Rate-Equilibrium Relationships for the Deprotonation of 4-Phenacylpyridines and 4-Phenacylpyridinium Cations

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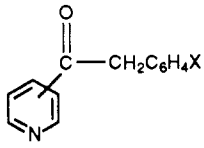
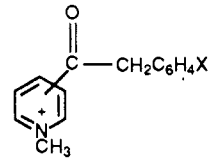
Abstract: Substituent effects upon the equilibria and kinetics of enolate ion formation from eight 4-(X-phenacyl)pyridines (**5**), eight 1-methyl-4-(X-phenacyl)pyridinium cations (**6**), five 1-benzyl-4-(X-phenacyl)pyridinium cations (**7**), and eight 1-(X-benzyl)-4-phenacylpyridinium cations (**8**) have been measured in aqueous solution at 25 °C and ionic strength 0.1. The pK_a values for deprotonation of these ketones correlate with Hammett σ constants for the X substituents, with ρ = 2.03, 1.38, 1.43, and 0.47 for **5**–**8**, respectively; deviations are observed for the 4-methoxy and 4-nitro substituents for both **5** and **6**. Brønsted α values (log k_{OH} vs pK_a) are 0.40, 0.45, 0.42, and 0.35 for **5**–**8**, respectively. These data are analyzed in terms of charge imbalances that are present in the transition-state species in these deprotonation reactions. Comparisons of the current data with the previously reported studies of the deprotonation of the isomeric phenylacetyl pyridines and pyridinium cations establish that there are no general rate–equilibrium correlations for the deprotonation of different series of ketones, even when all substitution is remote from the site of deprotonation.

We have recently shown[1] that the 3- and 4-(X-phenylacetyl)pyridines (**1** and **2**) and their *N*-methyl cations (**3** and **4**) are reasonably strong carbon acids, and that their kinetic and thermodynamic acidities are readily measured in aqueous solution. Furthermore, these four series of ketones display quite distinct Brønsted relationships (log k_{OH} vs pK_a), with Brønsted α values that vary systematically with the acidities of the parent ketones.



1 = 3-phenylacetyl
2 = 4-phenylacetyl



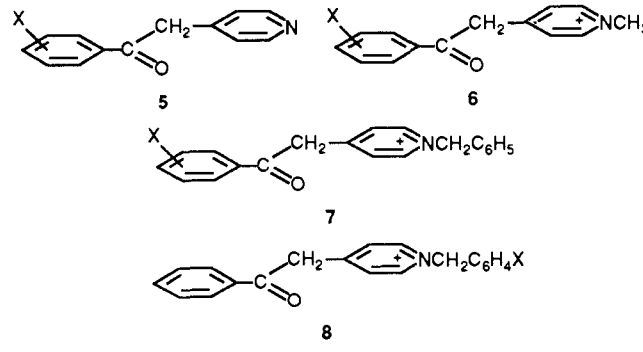
3 = 3-phenylacetyl
4 = 4-phenylacetyl

Katritzky and co-workers have reported[2] acidities for the parent 2-, 3-, and 4-phenacylpyridines that are similar to those found[1] for their isomers **1** and **2**; e.g. 4-phenacylpyridine (**5**, X = H) has pK_a = 12.46 in aqueous solution and is of similar acidity to **2** (pK_a = 12.26). N-methylation of **5** gives a ketone that is significantly more acidic than **4** (pK_a = 9.02); the 1-methyl-4-phenacylpyridinium cation (**6**, X = H) was reported[2] to have pK_a = 7.58 in aqueous solution. Since the 4-phenacylpyridines (**5**) are readily synthesized, it seemed worthwhile to extend our earlier study[1] of the Brønsted relationships for the deprotonation of **1**–**4** to their isomeric series of ketones **5** and **6**. Furthermore, the two series of ketones 7 and 8 would allow a probe of transition state structure via substituent effects at quite different sites in these carbon acids. Such a comparison should provide a direct method for the investigation of transition state imbalances in electron density distribution which may develop during the deprotonation of these ketones. We have therefore synthesized a variety of substituted ketones of the types **5**–**8**, and report a study of their pK_a values in aqueous solution and also the second-order rate constants for their deprotonation by hydroxide ion.

We have found that the 4-phenacyl and 4-phenylacetyl ketones and their *N*-methyl cations display major differences in several aspects of both their thermodynamic and kinetic carbon acidities. These differences are reflected in significant effects upon Hammett ρ values, Brønsted α parameters, and the influence of N-methylation upon the kinetic acidities of these ketones.

Experimental Section

Synthesis of 4-Phenacylpyridines (5). The ketones **5a**–**5e** were synthesized via a slightly modified version of a route described by Screttas



5 6 7 8

and co-workers.[3] This modification involved the use of lithium diisopropylamide rather than 2-thienyllithium for the metalation of 4-methylpyridine and is described below for the preparation of **5a**. Attempts to prepare the ketones **5f**–**5i** by this same general method were unsuccessful. In these latter cases, a black insoluble product was produced during the addition of the appropriately substituted benzonitrile to the metalated 4-methylpyridine. This complication was not explored in detail, since these ketones were also readily accessible by the method of Zimmer and Bercz,[4] which we also previously used[1] for the synthesis of (phenylacetyl)pyridines.

4-Phenacylpyridine (5a). A solution of lithium diisopropylamide in anhydrous tetrahydrofuran (100 mL) was prepared from *n*-butyllithium [49 mmol; 19.6 mL of a 2.5 M solution in hexane (Aldrich Chemical Co.)] and diisopropylamine (7.22 mL; 51.1 mmol) in a dry three-necked 500-mL flask under a positive pressure of nitrogen at −78 °C. A solution of 4-methylpyridine (5 g; 53.7 mmol) in tetrahydrofuran (50 mL) was then added over 30 min, and the resulting deep red solution was then stirred for a further 30 min at 0 °C. Benzonitrile (7.1 g; 60.6 mmol) in tetrahydrofuran (50 mL) was added over 40 min at −78 °C. Stirring was continued for 2 h at −78 °C and then a further 16 h at room temperature. The dark brown mixture was treated with water (100 mL) and then acidified with 48% hydrobromic acid. The tetrahydrofuran was removed on the rotary evaporator and the resulting acidic aqueous solution was refluxed for 2 h. The cooled aqueous solution was extracted several times with diethyl ether, and upon neutralization of the acidic aqueous layer, the 4-phenacylpyridine precipitated as a yellow solid. The product (**5a**) was recrystallized several times from hexane; yield 95%.

The substituted ketones **5b**–**5e** were prepared via this same general procedure in 40–70% yields. All of the ketones **5** were purified by several recrystallizations from a mixture of hexane and ethyl acetate. The melting points and ^1H NMR spectra of all **5** are listed in Table I. Elemental analyses (C, H, N) of all ketones in this table were consistent with the molecular formulas.

Synthesis of the Bromide Salts of 6. All **6**·Br^- were prepared by treatment of the appropriate **5** with methyl bromide in acetone solution

(1) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1988**, *110*, 4008.
(2) Katritzky, A. R.; Kucharska, H. Z.; Rowe, J. D. *J. Chem. Soc.* **1965**, 3093.
(3) Screttas, C. G.; Estham, J. M.; Kamienski, C. W. *Chimia* **1970**, *24*, 109.
(4) Zimmer, H.; Bercz, J. P. *Justus Liebigs Ann. Chem.* **1965**, *686*, 107.

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Table I. Characterization of 4-(X-Phenacyl)pyridines (5)

ketone	X	mp, °C	^{1}H NMR,[a] δ
5a	H	114–115[b]	5.00 (2 H, s), 7.58–7.95 (3 H, m), 8.17–8.33 (4 H, m), 8.92 (2 H, m)
5b	4-OCH_3	99–100	4.13 (3 H, s), 4.96 (2 H, s), 7.20 (2 H, d), 8.17–8.40 (4 H, m), 9.00 (2 H, m)
5c	4-CH_3	105–106	2.60 (3 H, s), 4.97 (2 H, s), 7.52 (2 H, d), 8.00–8.30 (4 H, m), 8.80–9.07 (2 H, m)
5d	4-Cl	92–93	4.97 (2 H, s), 7.63 (2 H, d), 8.03–8.33 (4 H, m), 8.90 (2 H, m)
5e	3-Cl	103–104	5.00 (2 H, s), 7.58–7.92 (2 H, m), 8.00–8.37 (4 H, m), 8.93 (2 H, m)
5f	4-CF_3	96–97	5.03 (2 H, s), 7.96 (2 H, d), 8.17–8.53 (4 H, m), 8.90 (2 H, m)
5g	3-NO_2	83–85	5.10 (2 H, s), 7.92 (2 H, d), 8.10–8.40 (2 H, m), 8.57–9.20 (4 H, m)
5h	3-NO_2, 4-Cl	95–96	5.10 (2 H, s), 7.95 (1 H, d), 8.27–8.67 (3 H, m), 8.83–9.23 (3 H, m)
5i	4-NO_2	173–175	5.13 (2 H, s), 8.32 (2 H, d), 8.43–8.77 (4 H, m), 9.03 (2 H, m)

[a] In trifluoroacetic acid; all chemical shifts are relative to tetramethylsilane. [b] Lit.[3] mp 112–113 °C.

Table II. Characterization of the Bromide Salts of 6

bromide salt	X	mp, °C	^{1}H NMR,[a] δ
6a	H	198–199	4.58 (3 H, s), 4.97 (2 H, s), 7.63–7.88 (3 H, m), 8.13–8.23 (4 H, m), 8.80 (2 H, d)
6b	4-OCH_3	177–178	4.10 (3 H, s), 4.60 (3 H, s), 4.97 (2 H, s), 7.20 (2 H, d), 8.20–8.40 (4 H, m), 8.92 (2 H, d)
6d	4-Cl	232 dec	4.63 (3 H, s), 5.02 (2 H, s), 7.60 (2 H, d), 8.13–8.33 (4 H, m), 8.95 (2 H, d)
6e	3-Cl	195–196	4.58 (3 H, s), 5.00 (2 H, s), 7.67 (2 H, d), 8.03–8.25 (4 H, m), 8.90 (2 H, d)
6f	4-CF_3	176–177	4.50 (3 H, s), 4.96 (2 H, s), 7.83–8.40 (6 H, m), 8.83 (2 H, d)
6g	3-NO_2	205 dec	4.63 (3 H, s), 5.06 (2 H, s), 7.83–8.33 (3 H, m), 8.58–9.03 (5 H, m)
6h	3-NO_2, 4-Cl	210 dec	4.67 (3 H, s), 5.10 (2 H, s), 7.83–8.97 (7 H, m)
6i	4-NO_2	204 dec	4.67 (3 H, s), 5.10 (2 H, s), 8.22 (2 H, d), 8.53 (4 H, s), 8.95 (2 H, d)

[a] In trifluoroacetic acid; all chemical shifts relative to tetramethylsilane.

as previously described.[1] The ^{1}H NMR spectra and melting points of these salts are listed in Table II.

Synthesis of the Bromide Salts of 7 and 8. A mixture of the appropriate 4-phenacylpyridine (1 g) and the substituted benzyl bromide (1.1 equiv) was refluxed in acetone solution for 24 h. The bromide salt of **7** or **8** precipitated from the cooled solution and was purified by recrystallization from 2-propanol. The melting points and ^{1}H NMR spectra of **7**·Br^- and **8**·Br^- are listed in Table III.

pK_a Values. The pH-dependent spectral changes of the cations **6–8** occur in the vicinity of neutral pH. It was found that the absorption spectra of the conjugate bases of these cationic ketones were not stable when the pH of an aqueous solution of these cations was maintained by a phosphate buffer. We have not investigated this instability in these phosphate buffer solutions; however, stable spectra were obtained in this pH range when either *N*-(2-hydroxyethyl)piperazine-*N*'-(2-ethanesulfonic acid) (HEPES; pK_a = 7.5) or 2-(*N*-morpholino)ethanesulfonic acid (MES; pK_a = 6.1) was used as the buffering species. The pH-dependent spectral changes were cleanly reversible upon acidification of such buffered solutions. The absorbances as a function of pH at the long-wavelength absorption maxima were consistent with a clean acid–base equilibration, and pK_a values were evaluated from these data by the general method of Albert and Serjeant[5] at 25 °C and ionic strength 0.1. Since the enolate conjugate bases of some **7** tended to precipitate even at concentrations as low as 0.01 mM, it was found necessary to add up to 1.5% acetonitrile to these solutions in order to maintain solution homogeneity in these studies. The pK_a values of **6a**, **6b**, and **6e** were also confirmed by potentiometric titration[6] of aqueous solutions of these ketones (10 mM); however, the conjugate bases of all other cations precipitated during attempts to determine pK_a values by such potentiometric titrations at concentrations of ≥1 mM.

(5) Albert, A.; Serjeant, E. P. *Ionization Constants of Acids and Bases*; Methuen: London, 1962; Chapter 4.
(6) Albert, A.; Serjeant, E. P. Reference 5, Chapters 2 and 3.

Table III. Characterization of the Bromide Salts of 7 and 8

bromide salt	X	mp, °C	^{1}H NMR,[a] δ
7a[b]	H	154–155	4.93 (2 H, s), 5.85 (2 H, s), 7.52–7.80 (8 H, m), 8.03–8.23 (4 H, m), 8.83 (2 H, d)
7d	4-Cl	202–204	5.04 (2 H, s), 6.01 (2 H, s), 7.59–7.87 (7 H, m), 8.27 (4 H, m), 9.35 (2 H, m)[c]
7e	3-Cl		5.08 (2 H, s), 6.00 (2 H, s), 7.59–7.96 (7 H, m), 8.22 (4 H, m), 9.35 (2 H, d)[c]
7f	4-CF_3	161–163	4.96 (2 H, s), 5.86 (2 H, s), 7.55 (5 H, m), 7.92 (2 H, d), 8.10 (2 H, d), 8.28 (2 H, d), 8.83 (2 H, d)
7g	3-NO_2		5.19 (2 H, s), 5.96 (2 H, s), 7.60 (5 H, m), 8.03–9.11 (6 H, m), 9.22 (2 H, s)[c]
8a[b]	H		
8b	3-CH_3	169–170	2.50 (3 H, s), 5.02 (2 H, s), 5.85 (2 H, s), 7.50 (4 H, s), 7.67–8.00 (3 H, m), 8.17–8.33 (4 H, m), 8.92 (2 H, d)
8c	4-CH_3	172–174	2.42 (3 H, s), 4.92 (2 H, s), 5.83 (2 H, s), 7.40 (4 H, s), 7.55–7.80 (3 H, m), 8.03–8.20 (4 H, m), 8.87 (2 H, d)
8d	3-Cl	163–164	5.00 (2 H, s), 5.87 (2 H, s), 7.17–7.90 (7 H, m), 8.10–8.30 (4 H, m), 8.93 (2 H, d)
8e	4-Br	174–175	5.02 (2 H, s), 5.88 (2 H, s), 7.33–7.87 (7 H, m), 8.13–8.30 (4 H, m), 8.95 (2 H, d)
8f	3-NO_2	188–190	5.07 (2 H, s), 6.18 (2 H, s), 7.58–8.75 (11 H, m), 9.12 (2 H, d)
8g	4-NO_2	207 dec	5.12 (2 H, s), 6.20 (2 H, s), 7.67–8.03 (5 H, m), 8.17–8.58 (6 H, m), 9.12 (2 H, d)
8h	3,5-$(NO_2)_2$	222 dec	5.10 (2 H, s), 6.35 (2 H, s), 7.50–7.97 (3 H, m), 8.13–8.43 (4 H, m), 8.85–9.38 (5 H, m)

[a] In trifluoroacetic acid unless otherwise indicated; all chemical shifts are relative to tetramethylsilane. [b] **7a** ≡ **8a**. [c] In dimethyl sulfoxide containing two drops of trifluoroacetic acid.

The pK_a values of the neutral ketones **5** were evaluated from the pH dependences of the absorbances of equilibrated solutions, which were formed from the mixing of an aqueous solution of the ketone with standard potassium hydroxide solutions in the Durrum-Gibson stopped-flow spectrophotometer. All pH measurements in these studies were made on a Radiometer PHM82 pH meter using a GK2401B combination electrode. pH measurements of solutions in the stopped-flow studies were made by mixing equal volumes of the ketone stock solution in water with the double-strength buffer solutions.

Kinetic Studies. All kinetic data were obtained on the stopped-flow spectrophotometer in aqueous solution at 25 °C and ionic strength 0.1 (KOH + KCl), by mixing equal volumes of an aqueous solution of the ketone (0.01 mM) with KOH + KCl solutions of ionic strength 0.2. The equilibration of the ketone and its enolate ion conjugate base was monitored at the long-wavelength absorption maxima of the enolate ions that are listed in Table IV. The neutral ketones **5** were investigated over the range pH 10.8–13.0, while kinetic studies of the cationic ketones **6–8** were restricted to pH 10.6–11.6 since the rates of these latter reactions became too rapid for stopped-flow spectrophotometry in more basic solutions.

Pseudo-first-order rate constants at each pH were based upon the average value obtained from at least six repetitive runs at that pH. Data collection involved the automatic digitization of the photomultiplier output into 118 data points with transfer of these data to a Tektronix 4051 computer for data collection and kinetic analysis. All reactions were found to be kinetically first order in carbon acid for at least the first 95% of the overall reaction.

Results

Each of the ketones **5–8** displays a pH-dependent electronic absorption spectrum in aqueous solution. Typical spectral changes are indicated in Figure 1. In all cases the ultraviolet absorption spectra of these aromatic ketones are converted into spectra having intense long-wavelength absorption maxima in more basic solutions (log $\epsilon \approx 4.3$ for **5**; log $\epsilon \approx 4.6$ for **6–8**).[2] Fixed-wavelength absorbances as a function of pH describe clean acid–base equilibrations. The pK_a values that were measured for all of the ketones studied are given in Table IV. This table also includes

Table IV. Kinetic and Thermodynamic Acidities of 4-Phenacylpyridines and 4-Phenacylpyridinium Cations

ketone	X	pK_a	k_{OH}, 10^4 M^{-1} s^{-1}	λ_{max},[b] nm
5a	H	12.47[c]	0.0220	353
5c	4-CH_3	12.87	0.0148	355
5d	4-Cl	12.06	0.0344	356
5e	3-Cl	11.73	0.0456	355
5f	4-CF_3	11.39	0.0606	356
5g	3-NO_2	11.02	0.0836	356
5h	3-NO_2, 4-Cl	10.64	0.117	356
5i	4-NO_2	10.59	0.102	360
6a	H	7.66[d]	3.93	405
6b	4-OCH_3	8.27	2.52	410
6d	4-Cl	7.33	5.11	405
6e	3-Cl	7.14	6.29	407
6f	4-CF_3	6.88	8.15	405
6g	3-NO_2	6.66	11.4	404
6h	3-NO_2, 4-Cl	6.38	14.0	406
6i	4-NO_2	6.33	13.0	422
7a[e]	H	7.28	4.81	410
7d	4-Cl	6.96	6.63	410
7e	3-Cl	6.70	8.56	411
7f	4-CF_3	6.50	10.1	410
7g	3-NO_2	6.27	12.8	410
8a[e]	H			
8b	3-CH_3	7.29	4.84	411
8c	4-CH_3	7.37	4.48	410
8d	3-Cl	7.10	5.68	410
8e	4-Br	7.17	5.28	411
8f	3-NO_2	6.96	6.44	410
8g	4-NO_2	6.93	6.54	413
8h	3,5-$(NO_2)_2$	6.59	8.24	413

[a] All rate and equilibrium constants in aqueous solution at 25 °C and ionic strength 0.1; standard deviations in pK_a are ≤0.02, and less than ±4% in k_{OH}. [b] Absorption maximum of the enolate ion conjugate base of this ketone. [c] Literature[2] value, 12.46. [d] Literature[2] value, 7.58. [e] **7a** ≡ **8a**.

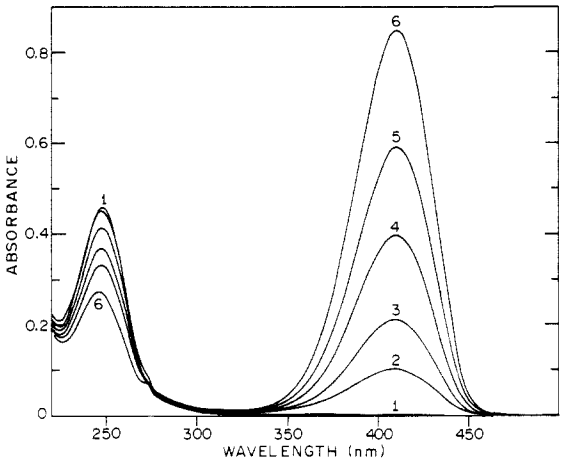


Figure 1. pH dependence of the electronic absorption spectrum of **7a** (0.025 mM) in aqueous solution: Curve: 1, pH 3.0; 2, pH 6.32; 3, pH 6.72; 4, pH 7.09; 5, pH 7.41; 6, pH 7.85.

the wavelengths of the visible absorption maxima in the spectra of the enolate ion conjugate base species.

The equilibration of each of the ketones **5–8** with their conjugate bases is readily observable upon mixing aqueous solutions of these ketones with aqueous KOH solutions in the stopped-flow spectrophotometer. The time dependences of the absorbance at wavelengths in the vicinity of the absorption maxima in Table IV were cleanly first order in ketone concentration. Pseudo-first-order rate constants were strictly linear in hydroxide ion concentration in all cases (e.g., Figures 2 and 3), and second-order rate constants (k_{OH}) were evaluated from the slopes of such plots, from the relationship $k_{obs} = k_{OH}[^-OH] + k_{H_2O}$. For the cationic ketones **6–8**, k_{H_2O} was in all cases within experimental error of zero over the pH range that was accessible in these studies. All second-order

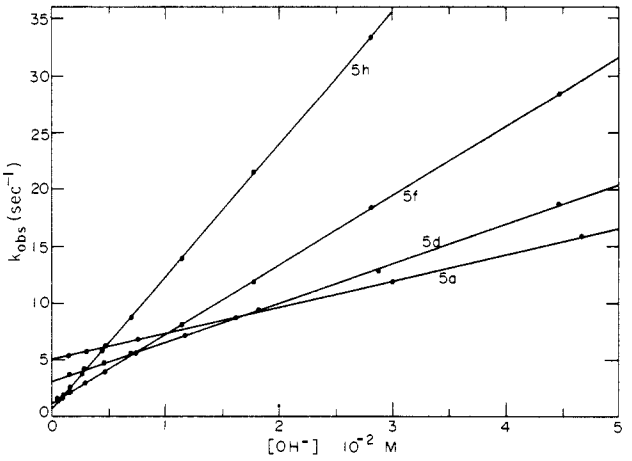


Figure 2. pH dependence of the pseudo-first-order rate constants for the equilibration of selected **5** with their enolate anion conjugate bases (25 °C, ionic strength 0.1).

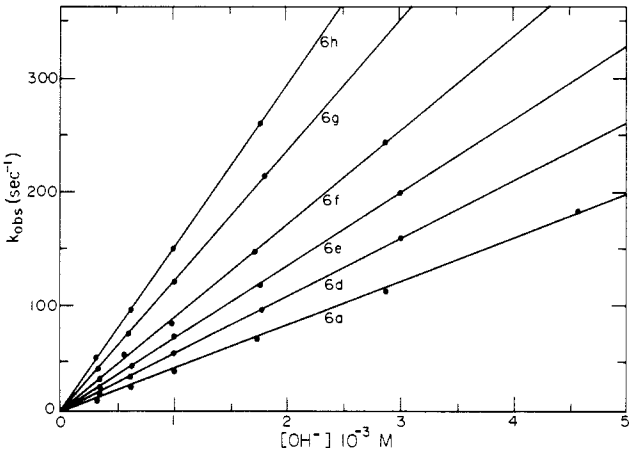


Figure 3. pH dependence of the pseudo-first-order rate constants for the deprotonation of selected **6** in aqueous solution (25 °C, ionic strength 0.1).

rate constants are summarized in Table IV.

The presence of significant quantities of either the enols or hydrates of these ketones would influence the thermodynamic and kinetic parameters that are obtained in this study. The following ^{13}C NMR experiment was therefore performed to evaluate the possible presence of such species. A saturated solution of the salt **6a** was prepared in H_2O and adjusted to pH 3.5 with HCl. A 100-MHz ^{13}C NMR spectrum (Varian XL-400 spectrometer) was obtained by using a delay time of 2 s between each pulse for 8000 pulses. Under these conditions the resulting ^{13}C NMR spectrum has a signal-to-noise ratio of 1542. The major peaks were readily assignable to the carbon atoms of the ketone **6a** (δ 45.1, 48.4, 129.0, 129.6, 130.1, 135.2, 135.8, 144.9, 155.1, 197.9 relative to the nitrile carbon atom of CH_3CN at δ 119.7). The ratio of the intensities of the major to the minor peaks was greater than 500:1; this corresponds to a maximum concentration of less than 1% for any species other than **6a**. There are thus no significant amounts of enol or *gem* diol (hydrate) present in these aqueous solutions at concentrations that would significantly influence our quantitative rate and equilibrium measurements. A very low equilibrium enol content for ketones of this type has also been demonstrated by other workers.[1,7]

Discussion

Acidities. The intense absorption maxima that are observed (Table IV) in the spectra of the enolate ion conjugate bases of

(7) (a) Fukata, G.; O'Brien, C.; More O'Ferrall, R. A. *J. Chem. Soc., Perkin Trans. 2* **1979**, 792. (b) Carey, A. R. E.; Al-Quatami, S.; More O'Ferrall, R. A.; Murray, B. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1097.

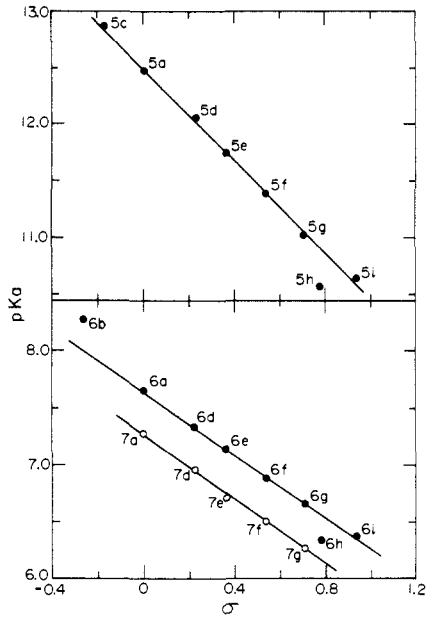
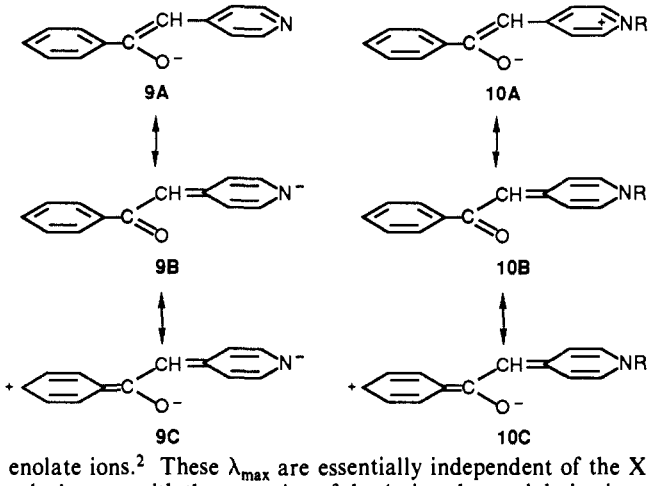


Figure 4. Hammett plots for the substituent dependence of the pK_a values for **5**, **6**, and **7**.

each of **5–8** are indicative of the importance of extended conjugation (**9A–9C** and **10A–10C**) to the electronic structures of these



enolate ions.[2] These λ_{max} are essentially independent of the X substituents, with the exception of the 4-nitrophenacyl derivatives, which show longwavelength shifts of about 5 and 15 nm for **5** and **6**, respectively. The spectra of the zwitterionic enolate ions of **6**, **7**, and **8** are almost exactly 50 nm red-shifted relative to those of the anionic enolate ions from **5**. The former are also considerably more intense than the latter. The λ_{max} in the vicinity of 355 nm that are observed for the enolate ions of **5** are very similar to the absorption maxima observed for the enolate ions of **1** (λ_{max} = 340 nm), **2** ($\lambda_{max} \approx$ 360 nm), and **3** (λ_{max} = 360 nm) when these enolate ions lack further resonance interactions from substituents.[1] All of these observations point to the importance of contributions from **9C** and **10C** to the electronic structures of the conjugate bases of the present study.

The pK_a values for each series of ketones may be correlated with the Hammett σ constants for benzoic acid ionization, although the 4-nitro and 4-methoxy derivatives of **5**, **6**, and **7** do show deviations (Figure 4) and have been ignored in calculating the correlation eqs 1–4. Deviations for the 4-nitro substituent are in the direction of a contribution from σ^-, while deviations for the 4-methoxy substituent require a contribution from σ^+.

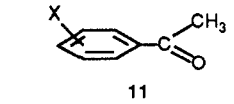
$$pK_a^5 = -2.03\ (\pm 0.03)\sigma + 12.50\ (\pm 0.03) \quad r = 0.9994 \quad (1)$$

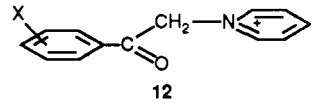
$$pK_a^6 = -1.38\ (\pm 0.02)\sigma + 7.64\ (\pm 0.02) \quad r = 0.9994 \quad (2)$$

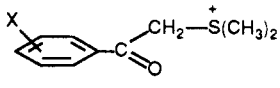
$$pK_a^7 = -1.43\ (\pm 0.05)\sigma + 7.27\ (\pm 0.03) \quad r = 0.998 \quad (3)$$

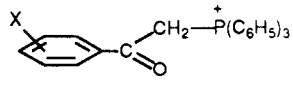
$$pK_a^8 = -0.47\ (\pm 0.01)\sigma + 7.28\ (\pm 0.02) \quad r = 0.998 \quad (4)$$

From eqs 1 and 2 it can be seen that N-methylation increases the acidity of **5** (X = H) by 4.86 pK_a units, while the *N*-benzyl cation is a further 0.37 unit more acidic (eq 3). This increase in acidity upon N-methylation is greater than the differences in acidity that are observed[1] upon the methylation of the 3- and 4-(phenylacetyl)pyridines (ΔpK_a = 2.9 and 3.24 upon N-methylation of **1** and **2**, respectively). The Hammett ρ value for **6** is smaller than for **5** (eqs 1 and 2) and these data follow the general trend reported[1] for the 3- and 4-(phenylacetyl)pyridines and their *N*-methyl cations. The ρ values of 1.38 and 1.43 that are observed for **6** and **7**, respectively, are similar in magnitude to ρ = 1.44 for **3** and ρ = 1.29 for **4**. The ρ = 2.03 for **5** is significantly larger than the ρ = 1.70 that was found for **1** and **2**, despite the fact that the X substituents are closer to the site of deprotonation in **1** (and **2**) than in **5**. This ρ value for **5** is, however, very similar to ρ = 1.95 (±0.19) reported by Guthrie and co-workers[8] for the deprotonation of ring-substituted acetophenones (**11**). The ρ = 2.03 for **5** is also similar to the ρ values in the range 2.1–2.3 that have been reported[9,10] for the substituent effects upon the pK_a values of the similarly substituted ketones **12–14**, although it should be noted that the data for **12–14** are for alcoholic solutions.

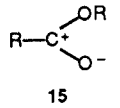


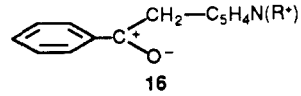






The relative magnitudes of these Hammett ρ values are quite unexpected[8] if one were to use the analogy that substituent effects upon the deprotonation of **1–4** should most closely resemble substituent effects upon phenol ionization (ρ = 2.15),[1] while substituent effects upon **5–7** should be more reasonably modeled by benzoic acid ionization (ρ = 1.0). The ρ values for **1–4** are less than ρ = 2.15 for phenol ionization, consistent with the additional stabilization of charge that is provided by delocalization onto the oxygen atom and into the pyridine ring. However, the large ρ values for **5–7** require a more direct effect for the influence of the electronic properties of substituents in the phenyl ring than is obvious from the structures **5–7** for the acid species and structures such as **9** and **10** for the conjugate bases. We suggest that a rationalization for these relatively large substituent effects can be found in terms of the recent conclusions[11–13] that have been drawn from theoretical calculations of the electron density distributions in carbonyl-containing functional groups. These studies are only consistent with **15** being the dominant resonance con-





tributor to the electronic structures of esters and carboxylic acids. The large magnitudes of the ρ values for **5–7** seem to indicate that the analogous structure **16** is a major contributor to the electronic structure of these ketones. Certainly **16** allows a ready rationalization of the deviation of the 4-methoxy derivatives from Hammett correlations in these series. Such deviations are in the direction of a contribution from σ^+ for the 4-methoxy substituent.

The ρ = 0.47 for substituents in the *N*-benzyl group in **8** is quite large considering the distance of these substituents from the re-

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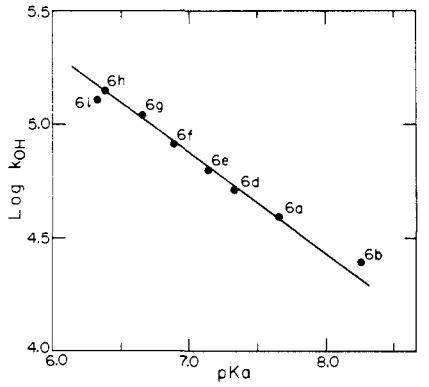
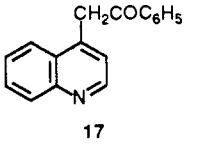


Figure 5. Brønsted plot for the hydroxide ion catalyzed deprotonation of **6**.

action center and further dramatizes the importance of resonance contributors such as **10B** to the structure of these enolate anions. This $\rho = 0.47$ for **8** should be compared with $\rho = 1.14$ for the pK_a values for deprotonation of ring-substituted *N,N*-(dimethylbenzyl)ammonium cations ($XC_6H_4CH_2NH(CH_3)_2^+$).[14] These ρ values suggest at least 40% neutralization of the positive charge on the ring nitrogen atom upon enolate ion formation from **8**.

Kinetic Studies. As far as we are aware, the present work represents the first kinetic investigation of the deprotonation of any of the ketones **5–8**, although More O'Ferrall and co-workers[15] have studied the rates of deprotonation of 4-phenacylquinoline (**17**; $pK_a = 12.37$) and its *N*-methyl derivative (**18**; $pK_a = 7.02$)



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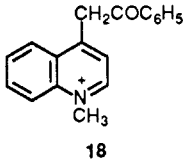

18

and the 2-phenacyl isomers of **17** and **18** in aqueous solution. These workers reported $k_{OH} = 185\ M^{-1}\ s^{-1}$ for **17** and $k_{OH} = 2.68 \times 10^4\ M^{-1}\ s^{-1}$ for **18** at 25 °C. Both the thermodynamic and kinetic acidities of these quinoline carbon acids are similar to those of their 4-phenacylpyridine analogues (**5a** and **6a** in Table IV).

The dependence of log k_{OH} upon pK_a produces four distinct linear Brønsted plots for the ketones **5–8** although the 4-nitro and 4-methoxy substituents deviate in the series **5** and **6** (Figure 5). These plots are defined by the correlation eqs 5–8 when these deviant data points are ignored.

$$\log k_{OH}^5 = -0.40\ (\pm 0.01)\ pK_a^5 + 7.34\ (\pm 0.02) \quad r = 0.998 \quad (5)$$

$$\log k_{OH}^6 = -0.45\ (\pm 0.02)\ pK_a^6 + 8.02\ (\pm 0.02) \quad r = 0.995 \quad (6)$$

$$\log k_{OH}^7 = -0.42\ (\pm 0.01)\ pK_a^7 + 7.72\ (\pm 0.01) \quad r = 0.9992 \quad (7)$$

$$\log k_{OH}^8 = -0.35\ (\pm 0.01)\ pK_a^8 + 7.20\ (\pm 0.01) \quad r = 0.997 \quad (8)$$

Equations 5–8 indicate that if one compares **5–8** at a constant pK_a, then the relative order of reactivities of k_{OH} is *N*-methyl (**6**) > *N*-benzyl (**7**) > N (**5**). If one chooses to make such a comparison at $pK_a = 9$, which was used for this type of analysis in our previous study[1] of the (phenylacetyl)pyridines ($pK_a = 9.02$ for **4**; X = H), then one obtains the extrapolated rate constants in Table V. Note that methylation of **1** and **2** leads to a lower reactivity, whereas methylation of **5** leads to an enhanced reactivity. At present, we have no simple explanation for this apparently trivial observation, although it is presumably another manifestation of the characteristic α values that are discussed below for these various classes of ketones.

Table V. Kinetic Acidities of Related Ketones for $pK_a = 9.0$[a]

ketone	k_{OH}, $M^{-1}\ s^{-1}$	k_{OH}^{Rel}	k_{OH}^{NMe}/k_{OH}^{N}
1	2×10^4	25	
2	1×10^4	13	
3	6×10^3	7.5	0.3
4	8×10^2	(1)	0.08
5	5.5×10^3	6.9	
6	9.3×10^3	12	1.7
7	8.8×10^3	11	
8	1.1×10^4	14	

[a] Calculated by extrapolation of Brønsted plots to $pK_a = 9.0$. Data for **1–4** are from ref 1; data for **5–8** are calculated from eqs 5–8. k_{OH}^{NMe}/k_{OH}^{N} reflects the relative reactivities of a pyridine ketone (k_{OH}^{N}) and its *N*-methyl derivative (k_{OH}^{NMe}).

Table VI. Marcus Theory Evaluation of the Deprotonation of Ketones **5–8** by Hydroxide Ion[a]

ketone	$\Delta G_0^{\ddagger}$	α_M	α	A	B
5	15.29	0.48	0.40	15.13 (±0.03)	−0.08 (±0.01)
6	15.21	0.43	0.45	15.49 (±0.03)	0.03 (±0.02)
7	15.31	0.43	0.42	15.29 (±0.01)	−0.00 (±0.01)
8	15.31	0.43	0.35	14.59 (±0.01)	−0.08 (±0.01)

[a] Parameters are evaluated as described in the text. $\Delta G_0^{\ddagger}$ and A are in kcal/mol.

All Brønsted α values in eqs 5–8 are less than 0.5, which is as expected based upon the prediction from Marcus theory that $\alpha < 0.5$ for $\Delta G° < 0$. This result contrasts with the observation[1,16] of "anomalous" α values in the range 0.66–0.76 for the deprotonation of the ketones **1–4** by hydroxide ion. However, a more detailed consideration of the α values of eqs 5–8 in the light of Marcus theory shows that all is not normal. In Table VI, we list the intrinsic barriers ($\Delta G_0^{\ddagger}$) calculated from Marcus theory (eq 9) for the unsubstituted ketone (X = H) of each of the series **5–8**,

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger}\ (1 + \Delta G°/4\Delta G_0^{\ddagger})^2 \quad (9)$$

$$\alpha_M = 0.5(1 + \Delta G°/4\Delta G_0^{\ddagger}) \quad (10)$$

and also the Brønsted α value (α_M) that is predicted from these intrinsic barriers according to eq 10. It is clear that while the experimental α values for **6** and **7** are predicted reasonably well by Marcus theory, the series **5** and **8** show much larger discrepancies between α and α_M than is consistent with experimental error.

In our earlier work we have shown[1,16] that such discrepancies can be rationalized by modifying the usual form of the Marcus equation (eq 9) to include a variable intrinsic barrier that is defined by eq 11. Calculation of $\Delta G_0^{\ddagger}$ and $\Delta G°$ for the deprotonation

$$\Delta G_0^{\ddagger} = A + B\Delta G° \quad (11)$$

of each ketone in the current study (excepting the 4-NO_2 and 4-OCH_3 derivatives, which deviate from the simple Brønsted plots), and then least-squares fitting of the data to eq 11, gives the A and B parameters in Table VI. Note that in general $B \approx (\alpha - \alpha_M)$, and that A varies between 14.6 and 15.5 for the four series of ketones. These latter intrinsic barriers are less than the range of 16.0–18.9 that was found[1] for A in the series **1–4**.

It is particularly noteworthy that the experimental α values for the ketone series **7** and **8** are not identical. To a first approximation, one can describe the deprotonation of the ketones **5–8** in terms of three major reaction events: (1) proton transfer from the methylene group with generation of carbanionic character at this carbon atom; (2) electron delocalization from this carbanionic center into the pyridine ring; (3) electron delocalization onto the oxygen atom of the carbonyl group.

If these three reaction events were completely synchronous processes, then the rate–equilibrium correlations for **7** and **8** should produce identical Brønsted coefficients in eqs 7 and 8. Fur-

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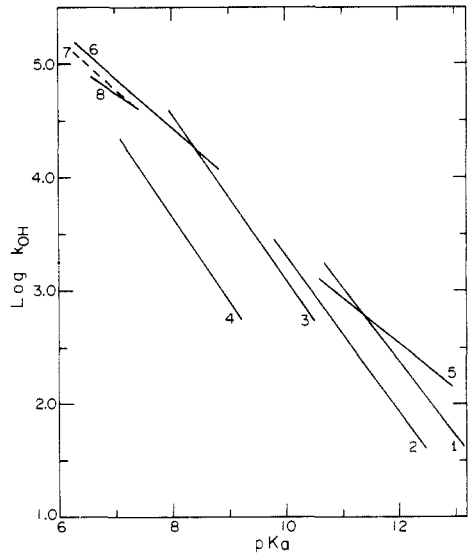

Figure 6. Brønsted plots for the hydroxide ion catalyzed deprotonation of the ketone series **1–8**. The lines cover the pK_a ranges for which data are available in each ketone series.

thermore, the magnitude of this α value should be consistent with the value of α_M predicted by Marcus theory. The fact that these latter two conditions do not hold, indicates that these three major reaction events are not completely synchronized processes. This same result is also indicated by the different A values (Table VI) that are found for the two series **7** and **8**, despite the fact that the unsubstituted member of each of these two series is the *same* ketone. It is therefore clear that substituent effects in **7** and **8** are sampling different aspects of the electronic reorganization that occurs upon the formation of the transition-state species.

The experimental α value for the deprotonation of **8** is directly related to the electron delocalization into the pyridine ring in the transition state (event 2 above). The magnitude of $\alpha = 0.35$ for this process is 0.08 unit lower than α_M calculated from Marcus theory and is also lower than $\alpha = 0.42$ that is found for **7**. This suggests that electron delocalization into the pyridine ring lags behind other reaction events in the transition state for deprotonation of **6–8**. Such a lag in electron delocalization into the pyridinium ring suggests a buildup of negative charge on the carbanionic carbon atom in the transition-state species. Such a buildup would presumably also affect the transition-state delocalization of negative charge onto the carbonyl oxygen atom (event 3 above).

Although we have presented reaction events 1–3 as individual phenomena, it is clear that any lag in the development of any one of these transition-state events will have consequences for each of the other events, since all events are linked via the delocalization of the same developing negative charge. In this sense the approximately "normal" α values that are experimentally observed for **6** and **7** may be more a case of an accidental offsetting of contributions from several different events rather than any inherent applicability of the ideal Marcus relationship (eq 9) in the cases of **6** and **7** as opposed to a requirement for variable intrinsic barriers for **5** and **8**. In other words, the B parameters appear to contain contributions from a number of reaction events, and these may sometimes fortuitously result in $B \approx 0$, and consequently the applicability of the ideal Marcus relationship.

Unfortunately, systems in which two quite different sets of remote substituent effects in the same reactant may be independently analyzed (such as **7** and **8**) are relatively uncommon. However, we feel that the current work clearly demonstrates the value of such multiple substituent effect studies in connection with the evaluation of the properties and structure of transition-state species. It should be noted that the transition-state imbalances that are found in comparisons of series such as **7** and **8** are different in principle from the transition-state imbalances that have been extensively probed by Bernasconi and co-workers[17] in related reactions. These latter workers explored transition-state imbalances in electron density distribution via comparisons of substituent effects in the carbon acid with those in the general-base catalyst. We have observed[18] similar imbalances for the deprotonation of the ketones **1–8** by amine and phenoxide ion bases.

When the current study is combined with our recent report,[1] we have now evaluated rate–equilibrium relationships for the deprotonation of eight series of benzylic ketones (**1–8**) by hydroxide ion. All of these series of ketones are as closely matched as it is possible to imagine in terms of the steric requirements at the site of deprotonation. Yet it is clear from Figure 6 that these eight series of ketones display eight distinct Brønsted correlations. This result clearly establishes that there can be no unique rate–equilibrium correlation that will adequately describe the deprotonation of all ketonic carbon acids. Although approximate correlations of this type covering many pK_a units have been presented[19-21] (but showing considerable scatter), we feel that Figure 6 is a clear warning that no significant conclusions can be drawn from such general correlations. In particular, we feel that arguments are not well-founded when based upon the interpretation of apparent curvature in such extended Brønsted plots.

While it may be objected that much of the nonconformity to a single correlation in Figure 6 can be traced to specific resonance interactions in the different series of ketones, it must be remembered that such variable resonance stabilization of conjugate base species is really the only possible way that one can obtain a broad range of acidities of carbon acids. Not only do extended Brønsted correlations contain pronounced contributions from resonance phenomena, they are usually also strongly influenced by significant steric and solvation effects when structural changes are made either close to, or at, the site of deprotonation.

We feel that we have demonstrated that greater insights into the physical organic chemistry of the deprotonation of carbon acids will be obtained through systematic studies of remote substituent effects covering limited ranges of acidity, than from studies of major structural changes in the vicinity of the acidic C–H bond. In this regard, the difference in the experimental α values for **8** ($\alpha = 0.35$) and **1–4** ($\alpha = 0.66 - 0.76$) is particularly intriguing, since the X substituents in **8** are apparently sampling (via the electron density at the ring nitrogen atom) the transition structure electron delocalization in a system that is π isoelectronic to that which is being sampled by the X substituents in the phenyl rings of **1–4**. These differences in α values are presumably a direct reflection of the relative contributions of resonance delocalization and solvation effects to transition-state stabilization in these systems, but a simple physical interpretation in terms of these phenomena is not obvious at present.

Acknowledgment. We appreciate the continued financial support of this work by the Natural Sciences and Engineering Research Council of Canada.

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