

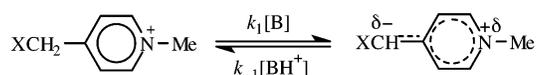
Kinetics of Proton Transfer from Cationic Carbon Acids in Water and Aqueous DMSO. Effect of Activating Groups and Solvent on Intrinsic Rate Constants

Claude F. Bernasconi,* Douglas E. Fairchild, Robert L. Montañez, Perdran Aleshi, Huaiben Zheng, and Edward Lorance

Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064

bernasconi@chemistry.ucsc.edu

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X = PhCO : $\log k_0 = 2.3$ (resonance effect of PhCO lowers k_0)

X = PhSO₂ : $\log k_0 = 4.0$ (inductive effect of PhSO₂ increases k_0)

Acidity constants and rates of reversible deprotonation of acetyltriphenylphosphonium ion (**1H**⁺), phenacyltriphenylphosphonium ion (**2H**⁺), *N*-methyl-4-phenacylpyridinium ion (**3H**⁺), and *N*-methyl-4-(phenylsulfonylmethyl)pyridinium ion (**4H**⁺) by amines in water, 50% DMSO–50% water (v/v), and 90% DMSO–10% water (v/v) have been determined. From the respective Brønsted plots, $\log k_0$ values for the *intrinsic* rate constants of the various proton transfers were obtained. Solvent transfer activity coefficients of the carbon acids and their respective conjugate bases were also determined which helped in understanding how the pK_a values and intrinsic rate constants depend on the solvent. Some of the main conclusions are as follows: (1) The pK_a values of **1H**⁺, **2H**⁺, and **3H**⁺ are significantly higher than that of **4H**⁺ because of a stronger resonance stabilization of the corresponding conjugate bases **1**, **2** and **3**, respectively. (2) The electronic effects of the PPh₃⁺ and the *N*-methyl-4-pyridylum group are similar but the mix between inductive and resonance effect is different. (3) All four acids become more acidic upon addition of DMSO to the solvent. In all cases, the main factor is the stronger solvation of H₃O⁺ in DMSO; for **1H**⁺, **2H**⁺, and **3H**⁺ but not **4H**⁺ this factor is significantly attenuated by stronger solvation of the carbon acid in DMSO. (4) The *intrinsic* rate constants for proton transfer are relatively high for all four carbon acids and show little solvent dependence; this contrasts with nitroalkanes which have much lower intrinsic rate constants and show a strong solvent dependence. These results can be understood by a detailed analysis of the interplay between inductive, resonance, and solvation effects.

Introduction

The study of proton transfers from carbon acids has provided numerous insights about the factors that affect intrinsic barriers (ΔG_0^\ddagger)¹ or intrinsic rate constants (k_0)¹ of chemical reactions.⁴ An important conclusion is that product-stabilizing factors such as charge delocalization/

resonance or solvation have a disproportionately small effect on the transition state because their development in a product lags behind bond changes or their loss from a reactant is ahead of bond changes (“transition state imbalance”). As a result, the intrinsic barriers are higher (or the intrinsic rate constants are lower) for reactions that lead to more delocalized or more solvated products. On the other hand, inductive effects by electron-withdrawing substituents that are close to the reaction site tend to decrease ΔG_0^\ddagger or increase k_0 due to the imbalance because their stabilizing effect on the transition state is disproportionately large.

Most studies of proton transfers at carbon have dealt with neutral carbon acids that are activated by one or two π -acceptor groups.^{4c} Cationic carbon acids have received less attention, although kinetic data on several

(1) The intrinsic barrier (intrinsic rate constant) of a reaction with a forward rate constant k_1 and a reverse rate constant k_{-1} is defined as $\Delta G_0^\ddagger = \Delta G_1^\ddagger = \Delta G_{-1}^\ddagger$ when $\Delta G^\circ = 0$ (as $k_0 = k_1 = k_{-1}$ when $K_1 = 1$).^{2,3} For proton transfers statistical factors are usually included.³

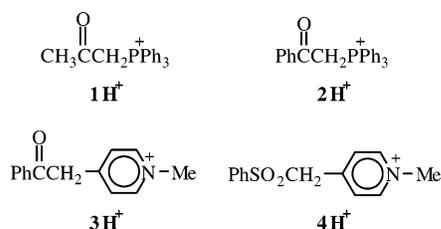
(2) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891.

(3) Keeffe, J. R.; Kresge, A. J. In *Investigation of Rates and Mechanisms of Reactions*; Bernasconi, C. F., Ed.; Wiley-Interscience: New York, 1986; Part I, p 747.

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

1-methyl-3-(phenylacetyl)pyridinium,⁵ 1-methyl-4-(phenylacetyl)pyridinium,⁵ 4-phenacylpyridinium,⁶ 4-(phenylsulfonyl)methylpyridinium cations,⁷ dimethyl-9-fluorenylsulfonium ions,⁸ triphenyl-9-fluorenylphosphonium,⁹ 2-acetyl-1-methylpyridinium ion,¹⁰ and several cationic rhenium Fischer carbene complexes^{11,12} have been reported.

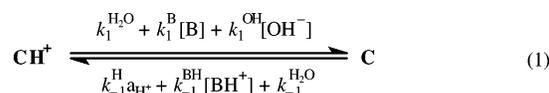
In this paper, we present rate data on the reversible deprotonation of two triphenylphosphonium ion derivatives (**1H⁺**, **2H⁺**) and two *N*-methylpyridinium ion derivatives (**3H⁺**, **4H⁺**) by amines in water, 50% DMSO–50% water (v/v), and/or 90% DMSO–10% water (v/v).



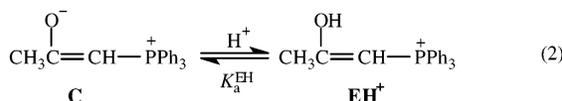
The main focus is on the determination of intrinsic rate constants. We are particularly interested in the effect of the interplay between cationic substituent and π -acceptor and also on the solvent effect on the intrinsic rate constants. The determination of solvent activity coefficients of the carbon acids and their respective conjugate bases will be used to analyze the various contributions to the solvent dependence of the intrinsic rate constants and the pK_a values of the four carbon acids.

Results

General Features. The reactions of **1H⁺**–**4H⁺** with amine buffers can be described by eq 1 where **CH⁺** refers to the cationic carbon acid, **C** to its conjugate base, **B** to the amine, and **BH⁺** to its respective conjugate acid. For



1H⁺–**3H⁺**, enol formation (**EH⁺**) by rapid protonation of the enolate oxygen, e.g., eq 2, might, in principle, play a role in the kinetics at low pH. However, under our



reaction conditions no evidence for the involvement of the enol could be found, indicating that $\text{pH} \gg pK_a^{\text{EH}}$ under all conditions. Hence, the observed pseudo-first-order rate

constants for equilibrium approach are given by eq 3 for all carbon acids of this study.

$$k_{\text{obsd}} = k_1^{\text{H}_2\text{O}} + k_{-1}^{\text{H}}\alpha_{\text{H}^+} + k_1^{\text{OH}}[\text{OH}^-] + k_{-1}^{\text{H}_2\text{O}} + k_1^{\text{B}}[\text{B}] + k_{-1}^{\text{BH}}[\text{BH}^+] \quad (3)$$

The pK_a^{CH} values of the various carbon acids were determined spectrophotometrically via eq 4 where A_{C} and A_{CH^+} refer to the absorbance of **C** ($\text{pH} \gg pK_a^{\text{CH}}$) and **CH⁺** ($\text{pH} \ll pK_a^{\text{CH}}$), respectively, and A to the absorbance of 6–9 solutions of intermediate pH close to pK_a^{CH} .

$$\text{p}K_a^{\text{CH}} = \text{pH} + \log \frac{A_{\text{C}} - A}{A - A_{\text{CH}^+}} \quad (4)$$

Kinetic Results for Acetonyltriphenylphosphonium Ion (1H⁺) and Phenacyltriphenylphosphonium Ion (2H⁺). Kinetic measurements were performed in water, 50% DMSO–50% water (v/v), and 90% DMSO–10% water (v/v). The choice of amines was limited by the time resolution of the stopped-flow apparatus. For the purpose of comparison with other carbon acids (see the Discussion) where most of the relevant literature data refer to reactions with alicyclic secondary amines, measurements with such secondary amines would have been desirable. However, the reactions with these amines were too fast for the stopped-flow method. The same was true for *n*-butylamine in water and 90% DMSO, but measurements with *n*-butylamine and morpholine were feasible in 50% DMSO. In 90% DMSO even the reaction with 2-methoxyethylamine was too fast.

Under our reaction conditions, the contribution of the $k_1^{\text{H}_2\text{O}}$, $k_{-1}^{\text{H}}\alpha_{\text{H}^+}$, $k_1^{\text{OH}}[\text{OH}^-]$, and $k_{-1}^{\text{H}_2\text{O}}$ terms to k_{obsd} was either small or negligible; since the amine dependence of k_{obsd} was determined at constant pH, eq 3 simplifies to eq 5 with C being a constant.

$$k_{\text{obsd}} = C + k_1^{\text{B}}[\text{B}] + k_{-1}^{\text{BH}}[\text{BH}^+] \quad (5)$$

Plots of k_{obsd} versus $[\text{B}]$ yielded slopes given by eq 6 from which k_1^{B} could be calculated since K_a^{CH} is known; k_{-1}^{BH} was calculated as $k_1^{\text{B}}K_a^{\text{BH}}/K_a^{\text{CH}}$. The various rate constants and pK_a^{CH} values are summarized in Table 1.

$$\text{slope} = k_1^{\text{B}} + k_{-1}^{\text{BH}} \frac{\alpha_{\text{H}^+}}{K_a^{\text{BH}}} = k_1^{\text{B}} \left(1 + \frac{\alpha_{\text{H}^+}}{K_a^{\text{CH}}} \right) \quad (6)$$

***N*-Methyl-4-phenacylpyridinium Ion (3H⁺) and *N*-Methyl-4-(phenylsulfonylmethyl)pyridinium Ion (4H⁺).**¹³ Kinetic determinations were made in water, 50% DMSO–50% water (v/v), and 90% DMSO–10% water (v/v) with piperidine, piperazine, 1-(2-hydroxyethyl)piperazine (PZ-CH₂CH₂OH), and morpholine. For **4H⁺** rates in water and 50% DMSO–50% water were also measured with *n*-butylamine, 2-methoxyethylamine, 2-chloroethylamine, and glycylamide. Data analysis was performed as described for **1H⁺** and **2H⁺**. The results are summarized in Table 2.

Solvent Transfer Activity Coefficients. To assess how changes in the solvation of **CH⁺**, **C** and **H⁺** may

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(13) Rates of deprotonation of **3H⁺** and **4H⁺** by OH^- and pK_a values in water have been reported by Bunting et al.^{6,7}

TABLE 1. Rate Constants and pK_a^{CH} Values for the Reversible Deprotonation of Acetyltriphenylphosphonium Ion ($1H^+$) and Phenacyltriphenylphosphonium Ion ($2H^+$) in Water, 50% DMSO–50% Water (v/v), and 90% DMSO–10% Water (v/v) at 20 °C^a

Base	pK_a^{BH}	$\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{PPh}_3^+$ ($1H^+$)		$\text{PhC}(\text{O})\text{CH}_2\text{PPh}_3^+$ ($2H^+$)	
		k_1^B ($M^{-1} s^{-1}$)	k_{-1}^{BH} ($M^{-1} s^{-1}$)	k_1^B ($M^{-1} s^{-1}$)	k_{-1}^{BH} ($M^{-1} s^{-1}$)
		$pK_a^{CH}(1H^+) = 7.83 \pm 0.03$		H_2O^b	$pK_a^{CH}(2H^+) = 7.08 \pm 0.03$
MeOCH ₂ CH ₂ NH ₂	9.83	1.46×10^5	1.46×10^3		2.00×10^5 3.56×10^2
EtOOCCH ₂ NH ₂	7.95	1.19×10^4	9.03×10^3		1.99×10^4 2.68×10^3
NCCH ₂ NH ₂	5.57	6.98×10^2	1.27×10^5		6.97×10^2 2.26×10^4
		$pK_a^{CH}(1H^+) = 7.21 \pm 0.03$		50% DMSO ^b	$pK_a^{CH}(2H^+) = 6.33 \pm 0.02$
morpholine	8.70	7.59×10^4	2.45×10^3		1.47×10^5 6.28×10^2
<i>n</i> -BuNH ₂	10.68	4.47×10^5	1.51×10^2		
MeOCH ₂ CH ₂ NH ₂	9.63	9.96×10^4	3.79×10^2		1.63×10^5 8.15×10^1
EtOOCCH ₂ NH ₂	7.88	2.13×10^4	5.12×10^3		4.31×10^4 1.63×10^3
NCCH ₂ NH ₂	5.39	7.94×10^2	5.25×10^4		1.66×10^3 1.45×10^4
		$pK_a^{CH}(1H^+) = 6.97 \pm 0.03$		90% DMSO ^c	$pK_a^{CH}(2H^+) = 5.62 \pm 0.04$
H ₂ NCOCH ₂ NH ₂	9.19	1.28×10^5	7.71×10^2		
EtOOCCH ₂ NH ₂	8.22	5.09×10^4	2.86×10^3		1.73×10^5 4.35×10^2
NCCH ₂ NH ₂	5.95	1.38×10^3	1.45×10^4		2.10×10^4 9.32×10^3
MeONH ₂	5.15				4.61×10^3 1.36×10^4

^a Error limits in k_1^B and $k_{-1}^{BH} \pm 6\%$ or better. ^b $\mu = 0.5$ M (KCl). ^c $\mu = 0.06$ M (KCl).

affect the solvent effects on pK_a^{CH} and $\log k_o$, we determined the solvent transfer activity coefficients, ${}^I\gamma_{CH}^{II}$, for the transfer of **C** from solvent I to solvent II, e.g., I = H₂O, II = 90% DMSO–10% water (v/v). These determinations were made by carrying out distribution experiments between *n*-heptane and the various solvents of interest, as described by Watarai¹⁴ and by Bernasconi and Bunnell.¹⁵ These experiments yielded partition coefficients from which $\log {}^I\gamma_C^{II}$ was calculated as described in the Experimental Section. From these ${}^I\gamma_C^{II}$ values, the solvent activity coefficient, ${}^I\gamma_{CH^+}^{II}$, for the transfer of CH^+ from solvent I to solvent II, could then be obtained by applying the Parker¹⁶ formalism of eq 7.

$${}^I\Delta^{II}pK_a^{CH} = \log {}^I\gamma_C^{II} + \log {}^I\gamma_{H^+}^{II} - \log {}^I\gamma_{CH^+}^{II} \quad (7)$$

In this equation ${}^I\Delta^{II}pK_a^{CH}$ represents the difference between the pK_a^{CH} values in the two solvents, i.e., ${}^I\Delta^{II}pK_a^{CH} = pK_a^{CH}(II) - pK_a^{CH}(I)$, while $\log {}^I\gamma_{CH^+}^{II}$, $\log {}^I\gamma_C^{II}$ and $\log {}^I\gamma_{H^+}^{II}$ are related to the standard free energies of transfer by eqs 8–10, respectively; $\log {}^I\gamma_{H^+}^{II}$ is known

from Well's work.¹⁷

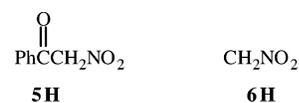
$${}^I\delta^{II}\Delta G_{tr}^\circ(CH^+) = 2.303RT \log {}^I\gamma_{CH^+}^{II} \quad (8)$$

$${}^I\delta^{II}\Delta G_{tr}^\circ(C) = 2.303RT \log {}^I\gamma_C^{II} \quad (9)$$

$${}^I\delta^{II}\Delta G_{tr}^\circ(H^+) = 2.303RT \log {}^I\gamma_{H^+}^{II} \quad (10)$$

Discussion

pK_a^{CH} Values. The pK_a^{CH} values and relevant solvent transfer activity coefficients for $1H^+$ – $4H^+$ in water, 50% DMSO–50% water (v/v), and 90% DMSO–10% water (v/v) are summarized in Table 3 along with the previously reported pK_a^{CH} values and activity coefficients $5H^+$ ¹⁸ and $6H^+$ ¹⁵ in the same solvents. The following points are noteworthy.



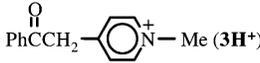
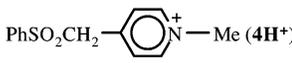
(1) The pK_a^{CH} values in water of the three cationic acids $1H^+$, $2H^+$, and $3H^+$ are quite similar but significantly lower than the pK_a^{CH} of $4H^+$.¹⁹ This reflects the stronger π -acceptor effect of the acyl groups compared to the

(14) (a) Watarai, H.; Suzuki, N. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1848. (b) Watarai, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3019.

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TABLE 2. Rate Constants and pK_a^{CH} Values for the Reversible Deprotonation of *N*-Methyl-4-phenacylpyridinium Ion ($3H^+$) and *N*-Methyl-4-(phenylsulfonylmethyl)pyridinium Ion ($4H^+$) in Water, 50% DMSO–50% Water (v/v), and 90% DMSO–10% Water (v/v) at 20 °C^a

Base	pK_a^{BH}				
		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)
		$pK_a^{CH}(3H^+) = 7.72 \pm 0.02$		H_2O^b	$pK_a^{CH}(4H^+) = 11.54 \pm 0.03$
<i>n</i> -BuNH ₂	11.12				3.72×10^3 9.78×10^3
MeOCH ₂ CH ₂ NH ₂	9.83				1.93×10^2 9.91×10^3
ClCH ₂ CH ₂ NH ₂	8.77				1.23×10^2 7.26×10^4
H ₂ NCOCH ₂ NH ₂	8.29				4.02×10^1 7.16×10^4
piperidine	11.53	5.90×10^3	9.14×10^{-1}		1.61×10^4 1.65×10^4
piperazine	10.12	2.77×10^3	1.10×10^1		2.05×10^3 5.35×10^4
PZ-CH ₂ CH ₂ OH ^d	9.45	1.26×10^3	2.37×10^1		1.15×10^3 1.42×10^5
morpholine	8.90	6.05×10^2	4.00×10^1		2.62×10^2 1.09×10^5
		$pK_a^{CH}(3H^+) = 6.62 \pm 0.07$		50% DMSO ^b	$pK_a^{CH}(4H^+) = 9.69 \pm 0.04$
<i>n</i> -BuNH ₂	10.68				6.80×10^3 6.69×10^2
MeOCH ₂ CH ₂ NH ₂	9.63				2.19×10^3 2.52×10^3
ClCH ₂ CH ₂ NH ₂	9.14				1.12×10^3 8.05×10^3
H ₂ NCOCH ₂ NH ₂	8.28				3.91×10^2 1.01×10^4
piperidine	11.02	1.82×10^4	7.25×10^{-1}		6.84×10^4 3.03×10^2
piperazine	9.90	1.18×10^4	6.20		2.30×10^4 1.42×10^4
PZ-CH ₂ CH ₂ OH ^d	9.51	4.99×10^3	6.43		1.20×10^4 1.81×10^4
morpholine	8.72	2.43×10^3	1.94×10^1		3.58×10^3 3.34×10^4
		$pK_a^{CH}(3H^+) = 5.61 \pm 0.05$		90% DMSO ^c	$pK_a^{CH}(4H^+) = 7.94 \pm 0.06$
piperidine	10.74	1.12×10^5	8.30×10^{-1}		2.44×10^5 3.86×10^2
piperazine	10.23	9.84×10^4	2.36		2.19×10^5 1.12×10^3
PZ-CH ₂ CH ₂ OH ^d	9.53	3.39×10^4	4.07		7.68×10^4 1.97×10^3
morpholine	8.91	1.51×10^4	7.57		2.72×10^4 2.91×10^3
N-methylmorpholine	6.92	4.59×10^3	2.25×10^2		5.99×10^3 6.27×10^4

^a Error limits in k_1^B and $k_{-1}^{BH} \pm 6\%$ or better. ^b $\mu = 0.5$ M (KCl). ^c $\mu = 0.06$ M (KCl). ^d 1-(2-Hydroxyethyl)piperazine.

phenylsulfonyl group ($\sigma_R(\text{CH}_3\text{CO}) = 0.16$,²¹ $\sigma_R(\text{PhCO}) = 0.16$,²¹ $\sigma_R(\text{PhSO}_2) = 0.12$ ²¹); the stronger inductive effect of the PhSO₂ group ($\sigma_F(\text{CH}_3\text{CO}) = 0.25$,²¹ $\sigma_F(\text{PhCO}) = 0.29$,²¹ $\sigma_F(\text{PhSO}_2) = 0.59$ ²¹) is not able to offset its weaker

π -acceptor effect.²² The somewhat lower pK_a^{CH} of $2H^+$ compared to that of $1H^+$ is apparently the result of the somewhat stronger inductive effect of the PhCO group relative to that of the CH₃CO group.

(2) The acidifying effects of the PPh₃⁺ and the *N*-methyl-4-pyridylium groups lead to decreases in pK_a^{CH} by

(17) Wells, C. F. In *Thermodynamic Behavior of Electrolytes in Mixed Solvents*; Furter, W. F., Ed.; Advances in Chemistry 177; American Chemical Society: Washington, DC, 1979; p 53.

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(19) At 25 °C, $\mu = 0.1$ M, $pK_a^{CH}(3H^+) = 7.66$ and $pK_a^{CH}(4H^+) = 11.34$.²⁰

(20) Wodzinski, S.; Bunting, J. W. *Can. J. Chem.* **1992**, *70*, 2635.

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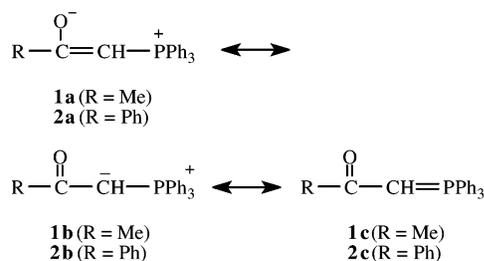
(22) A reviewer has suggested that the differences between $\sigma_R = 0.16$ for PhCO and 0.12 for PhSO₂ does not seem sufficient to account for the large difference in the pK_a values of the respective compounds ($3H^+$ and $4H^+$). In view of the close proximity of the PhCO and PhSO₂ groups to the reaction center one actually should expect a rather large difference in the pK_a values.

TABLE 3. Solvent Transfer Activity Coefficients and pK_a^{CH} Values at 20 °C^a

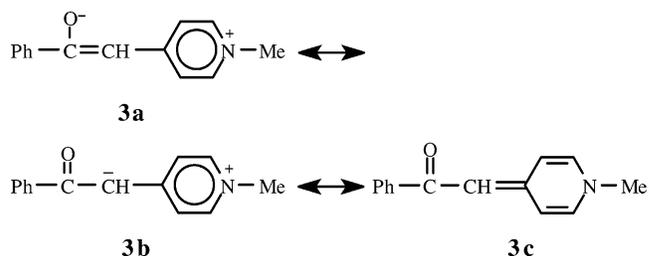
Solvent	pK_a^{CH}	$\log^0 \gamma_C^{50b}$	$\log^0 \gamma_{\text{CH}^+}^{50b}$	$\log^0 \gamma_C^{90b}$	$\log^0 \gamma_{\text{CH}^+}^{90b}$
 CH ₃ C(=O)CH ₂ PPh ₃ ⁺ (1H ⁺)					
H ₂ O	7.83				
50% DMSO	7.21	-0.24	-1.55		
90% DMSO	6.97			-1.43	-3.62
 PhC(=O)CH ₂ PPh ₃ ⁺ (2H ⁺)					
H ₂ O	7.08				
50% DMSO	6.33	-0.39	-1.57		
90% DMSO	5.62			-2.14	-3.72
 PhC(=O)CH ₂ -N ⁺ (Me)Py (3H ⁺)					
H ₂ O	7.72				
50% DMSO	6.62	-0.88	-1.64		
90% DMSO	5.61			-0.95	-1.89
 PhSO ₂ CH ₂ -N ⁺ (Me)Py (4H ⁺)					
H ₂ O	11.54				
50% DMSO	9.69	-0.23	-0.31		
90% DMSO	7.94			-0.28	0.27
 PhC(=O)CH ₂ NO ₂ (5H) ^c					
H ₂ O	5.27				
50% DMSO	5.47	1.00	-1.13		
90% DMSO	6.99			1.67	-3.10
 CH ₃ NO ₂ (6H) ^d					
H ₂ O	10.28				
50% DMSO	11.32	2.87	-0.10		
90% DMSO	14.80			6.70	-0.87

^a $\log^0 \gamma_{\text{H}^+}^{50} = -1.93$; $\log^0 \gamma_{\text{H}^+}^{90} = -3.05$, Reference 17. ^b For **5H** and **6H** the acid form is neutral ($\log^0 \gamma_{\text{CH}}^{\text{H}}$) and the conjugate base is anionic ($\log^0 \gamma_{\text{C}^-}^{\text{H}}$). ^c Reference 18. ^d Reference 15.

10.5–11.5 pK_a units relative to the respective reference ketones ($pK_a^{\text{CH}}(\text{CH}_3\text{COCH}_3) = 19.3$,²³ $pK_a^{\text{CH}}(\text{PhCOCH}_3) = 18.3$ ²⁴). There is very little difference in the overall electronic effect of the two groups, although the mix between inductive and resonance effects is different: for **1H**⁺ and **2H**⁺ the inductive effect exerted by the positively charged PPh₃ group is probably dominant, i.e.,

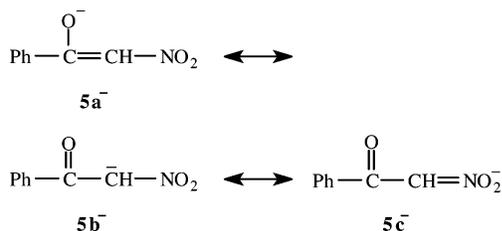


besides the large weight of **1a** (**2a**), the contribution of **1b** (**2b**) to the structure of the conjugate base is more important than that of **1c** (**2c**).^{25,26} In contrast, for **3H**⁺ the resonance effect symbolized by **3c** is dominant while **3b** is probably less important.



However, as the still lower pK_a^{CH} of **5H** indicates, neither the ⁺PPh₃ nor the *N*-methylpyridyl group is as

effective as the nitro group in stabilizing the respective conjugate base. This is undoubtedly the result of the strong resonance effect of the nitro group where $5c^-$ is the dominant resonance structure.¹⁸



Solvent Effects on pK_a^{CH} . The four cationic acids, $1\text{H}^+ - 4\text{H}^+$, become more acidic in the presence of DMSO while the two neutral acids, 5H and 6H , become less acidic. These solvent effects on the pK_a^{CH} values are most easily understood by considering the solvent transfer activity coefficients (Table 3) which measure the solvational stabilization/destabilization of the various species that results from changing the solvent; note a positive value of $\log {}^1\gamma_X^{\text{II}}$ means that species X becomes less solvated and hence destabilized upon transfer from solvent I to solvent II while a negative value means the opposite. The relationship between the solvent effect on the pK_a^{CH} value and the various activity coefficients is given by eq 7. Applied, e.g., to the change from water to 90% DMSO, eq 7 becomes eq 11. For the six acids, $1\text{H}^+ - 4\text{H}^+$, 5H and 6H , the numerical results of an analysis according to eq 11 are summarized in eqs 12–17.

$${}^0\Delta^{90}pK_a^{\text{CH}} = pK_a^{\text{CH}}(90) - pK_a^{\text{CH}}(0) = \log {}^0\gamma_{\text{C}}^{90} + \log {}^0\gamma_{\text{H}^+}^{90} - \log {}^0\gamma_{\text{CH}^+}^{90} \quad (11)$$

$${}^0\Delta^{90}pK_a^{\text{CH}}(1\text{H}^+) = -0.86 = -1.43 - 3.05 + 3.62 \quad (12)$$

$${}^0\Delta^{90}pK_a^{\text{CH}}(2\text{H}^+) = -1.46 = -2.14 - 3.05 + 3.72 \quad (13)$$

$${}^0\Delta^{90}pK_a^{\text{CH}}(3\text{H}^+) = -2.11 = -0.95 - 3.05 + 1.89 \quad (14)$$

$${}^0\Delta^{90}pK_a^{\text{CH}}(4\text{H}^+) = -3.60 = -0.28 - 3.05 - 0.27 \quad (15)$$

$${}^0\Delta^{90}pK_a^{\text{CH}}(5\text{H})^{27} = 1.72 = 1.67 - 3.05 + 3.10 \quad (16)$$

$${}^0\Delta^{90}pK_a^{\text{CH}}(6\text{H})^{27} = 4.52 = 6.70 - 3.05 + 0.87 \quad (17)$$

The following points are of interest.

(1) The stronger solvation of the hydronium ion in 90% DMSO than in water ($\log {}^0\gamma_{\text{H}^+}^{90} = -3.05$) leads to an acidifying effect of 3.05 pK_a units for all acids.

(2) For 1H^+ , 2H^+ , and 3H^+ , both the acid (CH^+) and their respective conjugate base (C) are significantly better

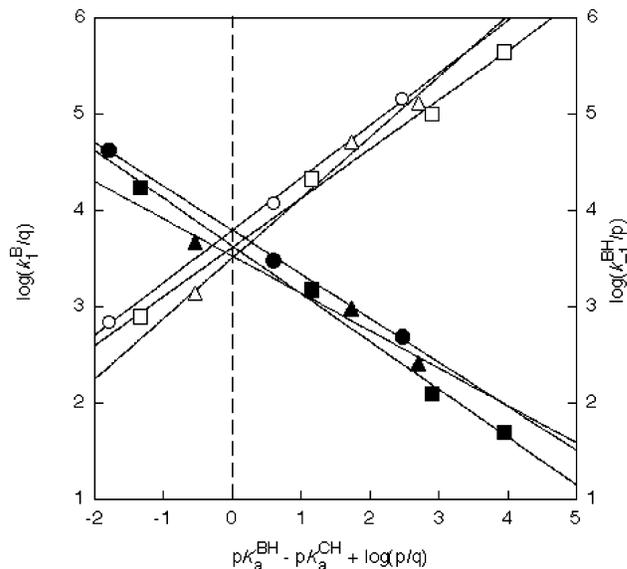
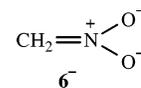


FIGURE 1. Brønsted plots for the reaction of 1H^+ with primary aliphatic amines in water (\circ , \bullet), 50% DMSO–50% water (\square , \blacksquare), and 90% DMSO–10% water (\triangle , \blacktriangle).

solvated in 90% DMSO. Hence, these two effects partially offset each other but, since the stabilization of CH^+ in 90% DMSO is stronger than that of C , the net result is to decrease the acidity in 90% DMSO and thus to attenuate the effect of the stronger solvation of the hydronium ion on ${}^0\Delta^{90}pK_a^{\text{CH}}$. The enhanced solvation of CH^+ in 90% DMSO is consistent with the well-known properties of DMSO as a cation-solvating medium^{16,28} while the enhanced solvation of C is simply a manifestation of the better solubility of neutral organic molecules in DMSO than in water. It is noteworthy that for the *N*-methylpyridinium derivative 3H^+ the solvational stabilization of both the acid and the conjugate base is much weaker than for the phosphonium derivatives 1H^+ and 2H^+ ; however, because the effects on CH^+ and C again partially offset each other, ${}^0\Delta^{90}pK_a^{\text{CH}}(3\text{H}^+)$ is not dramatically different from, say, ${}^0\Delta^{90}pK_a^{\text{CH}}(2\text{H}^+)$.

(3) For 4H^+ , neither CH^+ nor C is strongly affected by the change in solvent; interestingly CH^+ is slightly less solvated in 90% DMSO which contributes to the acidifying effect in this solvent. The small $\log {}^0\gamma_{\text{CH}^+}^{90}$ and $\log {}^0\gamma_{\text{C}}^{90}$ values in this case may be traced to the sulfonyl group: the oxygen atoms of this group carry a significant partial negative charge which is better solvated by water than by DMSO. Hence the features that enhance solvation in DMSO for $1\text{H}^+ - 3\text{H}^+$ and their respective conjugate bases are offset by the counter effect of the sulfonyl group.

(4) For 5H and 6H , the conjugate base which is an anion, is destabilized in 90% DMSO which leads to a decrease in acidity. This destabilization is particularly strong for the conjugate base of 6H (6^-) which has a highly concentrated negative charge on the oxygens and is much more strongly solvated by hydroxylic solvents than by DMSO ($\log {}^0\gamma_{\text{C}}^{-90} = 6.70$); the more dispersed negative charge in 5^- reduces this effect ($\log {}^0\gamma_{\text{C}}^{-90} = 1.67$).



(23) Chiang, Y.; Kresge, A. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1989**, *111*, 3977.

(24) Chiang, Y.; Kresge, A. J.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 6392.

(25) Johnson, A. W. *Ylid Chemistry*; Academic Press: New York, 1966; p 292.

(26) Schlosser, M.; Titus, J.; Schaub, B. *Heteroatom Chem.* **1990**, *1*, 151.

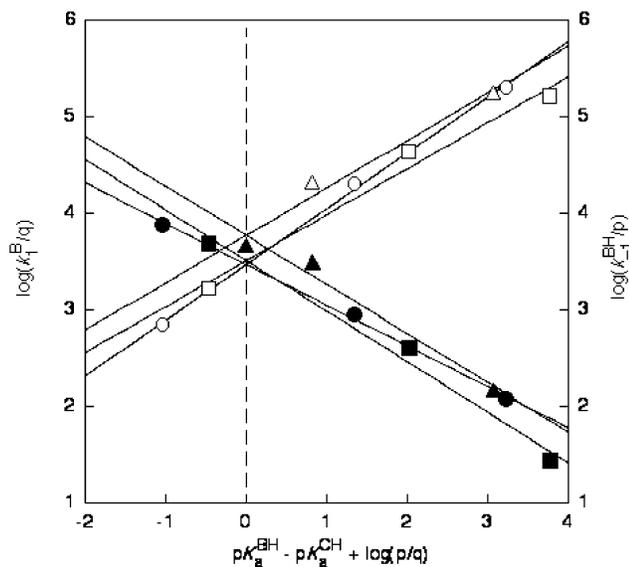


FIGURE 2. Brønsted plots for the reaction of 2H^+ with primary aliphatic amines in water (○, ●), 50% DMSO–50% water (□, ■), and 90% DMSO–10% water (△, ▲).

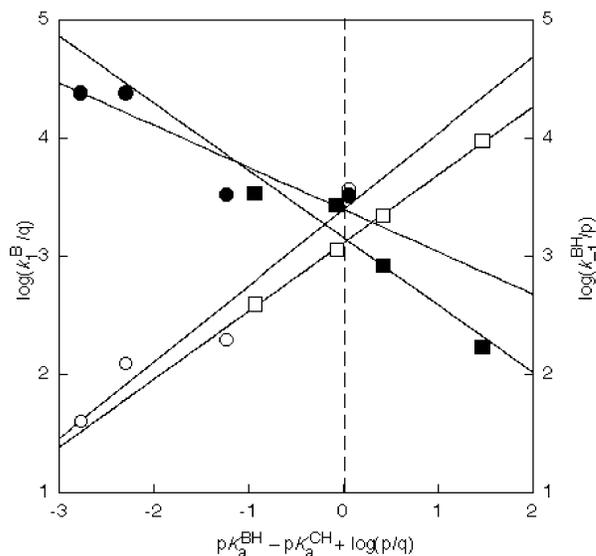


FIGURE 4. Brønsted plots for the reaction of 4H^+ with primary aliphatic amines in water (○, ●) and 50% DMSO–50% water (□, ■).

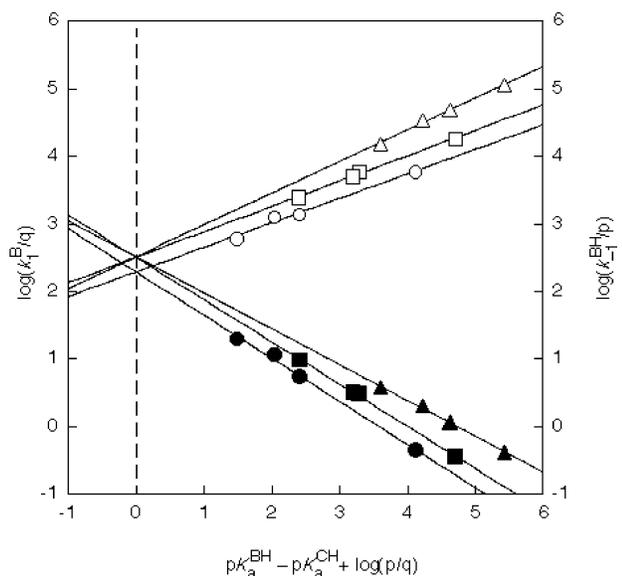


FIGURE 3. Brønsted plots for the reaction of 3H^+ with secondary alicyclic amines in water (○, ●), 50% DMSO–50% water (□, ■), and 90% DMSO–10% water (△, ▲).

Intrinsic Rate Constants. The proton-transfer rate constants for 1H^+ and 2H^+ are reported in Table 1, those for 3H^+ and 4H^+ in Table 2. Figures 1–5 show the respective Brønsted plots where q and p represent statistical factors.^{3,29} The Brønsted coefficients and $\log k_0$ values for the intrinsic rate constants are summarized in Table 4; the latter values were obtained as $\log k_0 = \log(k_1^B/q) = \log(k_{-1}^B/p)$ at $\text{p}K_a^{\text{BH}} - \text{p}K_a^{\text{CH}} + \log(p/q) = 0$.

Most Brønsted coefficients are in the range of 0.4–0.6 which is typical for proton transfer at carbon. There is a small trend toward increasing α and decreasing β values as DMSO is added to the solvent; this trend is seen for

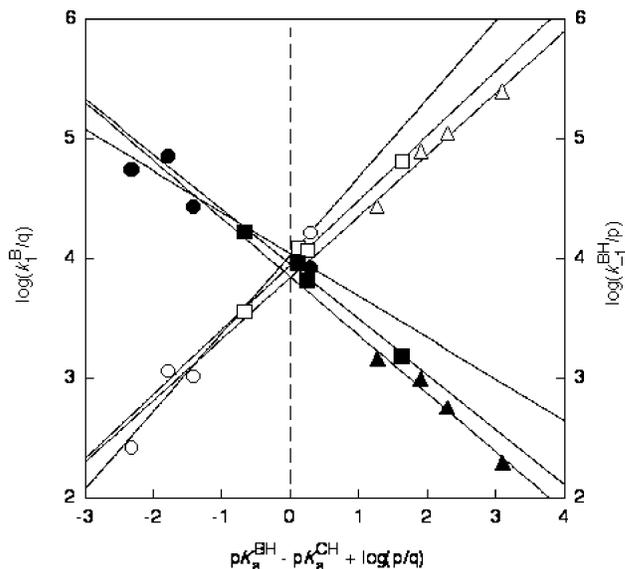


FIGURE 5. Brønsted plots for the reaction of 4H^+ with secondary alicyclic amines in water (○, ●), 50% DMSO–50% water (□, ■), and 90% DMSO–10% water (△, ▲).

1H^+ , 3H^+ , 4H^+ , 5H , and 6H but not for 2H^+ . We do not attach much significance to these trends which are difficult to interpret.³⁰

As is typical for proton transfers involving carbon acids that have resonance stabilized conjugate bases, the $\log k_0$ values are much lower⁴ than for the proton transfers involving “normal” acids.³³ However, there are sig-

(29) q is the number of equivalent basic sites on the amine, while p is the number of equivalent protons on the protonated amine.

(30) For example, for the cationic acids 1H^+ , 3H^+ , and 4H^+ the increased acidity in the presence of DMSO means that the deprotonation becomes thermodynamically more favorable; according to the Hammond³¹–Leffler³² postulate, this should lead to a transition state with less proton transfer which is consistent with a smaller β value. However, for the two neutral acids 5H and 6H DMSO decreases the acidity, and hence, the observed trend in β is inconsistent with the Hammond–Leffler postulate.

(31) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

(27) For 5H and 6H , the acid is neutral (CH) and its conjugate base (C^-) is anionic.

(28) Buncl, E.; Wilson, H. *Adv. Phys. Org. Chem.* **1977**, *14*, 133.

TABLE 4. Brønsted Coefficients and Intrinsic Rate Constants at 20 °C

Solvent	RNH ₂			R ₂ NH		
	α	β	log <i>k</i> ₀	α	β	log <i>k</i> ₀
	 CH ₃ CCH ₂ PPh ₃ ⁺ (1H ⁺)					
H ₂ O	0.54 ± 0.02	0.46 ± 0.02	3.79 ± 0.03			
50% DMSO	0.51 ± 0.03	0.49 ± 0.03	3.63 ± 0.08			
90% DMSO	0.62 ± 0.07	0.38 ± 0.07	3.51 ± 0.12			
	 PhCCH ₂ PPh ₃ ⁺ (2H ⁺)					
H ₂ O	0.58 ± 0.02	0.42 ± 0.02	3.46 ± 0.05			
50% DMSO	0.48 ± 0.07	0.52 ± 0.07	3.51 ± 0.18			
90% DMSO	0.49 ± 0.09	0.51 ± 0.09	3.77 ± 0.16			
	 PhCCH ₂ - (3H ⁺)					
H ₂ O				0.36 ± 0.03	0.64 ± 0.03	2.29 ± 0.09
50% DMSO				0.38 ± 0.02	0.62 ± 0.02	2.50 ± 0.06
90% DMSO				0.47 ± 0.03	0.53 ± 0.03	2.51 ± 0.11
	 PhS(=O) ₂ CH ₂ - (4H ⁺)					
H ₂ O	0.36 ± 0.12	0.64 ± 0.12	3.39 ± 0.24	0.35 ± 0.09	0.65 ± 0.09	4.03 ± 0.14
50% DMSO	0.48 ± 0.02	0.52 ± 0.02	3.09 ± 0.02	0.46 ± 0.03	0.54 ± 0.03	3.95 ± 0.03
90% DMSO				0.51 ± 0.06	0.49 ± 0.06	3.85 ± 0.13
	 PhCCH ₂ NO ₂ (5H) ^a					
H ₂ O				0.45	0.55	1.57
50% DMSO				0.45	0.55	1.87
90% DMSO				0.53	0.47	2.75
	 CH ₃ NO ₂ (6H) ^b					
H ₂ O				0.59	0.41	-0.59
50% DMSO				0.62	0.38	0.73
90% DMSO				0.69	0.31	3.06

^a Reference 18. ^b Bernasconi, C. F.; Kliner, D. A. V.; Mullin, A. S.; Ni, J.-X. *J. Org. Chem.* **1988**, *53*, 3342.

nificant differences in the log *k*₀ values as well as their solvent dependence.

(1) For **1H**⁺, **2H**⁺, and **4H**⁺ the log *k*₀ values are relatively high and, for the reactions with primary amines, range from about 3.1–3.8. For **4H**⁺, data with secondary alicyclic amines are also available. As is typical for such proton transfers, the log *k*₀ values for the secondary amines are 0.7–0.9 log units higher than for the

primary amines.^{4c,35} These results show that for a given family of amines, the intrinsic rate constants for **1H**⁺, **2H**⁺, and **4H**⁺ are significantly higher than for **3H**⁺ and, in the more aqueous solvents, also higher than for **5H** and **6H**.

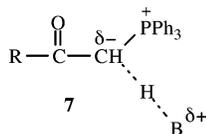
(34) (a) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *1*, 3. (b) Ahrens, M.-L.; Maass, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 818.

(35) The higher *k*₀ values are the result of differences in the solvation energies of the respective protonated amines and the fact that at the transition state solvation of the incipient protonated amines lags behind proton transfer.^{4c,36,37}

(32) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963; p 156.

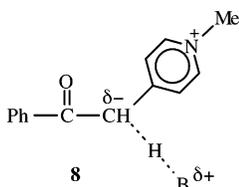
(33) For normal acids, log *k*₀ is typically in the range of 8.5–9.5.³⁴

For the reactions of 1H^+ and 2H^+ the transition state may be described by **7**. Since, due to the lag in delocalization,⁴ the incipient negative charge on **7** is mainly localized on the carbon, the positively charged PPh_3 group stabilizes this charge by its inductive effect. This results



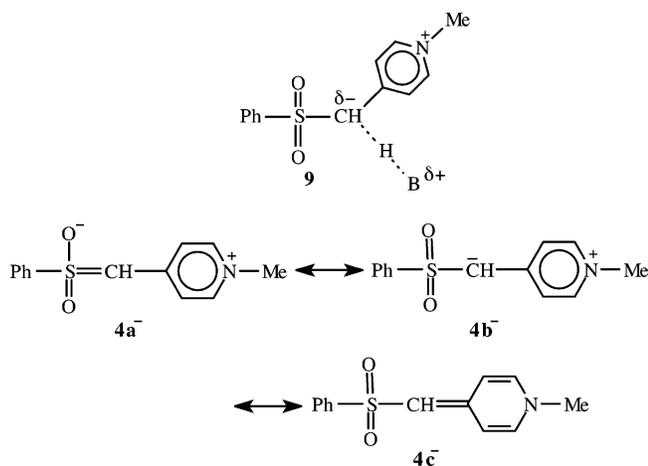
in an increase in k_o because in the conjugate base, where the resonance structure **1a** (**2a**) is dominant, the inductive effect is diminished and thus the effect on the $\text{p}K_{\text{a}}^{\text{CH}}$ is rather small. This increase in k_o by the inductive effect thus counteracts the typical k_o -lowering effect of the lag in the resonance development behind the proton transfer.

(2) For the reaction of 3H^+ the transition state can be represented as **8**. In this case, there is at best a minimal transition state stabilization by the inductive effect of the *N*-methylpyridyl group because the positive charge is farther away from the negative carbon than in **7**, and hence, there is no significant counter effect to the k_o -lowering resonance effect of the conjugate base. This



feature, in combination with the greater resonance stabilization of the conjugate base because of *two* major resonance structures (**3a** and **3c**) explains why k_o is lower than for 1H^+ and 2H^+ .

For the reactions of 4H^+ the transition state and conjugate base are shown as **9** and **4c⁻**, respectively, with **4c⁻** being the dominant resonance structure. In this case,



it is mainly the electron-withdrawing inductive effect of the PhSO_2 group which stabilizes the incipient negative charge at the transition state and offsets the k_o -lowering effect of the lag in resonance development involving the *N*-methylpyridinium system. Furthermore, since the PhSO_2 group is a weaker π -acceptor than the RCO groups, it participates only minimally in the resonance

stabilization of the conjugate base (**4a⁻**) and hence there is diminished overall resonance stabilization of the conjugate base. This reduces the k_o -lowering resonance effect and contributes to the relatively high k_o values.

(4) The low k_o values for the reactions of **5H** in water and 50% DMSO–50% water is mainly the result of the strong resonance stabilization of the corresponding carbanion (**5a⁻** and **5c⁻**) which is reflected in the high acidity of **5H** discussed above. Hydrogen bonding solvation by water which, like resonance/delocalization, lags behind proton transfer at the transition state,⁴ contributes to the lowering of k_o . This latter factor becomes even more prominent for **6⁻** and explains why k_o for nitromethane is so low in the two most aqueous solvents (more on this below).

Solvation Effect on k_o . As discussed in much detail elsewhere,^{4c} solvation of products and desolvation of reactants which are not synchronous with proton transfer at the transition state can have a significant effect on intrinsic rate constants and hence on their solvent dependence. More specifically, solvation of incipient products invariably lags behind proton transfer (develops “late”) at the transition state while desolvation of reactants is ahead of proton transfer (lost “early”). Even though both of these effects lower the intrinsic rate constants, a change in solvent can lead either to an increase or decrease in k_o . Following the formalism developed earlier for the analysis of the solvent effect on the intrinsic rate constant^{4c} we can write eq 18 for the reaction of a cationic carbon acid and eq 19 for a neutral carbon acid with a neutral base.

$${}^{\text{I}}\delta^{\text{II}}\log k_o = \delta_{\text{CH}^+} + \delta_{\text{B}} + \delta_{\text{C}} + \delta_{\text{BH}^+} + \delta_{\text{TS}} \quad (18)$$

$${}^{\text{I}}\delta^{\text{II}}\log k_o = \delta_{\text{CH}} + \delta_{\text{B}} + \delta_{\text{C}^-} + \delta_{\text{BH}^+} + \delta_{\text{TS}} \quad (19)$$

${}^{\text{I}}\delta^{\text{II}}\log k_o = \log k_o(\text{II}) - \log k_o(\text{I})$ represents the difference between the $\log k_o$ values in the two solvents, δ_{CH^+} (δ_{CH}), δ_{B} , δ_{C} (δ_{C^-}) and δ_{BH^+} are the contribution to the solvent effect from the early desolvation of the carbon acid, the early desolvation of the amine base, the late solvation of the deprotonated carbon acid and the late solvation of the protonated amine, respectively, while δ_{TS} includes possible effects other than those arising from nonsynchronous solvation/desolvation.³⁸

The contributions of δ_{B} and δ_{BH^+} have been shown to be small and quite independent of the specific reaction; for $\text{H}_2\text{O} \rightarrow 50\% \text{ DMSO}$: $\delta_{\text{B}} \approx -0.03$, $\delta_{\text{BH}^+} \approx -0.16$; for $\text{H}_2\text{O} \rightarrow 90\% \text{ DMSO}$: $\delta_{\text{B}} \approx -0.01$, $\delta_{\text{BH}^+} \approx -0.25$.^{4c} For the reaction of nitromethane (**6**), δ_{CH} , δ_{C^-} , and δ_{TS} for the change from water to 90% DMSO were estimated as -0.08 , 3.15 , and 0.84 , respectively.^{4c} This means that the solvent effect on $\log k_o$ (${}^{\text{O}}\delta^{\text{90}} \log k_o = 3.65$; Table 4) is dominated by the δ_{C^-} term. This is consistent with the very large $\log {}^{\text{O}}\gamma_{\text{C}^-}^{\text{90}}$ value of 6.70 (Table 3) which indicates very much weaker solvation of the nitronate ion in

(36) Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, 1973; Chapter 10.

(37) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1968; p 178.

(38) A further breakdown of δ_{CH^+} (δ_{C}), δ_{B} , δ_{C} (δ_{C^-}), δ_{BH^+} , and δ_{TS} into components that include the respective solvent activity coefficient and a measure of the imbalance between solvation/desolvation and proton transfer discussed in ref 4c is not necessary for the present discussion and will not be attempted here.

90% DMSO than in water, i.e., the k_o depressing effect of the late solvation is strongly attenuated in the less solvating solvent.

In light of the results for nitromethane the following conclusions may be drawn for the other systems. (1) The only other case where $\log k_o$ increases significantly in 90% DMSO (${}^0\delta^{90} \log k_o = 1.18$) is **5H** which is the only other system where $\log {}^0\gamma_C^{90}$ is positive (1.67). This implies that in this case, too, the late solvation of the conjugate base is the dominant factor while the other terms in eq 19 play a minor role. (2) The solvent effect on k_o for all the four cationic carbon acids is very small. This could be due to a near cancellation of the various terms in eq 18. However, since there are large variations in the $\log {}^1\gamma_C^{II}$ and $\log {}^1\gamma_{CH^+}^{II}$ values for the various systems, it seems more likely that none of the terms in eq 18 are large. Hence, strong solvent effects only seem to occur when the conjugate base is an anion that is prone to strong hydrogen bond solvation in water.

Experimental Section

Substrates. **1H**⁺ was purchased from Aldrich as the neutral ylide **1**. A hot methanolic solution of this material was vacuum filtered to remove some insoluble gray solids. The filtrate was diluted with water and chilled for 2 h. A crystalline solid was collected and recrystallized from 2:1 water/methanol (v/v) to give white crystals, mp 203–204 °C (lit.³⁸ mp 205–206 °C).

The bromide salt of **2H**⁺ was synthesized according to the procedure of Ramirez and Dershowitz³⁹ using bromoacteoephene⁴⁰ as precursor.

The iodide salt of **3H**⁺ was obtained by following the procedure of Stefanidis and Bunting^{5,6} except that the methylation step was carried out with iodomethane instead of

bromomethane. ¹H NMR δ (250 MHz, DMSO-*d*₆): 4.36 (s, 3H, CH₃), 4.94 (s, 2H, CH₂), 7.5–7.8 (m, H, Ph), 8.0–8.1 (m, 4H, pyr).

The iodide salt of **4H**⁺ was synthesized as described by Wodzinski and Bunting²⁰ except that the methylation step was carried out with iodomethane instead of bromomethane. ¹H NMR δ (250 MHz, DMSO-*d*₆): 4.34 (s, 3H, CH₃), 5.22 (s, 2H, CH₂), 7.65–7.93 (m, 7H, ph and pyr), 8.95 (d, 2H, pyr).

Buffers and Other Reagents. Amines were obtained from Aldrich as analytical grade and purified as follows. Piperidine, morpholine, *n*-butylamine, 1-(2-hydroxyethyl)piperazine, and 2-methylethylamine were refluxed over CaH₂ for 1 h and distilled under nitrogen. Aminoacetonitrile hydrochloride, methoxyamine hydrochloride, glycineamide hydrochloride, and glycineethyl ester hydrochloride were recrystallized twice from 1:1 2-propanol/ethanol; piperazine was used without further purification. Reagent grade DMSO was obtained from Fisher Scientific. KOH and HCl solutions originated from “DILUT-IT” analytical concentrates (J. T. Baker). Ultrapure water was obtained from a Millipore MILLI-Q Plus water system.

General Procedures. The kinetic methodology, solution preparation, pH measurements, pK_a^{CH} determinations, and measurements of solvent transfer activity coefficients were essentially the same as described in ref 18. In most cases, the pK_a of the carbon acid was low enough that the rates could be measured after mixing the carbon acid with the appropriate amine buffer. For **4H**⁺ in water the pK_a was too high for such methodology; in this case, **4** was generated in a dilute KOH solution of **4H**⁺ and this solution was subsequently mixed with the amine buffer in a double-mixing stopped-flow apparatus.

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JO051166R

(39) Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41.

(40) Cooper, R. M.; Davidson, L. H. In *Organic Synthesis*; Blatt, E. H., Ed.; Wiley: New York, 1943; Collect. Vol. II, p 480.