Determination of the pK_a of Ethyl Acetate: Brønsted Correlation for Deprotonation of a Simple Oxygen Ester in Aqueous Solution

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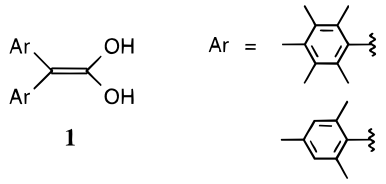
Received October 31, 1995[⊗]

Abstract: The rate constants for deprotonation of ethyl acetate by 3-substituted quinuclidines are correlated by $\beta = 1.09 \pm 0.05$. The limits of $k_{BH} = 2-5 \times 10^9$ M^{-1} s^{-1} for the encounter-limited reaction of the simple oxygen ester enolate with protonated quinuclidine (p$K_{BH} = 11.5$) were combined with $k_B = 2.4 \times 10^{-5}$ M^{-1} s^{-1} for deprotonation of ethyl acetate by quinuclidine, to give p$K_a^K = 25.6 \pm 0.5$ for ionization of ethyl acetate as a carbon acid in aqueous solution. A rate−equilibrium correlation for proton transfer from methyl and benzylic monocarbonyl compounds to hydroxide ion has been extended by 6 pK units in the thermodynamically unfavorable direction, and it is shown that the absence of curvature of this correlation is inconsistent with a constant Marcus intrinsic barrier for the enolization of simple carbonyl compounds.

The enols/enolates of simple[1] carboxylic acids, which are modeled by the corresponding oxygen esters, are proposed intermediates of many biologically important elimination and racemization reactions.[2−4] In aqueous solution, such enol(ate)s are highly unstable relative to their keto tautomers,[5] and this had led to recent examinations of the mechanistic imperatives for their formation as intermediates of enzyme-catalyzed reactions.[6−11] Gerlt and Gassman have proposed that the key high-energy intermediates are "enolic" species which are stabilized by formation of a strong "low-barrier" hydrogen bond[12,13] to an acidic amino acid in the enzyme active site.[7−10] On the other hand, Guthrie and Kluger argue that stabilization of an enolate by an enzyme is the result of electrostatic interactions with charged amino acid side chains in the active site or an enzyme-bound metal ion.[11] However, a critical unknown is the thermodynamic barrier to formation of the enol(ate)s of simple carboxylic acid derivatives in aqueous solution.

Direct observation of the enol(ate)s of carboxylic acid derivatives has been limited to those in which the enol(ate) is stabilized either kinetically or thermodynamically by special structural features. For example, the bulky β-aryl substituents at the "Fuson"-type enols **1**, generated as intermediates in the hydrolysis of the corresponding ketenes in aqueous acetonitrile, stabilize these species toward ketonization.[5,14]



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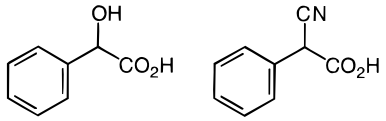
Kresge and co-workers have pioneered the generation of enols in larger than equilibrium amounts, as products of the decay of reactive intermediates generated by laser flash photolysis.[15−18] These techniques provided the carbon acid acidities of mandelic acid (**2**, p$K_a^K = 22$)[19,20] and α-cyano-α-phenylacetic acid (**3**, p$K_a^K = 8.22$)[21] in aqueous solution. The recently reported



2 **3**

acidity constants of 9-acylfluorenyl derivatives, **4-X**, determined

[⊗] Abstract published in *Advance ACS Abstracts,* March 15, 1996.

(1) We define a "simple" carboxylic acid or oxygen ester to be one in which the carbonyl group is adjacent to a carbon atom bearing only alkyl substituents.

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(20) The following notation is used for the equilibria relating to carbonyl compounds (Scheme 7): K_a^K, ionization constant for the α-proton(s) of the keto tautomer; K_a^E, ionization constant for the hydroxyl proton of the enol tautomer; K_E, equilibrium constant for formation of the enol from the keto tautomer.

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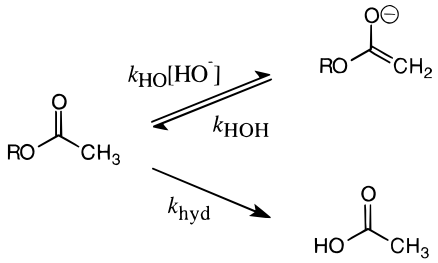
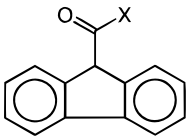
Scheme 1



using conventional stopped-flow techniques,[22] provides a comparison of the thermodynamic barrier to formation of the enolates of related oxygen (X = OMe, $pK_a^K = 11.5$) and thiol (X = SMe, $pK_a^K = 10.5$) esters in aqueous solution. However, these enolates are stabilized by the strongly acidifying 9-fluorenyl group (*cf.* $pK_a^K = 21.0$ for ethyl thioacetate[23]), so that there may be strong attenuation of the effects of substituents on the stability of the enolates of **4-X** compared with those for simple acetyl systems.



4-X

By contrast, there are very few experimental data pertaining to the stability of the enol(ate) tautomers of *simple* unsubstituted carboxylic acids or oxygen esters in aqueous solution. In principle, the pK_a^K for ionization of the latter carbon acids can be obtained from the rate constants for their hydroxide ion catalyzed enolization ($k_{HO}[HO^-]$, Scheme 1) and the uncatalyzed ketonization of the enolates (k_{HOH}, Scheme 1). However, such experiments have never been carried out for a simple oxygen ester in aqueous solution, because these esters undergo competing hydrolysis induced by hydroxide ion to give the corresponding carboxylic acids (k_{hyd}, Scheme 1). Thus, while Bonhoeffer *et al*. were able to obtain kinetic data for exchange of the α-protons of acetate anion in D_2O, they concluded that "the ionization constants of the esters of acetic acid are not yet known, because hydrolysis proceeds much faster than exchange in alkaline deuterium oxide".[24] The estimates of $pK_a^K = 24$ for acetic acid and $pK_a^K = 24.5$ for ethyl acetate made by Pearson and Dillon[25] have been propagated in the literature and are quoted in organic textbooks,[26−28] but these values lack direct experimental corroboration. The former was obtained by extrapolation of a rate−equilibrium correlation using rate constants for exchange of deuterium into acetic acid/acetate determined by Bonhoeffer *et al*., but the origin of the acidity constant for ethyl acetate was not documented.[25]

We report here experiments to determine the thermodynamic and kinetic stability of the enolate tautomer of a simple oxygen ester, ethyl acetate, *in aqueous solution*. We recently reported a general method for the determination of rate constants for deprotonation of carbon acids in D_2O, in which the incorporation of a single deuterium is monitored by exploiting the ^2H perturbation of ^1H chemical shifts.[23] Using this method, we have now determined rate constants for deprotonation of ethyl acetate by a homologous series of tertiary amines in aqueous solution, by monitoring small amounts of deuterium exchange (1−10% of the first α-proton) against the background of competing ester hydrolysis. These rate constants are correlated by a Brønsted coefficient of $\beta = 1.09 \pm 0.05$, and there is good evidence that the reverse reaction of the enolate with tertiary ammonium ions takes place at the encounter limit. These reactions of ethyl acetate with tertiary amines constitute the first examples of proton transfer reactions in which a carbonyl compound acts as a "normal" acid. Our data allow us to determine both the thermodynamic stability of the enolate of ethyl acetate, as $pK_a^K = 25.6$ for ionization of ethyl acetate, and its kinetic stability, as $k_{HOH} = 5 \times 10^8\ s^{-1}$ for reaction of the enolate with a solvent of bulk water.

Experimental Section

Materials. Ethyl acetate (HPLC grade), 3-quinuclidinone hydrochloride, 3-chloroquinuclidine hydrochloride, quinuclidine hydrochloride, 3-quinuclidinol, and potassium deuterioxide (40% wt, 98+% D) were from Aldrich. Deuterium oxide (99.9% D), deuterium chloride (35% w/w, 99.5% D), and deuteriated chloroform (99.8% D) were from Cambridge Isotope Laboratories. The 3-substituted quinuclidines were recrystallized from the following solvents: 3-quinuclidinone hydrochloride, ethanol/water; 3-chloroquinuclidine hydrochloride, 1:1 (v:v) methanol/propanol; quinuclidine hydrochloride, ethanol; 3-quinuclidinol, acetone. All other chemicals were reagent grade and were used without further purification.

Preparation of Solutions. The acidic protons of the hydrochlorides of 3-quinuclidinone, 3-chloroquinuclidine, and quinuclidine were exchanged for deuterium before use, as described previously.[23] Stock solutions of deuterium chloride and potassium deuterioxide were prepared by dilution of commercial concentrated solutions. Stock solutions of buffers were prepared by dissolving the 3-substituted quinuclidine hydrochlorides or neutral 3-quinuclidinol and KCl in D_2O, followed by addition of an appropriate amount of a stock solution of KOD or DCl, to give solutions of buffer at various acid:base ratios and $I = 1.0$ (KCl).

Determination of pH and pK_{BD}. Solution pH was determined at 25 °C using an Orion Model 601A pH meter equipped with a Radiometer GK2321C combination electrode that was standardized at pH 7.00 and 10.00. Values of pD were obtained by adding 0.40 to the observed pH meter reading.[29] The apparent activity coefficient of lyoxide ion under our experimental conditions, $\gamma_{OL} = 0.79$, was determined from the measured pH of solutions of known $[HO^-]$ in water at $I = 1.0$ (KCl) and 25 °C. For these measurements, the pH apparatus was standardized at 7.00 and at 12.47 with calcium hydroxide that was saturated at 21 °C.[30] The concentration of deuterioxide ion at any pD was then calculated from eq 1 using $K_w = 10^{-14.87}$ for the ion product of D_2O at 25 °C.[31] The apparent pK_as of the 3-substituted quinuclidinium cations in D_2O at $I = 1.0$ (KCl) and 25 °C, given by $pK_{BD} = pD - \log([B]/[BD^+])$, were determined from the pD of the gravimetrically prepared buffer solutions used for the exchange experiments and the stoichiometric concentrations of [B] and $[BD^+]$.

$$[DO^-] = \frac{10^{pD-pK_w}}{\gamma_{OL}} \quad (1)$$

Kinetic Methods. Rate constants for exchange for deuterium of the first α-proton of ethyl acetate in D_2O were determined by monitoring

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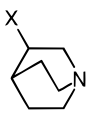
the disappearance of the α-CH_3 group of the substrate and the appearance of the α-CH_2D group of monodeuteriated ethyl acetate by the ^{1}H NMR method described previously.[23] All reactions were carried out at 25 °C and a constant ionic strength of 1.0 maintained with potassium chloride. Reactions in a volume of 4 mL were initiated by the addition of 8 μL of neat ethyl acetate, to give a final substrate concentration of 20 mM, and the pD of the reaction mixture was determined immediately. The reactions in 3-quinuclidinone buffers were protected from light by wrapping the reaction vials with aluminum foil, in order to minimize development of the yellow color of these solutions that was observed at longer times. Isotope exchange takes place against the background of the faster hydrolysis of ethyl acetate to give acetic acid, which leads to substantial decreases in the pDs of the reaction mixtures. Therefore, the pDs of the reaction mixtures were monitored closely, with the most frequent sampling at early reaction times where the velocity of formation of acetic acid is greatest, and any decreases in pD (≤0.05 units) were compensated for by the addition of an aliquot of 4.4 M KOD. In this way, the pDs of the reaction mixtures were maintained within ±0.05 units of the initial pD. The progress of isotope exchange was determined by withdrawal of 1 mL aliquots of the reaction mixtures, which were quenched with 1 mL of 2−2.6 M DCl. The ethyl acetate was then extracted by adding 1.2 mL of $CDCl_3$, followed by vortexing and removal of the aqueous layer with a Pasteur pipet. The organic layer was dried by filtration through a short column of $MgSO_4$ directly into an NMR tube. The samples so prepared were placed in a sealed plastic bag containing Drierite and were stored in a freezer until they could be analyzed by ^{1}H NMR.

^{1}H NMR Spectroscopy. ^{1}H NMR spectra at 500 MHz were recorded in $CDCl_3$ on a Varian VXR-500S spectrometer at the University of Kentucky. Approximate values of T_1 for the various protons of ethyl acetate in $CDCl_3$, determined using a sample prepared as described above, were determined to be 4−6 s. Spectra (128−512 transients) were obtained by using a sweep width of 4000 Hz, a 90° pulse angle, and an acquisition time of 8 s and zero-filling of the data to 128 000 data points. In all cases, the relaxation delay between pulses was at least 10-fold greater than the longest T_1 value (total acquisition times were 2−8 h). The spectra were referenced to $CHCl_3$ at 7.27 ppm. Baselines were subjected to a first-order drift correction before integration of the signals.

Results

The exchange for deuterium of a single α-proton of ethyl acetate was followed by monitoring the disappearance of the α-CH_3 group of the substrate and the appearance of the α-CH_2D group of monodeuteriated ethyl acetate by 500 MHz ^{1}H NMR spectroscopy, taking advantage of the ^{2}H perturbation of ^{1}H chemical shifts.[23] Figure 1 shows representative partial ^{1}H NMR spectra of recovered ethyl acetate obtained during exchange of 1−10% of the first α-proton for deuterium in the presence of 3-substituted quinuclidine buffers in D_2O at 25 °C and I = 1.0 (KCl). The isotope exchange reaction leads to disappearance



3-X Quinuclidines

of the singlet at 2.053 ppm due to the α-CH_3 group of unexchanged ethyl acetate, and appearance of an upfield triplet at 2.040 ppm due to the α-CH_2D group of monodeuteriated ethyl acetate, in which the remaining α-protons are coupled to the α-deuterium (J_{HD} = 2.2 Hz). The two peaks of equal intensity on either side of the large (offscale) singlet at 2.053 ppm (Figure 1) are the ^{13}C satellites of the signal for the α-CH_3 group of unexchanged ethyl acetate that arise from coupling of the α-CH_3 protons to the neighboring carbonyl carbon (J_{CH} = 7 Hz) in natural abundance ^{13}C═O ethyl acetate.

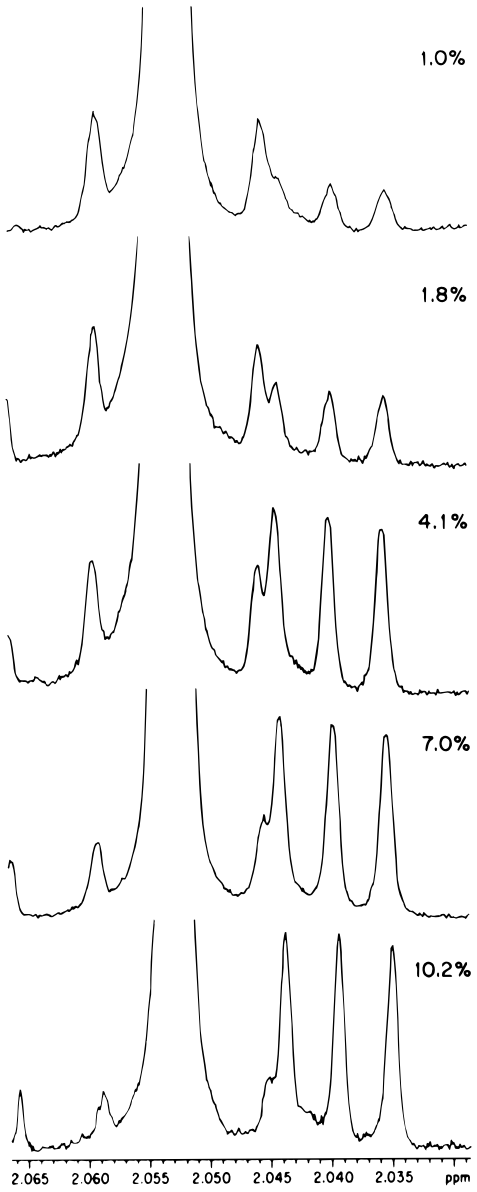


Figure 1. Representative partial ^{1}H NMR spectra at 500 MHz in $CDCl_3$ of recovered ethyl acetate obtained during exchange of the first α-proton for deuterium in the presence of 3-substituted quinuclidine buffers in D_2O at 25 °C and pD = 9.7−12.3. Deuterium incorporation leads to the disappearance of the large singlet at 2.053 ppm (offscale peak) due to the α-CH_3 group of ethyl acetate, and the appearance of an upfield triplet at 2.040 ppm (J_{HD} = 2.2 Hz) due to the α-CH_2D group of the monodeuteriated product. Details of the peak assignments are given in the text. The fraction of monodeuteriated ethyl acetate in each sample is indicated at the top right of the spectrum.

The deuterium exchange reaction proceeds against the background of hydrolysis of ethyl acetate to give acetic acid, which is 20−70-fold faster than isotope exchange (see Discussion). Consequently, only low levels of deuterium incorporation into ethyl acetate could be followed before there was extensive depletion of the substrate by the competing hydrolysis reaction.

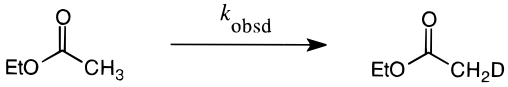
The kinetics of deuterium exchange were monitored by integration of the signals due to the α-CH_3 group of the substrate and the α-CH_2D group of the product during exchange of 1−10% of the first α-proton of ethyl acetate, which corresponds to 0.3−3% of the total α-protons. During this time period, the velocity of deuterium exchange was essentially constant, and there was no detectable formation of dideuteriated ethyl acetate. The difference in the chemical shifts of the protons of the α-CH_3 and α-CH_2D groups is very small (0.013 ppm), so that the

Table 1. Rate Constants for Exchange for Deuterium of the First α-Proton of Ethyl Acetate in 3-Substituted Quinuclidine Buffers in D_2O[a]

buffer base	pK_{BD}[b]	% free base	[buffer]/M	pD	k_{obsd}/s^{-1} [c]	k_o/s^{-1} [d]	$(k_B)_{obsd}/M^{-1}\ s^{-1}$ [e]
quinuclidine	12.1	60	0.50	12.26	1.19×10^{-5}	5.90×10^{-6}	1.20×10^{-5}
			0.25	12.31	8.90×10^{-6}		
		50	0.50	12.08	1.05×10^{-5}		
		10	0.80	11.05	2.25×10^{-6}		
			0.60	11.11	1.83×10^{-6}		
			0.40	11.14	1.38×10^{-6}		
3-quinuclidinol	10.7	50	0.50	10.69	4.64×10^{-7}	1.53×10^{-7}	6.24×10^{-7}
			0.25	10.71	3.11×10^{-7}		
			0.10	10.72	2.14×10^{-7}		
		25	0.40	10.25	1.65×10^{-7}		
3-chloroquinuclidine	9.7	50	0.25	9.67	2.44×10^{-8}	1.31×10^{-8}	4.48×10^{-8}
			0.20	9.68	2.15×10^{-8}		
			0.15	9.68	2.07×10^{-8}		
			0.10	9.69	1.72×10^{-8}		
3-quinuclidinone[f]	8.3	81	1.00	8.93	3.84×10^{-9}		
		77	1.00	8.82	3.02×10^{-9}		

[a] At 25 °C and $I = 1.0$ (KCl). Deuterium exchange was followed by ^1H NMR (see text). [b] Apparent pK_as of the 3-substituted quinuclidinium cations in D_2O at 25 °C and $I = 1.0$ (KCl), given by $pK_{BD} = pD - \log([B]/[BD^+])$, determined from the pD of the buffer solutions and the stoichiometric concentrations of [B] and $[BD^+]$. [c] Pseudo-first-order rate constant for exchange for deuterium of the first α-proton of ethyl acetate, determined from plots of reaction progress against time according to eq 2. Unless noted otherwise, values of k_{obsd} (s^{-1}) were obtained by least squares analysis of data for three or four reaction times that included a point for zero time. [d] Pseudo-first-order rate constant for solvent-catalyzed exchange at the pD of the experiment obtained from the intercept of a plot of k_{obsd} against [buffer] according to eq 4. [e] Observed second-order rate constant for buffer-catalyzed exchange obtained from the slope of a plot of k_{obsd} against [buffer] according to eq 4. [f] Values of k_{obsd} (s^{-1}) were calculated from the initial velocity of deuterium incorporation determined from a single time point and a point for zero time (see Results).

Scheme 2



upfield ^{13}C satellite of the singlet due to the α-CH_3 group of the substrate was not completely resolved from the most downfield peak of the triplet due to the α-CH_2D group of the product (see Figure 1). Therefore, the total integrated area of the triplet due to the α-CH_2D group of monodeuteriated ethyl acetate was obtained by integration of only the most upfield peak of this triplet, which was then multiplied by 3 to give A(α-CH_2D).

Observed pseudo-first-order rate constants for exchange for deuterium of the first α-proton of ethyl acetate, k_{obsd}, were obtained from the slopes of plots of reaction progress against time according to eq 2, derived for Scheme 2, where $f(CH_3)$ is the fraction of unexchanged ethyl acetate remaining at time t. The values of $f(CH_3)$ were calculated from eq 3, where A(α-CH_3) and A(α-CH_2D) are the total integrated areas of the peaks due to the α-CH_3 group of the substrate and the α-CH_2D group of the product, respectively.[32] Table 1 gives the values of k_{obsd} (s^{-1}), which were obtained by least squares analysis of the data for three or four reaction times that included a point for zero time, for which A(α-CH_2D) = 0. The reactions in the presence of 1.0 M 77% and 81% free base 3-quinuclidinone buffers were extremely slow: after *ca*. 60 days there was only *ca*. 1.7% exchange of the first α-proton of ethyl acetate. Therefore, the values of k_{obsd} (s^{-1}, Table 1) for these reactions were calculated from the initial velocity of deuterium incorporation determined from this single time point and a point for zero time.

$$\ln f(CH_3) = -k_{obsd}t \qquad (2)$$

$$f(CH_3) = \frac{A(\alpha\text{-}CH_3)}{A(\alpha\text{-}CH_3) + 1.5A(\alpha\text{-}CH_2D)} \qquad (3)$$

(32) A more complex treatment is required for reactions in which there is significant formation of dideuteriated products.[83] However, for the small extents of deuterium exchange studied here, there is no significant difference between the rate constants obtained using eqs 2 and 3 and those calculated using the more complex analysis.

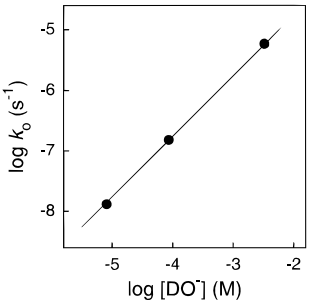


Figure 2. Logarithmic plot of pseudo-first-order rate constants for solvent-catalyzed exchange for deuterium of the first α-proton of ethyl acetate against the logarithm of the concentration of deuterioxide ion in 3-substituted quinuclidine buffers in D_2O at 25 °C and $I = 1.0$ (KCl) (eq 5 and Table 1). The values of $[DO^-]$ were calculated from the pD of the buffered reaction mixtures using eq 1. The line of unit slope drawn through the data was calculated using $k_{DO} = 1.7 \times 10^{-3}\ M^{-1}\ s^{-1}$ obtained from the intercepts of plots of k_{obsd} against [buffer] for 60% free base quinuclidine (pD = 12.29), 50% free base 3-quinuclidinol (pD = 10.71), and 50% free base 3-chloroquinuclidine (pD = 9.68) buffers (see text).

The values of k_{obsd} (s^{-1}, Table 1) were plotted against [buffer] according to eq 4, where k_0 (s^{-1}, Table 1) is the pseudo-first-order rate constant for solvent-catalyzed exchange at the pD of the experiment and $(k_B)_{obsd}$ ($M^{-1}\ s^{-1}$, Table 1) is the observed second-order rate constant for buffer-catalyzed exchange. For

$$k_{obsd} = k_0 + (k_B)_{obsd}[\text{buffer}] \qquad (4)$$

50% free base 3-quinuclidinol and 50% free base 3-chloroquinuclidine buffers these plots were linear for [buffer] ≤ 0.50 M (not shown). However, there is a 15% negative deviation of k_{obsd} for 1.0 M 50% free base 3-quinuclidinol from the correlation defined by [buffer] ≤ 0.50 M, which probably represents a medium effect. The plot of k_{obsd} against [buffer] for 10% free base quinuclidine was linear up to [buffer] = 0.08 M (not shown).

Figure 2 shows that the values of k_0 (s^{-1}, Table 1), obtained from the intercepts of the plots of k_{obsd} against [buffer] (eq 4), increase with increasing pD according to eq 5, where $[DO^-]$ is the concentration of deuterioxide ion at the pD of the experi-

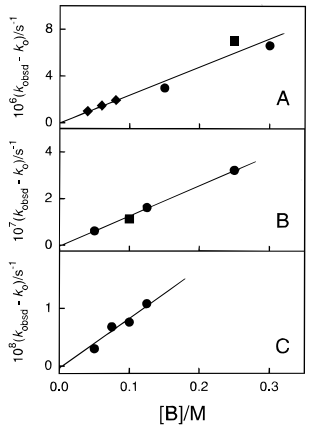


Figure 3. Plots of $k_{obsd} - k_0$ for exchange for deuterium of the first α-proton of ethyl acetate against the concentration of the basic form of 3-substituted quinuclidine buffers in D_2O at 25 °C and $I = 1.0$ (KCl), according to eq 6. (A) Data for quinuclidine buffers: ◆, 10% free base, pD = 11.10; ■, 50% free base, pD = 12.08; ●, 60% free base, pD = 12.29. (B) Data for 3-quinuclidinol buffers: ■, 25% free base, pD = 10.25; ●, 50% free base, pD = 10.71. (C) Data for 50% free base 3-chloroquinuclidine buffers, pD = 9.68.

ment, calculated from eq 1. The line of unit slope drawn

$$k_0 = k_{DO}[DO^-] \quad (5)$$

through the data in Figure 2 was calculated using $k_{DO} = (1.7 \pm 0.1) \times 10^{-3}$ M^{-1} s^{-1} as the second-order rate constant for exchange catalyzed by deuterioxide ion, obtained from the data in Table 1 for 60% free base quinuclidine (pD = 12.29), 50% free base 3-quinuclidinol (pD = 10.71), and 50% free base 3-chloroquinuclidine (pD = 9.68) buffers, which required less than a 1.5-fold extrapolation of the plots of k_{obsd} against [buffer] to [buffer] = 0 M.

The contribution of deuterioxide-catalyzed exchange (k_0) to k_{obsd} for the isotope exchange reaction in the presence of increasing concentrations of 3-substituted quinuclidine buffers was calculated from the pD of each reaction mixture and $k_{DO} = 1.7 \times 10^{-3}$ M^{-1} s^{-1} using eqs 1 and 5. Figure 3 shows plots of $k_{obsd} - k_0$ against the concentration of the basic form (B) of quinuclidine, 3-quinuclidinol, and 3-chloroquinuclidine buffers, according to eq 6. These data correspond to the following rate

$$k_{obsd} - k_0 = k_B[B] \quad (6)$$

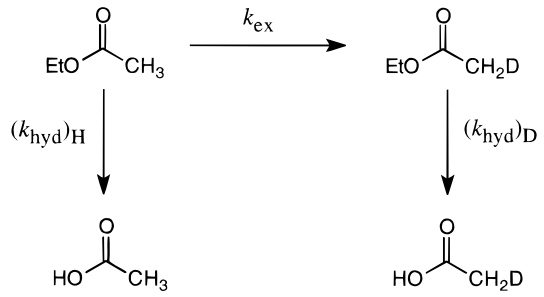
increases over the background deuterioxide-catalyzed reaction due to buffer catalysis: 0.80 M 10% free base quinuclidine, $k_{obsd}/k_0 = 4.4$; 0.50 M 60% free base quinuclidine, $k_{obsd}/k_0 = 2.0$; 0.50 M 50% free base 3-quinuclidinol, $k_{obsd}/k_0 = 3.0$; 0.25 M 50% free base 3-chloroquinuclidine, $k_{obsd}/k_0 = 1.9$. For quinuclidine (Figure 3A) and 3-quinuclidinol (Figure 3B), the data obtained at different buffer ratios [B]/[BD$^+$] (different pD) fall on the same correlation line, which shows that there is no significant catalysis of exchange by the acidic form of these buffers (BD$^+$). The slopes of the plots in Figure 3 are k_B (M^{-1} s^{-1}, Table 2), the second-order rate constants for catalysis of exchange for deuterium of the first α-proton of ethyl acetate by the basic form of the buffer. The value of k_B for 3-quinuclidinone (Table 2) is an average of the values determined in 1.0 M 77% and 81% free base 3-quinuclidinone buffers, with a correction of the values of $k_{obsd} - k_0$ based on the 16% negative deviation of the point for 1.0 M 50% free base 3-quinuclidinol from the correlation shown in Figure 3B.

Table 2. Second-Order Rate Constants for Deprotonation of Ethyl Acetate by 3-Substituted Quinuclidines in D_2O[a]

buffer base	pK_{BH}[b]	pK_{BD}[c]	k_B[d] (M^{-1} s^{-1})
quinuclidine	11.5	12.1	2.4×10^{-5}
3-quinuclidinol	10.0	10.7	1.3×10^{-6}
3-chloroquinuclidine	9.0	9.7	8.6×10^{-8}
3-quinuclidinone	7.5	8.3	1.9×10^{-9} [e]

[a] At 25 °C and $I = 1.0$ (KCl). [b] Apparent pK_as of the 3-substituted quinuclidinium cations in water at 25 °C and $I = 1.0$, given by pK_{BH} = pH − log([B]/[BH$^+$]), taken from ref 51. [c] Apparent pK_as of the 3-substituted quinuclidinium cations in D_2O at 25 °C and $I = 1.0$ (KCl), given by pK_{BD} = pD − log([B]/[BD$^+$]), determined from the pD of the buffer solutions and the stoichiometric concentrations of [B] and [BD$^+$]. [d] Second-order rate constant for base-catalyzed exchange for deuterium of the first α-proton of ethyl acetate, obtained from the slopes of the plots shown in Figure 3, unless noted otherwise. The least squares analyses included points for [B] = 0 M. [e] Average of values determined for 1.0 M 77% and 81% free base buffers, with a correction of the values of $k_{obsd} - k_o$ based on the 16% negative deviation of the point for 1.0 M 50% free base 3-quinuclidinol from the correlation shown in Figure 3B.

Scheme 3



Discussion

Ester Hydrolysis Competing with Deuterium Exchange. The lack of experimental data for the base-catalyzed enolization of simple oxygen esters in aqueous solution is due to the competing ester hydrolysis reaction, which is much faster than proton abstraction. We have determined rate constants for exchange for deuterium of the first α-proton of ethyl acetate in D_2O, using high-resolution ^{1}H NMR spectroscopy. Under our reaction conditions, the second-order rate constant for hydrolysis of ethyl acetate induced by deuterioxide ion is estimated to be $(k_{hyd})_H = 0.15$ M^{-1} s^{-1} (Scheme 3),[33] so that hydrolysis is 20−70-fold faster than the observed deuterium exchange reactions (Table 1). Our method for the determination of rate constants for deuterium exchange requires quantification of the fraction of monodeuteriated ethyl acetate present in the mixture of unexchanged substrate and monodeuteriated product, under conditions where up to *ca.* 95% of the substrate/product undergoes hydrolysis (Scheme 3). The secondary β-deuterium isotope effect on the hydrolysis of monodeuteriated ethyl acetate induced by deuterioxide ion in D_2O, $(k_{hyd})_H/(k_{hyd})_D = 0.96$, was estimated from $(k_{hyd})_H/(k_{hyd})_{3D} = 0.90$ for the isotope effect on the hydrolysis of trideuteriated ethyl acetate induced by hydroxide ion in water.[34] This isotope effect was then combined with the integrated rate law derived for Scheme 3,[35] to show

(33) $(k_{hyd})_H = 0.15$ H M^{-1} s^{-1} for hydrolysis of ethyl acetate induced by deuterioxide ion in D_2O under our experimental conditions was estimated from $(k_{hyd})_H = 0.11$ M^{-1} s^{-1} for hydrolysis induced by hydroxide ion in H_2O at 25 °C and $I = 1.0$ (KCl),[84] and $k_{HOH}/k_{DOD} = 0.75$ for the secondary solvent isotope effect on hydrolysis.[85]

(34) Bender, M. L.; Feng, M. S. *J. Am. Chem. Soc.* **1960**, *82*, 6318−6321.

(35) The integrated rate equation for Scheme 3 was derived assuming consecutive first-order reactions for the deuterium exchange (k_{ex}) and hydrolysis of the monodeuteriated product ($(k_{hyd})_D$) and a parallel first-order hydrolysis of unexchanged ethyl acetate ($(k_{hyd})_H$).

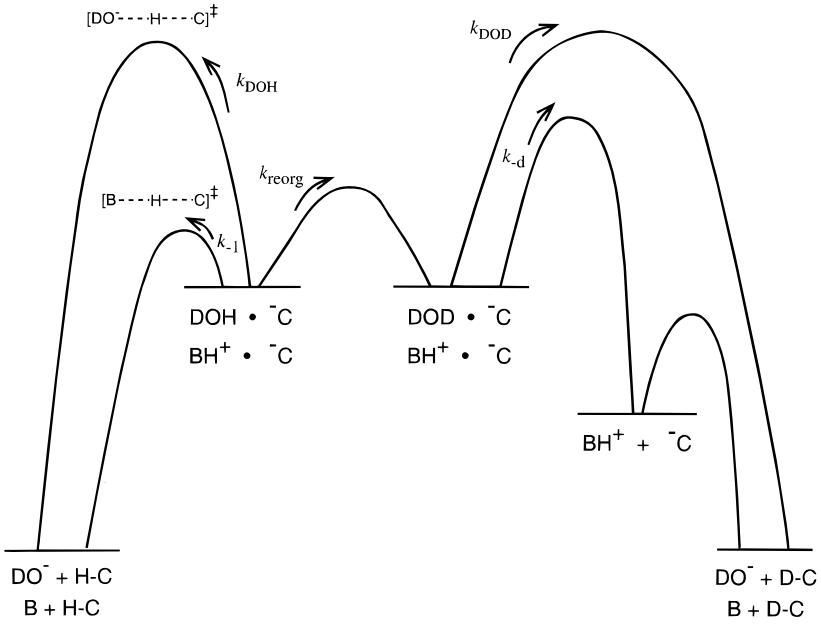
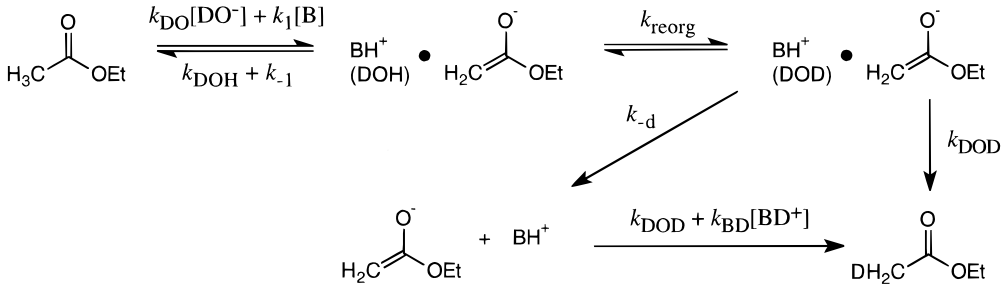


Figure 4. Relative free energy reaction coordinate profiles for exchange for deuterium of the first α-proton of ethyl acetate in D_2O, catalyzed by deuterioxide ion and buffer bases. The rate constants are defined in Scheme 4. The standard state for the buffer bases is defined to be 1 M, and the standard state for deuterioxide ion is defined to be its concentration at pD = pK_{BD}. This convention is useful because it provides a description of the overall catalysis of proton transfer by buffer bases.

Scheme 4



that the observed fractions of monodeuteriated ethyl acetate under our experimental conditions are less than 5% smaller than those expected in the absence of competing hydrolysis or for the case of $(k_{hyd})_H/(k_{hyd})_D = 1.0$. Therefore, the observed rate constants for exchange determined in our experiments (k_{obsd}, Scheme 2), in which there was up to 10% exchange of the first α-proton, differ from the absolute rate constants for exchange (k_{ex}, Scheme 3) by less than 5%, which is within the estimated error of these experiments.

Mechanism of Deuterium Exchange. The exchange for deuterium of the first α-proton of ethyl acetate in D_2O is catalyzed by deuterioxide ion and tertiary amines. The absence of upward curvature of the plots of k_{obsd} against [buffer] (not shown) shows that there is no significant exchange by a termolecular mechanism involving general acid−base catalysis of enolization.[36] Therefore, the results of this work on ethyl acetate, and our previous work on ethyl thioacetate,[23] provide no evidence that concerted formation of the enols of simple carboxylic acid derivatives is a significant pathway for proton abstraction from such compounds in aqueous solution.

Scheme 4 shows possible mechanisms for exchange for deuterium of the first α-proton of ethyl acetate in D_2O, and the corresponding relative reaction coordinate profiles for these pathways are illustrated in Figure 4. Proton transfer from ethyl acetate to deuterioxide ion ($k_{DO}[DO^-]$) or a buffer base ($k_1[B]$) leads to the intimate ion−dipole pair $DOH\cdot^{-}CH_2CO_2Et$ or ion pair $BH^+\cdot^{-}CH_2CO_2Et$, respectively. The subsequent fast reorganization of the local solvation shell of the ion−dipole pair by dielectric relaxation of the solvent ($k_{reorg} \approx 10^{11}$ s^{-1})[37−39] results in a new ion−dipole pair, $DOD\cdot^{-}CH_2CO_2Et$, in which a molecule of D_2O is placed to deliver a deuteron to the carbanionic center. Diffusional separation of the ion pair $BH^+\cdot^{-}CH_2CO_2Et$ (k_{-d}) leads to the free, diffusionally-equilibrated, oxygen ester enolate. Once formed, the free carbanion can react only with D_2O (k_{DOD}) or a molecule of deuteriated buffer acid ($k_{BD}[BD^+]$), resulting in a deuterium exchange event, because the concentrations of DOH and/or BH^+ in D_2O are negligible. The following observations show that deuterium exchange into ethyl acetate proceeds by formation of the free, diffusionally-equilibrated, oxygen ester enolate and does not arise from exchange within the first-formed intimate ion or ion−dipole pairs.

(1) Exchange catalyzed by deuterioxide ion does not take place by reorganization of the local solvation shell of the ion−dipole pair (k_{reorg}, Scheme 4 and Figure 4) followed by proton transfer from a molecule of D_2O *without* complete equilibration of the enolate, because diffusional equilibration of the enolate,

(36) Hegarty, A. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1975**, *97*, 7188−7189.

(37) Giese, K.; Kaatze, U.; Pottel, R. *J. Phys. Chem.* **1970**, *74*, 3718−3725.

(38) Kaatze, U. *J. Chem. Eng. Data* **1989**, *34*, 371−374.

(39) Kaatze, U.; Pottel, R.; Schumacher, A. *J. Phys. Chem.* **1992**, *96*, 6017−6020.

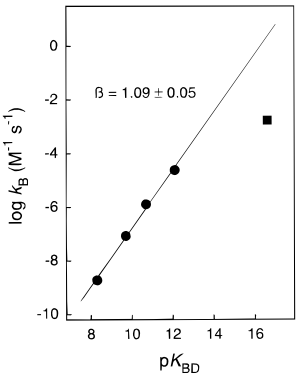


Figure 5. Brønsted correlation for deprotonation of ethyl acetate by 3-substituted quinuclidines in D_2O at 25 °C and $I = 1.0$ (KCl). pK_{BD} are the apparent pK_as of the 3-substituted quinuclidinium cations in D_2O under the experimental conditions, given by pK_{BD} = pD − log([B]/[BD^+]), calculated from the pD of the buffer solutions and the stoichiometric concentrations of [B] and [BD^+]. The data are correlated by $\beta = 1.09 \pm 0.05$ (solid line).[44] Deuterioxide ion (pK_{BD} = 16.6, ■) exhibits a 1600-fold negative deviation from the correlation for 3-substituted quinuclidines.

$k_{-d} \approx 1.6 \times 10^{10}$ s^{-1},[40] is substantially faster than its reaction with solvent, $k_{DOD} \leq k_{HOH} = 5 \times 10^8$ s^{-1} (see below).

(2) There is no significant exchange by reaction of the enolate within the intimate ion pair $BH^+ \cdot {}^-CH_2CO_2Et$ with a molecule of D_2O, because the principle of microscopic reversibility requires that the lowest-energy pathway for the breakdown of an intermediate be the reverse of the preferred pathway for its formation. The proton abstraction from ethyl acetate by a buffer base to give $BH^+ \cdot {}^-CH_2CO_2Et$ therefore requires the collapse of this enolate by proton transfer from the conjugate acid of the *same* buffer base.

(3) There is no significant exchange of the proton of BH^+ within the intimate ion pair $BH^+ \cdot {}^-CH_2CO_2Et$ by reaction with a molecule of D_2O or BD^+, because the diffusional separation of the ion pair, $k_{-d} \approx 1.6 \times 10^{10}$ s^{-1},[40] is faster than both proton exchange between protonated quinuclidines and water ($k_{exchange} < 10^3$ s^{-1})[41] and diffusional encounter with dilute BD^+, $k_d = 5 \times 10^9$ M^{-1} s^{-1}.[42]

(4) Exchange does not arise from the rotational motion of BH^+ within the intimate ion pair $BH^+ \cdot {}^-CH_2CO_2Et$ because tertiary ammonium ions have only one acidic proton. Isotope exchange by such a rotational mechanism is also not a significant pathway for the detritiation of phenylacetylene or of chloroform by primary amines in water.[43]

We conclude that the rate constants $k_{DO} = 1.7 \times 10^{-3}$ M^{-1} s^{-1} and k_B (M^{-1} s^{-1}, Table 2) for exchange for deuterium of the first α-proton of ethyl acetate are the rate constants for deprotonation of the α-methyl group of the substrate by deuterioxide ion and buffer bases, respectively, to give the *free* diffusionally-equilibrated simple oxygen ester enolate, $^-CH_2CO_2Et$.

Brønsted Correlation for Deprotonation of Ethyl Acetate. Figure 5 shows the Brønsted plot for deprotonation of ethyl acetate by 3-substituted quinuclidines in D_2O. The data for deprotonation catalyzed by this homologous series of bases are correlated by a line of slope $\beta = 1.09 \pm 0.05$.[44] General base catalysis of deprotonation of ethyl acetate is readily detectable in spite of this very large Brønsted exponent, because deuterioxide ion exhibits a 1600-fold negative deviation from the Brønsted correlation defined by 3-substituted quinuclidines (Figure 5). Part of the increased efficiency of these tertiary amines as catalysts of proton transfer from carbon might be due to the favorable electrostatic interaction between the negative charge at the enolate and the positive charge at the tertiary ammonium ion in the intimate ion pair $BH^+ \cdot {}^-CH_2CO_2Et$ (Scheme 4); this interaction is absent when the proton is abstracted by a negatively charged base such as deuterioxide ion to give $DOH \cdot {}^-CH_2CO_2Et$ (Scheme 4).[43,45−47] However, large negative deviations of the point for lyoxide ion from Brønsted correlations for anionic bases are also commonly observed. These deviations are manifestations of the well-known "lyoxide ion anomaly",[45,48] which may result in part from a requirement for desolvation of the very strongly basic deuterioxide ion.[48−50]

The large negative deviation (1600-fold) of deuterioxide ion from the Brønsted correlation for 3-substituted quinuclidines shown in Figure 5 strongly favors the hydrolysis of ethyl acetate over its deprotonation and deuterium exchange reactions when deuterioxide ion is the sole catalytic base, and it accounts for the failure to observe base-catalyzed deuterium exchange into ethyl acetate in an earlier study.[24] The change to 0.50 M quinuclidine at pD = pK_{BD} = 12.1 ([buffer] = 1.0 M) as the catalytic base results in a 4.3-fold increase in the observed rate constant for deuterium exchange over that for exchange catalyzed by deuterioxide ion alone. This advantage to the exchange catalyzed by tertiary amine over deuterioxide ion at pD = pK_{BD} is almost insensitive to the basicity of the amine, pK_{BD}, because the Brønsted exponent of close to unity requires that changes in pD result in equal changes in the pseudo-first-order rate constants for proton abstraction mediated by buffer bases and deuterioxide ion.

The Brønsted exponent $\beta = 1.09 \pm 0.05$ strongly suggests that proton transfer from ethyl acetate to tertiary amines is essentially complete in the rate-limiting transition state, so that the rates of these thermodynamically uphill proton transfers are limited by the diffusional separation of the intimate ion pairs $BH^+ \cdot {}^-C$ to give the free enolate and the solvated tertiary ammonium ions $BH^+ \cdot OH_2$ (k_{-d}, Scheme 5). In the reverse direction, this corresponds to an encounter-limited protonation of the free ester enolate by tertiary ammonium ions (k_{enc}, Scheme 5). The following considerations strongly support the conclusion that the reaction of the enolate of ethyl acetate with tertiary ammonium ions is limited by formation of the encounter complex $BH^+ \cdot {}^-C$ (k_{enc}) rather than the subsequent proton transfer step (k_p).

(1) The rate constant for deprotonation of ethyl acetate by 3-quinuclidinone (pK_{BH} = 7.5)[51] in D_2O, with a statistical correction for the number of acidic protons, is $k_B = 6.3 \times 10^{-10}$ M^{-1} s^{-1} (Table 2), which is (1.4×10^5)-fold smaller than the statistically-corrected rate constant for deprotonation of acetone by the same base, $k_B = 8.7 \times 10^{-5}$ M^{-1} s^{-1}.[23] The Brønsted

(40) The estimated rate constant for diffusional separation of a carbocation−anion ion pair is $k_{-d} = 1.6 \times 10^{10}$ s^{-1}.[92,93]

(41) Berg, U.; Jencks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 6997−7002.

(42) Rate constants of (5−7) × 10^9 M^{-1} s^{-1} for the diffusion-limited reactions of a wide range of benzylic carbocations with azide ion have been determined directly by laser flash photolysis.[89−91]

(43) Lin, A. C.; Chiang, Y.; Dahlberg, D. B.; Kresge, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 5380−5386.

(44) The slope of the Brønsted correlation that does not include the point for 3-quinuclidinone (pK_{BD} = 8.3) is $\beta = 1.01$.

(45) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475−503.

(46) Thibblin, A. *J. Am. Chem. Soc.* **1984**, *106*, 183−186.

(47) Richard, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 4926−4936.

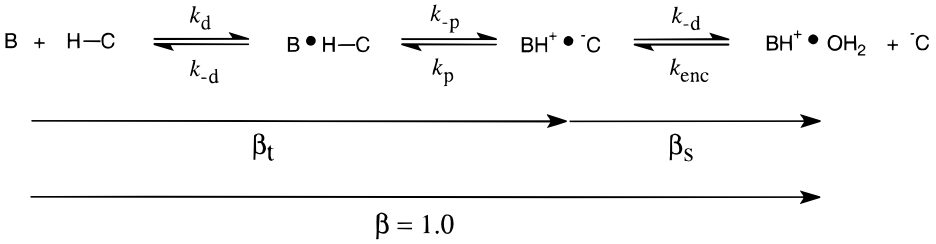
(48) Washabaugh, M. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 683−692.

(49) Hupe, D. J.; Wu, D. *J. Am. Chem. Soc.* **1977**, *99*, 7653−7659.

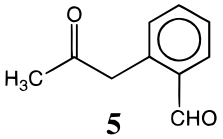
(50) Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, G.; Nakamura, C. *J. Am. Chem. Soc.* **1982**, *104*, 7045−7051.

(51) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963−6980.

Scheme 5



coefficient for deprotonation of acetone by 3-substituted quinuclidines has not been determined, but values of $\beta = 0.48$ and 0.53 for these bases have been determined for deprotonation of the hydroxymethyl group of dihydroxyacetone phosphate dianion ($pK_a^K \approx 18$)[47] and the methyl group of **5** ($pK_a^K \approx 19.6$),[52] respectively. The carbon acid acidities of these



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compounds are similar to that of acetone ($pK_a^K = 19.3$),[18,53] so that we estimate $\beta \approx 0.5$ for deprotonation of acetone by 3-substituted quinuclidines. The increase from $\beta \approx 0.5$ to $\beta = 1.09$ that accompanies a (1.4×10^5)-fold decrease in the reactivity of the substrate toward a base of $pK_{BH} = 7.5$ is substantially larger than the increase from $\beta = 0.48$ for deprotonation of acetylacetone[54] to $\beta = 0.88$ for deprotonation of acetone[55] by substituted carboxylate ions, for which there is an even larger, (2.6×10^6)-fold decrease in reactivity toward a base of $pK_{BH} = 7.5$.[56] A simple explanation for the unusually sharp increase in the structure−reactivity parameter β is that it is due to a change from rate-determining chemical steps for the formation and reaction of the enolate of acetone (k_{-p} and k_p, Scheme 5) to rate-determining transport steps, with rate constants that are independent of buffer reactivity (k_{-d} and k_{enc}, Scheme 5), for the formation and reaction of the enolate of ethyl acetate.

(2) A logarithmic plot of the rate constants for deprotonation of methyl and benzylic monocarbonyl compounds by hydroxide ion against the logarithm of their ionization constants, K_a^K, has a slope of 0.40.[18] This empirical correlation shows that approximately 40% of the equilibrium substituent effects are expressed in the transition state of the chemical step for formation of the enolates, so that the substituent effects on the chemical steps for formation and reaction of these enolates are roughly similar. The second-order rate constant for deprotonation of ethyl acetate by deuterioxide ion in D_2O, $k_{DO} = 1.7 \times 10^{-3}$ M^{-1} s^{-1} (see Results), can be combined with an estimated secondary solvent isotope effect of $k_{DO}/k_{HO} = 1.4$,[57] to give $k_{HO} = 1.2 \times 10^{-3}$ M^{-1} s^{-1} for deprotonation of ethyl acetate by hydroxide ion in H_2O. Therefore, the statistically corrected rate constant for deprotonation of acetone by hydroxide ion, $k_{HO} = 0.22/6 = 0.037$ M^{-1} s^{-1},[53] is 93-fold larger than that for deprotonation of ethyl acetate, $k_{HO} = 1.2 \times 10^{-3}/3 = 4.0 \times 10^{-4}$ M^{-1} s^{-1}. This suggests that, if proton transfer were the rate-determining step, then the rate constant for reaction of the enolate of ethyl acetate with protonated 3-quinuclidinone would be *ca.* 100-fold larger than $k_{BH} = 2 \times 10^8$ M^{-1} s^{-1} for reaction of the enolate of acetone with this buffer acid.[23] However, the hypothetical rate constant of $k_{BH} = 2 \times 10^{10}$ M^{-1} s^{-1} for activation-limited protonation of the ester enolate exceeds that for a diffusion-limited reaction,[42] so that this proton transfer reaction must proceed at the encounter-controlled limit, with $k_{BH} = k_{enc}$ (Scheme 5).

The conclusion that proton transfer from tertiary ammonium ions to the enolate of ethyl acetate is limited by formation of the encounter complex leads to the expectation that the Brønsted exponent for deprotonation of ethyl acetate by 3-substituted quinuclidines should be unity, so that, at first sight, the observed value of $\beta = 1.09$ appears anomalous. However, Brønsted exponents for variation of the buffer base that are greater than unity are possible when there are changes in the solvation of the conjugate acid of the base catalyst (BH^+) on moving from the encounter complex $BH^+ \cdot C^-$ to the free buffer acid $BH^+ \cdot OH_2$ in solution, which involves the formation of a hydrogen bond between BH^+ and water. These changes in solvation are sensitive to pK_{BH} with $\beta_s < 0$ (Scheme 5), so that the requirement $\beta_t + \beta_s = 1.0$ results in $\beta_t > 1.0$ for the proton transfer step (Scheme 5).[58−60] The value of $\beta = 1.09 \pm 0.05$ for deprotonation of ethyl acetate by 3-substituted quinuclidines is consistent with complete proton transfer in the rate-limiting step, with $\beta_t = 1.04$ to 1.14 and $\beta_s = -0.14$ to -0.04 for solvation ($=\alpha_d$ for desolvation) of the 3-substituted quinuclidinium cations. Similarly, the value of $\beta = 1.12 \pm 0.05$ for detritiation of chloroform by primary amines[43] is consistent with $\beta_s = -0.17$ to -0.07 for solvation of primary ammonium cations. These values of β_s are somewhat smaller in magnitude than $\alpha_d = -0.2$ estimated for the desolvation of substituted carboxylic acids.[58,59]

The value of $\beta = 1.09 \pm 0.05$ for deprotonation of ethyl acetate is the largest Brønsted exponent yet observed for proton transfer from a carbonyl-activated carbon acid, and the reactions of the simple oxygen ester enolate with tertiary ammonium ions

(52) Nagorski, R. W.; Mizerski, T.; Richard, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 4718−4719.

(53) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460−462.

(54) Bell, R. P.; Gelles, E.; Möller, E. *Proc. R. Soc. London, Ser. A* **1949**, *198*, 308−322.

(55) Bell, R. P.; Lidwell, O. M. *Proc. R. Soc. London, Ser. A* **1940**, *176*, 88−113.

(56) Estimated rate constants of 62 M^{-1} s^{-1} and 7.0×10^{-5} M^{-1} s^{-1} for deprotonation of acetylacetone and acetone, respectively, by a base of $pK_{BH} = 7.5$ were obtained by extrapolation of Brønsted plots for deprotonation of these compounds by chloroacetate, glycolate, acetate, and trimethylacetate ions. The Brønsted plots were constructed using the data of Bell for deprotonation of acetylacetone[54] and acetone[55] by these bases and values of pK_{BH} for the corresponding substituted acetic acids from the following: Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry and Molecular Biology (Physical and Chemical Data)*, 3rd ed.; Fasman, G. D., Ed.; CRC Press: Cleveland, OH, 1976; Vol. 1, pp 305−351.

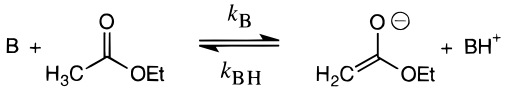
(57) Secondary solvent isotope effects of $k_{DO}/k_{HO} = 1.3-1.5$ have been determined for hydron transfer from carbon to lyoxide ion in several related systems: racemization of the anion of mandelic acid at 100 °C, $k_{DO}/k_{HO} = 1.4$;[86] detritiation of phenylacetylene at 25 °C, $k_{DO}/k_{HO} = 1.36$;[87] detritiation of chloroform at 25 °C, $k_{DO}/k_{HO} = 1.48$;[87] base-catalyzed bromination of acetone at 25 °C, $k_{DO}/k_{HO} = 1.46$.[88]

(58) Murray, C. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 7561−7563.

(59) Murray, C. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1990**, *112*, 1880−1889.

(60) Washabaugh, M. W.; Stivers, J. T.; Hickey, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 7094−7097.

Scheme 6



are the first examples of protonation of an enolate by a general acid that takes place at the encounter limit. These observations reflect the very large thermodynamic barrier to enolization of ethyl acetate, which takes place very far from $\Delta pK = pK_a^K - pK_{BH} = 0$ for thermoneutral proton transfer. The reactions of ethyl acetate with 3-substituted quinuclidines are an example, so far unique, of proton transfer from carbon in which a carbonyl compound acts as a "normal" acid.

Carbon Acid Acidity and Enol Content of Ethyl Acetate in Aqueous Solution. Scheme 6 shows that the pK_a^K for ionization of ethyl acetate as a carbon acid can be obtained from the rate constants for its deprotonation by buffer bases to give the free enolate (k_B) and for protonation of the free enolate by the corresponding conjugate acids of these bases (k_{BH}), according to eq 7. Values of k_B for deprotonation of ethyl acetate by

$$pK_a^K = pK_{BH} + \log(k_{BH}/k_B) \qquad (7)$$

3-substituted quinuclidines in D_2O have been determined in this work (Table 2), and as discussed above, k_{BH} are the rate constants for formation of the encounter complexes between the 3-substituted quinuclidinium cations and the enolate (k_{enc}, Scheme 5). However, the limiting rate constants for formation of such encounter complexes, which involves both diffusional encounter of a carbanion with a solvated tertiary ammonium ion $BH^+ \cdot OH_2$ and a desolvation step to give $BH^+ \cdot {}^-C$, are not known. If desolvation of the tertiary ammonium ion is kinetically significant, then k_{enc} ($=k_{BH}$) for the encounter-limited reactions of the enolate of ethyl acetate with 3-substituted quinuclidinium cations will lie below $k_d = 5 \times 10^9$ M^{-1} s^{-1} for a diffusion-limited reaction.[42]

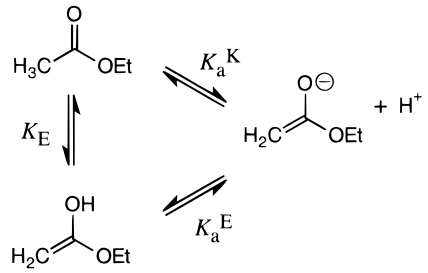
The value of $\beta = 1.09 \pm 0.05$ for deprotonation of ethyl acetate by 3-substituted quinuclidines corresponds to $\alpha = -0.09 \pm 0.05$ for reaction of the enolate of ethyl acetate with 3-substituted quinuclidinium cations, so that desolvation of these cations may be partially rate-limiting at least for those more acidic than the quinuclidinium cation ($pK_{BH} = 11.5$). By contrast, the value of $\alpha = 0.48$ for reaction of the enolate of the acetone analog **5** with 3-substituted quinuclidinium cations of $pK_{BH} = 7.5-11.5$[52] shows that the reactions of this more stable enolate are limited by the *chemical* barrier to the proton transfer step (k_p, Scheme 5) rather than the formation of the encounter complex ($k_{-d} \gg k_p$, eq 8 and Scheme 5). A change

$$k_{BH} = k_{enc}k_p/(k_{-d} + k_p) \qquad (8)$$

to partially rate-limiting encounter for these reactions would be most likely for protonated 3-quinuclidinone ($pK_{BH} = 7.5$), for which $k_{BH} = 8 \times 10^8$ M^{-1} s^{-1}.[61] However, the point for this catalyst exhibits a smaller than 2-fold (0.3 log unit) negative deviation from the correlation for the less acidic catalysts,[61] so that for protonated 3-quinuclidinone, $k_{enc} \geq 2k_{BH} = 1.6 \times 10^9$ M^{-1} s^{-1} ($k_{-d} \geq k_p$, eq 8 and Scheme 5). Rate-limiting desolvation of the less acidic protonated quinuclidine ($pK_{BH} = 11.5$) should be even less important than for protonated 3-quinuclidinone, so that we estimate $k_{enc} = k_{BH} = (2-5) \times 10^9$ M^{-1} s^{-1} for reaction of the enolate of ethyl acetate with protonated quinuclidine.

(61) Nagorski, R. W.; Mizerski, T.; Richard, J. P. Unpublished results.

Scheme 7



The limits of $k_{BH} = (2-5) \times 10^9$ M^{-1} s^{-1} and $k_B = 2.4 \times 10^{-5}$ M^{-1} s^{-1} for deprotonation of ethyl acetate by quinuclidine (Table 2) were substituted into eq 7 with $pK_{BH} = 11.5$[51] to give $pK_a^K = 25.6 \pm 0.5$ for ionization of ethyl acetate as a carbon acid in aqueous solution. This treatment neglects the secondary solvent isotope effect on k_B arising from its determination here in D_2O rather than in H_2O. However, a value of $k_B(H_2O)/k_B(D_2O) = 1.1$ has been determined for deprotonation of L-glyceraldehyde 3-phosphate dianion by 3-quinuclidinone,[47] and for detritiation of the 3-(cyanomethyl)-4-methylthiazolium ion by acetate ion,[62] so that this assumption does not lead to a significant error in our calculation of pK_a^K for ethyl acetate in H_2O.

Scheme 7 shows that if the acidity constants of both ethyl acetate, K_a^K, and its enol, K_a^E, are known, then the enol content of ethyl acetate in aqueous solution can be calculated as $K_E = K_a^K/K_a^E$. It is not possible to determine K_a^E for the highly reactive enol of ethyl acetate by any simple experiment. However, $pK_a^E \approx 7$ for this enol can be estimated from $pK_a^E = 6.6$ for the enol of mandelic acid,[19] using corrections based on the 1 pK unit greater acidity of the trans enol of phenylacetaldehyde ($pK_a^E = 9.5$) than of the enol of acetaldehyde ($pK_a^E = 10.5$),[18,63] and the 0.6 pK unit lesser acidity of the cis enol of 2′-methoxyacetophenone ($pK_a^E = 10.9$) than of the enol of acetophenone ($pK_a^E = 10.3$).[18,63] This analysis makes the assumptions that an α-ethoxy group is modeled by an α-hydroxy group, and that the effect of a β-hydroxy group on pK_a^E is similar to that of a β-methoxy group. The values of $pK_a^K = 25.6$ and $pK_a^E = 7$ then give $pK_E = 18.6$ ($K_E = 2.5 \times 10^{-19}$) for the enol content of ethyl acetate in aqueous solution (Scheme 7). Thus the enol content of ethyl acetate is 1600-fold smaller than the enol content of mandelic acid ($pK_E = 15.4$)[17,19] and 10 orders of magnitude smaller than the enol content of the simplest ketone, acetone ($pK_E = 8.33$).[18,53] Our estimate of $pK_E = 18.6$ for ethyl acetate is close to the values of $pK_E = 21.0$[64] and 19.4[65] for acetic acid and $pK_E = 19.4$ for methyl acetate[65] that were obtained using calculated free energies of formation of the enols of these compounds in aqueous solution.

Effects of Oxygen and Sulfur Substituents. The determination in this work of $pK_a^K = 25.6$ for ionization of ethyl acetate allows evaluation of the effects of oxygen and sulfur substituents attached to the carbonyl group on the acidity of simple carboxylic acid derivatives in aqueous solution. The data in Table 3 show that ethyl acetate is 4.6 pK units less acidic than ethyl thioacetate ($pK_a^K = 21.0$),[23] so that a change from a simple oxygen ester to the related thiol ester leads to a (4×10^4)-fold increase in the acidity of the carbon acid.

The only other acidity constants available for analogous oxygen and thiol esters are those for the 9-acylfluorenyl

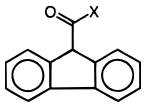
(62) Washabaugh, M. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 674−683.

(63) It is thought that $pK_a^E = 6.6$ for the enol of mandelic acid is for ionization of the enolic hydroxyl placed trans to the β-phenyl group and cis to the β-hydroxy group.[17,19]

(64) Guthrie, J. P. *Can. J. Chem.* **1993**, *71*, 2123−2128.

(65) Guthrie, J. P.; Liu, Z. *Can. J. Chem.* **1995**, *73*, 1395−1398.

Table 3. Effects of Oxygen and Sulfur Substituents on the Carbon Acid Acidity of Acetyl and 9-Acylfluorenyl Derivatives in Aqueous Solution[a]

	pK_a^{K} [b]		
carbon acids	X = CH_3	X = SR	X = OR
	19.3[c]	21.0[d]	25.6[e]
 **4-X**	9.9[f]	10.5[g]	11.5[g]

[a] At 25 °C. [b] pK_a for ionization of the carbon acid. [c] Data from refs 18 and 53 at $I = 0.1$. [d] R = Et. Data from ref 23 at $I = 1.0$ (KCl). [e] R = Et. Data from this work at $I = 1.0$ (KCl). [f] Data from ref 70. [g] R = Me. Data from ref 22 at $I = 0.1$.

Scheme 8

$$HO^- + H\text{-}C \underset{k_{HOH}/[HOH]}{\overset{k_{HO}}{\rightleftharpoons}} H_2O + {}^-C$$

$$K_{eq} = k_{HO}[HOH]/k_{HOH} = K_a^{K}/K_a^{w}$$

derivatives (**4-X**) recently reported by Kresge *et al*. (Table 3).[22] However, 9-acetylfluorene (**4-Me**) is 9.4 p*K* units more acidic than acetone (Table 3), which shows that the 9-fluorenyl nucleus provides considerable resonance stabilization of the enolate.[22,66,67] The data in Table 3 show that the effects of alkylthio and alkoxy substituents at the carbonyl group on the carbon acid acidities of **4-X** are much smaller than those for simple acyl derivatives, so that these substituent effects are strongly attenuated by the 9-fluorenyl group. The effect of the change from a methyl to an alkoxy substituent at **4-X** is similar to the 1.7 unit difference in the acidities of the doubly activated dicarbonyl compounds acetylacetone (pK_a^{K} = 8.9)[68] and ethyl acetoacetate (pK_a^{K} = 10.6),[69a] so that the attenuation of the effects of substituents at the carbonyl group on the acidity of simple acyl derivatives by the 9-fluorenyl group is similar to that of a second carbonyl group.

Rate−Equilibrium Relationships and Intrinsic Barriers for Enolization. Keeffe and Kresge have reported that a logarithmic plot of the statistically corrected rate constants for deprotonation of methyl and benzylic monocarbonyl compounds by hydroxide ion, log(k_{HO}/p), against the statistically corrected ionization constants of the carbon acids, log(K_a^{K}/p), where *p* is the number of acidic protons of the carbon acid, is linear with a slope of 0.40.[18] Therefore, approximately 40% of the substituent effect on the equilibrium constant for formation of the enolate (K_{eq}, Scheme 8) is expressed in the rate constant for its formation (k_{HO}, Scheme 8). The linearity of this empirical rate−equilibrium correlation, which spanned a range of 11 p*K* units and included both thermodynamically favorable and unfavorable reactions, stands in sharp contrast with the reports of changes in Brønsted exponents for variation of the base catalyst with changing pK_a^{K} of a wide range of carbon acids.[59,70−72]

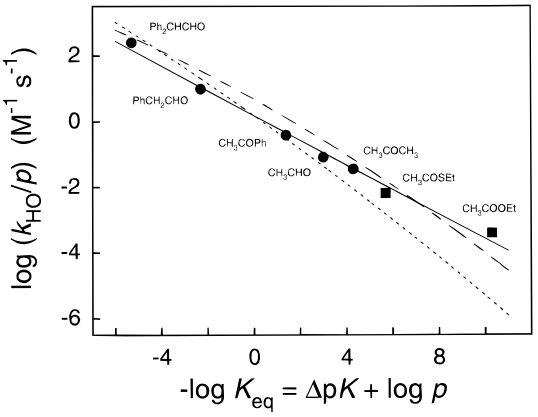


Figure 6. Rate−equilibrium correlation for deprotonation of simple monocarbonyl compounds by hydroxide ion in aqueous solution (Scheme 8), constructed using the data in Table 4. The rate constants, k_{HO} (M^{-1} s^{-1}), and the equilibrium constants, K_{eq}, have been corrected for the number of acidic protons of the carbon acid, *p*: ●, data from the earlier correlation of Keeffe and Kresge;[18] ■, data for simple carboxylic acid derivatives. The solid line through the data has a slope of −0.38. Dotted line: Theoretical correlation calculated from eq 9 with $w_r = 0$ and $\Lambda = 17.2$ kcal/mol (see text). Dashed line: theoretical correlation calculated from eq 9 with $w_r = 9.6$ kcal/mol and $\Lambda = 11.2$ kcal/mol (see text).

Table 4. Rate and Equilibrium Constants for Proton Transfer between Hydroxide Ion and Ethyl Acetate and Related Carbon Acids in Aqueous Solution (Scheme 8)[a]

carbon acid	pK_a^{K} [b]	$-\log K_{eq}$ [c] = pK_a^{K} + log *p* − 15.74	k_{HO} [d] (M^{-1} s^{-1})
CH_3COOEt [e]	25.6	10.3	1.2×10^{-3} [f]
CH_3COSEt	21.0[g]	5.7	0.02[h]
CH_3COCH_3	19.3	4.3	0.22
CH_3COPh	18.3	3.0	0.25
CH_3CHO	16.7	1.4	1.17
$PhCH_2CHO$ [i]	13.1	−2.3	20
Ph_2CHCHO	10.4	−5.3	254

[a] At 25 °C. Unless noted otherwise, data are taken from ref 18. [b] pK_a for ionization of the carbon acid. [c] Negative logarithm of equilibrium constant for deprotonation of the carbon acid by hydroxide ion, calculated using a statistical correction for the number of acidic protons of the carbon acid, *p*, and pK_a^{w} = 15.74 for ionization of water. [d] Observed second-order rate constant for deprotonation of the carbon acid by hydroxide ion. [e] Data from this work. [f] Calculated from $k_{DO} = 1.7 \times 10^{-3}$ M^{-1} s^{-1} in D_2O using a secondary solvent isotope effect of $k_{DO}/k_{HO} = 1.4$ (see text). [g] Data from ref 23. [h] Calculated from the data in ref 94. [i] Rate and equilibrium data refer to formation of the cis enolate.

Figure 6, constructed using the data in Table 4, shows an Eigen-type plot of the statistically corrected rate constants for proton transfer between hydroxide ion and simple monocarbonyl compounds, log(k_{HO}/p), against $\Delta pK = -\log K_{eq} = pK_a^{K} + \log p - 15.74$ (Scheme 8, where $K_a^{w} = 10^{-15.74}$ is the ionization constant of water). This figure includes representative data from the earlier correlation (●)[18] and new data for the simple carboxylic acid derivatives ethyl thioacetate and ethyl acetate (■) that extend the rate−equilibrium correlation by 6 p*K* units in the thermodynamically unfavorable direction. The good linear correlation, with a slope of −0.38 (Figure 6, solid line), is maintained even for enolization of ethyl acetate, which is

(66) Harcourt, M. P.; More O'Ferrall, R. A. *J. Chem. Soc., Chem. Commun*. **1987**, 822−823.
(67) Harcourt, M. P.; More O'Ferrall, R. A. *Bull. Soc. Chim. Fr*. **1988**, 407−414.
(68) Ahrens, M. L.; Eigen, M.; Kruse, W.; Maass, G. *Ber. Bunsen-Ges. Phys. Chem*. **1970**, *74*, 380−385.
(69) (a) Bunting, J. W.; Kanter, J. P. *J. Am. Chem. Soc*. **1993**, *115*, 11705−11715. (b) Bunting has pioneered the use of a variable Marcus intrinsic barrier to describe proton transfer from β-keto esters and amides and other carbon acids: See ref 69a and references therein.
(70) Argile, A.; Carey, A. R. E.; Fukata, G.; Harcourt, M.; More O'Ferrall, R. A.; Murphy, M. G. *Isr. J. Chem*. **1985**, *26*, 303−312.
(71) Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973; p 203.
(72) Guthrie, J. P. *Can. J. Chem*. **1979**, *57*, 1177−1185.

thermodynamically uphill by 14 kcal/mol and for which the expected late enolate ion like transition state would be expected to result in a relatively *large* expression of the equilibrium substituent effect.

The dotted line in Figure 6 shows that there is a poor fit of the data in Table 4 to the Marcus equation (eq 9, derived at 298 K) without the inclusion of a work term ($w_r = 0$) and with a constant intrinsic barrier of $\Lambda = 17.2$ kcal/mol obtained by linear interpolation of the data to $\Delta pK = 0$. However, the small

$$\log k_{HO} = \frac{1}{1.36}\left[17.44 - w_r - \Lambda\left(1 + \frac{1.36\Delta pK - w_r}{4\Lambda}\right)^2\right] \quad (9)$$

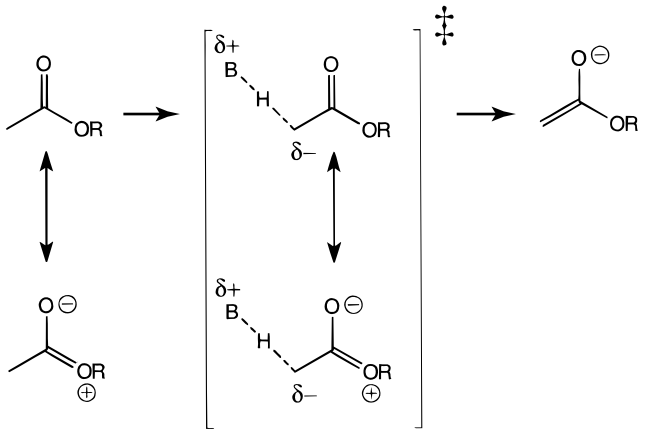
change in the slope of the tangent to this theoretical curve from -0.45 to -0.55 on moving from $\Delta pK = -5$ to $+5$ confirms the earlier conclusion that the large intrinsic barriers to these reactions result in indetectably small Marcus-type curvature over the more limited range of the original correlation.[18] There is no visible improvement of the fit of the data to eq 9 with the inclusion of a work term of $w_r = 9.6$ kcal/mol for formation of the encounter complex between the carbonyl compound and partially desolvated hydroxide ion[73] and a smaller intrinsic barrier of $\Lambda = 11.2$ kcal/mol, which results in more marked curvature of the theoretical correlation (Figure 6, dashed line).

These results strongly suggest that the expected increasingly sharp decreases in rate constant and increases in reaction barrier predicted by the Marcus equation as the proton transfer becomes increasingly uphill thermodynamically are offset or balanced by decreases in the intrinsic barrier to enolization. This results in increasingly large positive deviations of the observed rate constants for proton transfer from the theoretical correlations obtained by simple Marcus treatments with a constant intrinsic barrier, Λ (Figure 6). We suggest two closely related explanations for the gradual decrease in the intrinsic barrier to enolization on moving from the most reactive to the least reactive carbonyl compounds in Figure 6.[69b]

(1) There is very good direct evidence that the intrinsic barrier to proton transfer from carbon increases with increasing stabilization of the resulting carbanion by resonance, and this has been discussed extensively as the *principle of nonperfect synchronization*.[74−77] These increases in intrinsic barrier may be explained by a relatively small development of the resonance interactions present in the sp^2-hybridized carbanion in the transition state, where the developing carbanionic center is still partially sp^3-hybridized.[78] This causes the curvature of the energy surface on approach to the transition state to be steeper than that for a reaction in which the developing negative charge at carbon is not stabilized by resonance delocalization.[79] The most reactive carbonyl compounds in Figure 6 are those whose enolates are stabilized by one or two β-phenyl groups so that the intrinsic barrier to formation of their enolates is expected to be larger than that for the less reactive compounds.

(2) The intrinsic barrier to enolization may also decrease when the relative stability of the enolate is decreased by ground-state resonance stabilization of the keto tautomer, for example by electron donation from an α-alkoxy group to the carbonyl group (Scheme 9). An evaluation of this effect requires consideration of the fractional expression in the transition state of the resonance stabilization of both the keto reactant and the enolate product. There is good evidence that delocalization of developing negative charge in the transition state for proton transfer from carbon "lags" behind breaking of the C−H bond (see above).[74−77] This relatively late development of the resonance stabilization of the product enolate in the transition state will lead to a relatively *small loss* of the ground-state resonance stabilization of α-alkoxy carbonyl compounds such as ethyl acetate (Scheme 9). A simple application of the *principle of nonperfect synchronization*[74−77] then shows that the relatively late loss of this reactant stabilization will lead to a decrease in the intrinsic barrier to the reaction because the stabilization is largely maintained in the transition state.

Scheme 9

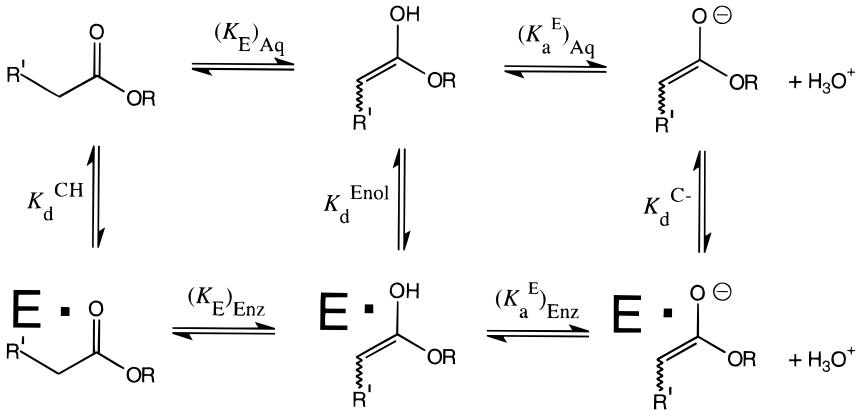


Lifetime of the Enolate of Ethyl Acetate. The rate constant for deprotonation of ethyl acetate by hydroxide ion, $k_{HO} = 1.2 \times 10^{-3}$ M^{-1} s^{-1} (Table 4), can be combined with $pK_a^K = 25.6$ for ionization of ethyl acetate to give $k_{HOH} = 5 \times 10^8$ s^{-1} for reaction of the enolate with bulk water (Scheme 8), so that the lifetime of the enolate of ethyl acetate in aqueous solution is *ca*. 10^{-9} s. However, the conclusion that the rate-limiting step for reaction of this enolate with 3-substituted quinuclidinium cations is the formation of the encounter complex $BH^{+}\cdot^{-}CH_2CO_2Et$ shows that proton transfer from tertiary ammonium ions to the enolate within an intimate ion pair, k_p (Scheme 5), is faster than the diffusional separation of the complex, $k_{-d} \approx 1.6 \times 10^{10}$ s^{-1}.[40] Therefore, the lifetime of a simple oxygen ester enolate in the presence of a general acid of $pK_{BH} \approx 7$, typical of those in the active sites of enzymes, is expected to be shorter than 10^{-10} s. This short lifetime suggests that either the enzyme provides considerable stabilization of these highly unstable carbanions or their formation is avoided by concerted reaction pathways that are enforced because the putative intermediate cannot exist for the time of even a single bond vibration.[6,80,81]

Enzymatic Catalysis. There is considerable interest in understanding the mechanism for catalysis of the enolization of simple oxygen esters and carboxylic acid derivatives, because the latter occurs as the first step of a number of enzymatic racemization and elimination reactions.[2−4] The importance of general acid catalysis in the mechanism of enzyme-catalyzed enolization has been emphasized.[7−10] However, it is even more important to understand that by far the largest barrier to formation of the enol of a simple oxygen ester in water is the *thermodynamic* barrier of *ca*. 25 kcal/mol determined in this work. The magnitude of this barrier is such that in 1.0 mL of a 17 mM solution of ethyl acetate in water there will be on average just a single molecule of the enol! This very large barrier to enolization in water cannot be reduced in an enzyme

(73) Guthrie, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 7249−7255.
(74) Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219−3234.
(75) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301−308.
(76) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119−238.
(77) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9−16.
(78) Kresge, A. J. *Can. J. Chem.* **1974**, *52*, 1897−1903.
(79) Richard, J. P. *Tetrahedron* **1995**, *51*, 1535−1573.
(80) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161−169.
(81) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345−375.

Scheme 10



active site simply by placing basic and acidic amino acid residues in appropriate positions to provide assistance by a concerted reaction mechanism. Rather, it is required that the enzyme bind the enol or enolate tautomer of the substrate more tightly than the keto tautomer (Scheme 10), and that the additional binding energy be utilized to stabilize the transition state for enolization.[82] This is illustrated by eqs 10 and 11 for reactions that proceed through enol and enolate intermediates, respectively (Scheme 10).

$$K_d^{enol}/K_d^{CH} = (K_E)_{aq}/(K_E)_{enz} \qquad (10)$$

$$K_d^{C-}/K_d^{CH} = (K_E)_{aq}(K_a^E)_{aq}/[(K_E)_{enz}(K_a^E)_{enz}] \qquad (11)$$

There are several ways in which an enzyme catalyst may achieve differential binding of a carbonyl compound and its enol and enolate:

(1) There may be specific stabilization of the enolate by its interaction with cationic amino acid side chains or a bound metal ion at the enzyme active site.[11] These interactions would have the effect of decreasing $p(K_a^E)_{enz}$ for ionization of the enolic hydroxyl group in the enzyme active site to below $p(K_a^E)_{aq}$ for its ionization in water (eq 11 and Scheme 10). We have shown that deprotonation of ethyl acetate by general bases is limited by the diffusional separation of the intimate ion pair $BH^{+}\cdot^{-}CH_2CO_2Et$, so that the transition state for proton transfer in water strongly resembles the enolate ion and enolization occurs at the maximum possible rate for a given thermodynamic barrier. Therefore, any structural features of an enzyme active site that provide stabilization of an oxyanion will be fully expressed in the transition state for formation of the enolate, so that electrostatic enzymatic catalysis will result in a maximal rate acceleration for a given increase in thermodynamic driving force.

(2) It has been noted that single-potential or "low-barrier" hydrogen bonds[12,13] to anions, with bond strengths of up to *ca*. 20 kcal/mol, may form in the gas phase, and it has been suggested that the formation of such hydrogen bonds might result in the specific stabilization of "enolic" intermediates of enzyme-catalyzed reactions.[7−10] However, it is difficult to understand how such interactions, although stabilizing in the gas phase, might lead to an increased affinity of an enolate (decrease in K_d^{C-}, Scheme 10) for an enzyme catalyst in water. These hydrogen bonds do not persist in water, a solvent which provides effective stabilization of localized negative charge. In order for hydrogen bonds of this type to form in an enzyme active site, it would be necessary to force the substrate into a binding pocket of low polarity and dielectric constant, where the negatively charged enolate will be intrinsically unstable. However, it is not clear that the energy price paid for this unfavorable transfer step will be returned in the formation of a low-barrier hydrogen bond. For example: (a) The barrier to transfer of the enolate of acetic acid from water to the gas phase is *ca*. 68 kcal/mol,[95] but no more than *ca*. 20 kcal/mol of this would be recovered by the formation of a hydrogen bond to a neutral acid. Such a hydrogen bond would be driven toward a single-potential structure, which allows the maximum dispersion of negative charge across the hydrogen bond donor and acceptor.[96] (b) Single-potential hydrogen bonds are significantly weaker in organic solvents than in the gas phase, and the former may serve as models for protein interiors of low effective dielectric constant.[97,98] There is only a 5 kcal/mol increase in the strength of the intramolecular hydrogen bond in the citraconic monoanion upon its transfer from water to chloroform.[99] However, once again, this increase in hydrogen bond strength may be due mainly to a greater stabilization of negative charge resulting from its increased dispersion in the organic solvent than in water.

Hydrogen bond formation is favored at an enzyme active site compared to solution, because the loss in translational and rotational entropy on proceeding from a free Brønsted acid in

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solution to a hydrogen-bonded species is expected to be larger than that for formation of the same type of hydrogen bond to an acidic amino acid side chain.[100] However, the *change* from a double- to a single-potential structure should not be strongly favored by the immobilization of acidic amino acid side chains at an enzyme active site. This would require that substrate binding eliminate a large entropic barrier to the interconversion of double- and single-potential hydrogen bonds in water; however, the two types of hydrogen bonds have similar structures and degrees of translational, rotational, and vibrational freedom and would therefore be expected to have similar entropies of formation.

It is interesting to note the results of a simple Coulomb's law calculation which shows that the strength of the interaction between an anion and a dication in the gas phase at a distance of 5 Å is 130 kcal/mol, which is much larger than that of low-barrier or single-potential hydrogen bonds.[12,13] Therefore, if it *were* possible to derive net catalysis by stabilization of an enolate anion in an active site of low effective dielectric constant, there would be a much larger advantage to electrostatic stabilization of the enolate by its interaction with an enzyme-bound metal ion such as Mg^{2+} than to its interaction with a hydrogen bond donor.

(3) There may be preferential stabilization by an enzyme of an enol and/or enolate resulting from increases in binding energy that are a direct consequence of the changes in bond angles that occur as the geometry of the α-carbonyl carbon changes from tetrahedral to planar on proceeding from the keto tautomer of the substrate to the enol(ate) intermediate.

Our data, which quantify the barrier to enolization of a simple oxygen ester in water, show that the thermodynamic barrier to this reaction is much larger than that to enolization of an aldehyde or ketone, so that a much larger rate acceleration will be required for efficient enzymatic catalysis of the former reaction. There is much that remains to be learned about the mechanism of these enzymatic reactions that results in the more efficient catalysis of enolization of simple carboxylic acid derivatives than of simple ketones.

Acknowledgment. We acknowledge the National Institutes of Health (Grant GM 39754) for support of this work. We thank Jiali Gao for helpful discussion.

JA953664V

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