Acidity and Tautomerism of β-Keto Esters and Amides in Aqueous Solution

John W. Bunting* and James P. Kanter

Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1, Canada

*Received July 1, 1993**

Abstract: The pH–rate profiles for the keto–enol tautomerization of 17 β-keto esters and amides ($RCOCH_2COX$: R = methyl; phenyl; 2-, 3-, and 4-pyridyl; 3(and 4)-(*N*-methylpyridinio); X = OCH_3, OC_2H_5, NH_2, or $N(CH_3)_2$) have been measured by stopped-flow spectrophotometry in aqueous solution (ionic strength 0.1, 25 °C) over the range pH = 2–12. Analysis of these profiles gives the microscopic rate constants for ketonization and enolization of each of these species in these aqueous solutions. Analysis of the pH dependence of the buffer catalysis for the general-acid-catalyzed protonation of these enolate conjugate bases allowed the evaluation of pK_a^E for the deprotonation of each enol species. In combination with pK_a^{eq}, these data in turn allow the calculation of the acidities of the keto tautomers (pK_a^K) and the equilibrium constants for enolization (K_E = [enol]/[keto]). In all cases, both the keto and enol tautomers of the amides are more acidic than the corresponding ester derivatives. The equilibrium enol/keto ratios (K_E) were found to decrease in the order: 2-pyridyl > 4-pyridyl > 3-pyridyl > 4-(*N*-methylpyridinio) > 3-(*N*-methylpyridinio) > methyl ≈ phenyl for both β-keto esters and amides. A simple linear correlation between pK_a^E and pK_a^K was observed for these series of β-keto esters and amides. Brønsted plots of second-order rate constants for deprotonation of the keto tautomer as a function of keto tautomer acidity were found to be linear, with α values in the range 0.37–0.54 for hydroxide ion, acetate ion, and several amine bases. However, the "water-catalyzed" reaction is unusual with Brønsted $\alpha = -0.17$. This α value is only readily explicable in terms of a combined general acid + general base catalysis involving two water molecules for the equilibration of the keto tautomer and the neutral enol species.

There have been relatively few studies of the carbon acidity or the keto–enol tautomerization of β-keto carboxylate esters or amides in aqueous solution, despite the fact that such species have pK_a values that are readily measured in the accessible pH region for aqueous media. Aqueous solutions of these species contain mixtures of the keto (KH) and enol (EH) tautomers (K_E = [EH]/[KH]). Deprotonation of either of these acidic species gives their common enolate anion conjugate base (E^-). These equilibria are summarized in Scheme I.

Titration of an equilibrium mixture of the keto and enol tautomers gives an apparent acid ionization constant, K_a^{eq} (eq 1), which is related to the individual ionization constants of the keto and enol tautomers by eqs 2 and 3. Thus, measurement of

$$K_a^{eq} = [H^+][E^-]/([KH] + [EH]) \quad (1)$$

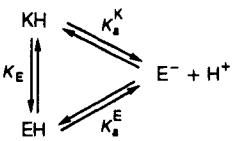
$$pK_a^{eq} = pK_a^K + \log(1 + K_E) \quad (2)$$

$$pK_a^{eq} = pK_a^E + \log(1 + 1/K_E) \quad (3)$$

pK_a^{eq} and any one of pK_a^K, pK_a^E, or K_E will allow the evaluation of all equilibrium constants in Scheme I.

There have been several reports of pK_a^{eq} for ethyl acetoacetate (**1**: R = H) in aqueous solution.[1-5] Brouillard and Dubois[5] report pK_a^{eq} = 10.65 (25 °C, ionic strength 0.1) in a kinetic investigation (temperature-jump technique) of the deprotonation reaction in aqueous base. These workers relied upon an earlier measurement

Scheme I



of K_E = 0.0039, which was reported by Schwarzenbach and Felder[6] from the titration of the enol species in the equilibrium mixture with bromine, to evaluate pK_a^E = 8.24 for the enol of ethyl acetoacetate. A similar K_E = 0.005 was reported for aqueous solution by Murthy and co-workers[7] from the electronic absorption spectrum of the enol species in the equilibrium mixture. However, a 10-fold larger K_E = 0.055 was found by Moriyasu et al.[8] by means of a high-performance liquid chromatographic separation of the tautomers in an equilibrated aqueous solution. Mills and Beak[9] also report an unreferenced literature value[10] of K_E = 0.07 for aqueous solutions of this ethyl ester. These latter values suggest that the only available literature value[5] of pK_a^E = 8.24 for the enol tautomer of ethyl acetoacetate may be underestimated by about 1 logarithmic unit.

$CH_3COCHRCO_2C_2H_5$ **1**

Brouillard and Dubois[5] also investigated a series of six substituted acetoacetate esters (**1**: R = alkyl) and reported rate and equilibrium constants for their equilibration with their enolate anions in aqueous base (pH = 10–13). Equilibrium constants

* Abstract published in *Advance ACS Abstracts*, November 1, 1993.

(1) Schwarzenbach, G.; Felder, E. *Helv. Chim. Acta* **1944**, *27*, 1701.
(2) Eidinoff, M. L. *J. Am. Chem. Soc.* **1945**, *67*, 2072.
(3) Walisch, W.; Ruppersberg, H. A. *Chem. Ber.* **1959**, *92*, 2622.
(4) Runipf, P.; Reynard, R. *C.R. Acad. Sci.* **1960**, 1501.
(5) Brouillard, R.; Dubois, J. E. *J. Org. Chem.* **1974**, *39*, 1137.
(6) Schwarzenbach, G.; Felder, E. *Helv. Chim. Acta* **1944**, *27*, 1044.
(7) Murthy, A. S. N.; Balasubramanian, A.; Rao, C. N. R.; Kasturi, T. R. *Can. J. Chem.* **1962**, *40*, 2267.
(8) Moriyasu, M.; Kato, A.; Hashimoto, Y. *J. Chem. Soc., Perkin Trans. II* **1986**, 515.
(9) Mills, S. G.; Beak, P. *J. Org. Chem.* **1985**, *50*, 1216.
(10) We have not been able to locate the source of this value.

0002-7863/93/1515-11705$04.00/0

for enolization of **1** (R = alkyl) were again estimated from the titration of the enol species in the equilibrium mixture with bromine. These studies appear to be the only attempt to systematically investigate the rates and equilibria for the deprotonation and tautomerism of β-keto esters in aqueous solution. Analogous data for the corresponding β-keto amides are also lacking.

Recent studies in our laboratory[11-14] have shown that the rates of deprotonation of a variety of benzylic ketones containing pyridine or pyridinium substituents are readily accessible in aqueous solution via stopped-flow spectrophotometry. Such species are readily soluble in aqueous solution, have pK_a values in the accessible pH region, and have conjugate bases which possess chromphores that are convenient for monitoring acid–base equilibration by spectrophotometry. As a follow up to these earlier studies, and as a contribution to the meager data that are currently available upon the influence of structural effects upon the deprotonation and tautomerism of β-keto esters and amides, we have now investigated the carbon acidities, the enolization, and the pH–rate profiles for acid–base equilibration for a series of β-keto methyl esters (**2**) and β-keto amides (**3** and **4**) derived from 2-pyridyl, 3-pyridyl, and 4-pyridyl ketones and their *N*-methyl cations as well as for the corresponding methyl esters and amides of benzoylacetic acid (**2a** and **3a**) and acetoacetic acid (**2g** and **3g**), and ethyl acetoacetate (**1**: R = H). The current work presents a complete analysis of the rates and equilibria for deprotonation and tautomerization of these species over the range pH = 2–12 in aqueous solution at 25 °C. These data lead to a relationship between the kinetic and thermodynamic acidities of these carbon acids and also suggest a simple relationship between the thermodynamic acidities of the keto and enol tautomers of these species. It has been found that equilibrium constants for the keto–enol tautomerism of these β-keto esters and amides are relatively independent of the acyl group in **2–4**, except for the case of R = 2-pyridyl in which hydrogen-bonding interactions are able to produce exceptional stabilization of the enol species. Keto–enol equilibrium ratios are also found to be quite similar for β-keto esters and the corresponding β-keto amides.

$RCOCH_2CO_2CH_3$ (**2**) $RCOCH_2CONH_2$ (**3**)

$RCOCH_2CON(CH_3)_2$ (**4**)

a: R = C_6H_5
b: R = 2-pyridyl
c: R = 3-pyridyl
d: R = 4-pyridyl
e: R = 3-(*N*-methylpyridinio)
f: R = 4-(*N*-methylpyridinio)
g: R = CH_3

Experimental Section

Materials. All reagents used in this study were purchased from Aldrich Chemical Co. unless otherwise specified. Ethyl picolinate, methyl nicotinate, methyl isonicotinate, methyl acetate, methyl benzoate, ethyl acetoacetate, acetoacetamide, bromomethane, and dimethylamine hydrochloride were of greater than 99% purity. Ammonium hydroxide used in the synthesis of the β-keto amides was an ACS reagent stated to assay 28–30% ammonia. Dimethyl sulfoxide-d_6 used as a solvent for proton NMR spectroscopy was an ACS reagent containing 99.5% deuterium.

For the buffer plots for the determination of rate constants, four types of buffers were used as follows: potassium acetate (98%)/acetic acid (99.7%), 2-picoline (distilled), tris(hydroxymethyl)aminomethane (Tris) (99.9%, ultrapure grade), and ethanolamine (distilled). For determination of some of the pK_a^{eq} values in the pH range 5–7, use was made of 2-(*N*-morpholino)ethanesulfonic acid purchased from Sigma Chemical Co. Buffer solutions of all the above amines were prepared using 1 M hydrochloric acid (BDH Chemicals). Spectrophotometric grade acetonitrile was used when required for solubility of methyl benzoylacetate and benzoylacetamide.

Syntheses. The detailed syntheses of the β-keto ester and amides derived from isonicotinic acid are described below. The syntheses of the picolinyl (R = 2-pyridyl), nicotinyl (R = 3-pyridyl), and benzoyl (R = phenyl) derivatives, and also methyl acetoacetate, followed the same general synthetic routes. All products were characterized by proton NMR spectroscopy on a Gemini 200-MHz spectrometer using deuterated DMSO as the solvent. All β-keto esters and amides existed as mixtures of the keto and enol tautomers in this solvent as previously reported for methyl nicotinylacetate[15] (**2c**). All product melting points were determined on a Mel-Temp II Fluke 51 K/J thermometer and are uncorrected.

Methyl 3-Oxo-3-(4-pyridyl)propanoate (2d). Methyl isonicotinate (2.50 g, 0.0182 mol) was dissolved in methyl acetate (10 mL) in a round-bottomed flask (100 mL). An 80% dispersion of sodium hydride in mineral oil (0.60 g, 0.02 mol) was added to this solution, with continuous stirring, over a period of 30 min. The mixture was stirred and refluxed for an additional 2.5 h during which time the solution changed from grey to bright yellow. After it had cooled to room temperature, the product mixture was poured into ice–water (40 mL). A clear solution was obtained after extraction of the aqueous mixture with diethyl ether (2 × 20 mL) and neutralization of the aqueous layer with concentrated HCl. Addition of a saturated sodium chloride solution (20 mL), followed by exhaustive extraction with dichloromethane, and drying of the dichloromethane layer with anhydrous magnesium sulfate resulted in a pale yellow solution. A yellow oil was obtained upon rotary evaporation of the dichloromethane solution. Addition of a small portion of diethyl ether and hexanes (10 mL each) followed by cooling overnight at approximately 5 °C gave large yellow crystals of the required β-keto ester, which was recrystallized from 2-propanol to give pale yellow crystals of **2d** in 82% yield; mp 141–3 °C (lit.[16] mp 136–8 °C).

Other β-keto esters prepared via a similar route are **2b**, mp 32–4 °C (lit.[16] mp 34–6 °C) and **2c**, mp 73–4 °C (lit.[15] mp 74–5 °C, lit.[16] mp 76–8 °C).

3-Oxo-3-(4-pyridyl)propanamide (3d). Methyl 3-oxo-3-(4-pyridyl)-propanoate (1 g, 0.006 mol) was dissolved in concentrated (28–30%) ammonium hydroxide (25 mL) in a pressure bottle. This solution was allowed to stir at room temperature for 4 days, during which time the solution changed from clear to pale yellow. Rotary evaporation of the excess ammonium hydroxide afforded a yellow powder, which gave fine yellow crystals of **3d** in 84% yield upon recrystallization from a mixture of ethanol/ethyl acetate; mp 174–5 °C.

Other β-keto amides prepared similarly are **3b**, mp 40–2 °C and **3c**, mp 102–4 °C.

***N,N*-Dimethyl 3-Oxo-3-(4-pyridyl)propanamide (4d).** Methyl 3-oxo-3-(4-pyridyl)propanoate (1 g, 0.006 mol) was dissolved in an aqueous solution (20 mL) containing potassium hydroxide (0.1 M) and dimethylamine hydrochloride (2 g, 0.026 mol). After 14 h of reflux and subsequent neutralization with concentrated HCl, a pale orange solution was obtained. After exhaustive extraction of this aqueous solution with dichloromethane, the organic layer was dried over anhydrous magnesium sulfate. Rotary evaporation of the dichloromethane layer gave an orange oil which could not be induced to crystallize from a variety of solvents. This oil was dried in a vacuum dessicator and, as for the other compounds in this study, appeared to be a mixture of the keto and enol tautomers by ^1H NMR spectroscopy in DMSO-d_6.

***N*-Methylpyridinium Bromide Salts.** Each of the nicotinyl and isonicotinyl β-keto esters and amides was methylated by treatment with methyl bromide in 100% excess over the substituted pyridine substrate. The two reagents were dissolved in acetone and stirred in a pressure bottle at room temperature for 16–24 h. The methyl bromide salts precipitated from these reaction mixtures in quantitative yield and were recrystallized from either 2-propanol or 1-butanol. Salts obtained by this method are **2e**·Br^-, mp 150–2 °C; **2f**·Br^-, mp 175–6 °C; **3e**·Br^-, mp 174–6 °C; **3f**·Br^-, mp 226–8 °C; and **4f**·Br^-, mp 182–3 °C.

(11) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1988**, *110*, 4008.
(12) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1990**, *112*, 779.
(13) Stefanidis, D.; Bunting, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 3163.
(14) Stefanidis, D.; Bunting, J. W. *J. Am. Chem. Soc.* **1991**, *113*, 991.
(15) Wenkert, E.; Orito, K.; Simmons, D. P.; Ardisson, J.; Kunesch, N.; Poisson, J. *J. Org. Chem.* **1983**, *48*, 5006.
(16) Stekhova, S. A.; Zagulyaeva, O. A.; Lapachev, V. V.; Mamaev, V. P. *Khim. Geterotsikl. Soedin.* **1980**, 822.

All attempts at methylating the 2-pyridyl derivatives with methyl bromide were unsuccessful. Attempted methylations of these latter species with either methyl iodide or dimethyl sulfate in refluxing nitrobenzene were also unsuccessful.

Equilibrium pK_a Values. The equilibrium pK_a values pK_a^{eq} of all β-keto esters and amides were measured at 25 °C in buffered aqueous solution using a Perkin-Elmer Lambda 2 UV/vis spectrophotometer by the general method of Albert and Serjeant[17] but with the computation of pK_a^{eq} values by fitting the measured absorbances (A) as a function of pH to eq 4 where

$$pH = pK_a^{eq} + \log[(A - A_{CH})/(A_C - A)] \quad (4)$$

A_{CH} and A_C are the absorbances of the acid (as the equilibrium mixture of the keto and enol tautomers) and the conjugate base, respectively, at the wavelength under study. The parameters A_{CH} and A_C and pK_a^{eq} were evaluated by an iterative fit to this equation via the Marquardt algorithm. Each solution contained buffer species and potassium chloride to a total ionic strength of 0.1. The pH of each solution was measured on a Radiometer PHM 82 pH meter, which had bee calibrated at 25 °C with BDH colorkey buffer solutions of pH = 4.00 ± 0.01, 7.00 ± 0.01, and 10.00 ± 0.01 as reference standards.

Kinetic Studies. All kinetic data were obtained in aqueous solutions of ionic strength 0.10 (KOH + KCl, buffer + KCl, or HCl + KCl) on a Durrum-Gibson stopped-flow spectrophotometer. Reactions of methyl benzoylacetate and benzoylacetamide were studied in the presence of 5% v/v acetonitrile/water for solubility reasons. All runs were carried out at 25.0(±0.1) °C, and the reactants were allowed to equilibrate at this temperature in the mixing syringes of the stopped-flow spectrometer for a minimum period of 10 min prior to each run. The photomultiplier output of the stopped-flow instrument was digitized and transferred to a Textronix 4051 computer for calculation of the pseudo-first-order rate constants k_{obs}. All reactions were found to be accurately pseudo first order for >4 half-lives. All k_{obs} values were obtained as averages of approximately six identical mixing experiments. Rates of equilibration of each carbon acid with its enolate ion conjugate base were measured by following both the deprotonation reaction (for pH > pK_{eq}) and also the protonation reaction of the enolate conjugate base (for pH < pK_{eq}). In all cases, data were collected over the pH range 2–12. Studies of the deprotonation reaction were made by mixing an aqueous solution of the substrate of concentration in the range 0.1–0.5 mM with a solution of potassium hydroxide or buffer base made up to ionic strength 0.2 with KCl; this resulted in an ionic strength of 0.10 in the mixed reaction solution. For studies of the protonation reaction, the substrate was initially deprotonated by the addition of 1 drop of 1 M KOH (the pH of the resulting solution was approximately 10.5) and this solution of the enolate base was mixed with a solution of HCl or buffer made up to an ionic strength of 0.20 with KCl. The pH of each reaction solution was measured on 1:1 mixtures of the reactant solutions on the Radiometer PHM 82 meter at 25 °C as described above.

The buffer species chosen for kinetic studies were potassium acetate/acetic acid (pH range = 3.5–5.5), 2-picoline/HCl (pH range = 5.5–7.2), tris(hydroxymethyl)aminomethane/HCl (pH range = 7.2–9.0), and ethanolamine/HCl (pH range = 9.0–10.8). All studies in buffered solution were carried out using approximately five solutions covering a 5-fold range in buffer concentration at each pH. Extrapolation of these data to zero buffer concentration gave buffer-independent rate constants at each pH.

Results

Absorption Spectra and pK_a^{eq}. The pH-dependent absorption spectra of **3c** and **2f** are shown in Figures 1 and 2, respectively. These figures are typical of the spectral observations for enolate formation from all species in the current study. In each case, the spectra of the N-methyl cations show clean isobestic points (e.g., Figure 2) and imply a clean equilibration of the acidic species with their conjugate bases. The spectra of the neutral β-keto esters and β-keto amides show no isobestic point in the observable spectral range, but λ_{max} smoothly increases with increasing pH of the buffer solution (e.g., Figure 1). Absorption maxima and extinction coefficients of the enolate ion conjugate base of each β-keto ester and amide are listed in Table I.

(17) Albert, A.; Serjeant, E. P. *Ionization Constants of Acids and Bases*; Methuen: London, 1962; p 69.

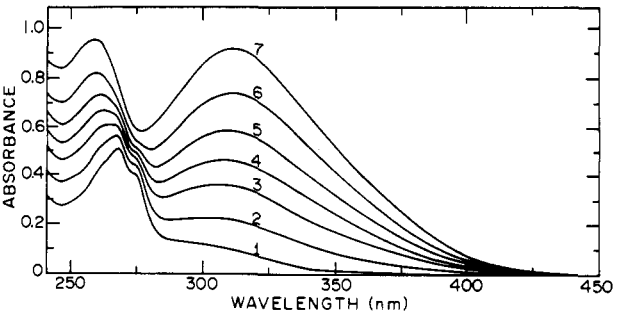


Figure 1. pH dependence of the electronic absorption spectrum of **3c** (2 × 10^{-4} M) in aqueous solution of ionic strength 0.1, 25 °C. Curves: 1, pH = 2.13 (spectrum of N-protonated **3c**); 2, pH = 7.13; 3, pH = 7.77; 4, pH = 8.17; 5, pH = 8.66; 6, pH = 9.02; and 7, pH = 11.17.

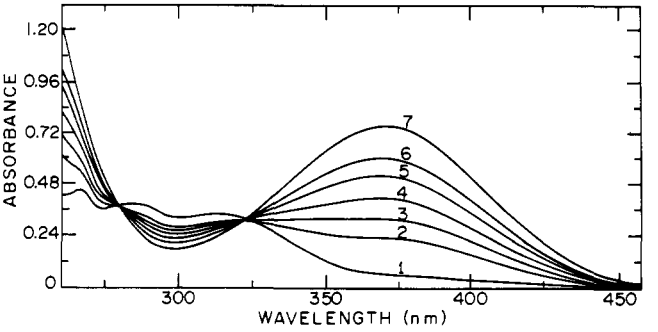


Figure 2. pH dependence of the electronic absorption spectrum of **2f** (1.5 × 10^{-4} M) in aqueous solution of ionic strength 0.1, 25 °C. Curves: 1, pH = 2.11; 2, pH = 5.64; 3, pH = 6.09; 4, pH = 6.44; 5, pH = 6.60; 6, pH = 6.82; and 7, pH = 12.42.

The pH dependence of the absorbance of each species at constant wavelength describes a clean titration curve consistent with eq 4. The pK_a^{eq} values, evaluated at several appropriate wavelengths (in the vicinity of λ_{max} for the enolate ion), were wavelength independent and accurate to within ±0.03 logarithmic unit in all cases. Values of pK_a^{eq} for each β-keto ester and amide are included in Table I.

Kinetic Studies. All pH-jump experiments indicated that the equilibration of the carbon acids with their enolate ion conjugate bases are strictly pseudo first order in the β-keto ester or amide species. Pseudo-first-order rate constants k_{obs} were evaluated for each reaction over the range pH = 2–12.

Figures 3, 4, and 5 show examples of each of the three types of pH–rate profiles that have been found in the current study. Figure 3 for methyl benzoylacetate is also typical of the pH–rate profiles obtained for benzoylacetamide and the esters and amide of acetoacetic acid. Figure 4 is typical of the pH–rate profiles that were observed for all neutral 3-oxo-3-pyridylpropanoate esters and amides. Figure 4 differs from Figure 3 in displaying an additional inflection in acidic solution. As discussed below, this inflection arises from the protonation of the pyridine nitrogen atom in acidic solution. Figure 5 is typical of the pH–rate profiles that are obtained for all β-keto esters and amides of N-methylpyridinium cations; all such species show kinetic saturation in basic solution.

In general, k_{obs} is the sum of the pseudo-first-order rate constants for enolization of the ketone (deprotonation of the methylene group of the β-keto ester or amide) and ketonization of the enol–enolate equilibrium mixture (protonation on carbon). A complete analysis of these profiles is presented below. At the present time, it should be noted that each pH–rate profile in Figures 3, 4, and 5 displays kinetic saturation in acidic solution. This saturation arises from the formation of the neutral enol species upon rapid acidification of a basic solution of the enolate anion (i.e., protonation on oxygen). Such O-protonation is a kinetically

Table I. pK_A Values for β-Keto Esters and Amides ($RCOCH_2COX$) and Their Enols and Derived Tautomeric Ratios[a]

no.	R	X	λ_{max}(log ε)[b]	pK_a^{eq}	pK_a^E	pK_a^K	K_E
2g	CH_3	OCH_3	271 (3.90)	10.61	9.48	10.60	0.080
	CH_3	OC_2H_5	271 (3.89)	10.63	9.51	10.57	0.087
2a	C_6H_5	OCH_3	278 (3.88)	10.31	9.19	10.28	0.081
2b	2-C_5H_4N	OCH_3	316 (3.78)	8.67	8.33	8.40	0.86
2c	3-C_5H_4N	OCH_3	304 (3.89)	9.04	8.16	8.98	0.15
2d	4-C_5H_4N	OCH_3	312 (3.81)	8.31	7.51	8.24	0.19
2e	3-($C_5H_4NCH_3^+$)	OCH_3	314 (3.67)	6.82	5.73	6.78	0.088
2f	4-($C_5H_4NCH_3^+$)	OCH_3	370 (3.80)	6.41	5.42	6.36	0.11
3g	CH_3	NH_2	272 (3.85)	10.46	9.46	10.41	0.11
3a	C_6H_5	NH_2	281 (3.87)	10.07	8.89	10.04	0.071
3b	2-C_5H_4N	NH_2	317 (3.50)	8.53	8.23	8.23	1.0
3c	3-C_5H_4N	NH_2	307 (3.89)	8.71	8.01	8.61	0.25
3d	4-C_5H_4N	NH_2	315 (3.75)	8.02	7.36	7.91	0.28
3e	3-($C_5H_4NCH_3^+$)	NH_2	317 (3.79)	6.56	5.60	6.51	0.12
3f	4-($C_5H_4NCH_3^+$)	NH_2	374 (3.49)	6.06	5.23	5.99	0.18
4d	4-C_5H_4N	$N(CH_3)_2$	319 (3.70)	7.86	7.32	7.75	0.40
4f	4-($C_5H_4NCH_3^+$)	$N(CH_3)_2$	374 (3.45)	5.98	5.24	5.91	0.22

[a] All data in aqueous solution of ionic strength 0.1 at 25 °C, except for methyl benzoylacetate and benzoylacetamide which are in 5% acetonitrile/95% water (v/v). The uncertainties in pK_a^{eq} were always less than ±0.03 logarithmic unit. The uncertainties in pK_a^K and pK_a^E were always less than ±0.07 logarithmic unit. [b] Absorbance maximum (nm) in the spectrum of the enolate ion conjugate base.

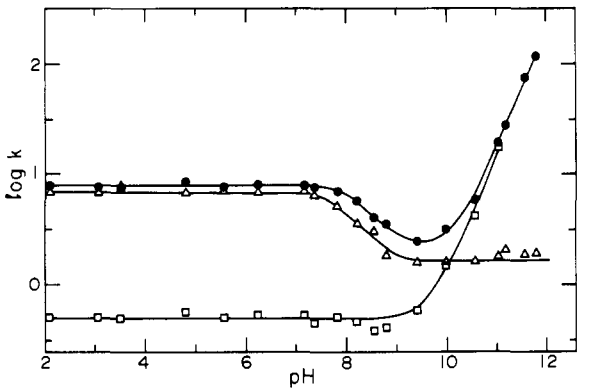


Figure 3. Dependence of log k_{obs} (solid circles), log k^E (squares), and log k^K (triangles) upon pH for methyl benzoylacetate (**2a**).

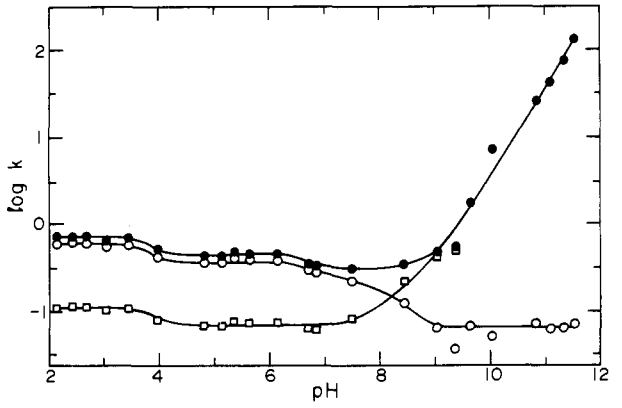


Figure 4. Dependence of log k_{obs} (solid circles), log k^E (squares), and log k^K (hollow circles) upon pH for **2d**.

controlled process which competes with the formation (by protonation on carbon) of the thermodynamically more stable keto tautomer. A complete kinetic analysis as described below of the buffer catalysis of ketonization in these solutions allows determination of pK_a^E for deprotonation of the enol species. With pK_a^E and pK_a^{eq} available, pK_a^K for deprotonation of the keto tautomer and the tautomerization equilibrium constant K_E = [enol]/[keto] can then be readily calculated using eqs 2 and 3.

Kinetic Analysis. When a solution of the enolate ion is rapidly mixed with acidic buffer, the enolate ion/enol equilibrium is rapidly established (within the mixing time of the instrument), and the measured k_p^{obs} represents the pseudo-first-order rate constant for ketonization of this equilibrium mixture. If k_p is the

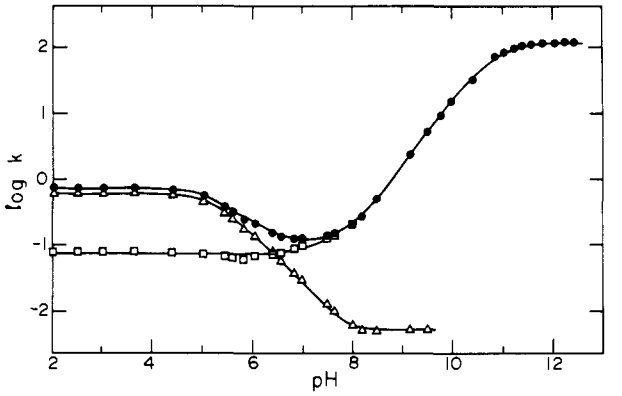


Figure 5. Dependence of log k_{obs} (solid circles), log k^E (squares), and log k^K (triangles) upon pH for **2f**.

pseudo-first-order rate constant for C-protonation of the enolate ion,[25] then:

$$k_p[E^-] = k_p^{obs}([E^-] + [EH])$$

$$= k_p^{obs}(1 + [H^+]/K_a^E)[E^-]$$

Thus,

$$k_p = k_p^{obs}(1 + [H^+]/K_a^E) \quad (5)$$

The rate constant k_p represents the sum of the pseudo-first-order rate constants for protonation of E^- by all of the acid species present in solution:

$$k_p = k_{H^+}[H^+] + k_{H_2O} + k_{HB}[HB]$$

where HB is the conjugate acid of the buffering species.

(18) Adolph, H. G.; Kamlet, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 4761.
(19) Chiang, Y.; Kresge, A. J.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 6392.
(20) Keeffe, J. R.; Kresge, A. J.; Toullec, J. *Can. J. Chem.* **1986**, *64*, 1224.
(21) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460.
(22) Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1992; Chapter 5.
(23) Equation 20 has been evaluated for R = phenyl, 3-pyridyl, or 4-pyridyl only, since the acetoacetic acid derivatives all appear to deviate from this correlation equation.
(24) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1989**, *111*, 5834.
(25) An acid-catalyzed pathway for enolization ($KH + H^+ \rightleftharpoons KH_2^+ \overset{H_2O}{\rightleftharpoons} EH + H_3O^+$) is likely in solutions which are much more acidic than those which have been investigated in this study.[26]

Table II. Rate Constants for the Protonation/Deprotonation Reactions of all $RCOCH_2COX$[a]

R	X	k_{OH}^E (10^5 M^{-1} s^{-1})	k_o^E (10^{-2} s^{-1})	k_o^K (10^{-2} s^{-1})	$k_{H^+}^K$ (10^7 M^{-1} s^{-1})	pK_z
CH_3	OCH_3	0.034	24	135	970	
CH_3	OC_2H_5	0.037	27	140	1020	
C_6H_5	OCH_3	0.062	37	120	700	
2-C_5H_4N	OCH_3	0.074	25	3.3	11	
3-C_5H_4N	OCH_3	0.19	14	18	14	
4-C_5H_4N	OCH_3	0.39	7.0	6.7	1.2	
3-($C_5H_4NCH_3^+$)	OCH_3	1.50	6.3	0.91	0.038	11.06
4-($C_5H_4NCH_3^+$)	OCH_3	2.80	8.6	0.64	0.019	10.50
CH_3	NH_2	0.047	43	120	1100	
C_6H_5	NH_2	0.080	57	87	620	
2-C_5H_4N	NH_2	0.086	50	1.5	8.5	
3-C_5H_4N	NH_2	0.23	7.6	5.8	3.4	
4-C_5H_4N	NH_2	0.44	7.9	3.6	0.64	
3-($C_5H_4NCH_3^+$)	NH_2	2.30	8.1	0.74	0.026	10.69
4-($C_5H_4NCH_3^+$)	NH_2	4.20	7.3	3.6	0.007	10.34
4-C_5H_4N	$N(CH_3)_2$	0.53	7.5	2.7	0.70	
4-($C_5H_4NCH_3^+$)	$N(CH_3)_2$	4.57	6.0	0.61	0.009	10.29

[a] All data at 25 °C in aqueous solutions of ionic strength 0.1; data for Ar = C_6H_5 in 5% CH_3CN/95% H_2O (v/v). Rate constants are defined by eqs 10, 11, and 12.

In the buffer solution:

$$[B]_T = [B] + [HB]$$

$$[HB] = [B]_T/(1 + K_{BH}/[H^+])$$

Therefore:

$$k_p = k_{H^+}[H^+] + k_{H_2O} + k_{HB}[B]_T/(1 + K_{HB}/[H^+]) \quad (6)$$

Combining eqs 5 and 6 gives

$$k_p^{obs} = (k_{H^+}[H^+] + k_{H_2O})/(1 + [H^+]/K_a^E) + k_{HB}[B]_T/[(1 + K_{HB}/[H^+])(1 + [H^+]/K_a^E)]$$

At constant pH:

$$k_p^{obs} = k_p^o + k_p^s[B]_T$$

and therefore, in a buffer dilution experiment at constant pH:

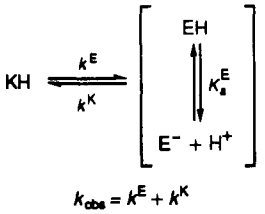
$$k_p^s = k_{HB}/[(1 + K_{HB}/[H^+])(1 + [H^+]/K_a^E)]$$

Rearranging this expression and taking its reciprocal:

$$1/[k_p^s(1 + K_{HB}/[H^+])] = 1/k_{HB} + [H^+]/(k_{HB}K_a^E) \quad (7)$$

Thus, evaluation of k_p^s as a function of $[H^+]$ allows the evaluation of k_{HB} and K_a^E. Experimental values of pK_a^E and the derived values of pK_a^K and K_E for each β-keto ester and amide are given in Table I.

Pseudo-first-order rate constants for ketonization k^K and enolization k^E may be defined by the following scheme (after extrapolation to zero buffer concentration):



At equilibrium:

$$k^E[KH] = k^K([E^-] + [EH])$$
$$= k^K[E^-](1 + [EH]/[E^-])$$
$$= k^K[E^-](1 + [H^+]/K_a^E)$$

Rearranging gives

$$k^E = k^K([E^-]/[KH])(1 + [H^+]/K_a^E)$$
$$= k^K(K_a^K/[H^+])(1 + [H^+]/K_a^E)$$

and:

$$k^K = k_{obs}/[1 + K_a^K(1/[H^+] + 1/K_a^E)]$$
$$= k^E[H^+]/[K_a^K(1 + [H^+]/K_a^E)] \quad (8)$$

therefore:

$$k^E = k_{obs}K_a^K(1/[H^+] + 1/K_a^E)/[1 + K_a^K(1/[H^+] + 1/K_a^E)] \quad (9)$$

Equations 8 and 9 can now be used to convert k_{obs} at each pH in Figures 3, 4, and 5 into the corresponding individual rate constants k^K and k^E as shown in these figures.

Derivatives of Acetoacetic and Benzoylacetic Acids. The pH–rate profiles for k^E and k^K in Figure 3 are described by

$$k^E = k_o^E + k_{OH}^E[^-OH] \quad (10)$$

$$k^K = k_o^K + k_{H^+}^K[H^+]/(1 + [H^+]/K_a^E) \quad (11)$$

Values of the parameters k_o^E, k_{OH}^E, $k_{H^+}^K$, and k_o^K have been evaluated for these esters and amides by fitting eqs 10 and 11 to the experimentally determined pH profiles for k^E and k^K; the values of these four parameters are listed in Table II. The values of k_{OH}^E and k_o^K for ethyl acetoacetate are each approximately 50% of the values reported for this ester by Brouillard and Dubois[5] under similar reaction conditions.

***N*-Methylpyridinio β-Keto Esters and Amides.** The pH–rate profiles of Figure 5 for these cationic β-keto esters and amides differ from those of Figure 3 in showing a kinetic saturation effect in k^E in the most basic solutions. The rate constant k^K is again described by eq 11 above; however, k^E requires eq 12

$$k^E = k_o^E + k_{OH}^E[^-OH]/(1 + K_z/[H^+]) \quad (12)$$

where K_z is a formal acid ionization constant defined by

$$H^+ + Z^- \rightleftharpoons KH \xrightarrow{k_{OH}^E[OH]} E^-$$
(K_z)

The parameters k_o^E, k_{OH}^E, $k_{H^+}^K$, k_o^K, and pK_z for each of these cationic β-keto esters and amides are listed in Table II.

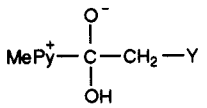
A similar kinetic saturation effect for k^E has been reported[11] in the deprotonation of (phenylacetyl)pyridinium cations in aqueous solution. In this latter case, pK_z was shown to be the formal acid dissociation constant for the equilibration of these ketones with the anions of their carbonyl hydrates (i.e., Z^- is **5**: Y = aryl). A similar interpretation seems appropriate in the

Table III. Second-Order Rate Constants for Buffer Catalysis of the Tautomerization of $RCOCH_2COX$[a-c]

R	X	k_B^{Eth}	k_{BH}^{Eth}	k_B^{Tris}	k_{BH}^{Tris}	k_B^{Pic}	k_{BH}^{Pic}	k_B^{Acet}	k_{BH}^{Acet}
CH_3	OCH_3	62	570	7.8	1960				
CH_3	OC_2H_5	65	550	8.3	1950				
C_6H_5	OCH_3	100	440	10.6	1240				
3-C_5H_4N	OCH_3	340	74	33	200	5.6	4900	0.124	2100
4-C_5H_4N	OCH_3	750	30	61	67	10.2	1610	0.36	1080
3-($C_5H_4NCH_3^+$)	OCH_3	2800	3.9	215	8.2	36	200	2.1	220
4-($C_5H_4NCH_3^+$)	OCH_3	4700	2.5	330	4.8	56	120	4.3	180
CH_3	NH_2	76	450	9.1	1470				
C_6H_5	NH_2	120	300	12	830				
3-C_5H_4N	NH_2	460	43	46	120	6.4	2400		
4-C_5H_4N	NH_2	980	18	84	43	13	980	0.45	640
3-($C_5H_4NCH_3^+$)	NH_2	3950	2.9	280	5.8	46	140		
4-($C_5H_4NCH_3^+$)	NH_2	6200	1.4	440	2.7			5.6	95
4-C_5H_4N	$N(CH_3)_2$	1130	14.5	98	35				
4-($C_5H_4NCH_3^+$)	$N(CH_3)_2$	7100	1.33	450	2.3				

[a] In aqueous solution of ionic strength 0.1 at 25 °C; Eth, Tris, Pic, and Acet are defined in eqs 24–27. [b] $pK_a^{Eth} = 9.64$, $pK_a^{Tris} = 8.20$, $pK_a^{Pic} = 6.04$, and $pK_a^{Acet} = 4.76$. [c] All second-order rate constants (M^{-1} s^{-1}).

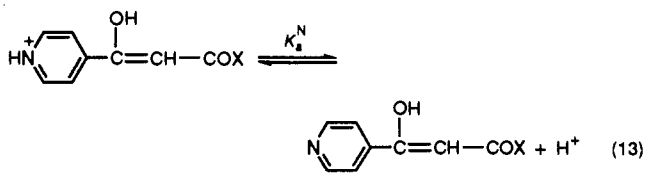
current study with Z^- represented by **5**: Y = CO_2CH_3, $CONH_2$, or $CON(CH_3)_2$.



5

Values of pK_z for these keto esters and amides range between 10.29 and 10.50 for the 4-pyridinio derivatives and 10.69 and 11.06 for the 3-pyridinio species. These pK_z values are less than pK_z = 11.81 and 12.32 that were found[11] for the 1-methyl-4-(phenylacetyl)pyridinium and 1-methyl-3-(phenylacetyl)pyridinium cations, respectively. These data are consistent with the expected greater electron-withdrawing inductive effect of methoxycarbonyl and aminocarbonyl substituents of these esters and amides relative to the phenyl substituents of the (phenylacetyl)-pyridinium cations. pK_z varies in the order $CON(CH_3)_2 \leq CONH_2 < CO_2CH_3$.

3-Oxo-3-pyridylpropanoate Esters and Amides. The pH–rate profiles for k^K and k^E in Figure 4 indicate that these neutral β-keto esters and amides show similar pH dependences to those of the benzoylacetic acid derivatives in Figure 3 in neutral and basic solutions. However, in acidic solution, a further acid–base equilibration is present due to the protonation of the pyridine ring nitrogen atom. There appears to be no simple analogy for the electronic effect of the substituent on the pyridine ring in eq 13; however, it should be electron withdrawing, and so, $pK_a^N < 5$.



(13)

The inflection in the vicinity of pH = 4 in Figure 4 is consistent with the N-protonation of this neutral enol species. The change in rate constant associated with this inflection is too small to allow a detailed quantitative analysis and, so, to derive pK_a^N. However, one may compare the pH-independent k_{obs} in the most acidic solutions for these species with the limiting k_{obs} in the most acidic solutions of the corresponding *N*-methyl cations. In all cases, these limiting rate constants agree within 20% for each pyridyl derivative and the corresponding *N*-methyl cation. This result supports the interpretation of this additional inflection in acidic solutions of these neutral pyridyl derivatives in terms of the acid–base equilibration of eq 13.

Buffer Catalysis. In buffered solutions, tautomerization is catalyzed by the acid and base species of the buffer that is present (eq 14).

$$KH \underset{k_{HB}[HB]}{\overset{k_B[B]}{\rightleftharpoons}} E^- \qquad (14)$$

Analysis of buffer dilution plots via eq 7, as discussed above, allows the evaluation of k_{HB} for each buffer species. At equilibrium:

$$k_B[B][KH] = k_{HB}[HB][E^-]$$

i.e.,

$$k_B = k_{HB}(K_a^K/K_{HB})$$

Thus, the second-order rate constant k_B for the general-base-catalyzed deprotonation of the keto tautomer is also available from these buffer-catalyzed equilibrations. Values of k_B and k_{HB} are summarized in Table III.

Discussion

Acidity of the Keto and Enol Tautomers. The pK_a values for the deprotonation of the keto and enol tautomers of each of the β-keto esters and amides in the current study are listed in Table I. Several systematic variations in pK_a^K and pK_a^E are apparent from these data. These variations may be summarized as follows.

(1) Although the differences are small, the acidities of amides are greater than those of esters for both the keto and enol tautomers of each species, with $\Delta pK_a^K(CONH_2 - CO_2CH_3) = -0.28 \pm 0.08$ and $\Delta pK_a^E(CONH_2 - CO_2CH_3) = -0.15 \pm 0.08$. A similar enhanced acidity for an amide-activated carbon acid relative to that of the corresponding ester species is also found for the only other direct quantitative comparison that we have been able to locate of the thermodynamic acidities of amides and esters in aqueous solution: nitroacetamide (pK_a = 5.18)[18] and ethyl nitroacetate (pK_a = 5.75).[18]

(2) For the two cases available, the keto tautomer of each *N*,*N*-dimethylamide is slightly more acidic than the corresponding unsubstituted amide. The acidity of the enol tautomers is the same within experimental error for the corresponding $CONH_2$ and $CON(CH_3)_2$ species. The corresponding equilibrium constants for the methyl and ethyl esters of acetoacetic acid are identical within experimental error.

(3) For both β-keto esters and amides, pK_a^K decreases in the order: methyl > phenyl > 3-pyridyl > 2-pyridyl > 4-pyridyl > 3-(*N*-methylpyridinio) > 4-(*N*-methylpyridinio). pK_a^E also follows this same general order with the exception of the 2-pyridyl enols which are less acidic than the 3-pyridyl enols for reasons that are discussed below.

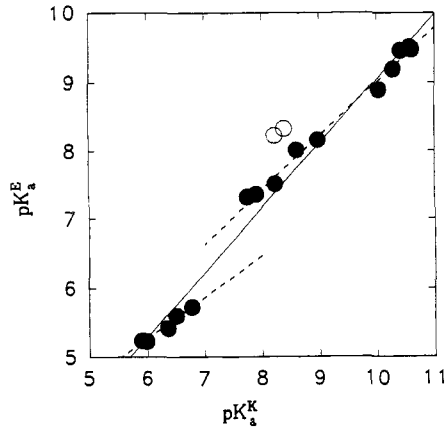


Figure 6. Relationship between pK_a^E and pK_a^K for all $RCOCH_2COX$. The open circles are for the 2-pyridyl species (**2b** and **3b**). The solid line represents eq 15, which is derived for all data points except **2b** and **3b**. The dashed lines are for cationic (lower line; eq 17) and neutral (upper line; eq 16) subcategories of β-keto esters and amides as described in the text.

(4) N-Methylation increases the acidity of the keto tautomer by 2.0 ± 0.1 logarithmic units relative to that of the corresponding neutral pyridyl species. N-Methylation of the enol tautomer similarly decreases pK_a^E by 2.2 ± 0.2 units.

The similar influences of structural effects that are observed upon pK_a^K and pK_a^E in each of the above comparisons imply a general relationship between the acidities of the keto and enol species of these β-keto esters and amides. Such a relationship is shown in Figure 6 and eq 15.

$$pK_a^E = 0.94(\pm0.03)pK_a^K - 0.3(\pm0.2)\ (r = 0.992) \quad (15)$$

Only the 2-pyridyl derivatives show significant deviations from this relationship; this case is discussed in more detail below under structural effects upon the enolization equilibria.

The broken lines in Figure 6 correspond to eqs 16 and 17 which are obtained if one considers neutral and cationic derivatives as two difference classes of β-keto esters and amides. The rationale for this subdivision is found in Figure 9 which implies two distinct classes of carbon acids when one considers the relationship between acidity and enolization equilibrium. Such a chemical classification of these two subclasses in Figure 6 is not supported by the statistical parameters reported in eqs 16 and 17 relative to those in eq 15. However, since the data for these two potential subclasses of β-keto esters and amides do not overlap in terms of the total range of acidities that is covered in Figure 6, we can reach no definite conclusion as to the potential existence of two such subcategories at the present time.

neutral species: $$pK_a^E = 0.79(\pm0.03)pK_a^K + 1.1(\pm0.1)\ (r = 0.995) \quad (16)$$

cations: $$pK_a^E = 0.60(\pm0.06)pK_a^K + 1.67(\pm0.04)\ (r = 0.984) \quad (17)$$

Figures 7 and 8 show the systematic variations in pK_a^K and pK_a^E, respectively, which are found for the β-keto ester and amide derivatives (eqs 18 and 19). These relationships indicate that structural variations in the acyl substituent in **2** and **3** have a similar effect in both the ester and amide series and are the basis for the inclusion of both esters and amides in the same correlation in eq 15. In Figures 7 and 8, the 2-pyridyl derivatives do not show significant deviations from the data for other derivatives; this confirms that the factor(s) responsible for the deviations of the 2-pyridyl derivatives in Figure 6 is common to esters and amides.

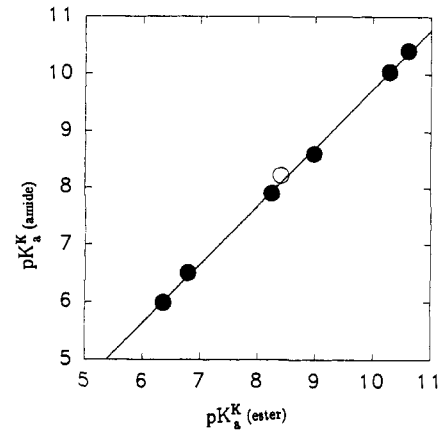


Figure 7. Relationship (eq 18) between pK_a^K (X = NH_2) and pK_a^K (X = OCH_3) for $RCOCH_2COX$. The open circle is for the 2-pyridyl species.

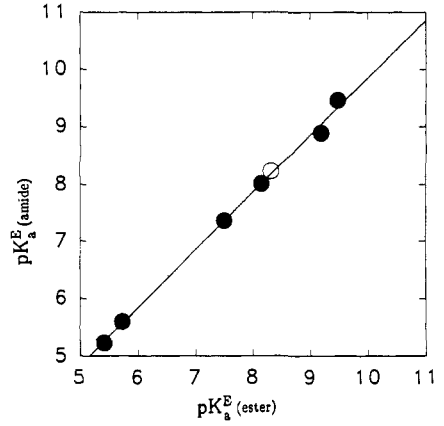
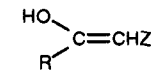


Figure 8. Relationship (eq 19) between pK_a^E (X = NH_2) and pK_a^E (X = OCH_3) for $RCOCH_2COX$. The open circle is for the 2-pyridyl species.

$$pK_a^K(CONH_2) = 1.03(\pm0.02)pK_a^K(CO_2CH_3) - 0.49(\pm0.08)\ (r = 0.999) \quad (18)$$

$$pK_a^E(CONH_2) = 1.01(\pm0.02)pK_a^E(CO_2CH_3) - 0.20(\pm0.09)\ (r = 0.998) \quad (19)$$

The enols of methyl benzoylacetate (**6**: R = C_6H_5, Z = CO_2CH_3) and benzoylacetamide (**6**: R = C_6H_5, Z = $CONH_2$) are 1.15 and 1.45 logarithmic units, respectively, more acidic than the enol of acetophenone (**6**: R = C_6H_5, Z = H; pK_a^E = 10.34).[19,20] Similarly, the enols of methyl acetoacetate (**6**: R = CH_3, Z = CO_2CH_3) and acetoacetamide (**6**: R = CH_3, Z = $CONH_2$) are 1.46 and 1.48 logarithmic units more acidic than the enol of acetone (**6**: R = CH_3, Z = H; pK_a^E = 10.94).[21] These



6

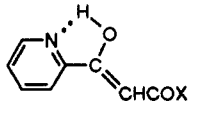
results are consistent with the expected acid-strengthening effects of the carboxyethyl and carboxamide electron-withdrawing substituents. An alternative comparison of these data indicates that the enols of the ester and the amide of benzoylacetic acid are more acidic than the corresponding derivatives of acetoacetic acid by similar amounts to the difference in acidities of the enols of acetophenone and acetone.

The pK_a^E = 9.51 for the enol of ethyl acetoacetate indicates that this species is considerably less acidic than implied by pK_a^E = 8.24 which is the only experimental value that we have been able to locate for the enol of any β-keto ester or amide.[5] This latter value was based upon K_E = 0.0039 for ethyl acetoacetate which was reported[6] more than 50 years ago. As discussed below, it is now clear that this earlier value of K_E for ethyl acetoacetate underestimates the enol content of aqueous solutions of this ester by a factor of approximately 20.

Enolization Equilibria. With the exception of the 2-pyridyl derivatives, the keto tautomer predominates over the enol tautomer for each of these β-keto esters and amides at equilibrium in aqueous solution, with K_E in the range 0.071–0.40 (Table I). In most cases, $K_E(CONH_2)$ is about 50% greater than $K_E(CO_2CH_3)$. Benzoylacetamide is the one exception to this generalization, with K_E for this amide being slightly smaller than that for the corresponding methyl ester. K_E decreases in the order: 2-pyridyl > 4-pyridyl > 3-pyridyl > 4-(*N*-methylpyridinio) > 3-(*N*-methylpyridinio) > methyl ≥ phenyl for both β-keto esters and amides. N-Methylation results in approximately a 45% decrease in K_E in each case. These relationships are a direct reflection of the similar structural effects noted above upon pK_a^K and pK_a^E and are required by the general relationship of eq 15.

The current K_E = 0.087 for ethyl acetoacetate is reasonably similar to the K_E = 0.055[8] reported from the separation of the keto and enol tautomers in an equilibrated aqueous solution of this ester by high-performance liquid chromatography as well as to the K_E = 0.07 of uncertain origin reported by Mills and Beak.[9,10] It thus appears that the earlier experimental value[6] of K_E = 0.0039, from the titration of the enol with bromine in equilibrated aqueous solutions of this ester, is indeed far too low.

The 2-pyridyl β-keto ester and amide each have significantly more enol species present in the equilibrium tautomeric mixture than do their 3- and 4-pyridyl isomers. A decreased acidity of the enol appears to be responsible for this phenomenon and is presumably attributable to the presence of hydrogen bonding between the enolic hydroxyl group and the 2-pyridyl ring nitrogen atom (**7**). The deviation of the 2-pyridyl β-keto ester and amide



7

from the correlation line in Figure 6 indicates the presence of a factor (which we assume to be intramolecular hydrogen bonding as in **7**) in this system which has no parallel in the tautomers of the other β-keto esters and amides that have been examined in the current study.

For monocarbonyl derivatives, Keeffe and Kresge[22] report an extended linear relationship (of slope 1.4) between pK_a^K and pK_E. This relationship extends over a 10^{10}-fold range in K_E. Figure 9 presents a similar analysis of the current data which cover a much smaller range in K_E. This figure indicates that two distinct linear correlations are required for the neutral (eq 20)[23] and

$$\text{neutral species (R = aryl):}\quad pK_a^K = 3.4(\pm0.5)pK_E + 6.2(\pm0.3)\ (r = 0.957) \quad (20)$$

$$\text{cations:}\quad pK_a^K = 2.2(\pm0.3)pK_E + 4.4(\pm0.1)\ (r = 0.965) \quad (21)$$

cationic (eq 21) β-keto esters and amides. The data for the neutral species actually cluster around the line shown for monocarbonyl derivatives, with the deviations from this line being no greater

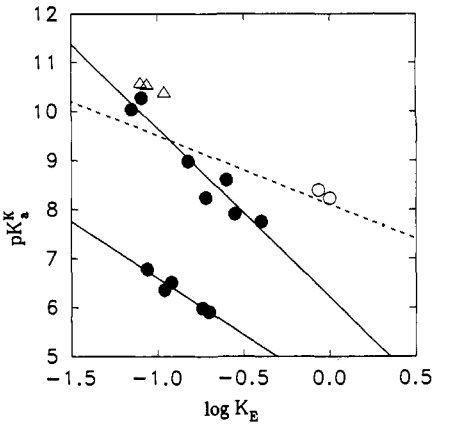


Figure 9. Relationship between pK_a^K and log K_E for cationic β-keto esters and amides (lower line; eq 21) and neutral β-keto esters and amides (upper line; eq 20). The open triangles are for the acetoacetic acid derivatives (see ref 23), and the open circles are for the 2-pyridyl derivatives. The dashed line is the relationship deduced in ref 22 for simple aldehydes and ketones.

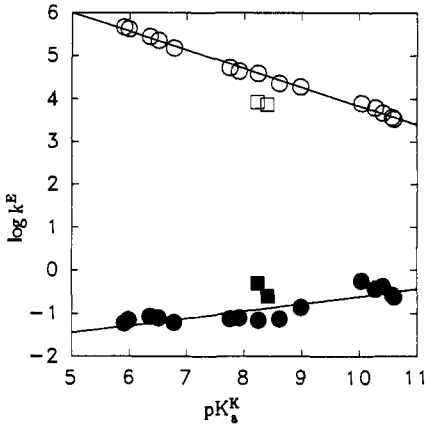


Figure 10. Brønsted plots of log k_{OH}^E (open symbols) and log k_o^E (filled symbols) against pK_a^K. The open and filled square symbols are for the 2-pyridyl species.

than those of some of the data points for the monocarbonyl derivatives considered by Keeffe and Kresge.[22] However, the slope of 3.4 in the correlation of eq 20 is much greater than that found for monocarbonyl derivatives (slope = 1.4) and suggests that these data for β-keto esters and amides should not be treated as a subset of the monocarbonyl species. The 2-pyridyl derivatives deviate from eq 20, with experimental K_E ratios that are 14-fold greater than those predicted for ketones of their measured acidities.

The linear correlations between pK_a^E and pK_a^K of eqs 15–17 suggest that pK_a^E should also correlate linearly with log K_E. In practice, such correlations appear to be somewhat less statistically acceptable than eqs 20 and 21.

Brønsted Relationships and Marcus Theory. The second-order rate constants (k_{OH}^E, k_o^E, and k_B) for the enolization of β-keto esters and amides depend upon the ketone acidity according to the Brønsted relationships of Figures 10 and 11 and eqs 22–27. In each Brønsted plot, β-keto esters and amides appear to define a single correlation line. The mechanistic implication of the unusual Brønsted α = –0.17 that is found for k_o^E is discussed below.

$$\log k_{OH}^E = -0.43(\pm0.01)pK_a^K + 8.17(\pm0.06)\ (r = 0.997) \quad (22)$$

$$\log k_o^E = 0.17(\pm0.03)pK_a^K - 2.3(\pm0.2)\ (r = 0.856) \quad (23)$$

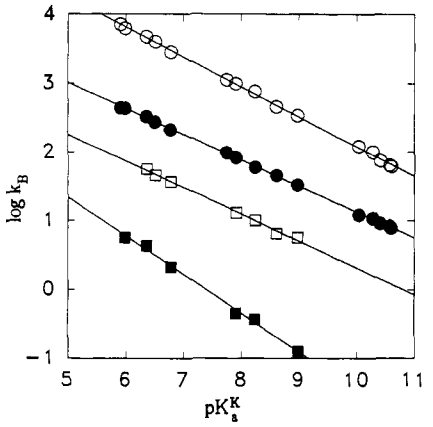


Figure 11. Brønsted plots of log k_B against pK_a^K. The filled squares are for acetate ion, the open squares for 2-picoline, the filled circles for tris(hydroxymethyl)aminomethane, and the open circles for ethanolamine.

For B = ethanolamine:

$$\log k_B^{Eth} = -0.43(\pm 0.01)pK_a^K + 6.41(\pm 0.02)\ (r = 0.999) \quad (24)$$

For B = tris(hydroxymethyl)aminomethane:

$$\log k_B^{Tris} = -0.38(\pm 0.01)pK_a^K + 4.92(\pm 0.02)\ (r = 0.999) \quad (25)$$

For B = 2-picoline:

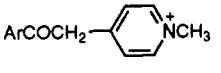
$$\log k_B^{Pic} = -0.39(\pm 0.01)pK_a^K + 4.21(\pm 0.03)\ (r = 0.997) \quad (26)$$

For B = acetate ion:

$$\log k_B^{Acet} = -0.56(\pm 0.02)pK_a^K + 4.2(\pm 0.1)\ (r = 0.998) \quad (27)$$

The value of $\alpha = 0.43$ for hydroxide ion (eq 22) is similar to $\alpha = 0.40$ that has been calculated for this same base reacting with a selected set from a structurally heterogeneous group of monocarbonyl derivatives.[22] However, the β-keto esters and amides of the current study are about 20-fold more reactive than predicted by the Brønsted correlation for monocarbonyl derivatives.

The Brønsted α values for hydroxide ion and tris(hydroxymethyl)aminomethane are similar to the values obtained for these bases reacting with a series of *N*-methyl-4-(substituted phenacyl)-pyridinium cations **8** in a previous study ($\alpha = 0.45$ for hydroxide



8

ion[13] and $\alpha = 0.41$ for tris(hydroxyethyl)aminomethane[14]). These 4-phenacylpyridinium cations are of similar thermodynamic acidity to the β-keto esters and amides of the current study. However, the β-keto esters and amides show 2- to 4-fold greater kinetic acidities than 4-phenacylpyridinium cations having the same pK_a^K.

Substituent effects upon the rate–equilibrium data for the deprotonation of 4-phenacylpyridinium cations have been extensively analyzed[13,14] in terms of a modified form of the Marcus relationship[11,24] which is given in eq 28. This relationship allows for a varible intrinsic barrier which is a function of the free energy of reaction. The current data for the general-base-catalyzed deprotonation of β-keto esters and amides have now also been analyzed in terms of eq 28. The intrinsic barrier as defined in terms of the usual form of the Marcus relationship (eq 29) was calculated for each carbon acid with each general base catalyst by solving the appropriate quadratic equation in $\Delta G_0^{\ddagger}$. For

$$\Delta G^{\ddagger} = (A + B\Delta G_0)[1 + \Delta G_0/4(A + B\Delta G_0)]^2 \quad (28)$$

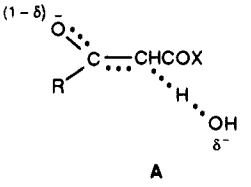
$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger}(1 + \Delta G_0/4\Delta G_0^{\ddagger})^2 \quad (29)$$

deprotonations employing either ethanolamine, tris(hydroxymethyl)aminomethane, or 2-picoline as the general base catalyst, it is clear that $\Delta G_0^{\ddagger}$ varies systematically with ΔG_0 (Figure 12 and Table IV), although such a variation is less certain for hydroxide ion (for which $\Delta G_0^{\ddagger}$ appears to vary randomly around the average value of 14.84 kcal/mol) and acetate ion (for which B is only marginally different from 0 within experimental error) as the general base catalysts. The negative B values that are obtained for the three amines in the current study are similar to the B values reported[14] for a variety of amine bases in the general base catalysis of the deprotonation of 4-phenacylpyridinium cations **8**.

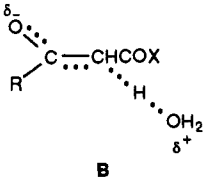
It can be concluded that the modified form of the Marcus relationship with the inclusion of a variable intrinsic barrier (eq 28) is applicable to the general-base-catalyzed deprotonation of β-keto esters and amides in aqueous solution. The empirically defined B parameter of eq 28 has been shown[24] to be a function of the work terms that are introduced in the more general treatments of reactions via Marcus theory and, as such, might be expected to contain contributions from structural factors in both the general base and the carbon acid species as well as various solvent reorganizational effects which are expected to be important in reaching the transition-state species. The similarities of the B parameters that are noted above for the reactions of amine bases with two relatively different structural classes of carbon acids are consistent with an interpretation in which similar solvent reorganizational phenomena in the vicinity of these general base catalysts is the controlling factor for the determination of the magnitude of the B parameter.

Mechanisms of Tautomerization. The pH–rate profiles that are presented in Figures 3, 4, and 5 indicate that there are at least two mechanistic pathways for the keto–enol tautomerization for these β-keto esters and amides in aqueous solution over the pH region that has been investigated in the current study. The pH dependence of k^E (eq 10 or 11) requires a pathway that is kinetically first order in hydroxide ion concentration (k_{OH}^E) and also an "uncatalyzed" pathway (k_o^E).[25]

The first of these pathways is only readily interpreted in terms of a direct abstraction of a proton from the methylene carbon atom of the keto tautomer by hydroxide ion (transition state **A**) to give the enolate ion conjugate base.[27] The microscopic reverse of this process then represents the protonation of the enolate ion by a water molecule (k_o^K). This transition state predominates in basic solution in all cases examined in the present work and is quite typical of the rate-determining transition states that have been established for hydroxide-ion-catalyzed deprotonations of simple aldehydes and ketones in aqueous base.[22]



A



B

By analogy with k_{OH}^E, the k_o^E term might be considered to represent the abstraction of a proton form the keto tautomer by a water molecule (transition state **B**). This reaction is the microscopic reverse of the protonation of the enolate ion by

(26) Pollack, R. M. *Tetrahedron* **1989**, *45*, 4913.

(27) The fractional charges in transition states A–E are assigned to maintain electrical neutrality. Charge delocalization in these species is likely to be more extensive than depicted in these oversimplified species.

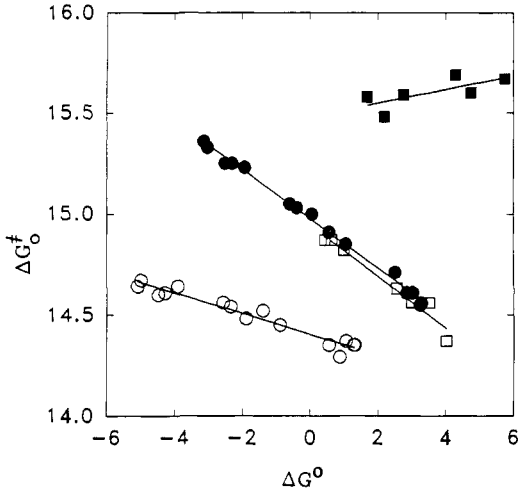


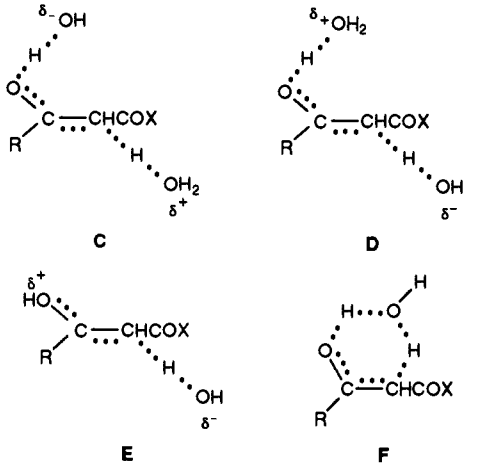
Figure 12. Dependence of the Marcus intrinsic barrier ($\Delta G^{\ddagger}_{o}$ calculated from eq 29) upon ΔG_o for ethanolamine (open circles), tris(hydroxymethyl)aminomethane (filled circles), 2-picoline (open squares), and acetate ion (filled squares).

Table IV. Modified Marcus Parameters for Deprotonation of $RCOCH_2COX$ by Hydroxide Ion and Buffer Bases

base	A (kcal/mol)	B
hydroxide ion	14.83 ± 0.09	0.00 ± 0.01
ethanolamine	14.40 ± 0.02	−0.05 ± 0.01
Tris	14.98 ± 0.02	−0.12 ± 0.01
2-picoline	14.94 ± 0.04	−0.12 ± 0.01
acetate	15.48 ± 0.06	0.03 ± 0.02

hydroxonium ion (k^{K}_{H+}) in the ketonization process. However, this simple interpretation of k^{E}_{o} is suspect, since although k^{E}_{OH} displays Brønsted α = 0.43, k^{E}_{o} is much less dependent upon carbon acidity and in fact displays an unusual α = −0.17 (eq 23). It seems unlikely that the lower basicity of water compared to that of the hydroxide ion could result in such a dramatic change in the α value in what is essentially the same transition-state species, especially since Brønsted α coefficients in the range 0.37–0.56 (eqs 24–27) have been found for the the deprotonation of these β-keto esters and amides by a variety of general base catalysts. In particular, it should be noted that acetate ion, which is closer in basicity to water than to hydroxide ion, produces α = 0.56. This suggests that the second-order rate constants k_B for the general-base-catalyzed processes are only readily interpreted as analogues of the k^{E}_{OH} process, i.e., transition-state species in which the general base replaces the hydroxide ion in transition state **A**.

Consequently, alternative transition-state species, which are kinetically equivalent to transition state **B**, should be considered for the k^{E}_{o} process and its microscopic reverse (k^{K}_{H+}) which predominate in neutral and acidic solutions. The only simple rationalization for α = −0.17 for k^{E}_{o} is that this value arises as the net result of two opposing electronic effects from the R substituent upon the stability of the rate-determining transition-state species. The only obvious opposing electronic effects of this type are (i) upon the protonation of the developing enolate ion (for which electron-withdrawing effects in R would promote such a protonation, i.e., negative α) and (ii) upon the development of such an anionic species during the deprotonation of the methylene group (which should be facilitated by electron-withdrawing effects in R, i.e., positive α). In this context, four closely related mechanisms (with rate-determining transition states **C–F**) which are kinetically equivalent to transition state **B** appear to be worthy of consideration for k^{E}_{o}. Each of the pathways represented by the transition states **C–F** is an example of what has been referred to as a "concerted" mechanism which involves synchronized protonation and deprotonation.[22,28,29] Each of **C–F** has the significant feature that structural effects in the R substituent, which would make protonation on oxygen less favorable, would also enhance the stabilization of the developing negative charge. Thus, the combination of these two opposing effects may potentially lead to $\alpha \approx 0$ for k^{E}_{o}.



In transition state **C**, deprotonation of the methylene group by a water molecule is assisted by a second water molecule which acts as a general acid catalyst for the protonation of the developing enolate ion to produce the neutral enol as the immediate reaction product. Alternatively, in transition state **D**, deprotonation by hydroxide ion is assisted by general-acid-catalyzed protonation of the developing enolate ion by a hydroxonium cation. Since enolization via **D** formally involves a termolecular reaction, this transition state may seem inherently unlikely, especially since two of the component species to the transition state are hydroxide ion and hydroxonium ion. The same type of termolecular reaction is also implied for ketonization via **C**. Of course, these formal termolecular transition states can be avoided by the assumption of a preassociation complex (presumably hydrogen bonded) between two of the reactant species.

Concerted mechanisms such as those that are implied by transition states **C** and **D** have been suggested for other keto–enol isomerizations of simple carbonyl compounds and have been the subject of considerable controversy.[22,30,31] The major evidence for such mechanisms is found in the observation of third-order kinetic terms in buffer-catalyzed enolizations. We have found no evidence for such terms in the buffer solutions on which the data in Table III are based; however, we have no extended our studies to high buffer concentrations in which such concerted mechanisms, if they exist, should be most readily diagnosed. We note that Keeffe and Kresge[22] concluded that "the concerted mechanism will be used only by acid–base pairs both of which are weak". Transition state **C** in which a water molecule is both the acid and base species certainly fulfils this criterion.

Transition state **E** represents a specific acid-catalyzed enolization process in which hydroxide ion deprotonates the preformed O-protonated conjugate acid of the keto tautomer. However, consideration of the basicity of the carbonyl oxygen atom of these keto tautomers readily allows one to discard transition state **E** in the following way. A reaction mechanism involving transition state **E** predicts that $k^{E}_{o} = k^{+}_{OH}K_w/K_a$, where K_a is the acid dissociation constant of the O-protonated conjugate acid of the keto tautomer and k^{+}_{OH} is the second-order rate constant for deprotonation of the methylene group of this O-protonated

(28) Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Chapman and Hall: London, 1973; p 149.
(29) Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 1.
(30) Capon, B.; Siddhanta, A. K.; Zucco, C. *J. Org. Chem.* **1985**, *50*, 3580.
(31) Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000.

conjugate acid by hydroxide ion. Now, the carbonyl oxygen atom of the keto tautomer should be less basic than the oxygen atom of acetophenone ($pK_{BH^+} = -4.16$).[32] Thus, $K_a > 10^4$ and $k_{OH}^+ > 0.37 \times 10^4/10^{-14} = 3.7 \times 10^{17}$ M^{-1} s^{-1} (using k_o^E for methyl benzoylacetate) which is well above the diffusion-controlled limit, and so, this effectively eliminates the specific acid-catalyzed route that is indicated by transition state **E**.

Transition state **F** represents a species in which a water molecule acts as both the base to deprotonate the methylene group as well as the source of a proton for the neutralization of the developing enolate negative charge. Variations on **F** in which more than one water molecule is involved are also conceivable. A transition state such as **F** was considered but subsequently ruled out for the "uncatalyzed" reaction in the tautomerization of simple carbonyl compounds.[33,34] It was concluded[34] that for simple ketones, the reaction equivalent to k_o^E in the current study occurs via a transition state analogous to **B**, above. However, Keeffe and Kresge[22] suggest that "the concerted mechanism is more likely to be used by systems whose enols are more stable". The enols of the β-keto esters and amides of Table I ($K_E \approx 0.1$) are certainly much more stable than the enols of simple monoketones (e.g., for acetophenone[20] $K_E = 10^{-7.96}$). As discussed above, we feel that the unusual α value that we have demonstrated for k_o^E is inconsistent with transition state **B** for β-keto esters and amides. We also note that $k_{H^+}^K$ (the microscopic reverse of k_o^E) for the most reactive compounds in the current study lies in the vicinity of 10^{10} M^{-1} s^{-1} (Table II) which is similar to $k_{H^+}^K$ in the vicinity of 5×10^9 M^{-1} s^{-1} reported[34] for the enols of acetone and acetophenone.

We conclude that each of the concerted routes implied by the transition states **C**, **D**, and **F** appears to be formally consistent with $\alpha \approx 0$ which is found for k_o^E. We see no simple way of distinguishing between these transition-state species on the basis of the data that are currently available.

Summary. The current work represents the most extensive study that is currently available of the deprotonation and the tautomerization of β-keto esters and amides in aqueous solution. In general, both the keto and enol tautomers of the β-keto amides are more acidic than for the analogous esters. The keto tautomers of the amides also show slightly greater kinetic acidities than those of the corresponding β-keto esters. Within the structurally related series of β-keto esters and amides represented by **2**, **3**, and **4**, it has been found that pK_a^E correlates linearly with pK_a^K. Both the keto and enol tautomers of methyl acetoacetate ($pK_a^K = 10.60$ and $pK_a^E = 9.48$) are less acidic than the keto and enol tautomers of acetylacetone[35] ($pK_a^K = 8.86$ and $pK_a^E = 8.09$ at 27.5 °C), with the enol content of this β-keto ester ($K_E = 0.080$) being approximately 50% of that in acetylacetone ($K_E = 0.17$) in aqueous solution. Interestingly, interpolation in eq 16 at $pK_a^K = 8.86$ gives $pK_a^E = 8.10$ and consequently $K_E = 0.17$ for a β-keto ester or amide having the same carbon acidity as acetylacetone. Similar interpolation in eq 22 gives $k_{OH} = 2.3 \times 10^4$ M^{-1} s^{-1} at 25 °C for a β-keto ester or amide of $pK_a^K = 8.86$; the value for acetylacetone[35] at 27.5 °C is 4×10^4 M^{-1} s^{-1}.

Brønsted α values have been obtained for the general-base-catalyzed deprotonation of these β-keto esters and amides for a number of general base catalysts. Substituent effects in these rate–equilibrium correlations are most readily reproduced by the use of a modified Marcus equation which incorporates a variable intrinsic barrier. This extends the applicability of this modified Marcus equation for the general-base-catalyzed deprotonation of carbon acids from the 4-(substituted phenacyl)pyridinium cations in a previous study to the β-keto esters and amides of the current study.

The uncatalyzed enolization reaction of these β-keto esters and amides displays an unusual Brønsted $\alpha = -0.17$. This implies a mechanistically more complex transition-state species than the simple deprotonation of the keto tautomer by a water molecule as the general base species. Transition states **C**, **D**, and **F** which involve the conversion of the keto tautomer to the neutral enol tautomer in a combined general acid + general base process appear to be appropriate rationalizations of the data for k_o^E and $k_{H^+}^K$. Analogous processes in the enzyme-catalyzed interconversion of neutral keto and enol tautomers have recently been discussed in some detail be Gerlt and Gassman[36,37] for reactions in which a carbon acid is deprotonated by an enzymic base which is much weaker than the enolate conjugate base of the carbon acid. The current k_o^E process, which involves a water molecule which is a weaker base than the enolate conjugate bases, seems to be a direct analogue of the general base + general acid catalysis that is proposed in such enzymic deprotonation reactions.

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

(32) Cox, R. A.; Smith, C. R.; Yates, K. *Can. J. Chem.* **1979**, *57*, 2952.
(33) Pruszynski, P.; Chiang, Y.; Kresge, A. J.; Schepp, N. P.; Walsh, P. A. *J. Phys. Chem.* **1986**, *90*, 3760.
(34) Chiang, Y.; Kresge, A. J.; Santaballa, J. A.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 5506.
(35) Ahrens, M. L.; Eigen, M.; Kruse, W.; Maass, G. *Ber. Bunsen-Ges. Phys. Chem.* **1970**, *74*, 380.
(36) Gerlt, J. A.; Kozarich, J. W.; Kenyon, G. L.; Gassman, P. G. *J. Am. Chem. Soc.* **1991**, *113*, 9667.
(37) Gerlt, J. A.; Gassman, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 5928.