gamma_{C^-}^{50}$ or $\log {}^{0}\gamma_{C^-}^{90} > 0$), as in the case of the nitroalkanes and β-diketones, the solvational lag enhances $\log k_o$; when the solvation of the carbanion is stronger in the Me_2SO-richer solvent ($\log {}^{0}\gamma_{C^-}^{50}$ or $\log {}^{0}\gamma_{C^-}^{90} < 0$), as is the case for all **2-X**, the fluorene derivatives and (α-cyanodiphenylmethane)bis(tricarbonylchromium(0)), the solvational lag decreases $\log k_o$. The second factor is a "classical" solvent effect[2b,35] which is best understood in terms of preferential solvation of the polarizable transition state by the polarizable Me_2SO. It increases $\log k_o$ and hence reinforces the $\log k_o$ enhancing effect of the first factor in the reactions of the nitroalkanes and β-diketones but more or less offsets the $\log k_o$ reducing effect of the first factor in the reactions of the **2-X**, the fluorene

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(30) (a) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*, Wiley: New York, 1963; p 156. (b) Kresge, A. *J. Acc. Chem. Res.* **1975**, *8*, 354.

(31) Pross, A. *J. Org. Chem.* **1984**, *49*, 1811. (b) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 4737. (c) Pross, A.; Shaik, S. S. *New J. Chem.* **1989**, *13*, 427.

(32) Based on data from reference 4.

(33) Note that in a reaction such as the deprotonation of arylnitromethanes where $\alpha_{CH} - \beta_B > 0$, eq 8 indicates that $\log k_o$ *increases* with increasing electron withdrawing strength of the phenyl substituent, as observed.[2a,2b]

(34) Note that this effect is on top of that of the delayed delocalization into the *ortho*-nitro group.

(35) See also Gandler, J. R.; Bernasconi, C. F. *J. Am. Chem. Soc.* **1992**, *114*, 631.

derivatives and (α-cyanodiphenylmethane)bis(tricarbonylchromium(0)).

Our results show that the hypothesis formulated in the Introduction according to which the solvent effect on k_o for the reactions of **2-NO₂** and the other **2-X** should be intermediate between the solvent effects on k_o for deprotonation of acetylacetone and 9-cyanofluroene is not confirmed. This hypothesis was based on the expectation that the solvation of **$2\text{-}NO_2^-$** in water should include *some* hydrogen bonding to the partially negative nitro groups (or the ortho-nitro group in **2-X** with X $\neq NO_2$) which would lead to log γ_C-values between those for 9-cyanofluorenyl anion ($\log {}^0\gamma_{C^-}^{90} = -4.02$, $\log {}^{50}\gamma_{C^-}^{90} = -2.65$) and acetylacetonate anion ($\log {}^0\gamma_{C^-}^{90} = 5.03$, $\log {}^{50}\gamma_{C^-}^{90} = 2.36$). However, $\log {}^0\gamma_{C^-}^{90} = -2.54$, and $\log {}^{50}\gamma_{C^-}^{90} = -1.93$ for **$2\text{-}NO_2^-$** are much closer to the corresponding values for 9-cyanofluorenyl anion than to those of the acetylacetonate anion. Apparently, Me_2SO is a better solvator than water for nitro groups that carry only a small fraction of charge (in contrast to a nitro group with a full negative charge as in $RCH{=}NO_2^-$). This conclusion is consistent with findings by Keeffe et al.[7] and others.[36,37]

A more quantitative treatment, based on a recently proposed formalism,[38] that takes other factors influencing the solvent effects on log k_o into account is presented under Supporting Information.[14] These factors include delayed solvation of the developing ammonium ion (protonated amine) and desolvation of the amine and carbon acid that is ahead of proton transfer. This quantitative treatment confirms the above qualitative conclusions.

Experimental Section

Materials. The synthesis of the various 4-X-2-nitrophenylacetonitriles was based on the method of Fairbourne and Fawson,[39] eq 9. NaOEt was generated by dissolving Na in ethanol.

$$NCCH_2COOEt \xrightarrow[EtOH]{NaOEt} NC\bar{C}HCOOEt \xrightarrow{ArCl(Br)} ArCH(CN)COOEt \xrightarrow{HCl} ArCH_2CN \quad (9)$$

The sodium salt of the ethylcyanoacetate anion was prepared as an approximately 0.5 M solution in ethanol by adding one equivalent of NaOEt to an ethanolic solution of ethylcyanoacetate (Aldrich). After adding 0.1 equivalents of neat ArCl to 100 mL of the above solution, the reaction mixtures were refluxed for up to 12 hours, acidified with nitric acid and extracted with methylene chloride. Evaporation of the solvent yielded ArCH(CN)COOEt as a reddish-brown oil in most cases although with Ar = 2-nitrophenyl-4-trifluoromethyl and 4-methylsulfonyl-2-nitrophenyl spontaneous crystallization occurred. The (4-X-2-nitrophenyl)ethylcyanoacetates were then added to a boiling ethanolic 3 M HCl solution and transformed to the 4-X-2-nitrophenylacetonitriles by refluxing for 4−6 h. Table 7 summarizes yields, melting points and ^1H NMR data; the latter were taken in $CDCl_3$ on a Brucker 250 MHz instrument. Further details were as follows.

2-4-Dinitrophenylacetonitrile (2-NO₂). This compound was available from a previous study[13] and recrystallized from CCl_4 prior to use, mp 88−89 °C (lit. mp 89 °C[39]).

(4-Methylsulfonyl-2-nitro)phenylacetonitrile (2-SO₂CH₃). Reflux time of the mixture of $NC\bar{C}HCOOEt$ with 4-chloro-3-nitromethylsulfonylbenzene and of ArCH(CN)COOEt with ethanolic HCl was for 4 h. After neutralization of the ethanolic HCl solution, **2-SO₂CH₃** formed crystals which were recrystallized several times from a 50% ethanol/50% water mixture.

Table 7. Summary of Melting Points, Yields, and Proton NMR Data for **2-X**

			NMR chemical shifts[a]			
2-X	mp (°C)	yield	3-position	5-position	6-position	CH_2
2-SO₂CH₃[b]	120−121	≈90%	8.73 (1.8)	8.28 (8.2; 1.8)	8.03 (8.2)	4.32
2-CN	94−95	≈40%	8.48 (1.6)	8.02 (8.1; 1.6)	7.95 (8.1)	4.31
2-CF₃	38−39	≈70%	8.66 (1.6)	8.12 (8.1; 1.6)	7.98 (8.1)	4.29
2-Br	109−110	≈40%	8.31 (2.0)	7.84 (8.3; 2.0)	7.62 (8.3)	4.16
2-Cl	84−85	≈35%	8.31 (1.9)	7.78 (8.3; 2.0)	7.71 (8.3)	4.19

[a] All spectra taken in $CDCl_3$ at 250 MHz. Numbers in parentheses are coupling constants in Hz; CH_2 protons give singlet. [b] Methyl group gives singlet at 3.15 ppm.

(2-Nitro-4-trifluoromethyl)phenylacetonitrile (2-CF₃). 4-Chloro-3-nitrobenzotrifluoride (Aldrich) was first distilled under reduced pressure. Reflux time of the mixture of $NC\bar{C}HCOOEt$ with ArCl was 8 h, and 4 h for the ethanolic HCl solution of ArCH(CN)COOEt. Upon neutralization and cooling of the ethanolic HCl solution the product appeared as an oil which was steam distilled and then recrystallized from 80% ethanol/20% water several times. HPLC showed a single peak.

(4-Cyano-2-nitro)phenylacetonitrile (2-CN). 4-Chloro-3-nitrobenzonitrile (ICN Chemicals) was used without purification. Reflux times were 8 h and 8 h. The product was extracted from the ethanolic solution into methylene chloride. A yellow oil was obtained after evaporation of the extract which subsequently solidified. The solid was recrystallized twice from low boiling (30−60 °C) petroleum ether. HPLC showed a single peak.

(4-Bromo-2-nitro)phenylacetonitrile (2-Br). 2,5-Dibromonitrobenzene (Eastman Kodak) was recrystallized from 80% ethanol prior to use. To 0.25 mol of $NC\bar{C}HCOOEt$ in 250 mL 0.02 mol of 2,5-dibromonitrobenzene was added. After 6 h reflux an additional 0.25 mol of $NC\bar{C}HCOOEt$ was added and refluxed for another 6 h; without the second reflux much of the 2,5-dibromonitrobenzene remained unreacted. Reflux time in ethanolic HCl was 6 h. The product was extracted into methylene chloride which yielded a brown oil after rotary evaporation. The oil was taken up in boiling ethanol and decolorized with charcoal. Water was then added to bring about a 80% ethanol/20% water mixture; crystallization took several days. The product was recrystallized from 80% ethanol/20% water.

(4-Chloro-2-nitro)phenylacetonitrile (2-Cl). 2,5-Dichloronitrobenzene (Eastman Kodak) was recrystallized from 80% ethanol prior to use. All procedures were the same as for the synthesis of **2-Br**.

Buffers and Other Reagents. Reagent grade piperidine and morpholine from Aldrich were refluxed over CaH_2, distilled and stored over P_2O_5 prior to use. Benzoic acid (Aldrich) was recrystallized from ethanol and stored over P_2O_5 prior to use. Chloroacetic acid (Mallinckrodt) was recrystallized from CCl_4 prior to use. The last three compounds were used as buffers to calibrate the pH-meter in DMSO/water mixture according to Hallé et al.[40]

Reagent grade KCl (Mallinckrodt) was used without further purification. Stock solutions of HCl and KOH, used to adjust the pH of solutions, were prepared from "Dilut It" (Baker Analytical) stock solutions. DMSO (Mallinckrodt) was distilled from CaH_2 under reduced pressure; the DMSO was generally used within one week of distillation.

Solutions and pH-Measurements. Solutions were prepared and their pH measured as described[41] before.

UV Spectra and Spectrophotometric pK_a^{CH} Determinations. The anions **$2\text{-}X^-$** absorb strongly in the visible region of the spectrum whereas **2-X** do not. Spectra were taken in a Hewlett-Packard diode array spectrophotometer; λ_{mas} and ϵ values are summarized in Table 8. The pK_a^{CH} values were determined by applying eq 10 where A, A_{C^-} and A_{CH} (≈ 0) are the absorbances at pH $\sim pK_a^{CH}$, pH $\gg pK_a^{CH}$ and pH

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(42) The average of the β_B values in the two solvents is used.

Table 8. Summary of UV/vis Spectral Data

	λ_{max} (ϵ)		
2-X	90% DMSO	50% DMSO	water
2-NO$_2$	442 (26 700)	442 (15 100)	442 (19 800)
2-SO$_2$CH$_3$	560 (9 400)	560 (10 000)	475 (9 800)
2-CN	570 (9 800)	580 (9 000)	580 (9 000)
2-CF$_3$	570 (8 500)	570 (11 000)	
2-Br	589 (10 900)	589 (9 900)	
2-Cl	589 (10 400)	589 (9 600)	

$\ll \mathrm{p}K_a^{CH}$, respectively.

$$\mathrm{p}K_a^{CH} = \mathrm{pH} + \log \frac{A_C - A}{A - A_{CH}} \tag{10}$$

Kinetic Measurements. All kinetic measurements were performed on a Durrum-Gibson stopped-flow spectrophotometer. For runs in the direction **2-X** + B → **2-X**$^-$ + BH$^+$, **2-X** was dissolved in 0.001 M HCl while the buffers were prepared with an excess of 0.001 M KOH. For reactions conducted in the direction **2-X**$^-$ + BH$^+$ → **2-X** + B, **2-X** was dissolved in 0.001 M KOH while the buffers were prepared with an excess of 0.001 M HCl. All rates were measured by monitoring the appearance or disappearance of **2-X**$^-$ at or near its λ_{max}.

Partition Coefficients. The procedures described earlier[9] were followed except that p-xylene instead of *n*-heptane was used as the partition solvent; none of the **2-X** were soluble enough in *n*-heptane to give meaningful results.

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Supporting Information Available: Figures S1 and S2, kinetic data; Tables S1 and S2, estimates of various contributions to solvent effects; and text, semi-quantitative treatment of solvent effects on intrinsic rate constants (10 pages). See any current masthead page for ordering and Internet access instructions.

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