

Intrinsic Rate Constants for Proton Transfer from a Monoketone to Amine Bases and Electrostatic Effects on the Intrinsic Rate Constants for the Deprotonation of Cationic Ketones by OH⁻

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Received September 16, 1998

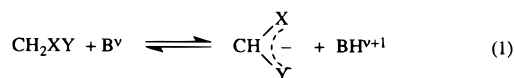
Abstract: Despite the central importance of monoketones as carbon acids, no intrinsic barriers or intrinsic rate constants for proton transfer to a standard family of bases such as amines have been reported. This paper presents the results of such determinations for the reaction of 2-acetyl-1-methylpyridinium ion (**1**) with secondary alicyclic amines. They yield $\log k_o = 0.92$ in water and $\log k_o = 1.70$ in 50% DMSO–50% water (v/v) at 20 °C. These intrinsic rate constants are lower than for any sterically unhindered carbon acids except for nitroalkanes, reflecting the strong π -acceptor character of the CO group as well as the strong solvation of the oxygen in the enolate ion. Rate constants, k_1^{OH} , for deprotonation of **1** by OH⁻ have also been determined in water and 50% DMSO–50% water, with somewhat different results than those reported by Tobin and Frey (*J. Am. Chem. Soc.* **1996**, *118*, 12253). The k_1^{OH} value in water shows a small positive deviation from a correlation of such rate constants with the corresponding $\text{p}K_a$ of 17 simple monoketones and aldehydes reported by Keeffe and Kresge; this deviation as well as the much larger positive deviation for the deprotonation of 1-methyl-3-pyridinioacetophenone (**7**) and 1-pyridinioacetophenone (**8**) can be attributed to electrostatic effects resulting from transition-state imbalance.

Introduction

The enolization of ketones has generated much recent interest,¹ with a strong focus on equilibrium ($\text{p}K_a$ of keto and enol forms, enolization constants) as well as on rate studies. The field has recently been authoritatively reviewed by Keeffe and Kresge¹ and by Toulllec.²

Keeffe and Kresge¹ have shown that a large body of data on the deprotonation of simple aldehydes and ketones by OH⁻ in water obey a linear correlation between $\log(k_{\text{OH}}/p)$ and $\log(K_a/p)$ of the keto form over a range of about 11 $\text{p}K_a$ units.³ The correlation line based on 17 points has a slope of 0.40 ± 0.01 and intercept of 6.47 ± 0.13 ($r = 0.9936$). There are also points with significant negative or positive deviations. The former can be attributed to transition-state imbalances and steric effects.¹ The positive deviations indicate reactions where there is particularly efficient charge delocalization into an aryl group attached to the α -carbon or where the transition state enjoys electrostatic or inductive stabilization by substituents close to the α -carbon (see Discussion).

Our own interest in proton transfers from carbon acids has been in determining intrinsic barriers (ΔG_o^\ddagger) or intrinsic rate constants (k_o)⁴ as a function of the activating groups (mainly π -acceptors) that are responsible for the acidity of the acids. There exists an extensive database on reactions of the type shown in eq 1 where B^v are primary and secondary amines or



carboxylate ions and CH₂XY include nitroalkanes, dinitroalkanes, diketones, diesters, phenacylpyridinium cations, 2-NO₂-4-substituted acetonitriles, 9-cyanofluorenes, Fischer carbene complexes such as (CO)₅Cr=C(OCH₃)CH₂R, and others.⁶ One class of carbon acids not represented on this list are monoketones or monoaldehydes that do not have an additional π -acceptor attached to the α -carbon as in 1,3-diketones,⁷ 4-phenacylpyridinium ions,⁸ or benzoylnitroalkanes.⁹ In view of the central importance of monoketones and monoaldehydes in chemistry, this is a gap that should be filled.¹⁰

The determination of k_o values⁴ for deprotonation of such monoketones by general bases is of interest because it would

(4) The intrinsic rate constant, k_o , for a reaction with the forward rate constant k_1 and reverse rate constant k_{-1} is defined as $k_o = k_1 = k_{-1}$ where the equilibrium constant $K_1 = 1$; the intrinsic barrier, ΔG_o^\ddagger , is defined as $\Delta G_o^\ddagger = \Delta G_1^\ddagger = \Delta G_{-1}^\ddagger$ where $\Delta G^\circ = 0$.⁵ For proton transfer, statistical factors are usually included.

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

(6) For a comprehensive review, see: Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119.

(7) (a) Bernasconi, C. F.; Paschalis, P. *J. Am. Chem. Soc.* **1986**, *108*, 2969. (b) Bernasconi, C. F.; Bunnell, R. D. *Isr. J. Chem.* **1985**, *26*, 420.

(8) Stefanidis, D.; Bunting, J. W. *J. Am. Chem. Soc.* **1991**, *113*, 991.

(9) (a) Bernasconi, C. F.; Montanez, R. L. *J. Org. Chem.* **1997**, *62*, 8162. (b) Moutiers, G.; El Fahid, B.; Collot, A.-G.; Terrier, F. *J. Chem. Soc., Perkin Trans. 2* **1996**, 49.

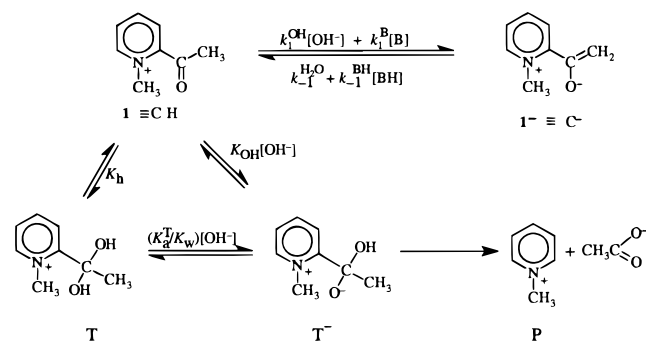
(10) Another important class of carbonyl-activated carbon acids without additional π -acceptor groups are the carboxylic esters; however the presence of the π -donor alkoxy group attached to the carbonyl carbon exerts a large intrinsic barrier-reducing effect, as recently reported by Amyes and Richard.¹¹

(1) Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1990; p 399.

(2) Toulllec, J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1990; p 323.

(3) p is the number of equivalent acidic protons of the carbonyl compounds.

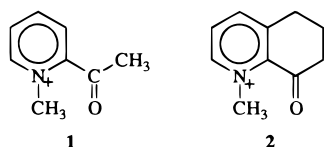
Scheme 1



provide a further important test of the suggested inverse correlation between k_o and the π -acceptor strength of the X,Y groups in CH_2XY (eq 1).^{6,12} Of particular interest is the comparison with nitroalkanes. According to the R^- substituent parameters, the π -acceptor strength of the CH_3CO group ($\text{R}^- = 0.51$)¹³ is not dramatically lower than that of the NO_2 group ($\text{R}^- = 0.62$).¹³ This suggests that k_o for the deprotonation of monoketones should be quite low, though probably not quite as low as for the nitroalkanes.

In this paper we report a kinetic study of the reversible deprotonation of 2-acetyl-1-methylpyridinium ion, **1**, by a series of secondary alicyclic amines in water and also in 50% DMSO–50% water (v/v), with the main objective to determine the respective intrinsic rate constants. There are two reasons why this ketone is particularly suitable for this purpose. First, its $\text{p}K_a$ (ca. 11 in water) is close to the range of $\text{p}K_a$'s of amine bases. This allows a determination of k_o without requiring a long extrapolation that can introduce significant errors.⁶ Second, the acidifying effect of the methylpyridinium group is not due to resonance delocalization in the enolate ion, i.e., **1** should approximate the characteristics of a “simple” monoketone.

A study of the deprotonation of **1** by OH^- and acetate ion has already been reported by Tobin and Frey.¹⁴ The main objective of these authors who also studied the deprotonation of **2** by the same bases was to assess the importance of



electrostatic effects on the $\text{p}K_a$ and deprotonation rate constants of these ketones; such electrostatic effects are potentially important in enzyme-catalyzed enolizations.¹⁵ In trying to reproduce their results we found discrepancies which, in part, are due to a faulty data treatment by these authors.

Results

General Features. As shown by Tobin and Frey¹⁴ (henceforth abbreviated T and F), when 2-acetyl-1-pyridinium ion (**1**) is placed into a basic solution, it not only undergoes reversible

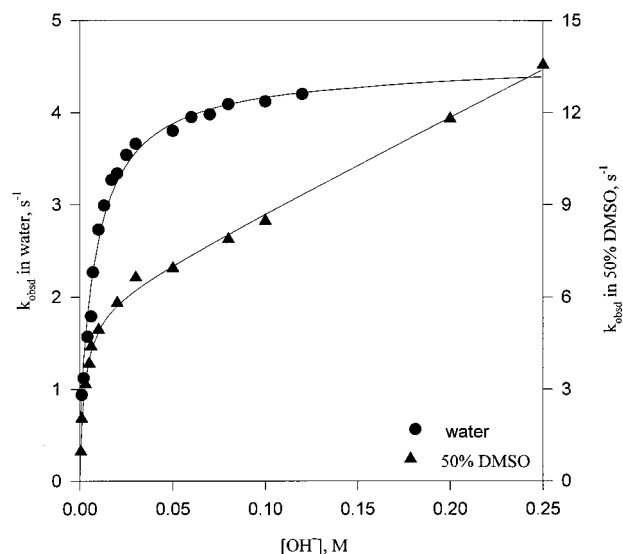


Figure 1. Reaction of **1** with KOH, k_{obsd} as function of $[\text{OH}^-]$. (●) left y-axis, in water at 25 °C, curve fit to eq 2; (▲) right y-axis, in 50% DMSO–50% water (v/v) at 20 °C, curve fit to eq 2 + linear term.

deprotonation but is also subject to hydration and deacylation. This is shown in Scheme 1. The ketone, its hydrate (T) and deprotonated hydrate (T^-) are in rapid equilibrium with each other, while the proton transfer is slow on the time scale of these equilibria. The deacylation which proceeds via T^- is much slower still; it does not interfere with the kinetics of proton transfer and manifests itself as a separate kinetic process to be discussed in a future report.

Kinetics of Proton Transfer in KOH Solution. Figure 1 shows a plot of the pseudo-first-order rate constants for proton transfer vs $[\text{KOH}]$ in water at 25 °C and an ionic strength of 0.1 M; the data are reported in Table S1 of the Supporting Information.¹⁶ These are the same conditions as in T and F's¹⁴ study except that they used NaOH as the base. According to Scheme 1, k_{obsd} is given by eq 2. Using $K_h = 0.047$ determined

$$k_{\text{obsd}} = \frac{k_1^{\text{OH}}[\text{OH}^-]}{1 + K_h + K_{\text{OH}}[\text{OH}^-]} + k_{-1}^{\text{H}_2\text{O}} \quad (2)$$

by ^1H NMR and fitting the k_{obsd} data to eq 2 yields $K_{\text{OH}} = 82.6 \pm 8.8 \text{ M}^{-1}$, $k_1^{\text{OH}} = 331 \pm 25 \text{ M}^{-1} \text{ s}^{-1}$ and $k_{-1}^{\text{H}_2\text{O}} = 0.72 \pm 0.08 \text{ s}^{-1}$. From $K_a^{\text{CH}} = K_1^{\text{OH}} K_w$ with $K_1^{\text{OH}} = k_1^{\text{OH}}/k_{-1}^{\text{H}_2\text{O}}$ and $K_w = 1.54 \times 10^{-14} \text{ M}^2$ ¹⁷ one obtains $\text{p}K_a^{\text{CH}} = 11.15 \pm 0.07$ for the acidity constant of **1**.

Similar data were also collected at 20 °C in water and in 50% DMSO–50% water at an ionic strength of 0.5 M (Tables S2 and S3).¹⁶ The results are summarized in Table 1. In 50% DMSO–50% water the plot of k_{obsd} vs $[\text{KOH}]$ did not reach a horizontal plateau but showed a linear increase (Figure 1). This linear increase is of unknown origin and could possibly be due to an increase in the activity coefficient of OH^- at high concentrations. The data were treated by adding a linear term to eq 2.

Spectrophotometric $\text{p}K_a^{\text{CH}}$ Determination. The method was based on measuring the absorbance as a function of pH. As shown by T and F,¹⁴ the absorbance is given by eq 3.

(11) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 3129.

(12) (a) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9.

(13) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(14) Tobin, J. B.; Frey, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 12253.

(15) (a) Guthrie, J. P.; Kluger, R. *J. Am. Chem. Soc.* **1993**, *115*, 11569.

(b) Halkides, C. J.; Frey, P. A.; Tobin, J. B. *J. Am. Chem. Soc.* **1993**, *115*, 3332.

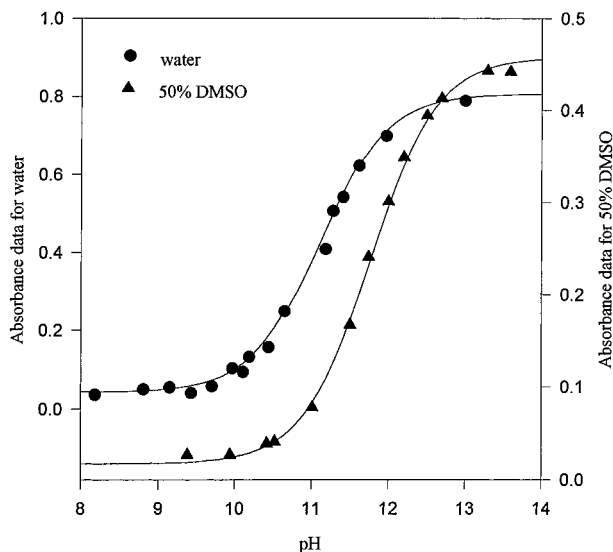
(16) See the paragraph concerning Supporting Information at the end of this paper.

(17) Harned, H. S.; Owen, B. B. *The Physical Chemistry of Electrolytic Solutions*; Reinhold: New York, 1950; p 487.

Table 1. Summary of Rate and Equilibrium Constants for the Reversible Deprotonation of **1** by OH⁻ and Hydration of **1**

parameter	H ₂ O, 25 °C ^{a,b}			
	this study	Tobin and Frey ^{c,d}	H ₂ O, 20 °C ^{e,f}	50% DMSO, 20 °C ^{e,g}
$k_1^{\text{OH}}, \text{M}^{-1} \text{s}^{-1}$	331 ± 25	187	165 ± 10	(2.37 ± 0.21) × 10 ³
$k_{-1}^{\text{H}_2\text{O}}, \text{s}^{-1}$	0.72 ± 0.08	1.32 ^h	0.45 ± 0.05	0.155 ± 0.020
$K_1^{\text{OH}} = k_1^{\text{OH}}/k_{-1}^{\text{H}_2\text{O}}, \text{M}^{-1}$	460 ± 85	142	367 ± 62	(1.53 ± 0.33) × 10 ⁴
$\text{p}K_a^{\text{CH}}(\text{kin})$	11.15 ± 0.07	11.66	11.33 ± 0.07	11.71 ± 0.08
$\text{p}K_a^{\text{CH}}(\text{spect})$	11.18 ± 0.02	11.13	11.35 ± 0.02	11.75 ± 0.02
K_h	0.047 ± 0.014	0.084	0.044 ± 0.013	0.058 ± 0.017
$K_{\text{OH}}, \text{M}^{-1}$	82.6 ± 8.8	19.1	68.2 ± 5.2	424 ± 93
$\text{p}K_a^{\text{T}i}$	10.57 ± 0.15		10.71 ± 0.14	12.03 ± 0.18

^a $\mu = 0.1 \text{ M}$ (KCl). ^b $1.54 \times 10^{-14} \text{ M}^2$, ref 17. ^c Ref 14. ^d $\mu = 0.1 \text{ M}$ (NaCl). ^e $\mu = 0.5 \text{ M}$ (KCl). ^f $K_w = 1.26 \times 10^{-14}$, ref 17. ^g $K_w = 1.29 \times 10^{-16} \text{ M}^2$, ref 34. ^h Erroneously interpreted as $k_1^{\text{H}_2\text{O}}$ by Tobin and Frey, see text. ⁱ $\text{p}K_a^{\text{T}} = -\log(K_{\text{OH}}K_w/K_h)$.

**Figure 2.** Plots of absorbance vs pH for **1** in KOH solutions: (●) in water at 25 °C, (▲) in 50% DMSO–50% water (v/v) at 20 °C.

$$A = \frac{(\epsilon_{\text{CH}} + \epsilon_{\text{T}}K_h)a_{\text{H}^+} + \epsilon_{\text{C}}K_a^{\text{CH}} + \epsilon_{\text{T}}K_{\text{OH}}K_w}{(1 + K_h)a_{\text{H}^+} + K_a^{\text{CH}} + K_{\text{OH}}K_w} [\text{CH}]_0 = \frac{Da_{\text{H}^+} + E}{Fa_{\text{H}^+} + G} [\text{CH}]_0 \quad (3)$$

Plots of A vs pH in water at 25 °C and in 50% DMSO–50% water at 20 °C are shown in Figure 2; the plot in water at 20 °C (not shown) is very similar to the one at 25 °C (data in Table S4).¹⁶ Curve fitting to eq 3 provides D , E , and G (F is known), and K_a^{CH} is found from eq 4. These spectrophotometric $\text{p}K_a^{\text{CH}}$

$$K_a^{\text{CH}} = G - K_{\text{OH}}K_w \quad (4)$$

values are reported in Table 1. The agreement with the kinetically determined $\text{p}K_a^{\text{CH}}$ values is very good for all three sets. In our further discussions we shall adopt the spectrophotometric values for which the standard deviations are smaller.

Kinetics of Proton Transfer with Amines Bases. Rates were determined in the presence of secondary alicyclic amines. In the presence of the amine buffers eq 2 contains two additional terms as shown in eq 5. Equation 5 can be rewritten as eq 6.¹⁸

(18) From $[\text{BH}] = [\text{B}][\text{H}^+]/K_a^{\text{BH}}$, $k_{-1}^{\text{BH}}/k_1^{\text{B}} = K_a^{\text{BH}}/K_a^{\text{CH}}$ and $K_w = [\text{H}^+][\text{OH}^-]$ one obtains $k_{-1}^{\text{BH}}[\text{BH}^+] = k_1^{\text{B}}K_w[\text{B}]/K_a^{\text{CH}}[\text{OH}^-]$, with K_a^{BH} being the acidity constant of BH^+ .

Table 2. Rate Constants for the Reversible Deprotonation of **1** by Secondary Alicyclic Amines

amine	$\text{p}K_a^{\text{BH}}$	$k_1^{\text{B}} (\text{M}^{-1} \text{s}^{-1})$	$k_{-1}^{\text{BH}^a} (\text{M}^{-1} \text{s}^{-1})$
H ₂ O, 25 °C, $\mu = 0.1 \text{ M}$, $\text{p}K_a^{\text{CH}} = 11.18$			
piperidine	11.12	13.03 ± 0.25	14.96 ± 0.99
piperazine	9.82	5.07 ± 0.05	(1.16 ± 0.07) × 10 ²
PZ-CH ₂ CH ₂ OH ^b	9.15	2.13 ± 0.06	(2.28 ± 0.17) × 10 ²
morpholine	8.59	0.84 ± 0.06	(3.31 ± 0.23) × 10 ²
H ₂ O, 20 °C, $\mu = 0.5 \text{ M}$, $\text{p}K_a^{\text{CH}} = 11.35$			
piperidine	11.53	13.51 ± 0.26	8.93 ± 0.59
piperazine	10.12	5.00 ± 0.18	84.9 ± 6.2
morpholine	8.90	0.86 ± 0.01	(2.42 ± 0.14) × 10 ²
50% DMSO–50% H ₂ O, 20 °C, $\mu = 0.5 \text{ M}$, $\text{p}K_a^{\text{CH}} = 11.75$			
piperidine	11.02	30.2 ± 0.6	(1.62 ± 0.11) × 10 ²
piperazine	9.90	15.6 ± 0.2	(1.10 ± 0.07) × 10 ³
PZ-CH ₂ CH ₂ OH ^b	9.51	6.54 ± 0.13	(1.14 ± 0.08) × 10 ³
morpholine	8.72	2.39 ± 0.02	(2.56 ± 0.14) × 10 ³

^a Calculated as $k_{-1}^{\text{BH}} = k_1^{\text{B}}K_a^{\text{BH}}/K_a^{\text{CH}}$. ^b 1-(2-hydroxyethyl)piperazine.

$$k_{\text{obsd}} = k_{\text{obsd}}(\text{eq 2}) + \frac{k_1^{\text{B}}[\text{B}]}{1 + K_h + K_{\text{OH}}[\text{OH}^-]} + k_{-1}^{\text{BH}}[\text{BH}^+] \quad (5)$$

$$k_{\text{obsd}} = k_{\text{obsd}}(\text{eq 2}) + k_1^{\text{B}} \left(\frac{1}{1 + K_h + K_{\text{OH}}[\text{OH}^-]} + \frac{K_w}{K_a^{\text{CH}}[\text{OH}^-]} \right) [\text{B}] \quad (6)$$

Hence plots of k_{obsd} vs. $[\text{B}]$ at constant pH have slopes given by eq 7. The k_1^{B} values are reported in Table 2 along with k_{-1}^{BH}

$$\text{slope} = k_1^{\text{B}} \left(\frac{1}{1 + K_h + K_{\text{OH}}[\text{OH}^-]} + \frac{K_w}{K_a^{\text{CH}}[\text{OH}^-]} \right) \quad (7)$$

obtained as $k_1^{\text{B}}K_a^{\text{BH}}/K_a^{\text{CH}}$ with K_a^{BH} being the acidity constant of BH^+ .

With piperidine in water at 25 °C additional runs were conducted at different pH values as a check of our results for internal consistency with respect to $\text{p}K_a^{\text{CH}}$. A plot of the slopes vs $[\text{OH}^-]$ is shown in Fig. S1.¹⁶ A curve fit to eq 7 with k_1^{B} and K_a^{CH} as the unknowns yielded $k_1^{\text{B}} = 15.5 \pm 4.2 \text{ M}^{-1} \text{ s}^{-1}$ and $\text{p}K_a^{\text{CH}} = 11.05 \pm 0.17$. Even though the standard deviation of this $\text{p}K_a^{\text{CH}}$ is considerably larger than that for the $\text{p}K_a^{\text{CH}}$ values determined spectrophotometrically and based on the OH⁻ reaction (Table 1), the agreement with these latter values is satisfactory.

Discussion

Comparison with Tobin and Frey's Results. There is excellent agreement between our spectrophotometrically deter-

mined pK_a^{CH} (11.18) T and F's value (11.13),¹⁴ but the agreement between the k_1^{OH} , $k_{-1}^{\text{H}_2\text{O}}$, K_1^{OH} , and K_{OH} values from the two laboratories is poor (Table 1). There are two reasons for this. One is that T and F¹⁴ treated their kinetic data with eq 8 instead of eq 2 and then multiplied the rate constants obtained

$$k_{\text{obsd}} = \frac{k_1^{\text{OH}}[\text{OH}^-] + k_1^{\text{H}_2\text{O}}}{1 + K_{\text{OH}}[\text{OH}^-]} \quad (8)$$

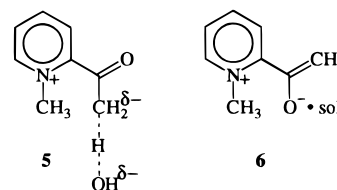
from the curve fit by the "correction factor $(1 + K_h)$."¹⁴ There are two problems with this treatment: (a) It erroneously equates the intercept of the plot of k_{obsd} vs $[\text{OH}^-]$ with the rate constant for deprotonation of **1** by water ($k_1^{\text{H}_2\text{O}}$) instead of the rate constant of protonation of **1**⁻ by water ($k_{-1}^{\text{H}_2\text{O}}$).¹⁹ (b) As seen in eq 2, K_h is only important at low $[\text{OH}^-]$ ($K_{\text{OH}}[\text{OH}^-] < (1 + K_h)$) but not at high $[\text{OH}^-]$ ($K_{\text{OH}}[\text{OH}^-] \gg (1 + K_h)$) and hence multiplying the rate constants by $(1 + K_h)$ is not correct.²⁰ The second reason for the poor agreement between the two laboratories has to do with insufficient data points in T and F's study at $[\text{NaOH}] \leq 0.02$ M. This is the most critical region in defining $k_{-1}^{\text{H}_2\text{O}}$, k_1^{OH} , and K_{OH} , and hence, insufficient data can lead to large errors in these parameters, irrespective of whether the correct equation (eq 2) is used.

With respect to the pK_a^{CH} values, it is perhaps surprising that T and F's spectrophotometric pK_a^{CH} agrees so well with ours since it depends on the value of K_{OH} (eq 4). However, because $K_{\text{OH}}K_w$ in eq 4 is much smaller than G , even a large error in K_{OH} barely affects pK_a^{CH} . On the other hand, the kinetic pK_a^{CH} (11.66) that one may calculate based on T and F's $k_1^{\text{OH}}/k_{-1}^{\text{H}_2\text{O}}$ ²¹ ratio agrees poorly with their spectrophotometric value (11.13), a direct result of the large errors in k_1^{OH} and $k_{-1}^{\text{H}_2\text{O}}$. This contrasts with the good agreement between the spectrophotometric pK_a^{CH} and two independently determined kinetic pK_a^{CH} values in the present study.

pK_a^{CH} and k_1^{OH} . The pK_a^{CH} value of 11.18 in water at 25 °C (11.35 at 20 °C) makes **1** one of the most acidic monoketones¹; it compares with $pK_a^{\text{CH}} = 19.27$ at 25 °C for acetone.²² The high acidity must be due to the combined electrostatic and inductive/field effects of the positive charge which stabilizes the enolate ion (**1**⁻). Along with the high acidity, k_1^{OH} for deprotonation by OH^- is also much higher than for most monoketones. With respect to Keeffe and Kresge's¹ correlation of $\log(k_1^{\text{OH}}/p)$ vs $\log(K_a^{\text{CH}}/p)$, our $\log(k_1^{\text{OH}}/p)$ value in water at 25 °C deviates positively from the correlation by 0.34 units. This deviation is small but significantly larger than the average deviation (~ 0.07 log units) of the 17 points that define the correlation; it suggests a somewhat enhanced intrinsic rate constant (k_o) for this compound.

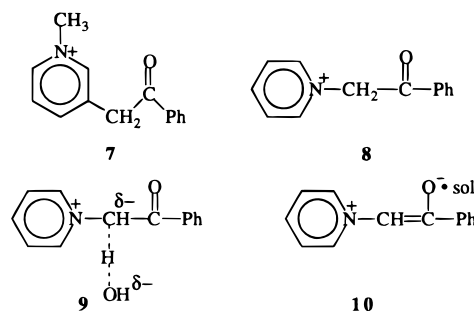
A possible explanation for the increase in k_o is that the transition state is stabilized by the favorable electrostatic interaction between OH^- and the positive charge on the nitrogen. However, in view of the large distance between the nitrogen and the OH^- (**5**), this effect is probably small. A more attractive interpretation is based on the assumption that, as is typical in the deprotonation of carbon acids activated by π -acceptors, the

transition state is imbalanced in that charge delocalization into the carbonyl group lags behind proton transfer.^{6,12} This leads to a concentration of the negative charge on the α -carbon as shown (in exaggerated form) in **5**. The conformation of the transition state is probably planar such as to maximize the proximity between the negative and positive charge, just as is the case for the enolate ion (**6**). Hence, even though the distance



between the α -carbon and the positive charge in the transition state is about the same as that between the oxygen and the positive charge in the enolate ion, to the extent that carbon is less able to support a negative charge than oxygen, the transition state derives a disproportionately large amount of stabilization from the positive charge compared to the enolate ion; the stabilization of this latter is further attenuated by strong solvation of the oxyanion (**6**). According to the principle of nonperfect synchronization,^{6,12} the result is an enhanced intrinsic rate constant.

Much larger enhancements have been observed for cationic ketones where the pyridinium group is attached to the α -carbon rather than to the carbonyl carbon, e.g., **7** (+1.47 log units)¹ or **8** (+2.96 log units).¹ Here the positive charge is much closer to the negative charge at the transition state (e.g. **9**) than in the corresponding enolate ion (e.g. **10**). This contrasts with the



situation in the deprotonation of **1** where the α -carbon at the transition state and carbonyl oxygen in the enolate ion have approximately the same distance from the positive charge. It should be noted that in the reaction of **8**, the favorable electrostatic interaction between the positive charge and OH^- at the transition state (**9**) probably contributes significantly to the enhanced intrinsic rate constant because, in contrast to **5**, the respective charges are much closer to each other.

Another interesting example is the deprotonation of **2** by OH^- where $\log k_{\text{OH}}/p$ deviates *negatively* from the Keeffe/Kresge correlation line by 0.85 units.²³ Part of this deviation may reflect the poorly understood depression of the intrinsic rate constant in the deprotonation of cyclohexanone.¹ A contributing factor may be related to the conformational rigidity of the system which prevents the α -carbon from getting into close proximity of the positive charge for optional transition-state stabilization (**11**) while the oxygen in the enolate ion (**12**) is close to the

(19) The pathway via deprotonation of **1** by water ($k_1^{\text{H}_2\text{O}}$) and its microscopic reverse (protonation of **1**⁻ by H^+ , k_{-1}^{H}) is negligible in the pH range of our and Tobin and Frey's study.

(20) In view of the small value of K_h (0.084),¹⁴ this error is relatively inconsequential.

(21) With Tobin and Frey's¹⁴ $k_1^{\text{H}_2\text{O}}$ value interpreted as k_{-1}^{H} .

(22) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460.

(23) This is based on $k_1^{\text{OH}} = 10.9 \text{ M}^{-1} \text{ s}^{-1}$ and $pK_a^{\text{CH}} = 11.90$ reported by Tobin and Frey.¹⁴ Inasmuch as k_1^{OH} was obtained from the wrong equation (eq 8), the true value is expected to be slightly different but not enough so as to affect this discussion.

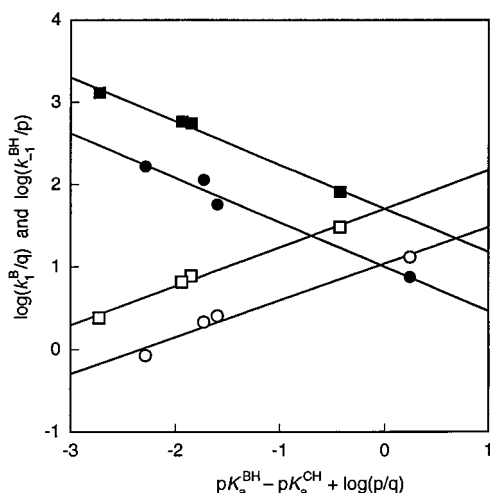
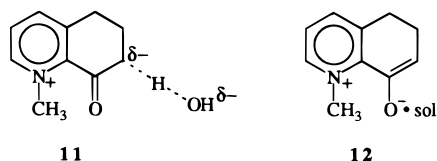


Figure 3. Brønsted plots in water at 25 °C (○, ●) and in 50% DMSO–50% water (□, ■); p is the number of equivalent protons on BH, q the number of equivalent basic sites on B.

Table 3. Brønsted Coefficients and Intrinsic Rate Constants for Proton Transfer from **1** to Secondary Alicyclic Amines

solvent	β_B	α_{CH}	$\log k_o$
H ₂ O, 25 °C, $\mu = 0.1$ M	0.45 ± 0.04	0.55 ± 0.04	1.02 ± 0.06
H ₂ O, 20 °C, $\mu = 0.5$ M	0.45 ± 0.02	0.55 ± 0.02	0.92 ± 0.03
50% DMSO, $\mu = 0.5$ M	0.47 ± 0.03	0.53 ± 0.03	1.70 ± 0.06



positive charge. As a result, the effect on the rate constant is disproportionately weak compared to the effect on the pK_a^{CH} , leading to a reduction in the intrinsic rate constant.

Solvent Effect on pK_a^{CH} and k_1^{OH} . The pK_a^{CH} of **1** in 50% DMSO–50% water (v/v) at 20 °C (11.75) is about 0.4 units higher than in water at the same temperature. This increase probably reflects mainly the reduced solvation of the enolate ion in 50% DMSO–50% water.²⁴ As to k_1^{OH} , it is 14.4-fold higher in 50% DMSO–50% water than in water whereas the equilibrium constant, K_1^{OH} , is 41.7-fold higher. The fact that k_1^{OH} increases by a factor that is only about 2.9-fold less than the increase in K_1^{OH} indicates that k_o is higher in 50% DMSO–50% water. This is reasonable because both OH[−] and the enolate ion are less solvated in 50% DMSO–50% water. This means that the k_o lowering effects of the early desolvation of OH[−]²⁵ and of the lagging solvation of the incipient enolate ion at the transition state are attenuated in 50% DMSO–50% water which translates into an enhanced k_o value.^{6,12}

Proton Transfer to Amines. The rate constants for the reversible deprotonation of **1** by secondary alicyclic amines are summarized in Table 2. Brønsted plots are shown in Figure 3. These plots yield β_B and α_{BH} from the slopes and $\log k_o = \log(k_1^B/q) = \log(k_1^{BH}/p)$ when $pK_a^{BH} - pK_a^{CH} + \log(p/q) = 0$; these parameters are summarized in Table 3. The β_B and α_{BH} values are within the typical range commonly observed for proton transfers from carbon acids.²⁶ The k_o values are the principal

focus of interest. As outlined in the Introduction, a major objective of this study was to obtain k_o for proton transfer from a simple monoketone that is strongly acidic but devoid of additional π -acceptor groups or other features that strongly influence k_o values.¹⁰ **1** comes close to this ideal; its pK_a^{CH} is quite low and, as indicated by the fact that the k_1^{OH} value deviates only modestly from the Keeffe/Kresge¹ correlation, the 1-methyl-2-pyridinio group is expected to have only a minor effect on k_o for the deprotonation by amines as well.²⁷

Table 4 lists $\log k_o$ values for proton transfers from a representative series of carbon acids to secondary alicyclic amines in water and in 50% DMSO–50% water. The list includes **1** and another monoketone, **13** (structure shown in Table 4), which was studied by Bunting and Stefanidis.²⁸ Even though no measurements with secondary alicyclic amines were carried out with **13**, a $\log k_o \approx 0.7$ may be estimated on the basis of data with primary aliphatic amines and the assumption that $\log k_o$ for the deprotonation of **13** by the alicyclic amines is about 0.7 log units higher than for the deprotonation by primary aliphatic amines.²⁹ The k_o values for **1** and **13** are quite similar, a feature to which we will return below.

In comparing **1** and **13** with the other carbon acids the following points are noteworthy. (1) The k_o values for **1** and **13** are among the lowest for carbon acids; only the nitroalkanes have significantly lower intrinsic rate constants. In particular, k_o for **1** and **13** is substantially lower than for 1,3-diketones such as acetylacetone and 1,3-indandione. (2) The change from water to 50% DMSO–50% water increases $\log k_o$ for **1** by 0.78; this change is smaller than for CH₃NO₂ (1.32) or PhCH₂NO₂ (0.97) but larger than for acetylacetone (0.15) or 1,3-indandione (ca. 0.16).

The trend toward lower k_o values for the carbon acids shown in Table 4 can be attributed to an increase in the stabilization of the respective carbanions by a combination of resonance and solvation effects.^{6,12} Because the development of both resonance and solvation lags behind proton transfer at the transition state, k_o is reduced and increasingly so the stronger the resonance and solvational stabilization of the carbanion. For carbanions that delocalize the negative charge onto oxygen atoms, the solvational component of the stabilization is particularly strong, especially in water. This is probably the reason all of the ketones and nitro compounds have lower k_o values than the carbon acids that lead to highly charge dispersed but weakly solvated carbanions (first five entries in Table 4).

Within the group of ketones and nitro compounds, the k_o values for **1** and **13** are lower than for the diketones because solvation of one oxygen with a high charge density is stronger than that of two oxygens with a low charge density; this apparently more than offsets the greater resonance stabilization of enolate ions derived from diketones and hence leads to a lower k_o value. For CH₃NO₂, the solvation of the anion is stronger still since there are two oxygens with a high charge density. Hence even if the resonance effects, as suggested by the R[−] substituent constants for NO₂ and CO groups, may not

(26) Numerous citations given in ref 9a.

(27) A referee has suggested that k_o could be reduced by the electrostatic repulsion between the positive charge on the pyridine nitrogen and the partial positive charge on the amine nitrogen at the transition state. In view of the large separation between these charges, the effect is likely to be small, just as the electrostatic stabilization between the positive charge and OH[−] in **5** is probably small.

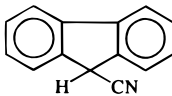
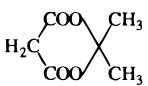
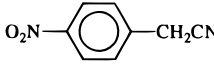
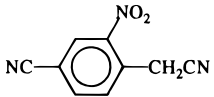
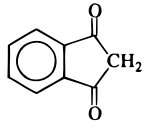
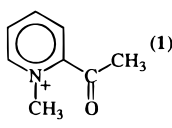
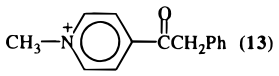
(28) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1990**, *112*, 779.

(29) A difference of 0.7 to 1.0 log units appears to be characteristic in k_o for the deprotonation of sterically *unhindered* carbon acids by secondary alicyclic vs primary aliphatic amines.^{7,30} **13** is probably not entirely devoid of steric hindrance; hence, the low value of 0.7 seems appropriate here.

(24) Bernasconi, C. F.; Bunnell, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 2900.

(25) Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, G.; Nakamura, G. *J. Am. Chem. Soc.* **1982**, *104*, 7045.

Table 4. Intrinsic Rate Constants for Proton Transfer from Carbon Acids to Secondary Alicyclic Amines

CH acid	log k_0	log k_0	log k_0	Ref.
	Water, 25°C	Water, 20°C	50% DMSO, 20°C	
CH ₂ (CN) ₂	ca. 7.0			b
			4.58	c
			3.90	d
			3.70	e
		3.20	3.15	f
		2.97 ^a	3.13	g
CH ₂ (COCH ₃) ₂		2.60	2.75	h
 (1)	1.02	0.92	1.70	i
 (13)	ca. 0.70			j
CH ₃ NO ₂		-0.59	0.73	k
PhCH ₂ NO ₂		-1.22	-0.25	k

^a In 10% DMSO–90% water. ^b Hibbert, F. *Compr. Chem. Kinet.* **1977**, *8*, 97. ^c Reference 30b. ^d Reference 6. ^e Reference 30a. ^f Bernasconi, C. F.; Wenzel, P. J. *J. Am. Chem. Soc.* **1996**, *118*, 11446. ^g Bernasconi, C. F.; Paschalis, P. *J. Am. Chem. Soc.* **1989**, *111*, 5893. ^h Bernasconi, C. F.; Bunnell, R. D. *Isr. J. Chem.* **1985**, *26*, 420. ⁱ This study. ^j Based on data in reference 28. ^k Reference 30c.

differ dramatically (see Introduction), the stronger solvation of CH₂ = NO₂⁻ must be the main reason log k_0 for CH₃NO₂ is 1.5 units lower than for **1**.

The foregoing interpretations are supported by the solvent effects on k_0 . The reduction in hydrogen-bonding solvation in going from water to 50% DMSO–50% water has the largest effect on the stability of the carbanion, and with it on k_0 , where this solvation is strong. This explains the solvent effects on k_0 in the order: nitroalkanes > **1** > diketones. Direct measurements of energies of transfer from water to 50% DMSO–50% water for CH₂ = NO₂⁻ (3.90 kcal/mol),²⁴ PhCH = NO₂⁻ (2.71 kcal/mol),²⁴ and 1,3-indandione anion (0.56 kcal/mol)²⁴ confirm this conclusion.^{30,31}

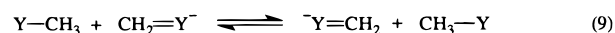
With respect to **1** and **13**, their k_0 values are quite comparable, with log k_0 for **13** being approximately 0.3 units lower than for

(30) (a) Bernasconi, C. F.; Hibdon, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 4363. (b) Bernasconi, C. F.; Terrier, F. *J. Am. Chem. Soc.* **1987**, *109*, 7115. (c) Bernasconi, C. F.; Kliner, D. A. V.; Mullin, A. S.; Ni, J. X. *J. Org. Chem.* **1988**, *53*, 3342.

(31) As pointed out in ref 6, the abnormally high transfer energy for the acetylacetonate ion (3.20 kcal/mol)²⁴ is likely to be the result of a faulty experiment.

1. Taking into account the standard deviation for log k_0 of **1** (± 0.06) and the fact that log k_0 for **13** is estimated, the actual difference between the two log k_0 values must be regarded as rather uncertain. Nevertheless, qualitatively it seems reasonable that k_0 for **13** should be somewhat lower than for **1**, due to the α -phenyl group. This is because, to the extent that the phenyl group contributes to the resonance stabilization of the enolate ion, it is expected to lower k_0 ,^{6,12} just as k_0 for PhCH₂NO₂ is lower than for CH₃NO₂.

Comparison with Gas-Phase Calculations. On the basis of the discussion of solvation effects one would expect that in aprotic solvents the k_0 values for monoketones and nitroalkanes should get much closer still than in 50% DMSO–50% water, although this prediction awaits experimental confirmation. Some recent gas phase ab initio calculations of the intrinsic barriers of the identity proton transfers shown in eq 9 are of interest in



this context. For Y = CHO, the intrinsic barrier is about 10 kcal/mol higher than for Y = NO₂,³² showing a dramatic

reversal compared to the solution phase barriers. As discussed in detail elsewhere,³² the barrier-increasing effect of resonance/imbalance which is a dominant factor in solution plays a minor role in the gas phase and is overshadowed by inductive/field and electrostatic effects. In the case at hand, the much stronger inductive/field effect of the nitro group compared to that of the carbonyl group leads to a greater transition-state stabilization when $Y = \text{NO}_2$ and hence to a lower barrier.

Summary and Concluding Remarks. Intrinsic rate constants for the deprotonation of monoketones by secondary alicyclic amines—a standard family of bases used to determine intrinsic rate constants—have not been available until now, despite the central importance of ketones as carbon acids. We have now determined such k_o values for **1** in water and in 50% DMSO–50% water (v/v). They are substantially lower than for the deprotonation of most carbon acids, including 1,3-diketones, but not as low as for the deprotonation of nitroalkanes. This is the result of the strong π -acceptor character of the carbonyl group and the strong solvation of the enolate ion; the solvational component apparently more than offsets the greater resonance stabilization of the diketone enolate ions. The still lower k_o values for the nitroalkanes are mainly the result of even stronger solvation of the nitronate ion. These conclusions are supported by the solvent effects on the k_o values.

Other points of interest can be summarized as follows.

(1) The higher intrinsic rate constants (lower intrinsic barriers) for deprotonation of monoketones compared to those for nitroalkanes contrast with the higher intrinsic barrier in the gas-phase reaction of eq 9 with acetaldehyde compared to the reaction of nitromethane.

(2) The rate constant for deprotonation of **1** by OH^- in water is 0.34 log units higher than expected based on the Keeffe/Kresge correlation. This suggests that the *intrinsic* rate constant is somewhat enhanced by the electrostatic effect of the positive charge because of transition imbalance. The effect is small because the distance between the centers of negative and positive charge are about the same in the transition state (**5**) and the enolate ion (**6**). When this distance is shorter in the transition state than in the enolate (e.g., **9** vs. **10**), there is a much greater enhancement of the intrinsic rate constant; when this distance is longer in the transition state than in the enolate ion (**11** vs. **12**), the imbalance lowers the intrinsic rate constant.

Experimental Section

Materials. 1-Methyl-2-acetylpyridine iodide was prepared as described by Cox,³³ mp 159–161 °C (lit.³³ 160–162 °C). The amines were refluxed over CaH_2 and distilled prior to use. DMSO was distilled

(32) Bernasconi, C. F.; Wenzel, P. J.; Keeffe, J. R.; Gronert, S. *J. Am. Chem. Soc.* **1997**, *119*, 4008.

(33) Cox, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 6823.

from CaH_2 and stored over 4 Å molecular sieves. KOH and HCl solutions were prepared from “dilut it” (Baker Analytical).

Kinetic Experiments. Rates of proton transfer were measured spectrophotometrically in a Durrum-Gibson stopped-flow apparatus. The reactions were monitored at 350 nm, a wavelength where **1**[−] but not **1** absorbs strongly. Typical substrate concentrations were about 5×10^{-4} M although at low [KOH] concentrations of **1** as low as 10^{-4} M were used to maintain pseudo-first-order conditions. The reactions with OH^- and with piperidine at pH > 11 were conducted by mixing a neutral solution of **1** with the base while the reactions with piperidine at pH < 11 and with all the other amines were conducted by mixing a basic solution of **1**[−] with the respective amine buffer.

pH and pK_a Measurements. The pH measurements in water were made with an Orion 611 pH meter equipped with an Orion Ross 810 glass electrode and an Orion Sureflow 80–03 reference electrode; in 50% DMSO–50% water an Orion 370 pH meter equipped with an Orion 9272BN combination electrode was used. Calibration of the pH meter in 50% DMSO–50% water was with buffers described by Hallé et al.³⁴ The pK_a^{BH} values of piperidine, piperazine, 1-(2-hydroxyethyl)-piperazine, and morpholine in water at 25 °C, $\mu = 0.1$ M (KCl) were determined potentiometrically; the pK_a^{CH} of these amines in water at 20 °C, $\mu = 0.5$ M (KCl), and in 50% DMSO–50% water at 20 °C, $\mu = 0.5$ M (KCl) were known from previous studies.^{9a} The pK_a^{CH} of **1** was determined spectrophotometrically in 10^{-3} M solutions of **1** at 350 nm as described in the Results. Absorbances measured at high pH were corrected for the onset of the deacylation reaction.

Determination of K_h . The K_h values in the different solvents were determined by ¹H NMR on a Varian 500 MHz instrument. Relative areas of the CH_3CO and the CH_3N protons of the ketone (3.0 and 4.59 ppm, respectively) and its hydrate (2.05 and 4.76 ppm, respectively) were determined in D_2O at 25 °C ($\mu = 0.1$ M), 20 °C ($\mu = 0.5$ M), and in 50% DMSO-*d*₆/50% D_2O at 20 °C ($\mu = 0.5$ M). The average of the [hydrate]/[ketone] ratios obtained from the CH_3CO and CH_3N protons afforded (K_h) _{D_2O} values. They yielded (K_h) _{H_2O} after applying the relationship (K_h) _{D_2O} /(K_h) _{H_2O} = ϕ^2 ³⁵ with $\phi = 1.08$ ³⁶ being the fractionation factor for the hydrogens of the OH groups in the hydrate.

Acknowledgment. This research was supported by Grants CHE-9307659 and CHE-9734822 from the National Science Foundation. L.L.H. was supported by Research Experience for Undergraduates Grant CHE-9619961 from the National Science Foundation. J.A.M. thanks the Fundação para a Ciência e a Tecnologia-Portugal (Praxis XXI/BD/5219/95) for a graduate student fellowship.

Supporting Information Available: Tables S1–S7 and Figure S1 (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(34) Hallé, J.-C.; Gaboriaud, R.; Schaal, R. *Bull. Soc. Chim. Fr.* **1970**, 2047.

(35) Chiang, Y.; Kresge, A. J.; Krogh, E. T. *J. Am. Chem. Soc.* **1988**, *110*, 2600.

(36) Bone, R.; Wolfenden, R. *J. Am. Chem. Soc.* **1985**, *107*, 4772.