Flash Photolysis of 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one in Aqueous Solution: Hydration of Acetylketene and Ketonization of Acetoacetic Acid Enol

Y. Chiang,[†] H.-X. Guo,[†] A. J. Kresge,*,[†] and O. S. Tee[‡]

Contribution from the Department of Chemistry, University of Toronto,
Toronto, Ontario M5S 1A1, Canada, and Department of Chemistry and Biochemistry,
Concordia University, Montreal, Quebec H3G 1M8, Canada

Received December 4, 1995[⊗]

Abstract: Acetylketene was produced by flash photolysis of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one in aqueous solution, and rates of hydration of the ketene to acetoacetic acid enol and subsequent ketonization of the enol were measured in this solvent across the acidity range $[H^+] = 1 - 10^{-13}$ M. Acetylketene proved to be a remarkably reactive substance, undergoing uncatalyzed hydration with the rate constant $k = 1.5 \times 10^6$ s^{-1}, some 10^4 times more rapidly than ketene itself; the acetylketene hydration reaction was also catalyzed weakly by hydroxide ion but not by hydrogen ion. Ketonization of acetoacetic acid enol was much slower with rates in the millisecond to second range. The reaction showed a complex rate profile that could be interpreted in terms of rate-determining carbon protonaton of the carboxylate-ionized form of the enol in the acid region and rate-determining carbon protonation of the doubly ionized carboxylate−enolate form in the basic region. Analysis of the data provided the acidity constant $pQ_a = 4.05$ for the carboxylic acid group of the enol and $pQ_a^E = 13.18$ for its enolic hydroxyl group. (These acidity constants are concentration quotients referring to an ionic strength of 0.10 M). Combination of the present results with information on the enolization of acetoacetic acid available from the literature gave $K_E = 5.6 \times 10^{-3}$, $pK_E = 2.25$, as an estimate of the keto−enol equilibrium constant.

Keto−enol isomerism of β-keto esters has been investigated for more than a century, and these systems consequently provide some of the most extensively documented examples of such tautomerism available today.[1] In striking contrast, very few studies of tautomerism in β-keto acids have been carried out,[2] and only one of these has dealt with the prototype substance acetoacetic acid.[2a] We wish to report that we have now generated the enol of acetoacetic acid in aqueous solution through the hydration of acetylketene (eq 1) and have examined its ketonization, (eq 2) under various conditions of acidity and

(1)

(2)
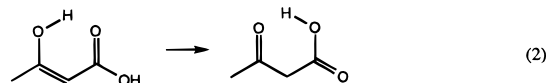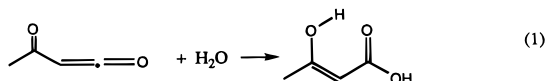
basicity. Our results provide values of acid dissociation constants for both the hydroxy and carboxylic acid groups of the enol, and together with a literature value of the rate of enolization,[2a] they also furnish an estimate of the keto−enol equilibrium constant for this system.

We produced acetylketene by flash photolysis of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**1**) (eq 3). This substance is

(3)
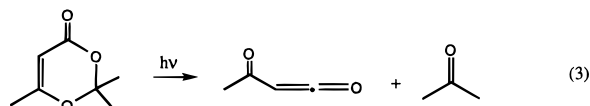
known to undergo thermolytic and photolytic retro-[2 + 4]-cycloaddition according to eq 3 in the gas phase, in organic solvents, and in low-temperature matrices.[3] We have found that this reaction occurs in aqueous solution as well, and we have measured rates of hydration of acetylketene in that medium. Our results show acetylketene to be a remarkably reactive substance. Although there is considerable current interest in the chemistry of acylketenes,[4] little quantitative information is available on their reactivity.

Acetoacetic acid contains both carboxylic acid and ketone functional groups, and it could, at least in principle, form a carboxylic acid enol (**1**) in addition to the ketone enol **2**. These
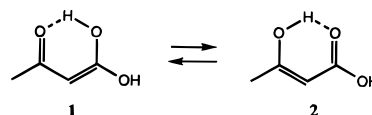
two isomeric enols can be interconverted by what must be a very facile proton transfer along a hydrogen bond. The ketone enol might be expected to be the much more stable isomer and


[†] University of Toronto.
[‡] Concordia University.
[⊗] Abstract published in *Advance ACS Abstracts,* March 15, 1996.

(1) For reviews of the early work, see: Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1969; pp 794−837. Wheland, G. W. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons: New York, 1960; pp 663−703. For a summary of more recent studies, see: Toullec, J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1990; pp 353−378.

(2) (a) Pedersen, K. J. *J. Phys. Chem.* **1934**, *38*, 999−1022. (b) Kirby, A. J.; Meyer, G. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1446−1451. (c) Bell, R. P.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1681−1686. Cox, B. G.; Hutchinson, R. E. *J. Chem. Soc., Perkin Trans. 2* **1974**, 613−616.

(3) Clemens, R. J.; Witzeman, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 2186−2193. Freiermuth, B.; Wentrup, C. *J. Org. Chem.* **1991**, *56*, 2286−2289. Kappe, C. O.; Wong, M. W.; Wentrup, C. *J. Org. Chem.* **1995**, *60*, 1686−1695.

(4) For recent reviews, see: Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, 1219−1248. Tidwell, T. T. *Ketenes*; John Wiley & Sons: New York, 1995. A recent theoretical study is provided by: Birney, D. M.; Wagenseller, P. E. *J. Am. Chem. Soc.* **1994**, *116*, 6262−6270.

the overwhelmingly predominant form in solution, inasmuch as keto−enol equilibrium constants for simple ketones are very much greater than those for simple carboxylic acids, *e.g.* pK_E = 8.33 for acetone[5] versus the estimate pK_E = 20 for acetic acid.[6] This difference must be due largely to a difference in initial state stability, for the keto form of acetic acid is stabilized strongly by interaction of its carbonyl group with the adjacent hydroxy substituent, an effect that is absent from the initial state of the acetone keto−enol equilibrium. In the case of acetoacetic acid, however, this initial state difference will be offset by a new vinylogous carbonyl−hydroxyl group interaction in the carboxylic acid enol through the enol double bond, and the relative abundances of the two enols at equilibrium may consequently not be as disparate as suggested by the acetone−acetic acid comparison.

Recent high-level, *ab initio*, molecular orbital calculations suggest that this is indeed the case: they give an energy difference of 11 kcal mol^{-1} between the ketone and acid enols, with the ketone enol (**2**) being the more stable species.[7] This difference is considerably less than that corresponding to the pK_E difference between acetone and acetic acid, which indicates that ketone and carboxylic acid enols are closer in stability than the acetone−acetic acid comparison would suggest. The calculations indicate, however, that the acetoacetic acid keto−enol equilibrium is an essentially completely ketone rather than carboxylic acid keto−enol system.

Experimental Section

Materials. 2,2,6-Trimethyl-4H-1,3-dioxin-4-one was purchased from Aldrich Chemical Co. and was distilled prior to use. All other materials were best available commercial grades and were used as received.

Flash Photolysis. Conventional and laser systems, whose details have already been described,[8] were used. The light pulse of the conventional system was provided by two xenon flash lamps and was *ca.* 50 μs wide at half-height. The laser system was a KrF excimer laser, which gave a 248-nm pulse of *ca.* 20-ns width at half-height. Some rates of reaction were too slow to be determined in even the conventional flash system, and measurements were therefore made with a Cary 2200 spectrophotometer using reaction mixtures that had been activated by a single flash from the conventional system.
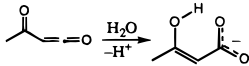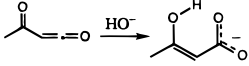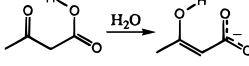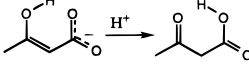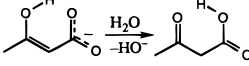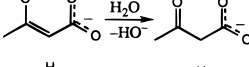
The temperature of all reaction mixtures was controlled at 25.0 ± 0.05 °C. The substrate was supplied as an acetonitrile stock solution, and the reaction mixtures consequently contained 0.03−0.04% acetonitrile; substrate concentrations in these reaction mixtures were *ca.* 1 × 10^{-5} M.
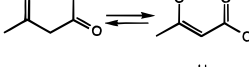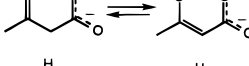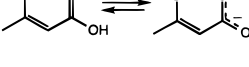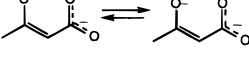
Observed rate constants were obtained by least squares fitting of exponential functions.

Results

Product Analysis. Acetoacetic acid was identified as one of the products formed in flash photolysis of 2,2,6-trimethyl-4H-1,3-dioxin-4-one by comparing rates of formation of its semicarbazone derivative. Control experiments with the dioxinone, acetone, and acetoacetic acid (the latter obtained through hydrolysis of ethyl acetoacetate)[2a] showed that all three substances form semicarbazones in aqueous semicarbazide buffer solutions and that their rates of reaction can be measured by monitoring an absorbance increase at λ = 234 nm. The dioxinone and acetone were found to react at comparable rates, whereas acetoacetic acid reacted 1 order of magnitude more

(5) Chiang, Y.; Kresge, A. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1989**, *111*, 3977−3980.

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

(7) Hoz, S.; Kresge, A. J. Unpublished work.

(8) (a) Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A. J.; Schepp, N.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000−4009. (b) Andraos, J.; Chiang, Y.; Huang, C.-G.; Kresge, A. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1993**, *115*, 10605−10610.

Table 1. Summary of Rate and Equilibrium Constants[a]

Process	Constant
acetylketene + H_2O / $-H^+$ → enol	$k_o = 1.54 \times 10^6$ s^{-1}
acetylketene + HO^- → enol	$k_{HO^-} = 1.86 \times 10^8$ M^{-1} s^{-1}
enol + H_2O → enol + H^+	$k_E = 6.42 \times 10^{-2}$ s^{-1}[b]
enol + H^+ → keto	$k_{H^+} = 1.28 \times 10^5$ M^{-1} s^{-1}
enol + H_2O / $-HO^-$ → keto	$k_o = 1.80 \times 10^{-2}$ s^{-1}
enolate + H_2O / $-HO^-$ → keto	$k_o' = 9.06 \times 10^2$ s^{-1}
keto ⇌ enol (OH)	$K_E = 5.62 \times 10^{-3}$; $pK_E = 2.25$
keto ⇌ enol	$K_E' = 1.22 \times 10^{-3}$; $pK_E' = 2.91$
enol (OH) ⇌ enolate + H^+	$Q_a = 8.93 \times 10^{-5}$ M; $pQ_a = 4.05$
enol ⇌ enolate + H^+	$Q_a^E = 6.63 \times 10^{-14}$ M; $pQ_a^E = 13.18$

[a] Temperature = 25 °C, ionic strength = 0.10 M. [b] Extrapolated from data at 0 and 18 °C reported in ref 2a.

rapidly. In these control experiments, semicarbazide was supplied in large excess; the reactions were therefore pseudo-first-order processes, and the kinetic data fit a single-exponential rate law well. Data obtained from reaction mixtures added to a large excess of semicarbazide buffer after the transients formed by flash photolysis had decayed, on the other hand, did not fit a single-exponential function but rather conformed to a double-exponential expression appropriate for two parallel first-order reactions occurring at different rates, and the two rate constants determined by fitting such an expression agreed with expectation for semicarbazone formation from acetoacetic acid and the dioxinone plus acetone. For example, in a semicarbazide 0.004 M buffer of buffer ratio [BH$^+$]/[B] = 3, the flash photolytic reaction mixture gave k = (2.20 ± 0.06) × 10^{-2} s^{-1} and (2.68 ± 0.27) × 10^{-3} s^{-1} (averages of eight separate determinations), whereas authentic samples of acetoacetic acid and acetone gave k = (2.13 ± 0.04) × 10^{-2} s^{-1} and (2.82 ± 0.27) × 10^{-3} s^{-1} (averages of four determinations), respectively.

These product studies were performed at initial dioxinone concentrations similar to those used in the flash photolytic work, *i.e. ca.* 10^{-5} M. The magnitude of the absorbance changes produced in semicarbazone formation suggested that *ca.* 10% of the dioxinone was being converted to photolysis products.

Ketene Hydration. Flash photolysis of aqueous solutions of 2,2,6-trimethyl-4H-1,3-dioxin-4-one produced a rapid rise in absorbance in the region 240−280 nm followed by a much slower decay. The known photochemistry of this dioxinone,[3] plus our identification of acetoacetic acid as a flash photolysis reaction product, suggests that the absorbance rise is due to the rapid hydration of acetylketene (eq 1), itself formed during the irradiation pulse according to eq 3, and that the absorbance decay
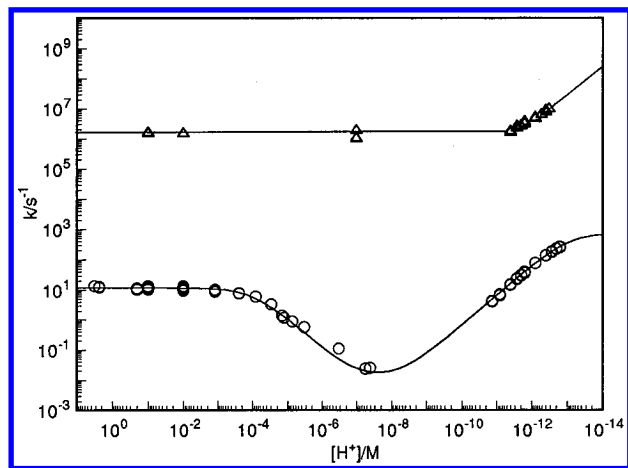
Figure 1. Rate profiles for the hydration of acetylketene ($\triangle$) and the ketonization of acetoacetic acid enol ($\bigcirc$) in aqueous solution at 25 °C.

is due to ketonization of the acetoacetic acid enol hydration product (eq 2). This assignment is supported by the response of the rates of these absorbance changes to changes in the acid−base and isotopic properties of the solvent, as detailed below: the chemistry revealed by these changes is typical of the behavior of ketene-hydration and enol−ketonization reactions.

Rates of hydration of acetylketene were measured in aqueous perchloric acid and sodium hydroxide solutions and also in water with no acid or base added. Acid and base concentrations were varied, but ionic strength was kept constant at 0.10 M. The data are summarized in Tables S1−S3[9] and are displayed as the upper rate profile of Figure 1.

These results show that the hydration of acetylketene is not acid-catalyzed up to an acidity of $[H^+] = 0.10$ M but is weakly catalyzed by the hydroxide ion. Such behavior is characteristic of ketene hydration reactions: their rate profiles commonly show large uncatalyzed regions with weak or nonexistent acid catalysis and weak base catalysis. Acid catalysis, when present, is known to occur by rate-determining proton transfer to the β-carbon atom of the ketene followed by rapid hydration of the ensuing acylium ion (eq 4).[10] Substituents such as phenyl that stabilize

$$\text{(4)}$$
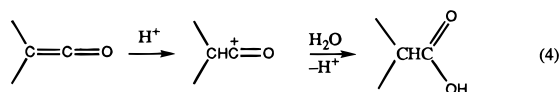
carbon−carbon double bonds impede this process by lowering the energy of the initial state, thus suppressing acid catalysis.[8b,11] Since acyl groups stabilize carbon−carbon double bonds,[12] acid catalysis of acetylketene hydration should also be suppressed, as observed.

The uncatalyzed and hydroxide-ion-catalyzed ketene hydration reactions occur by a different mechanism, one known to involve nucleophilic attack of water or hydroxide ion on the α-carbon atom of the ketene followed by ketonization of the carboxylic acid enol thus formed (eq 5).[13] The nucleophilic

(9) Supporting information; see paragraph at the end of this paper regarding availablility.

(10) (a) Allen, A. D.; Kresge, A. J.; Schepp, N. P.; Tidwell, T. T. *Can. J. Chem.* **1987**, *65*, 1719−1723. (b) Andraos, J.; Kresge, A. J. *J. Photochem. Photobiol. A* **1991**, *57*, 165−173.

(11) Allen, A. D.; Stevenson, A.; Tidwell, T. T. *J. Org. Chem.* **1989**, *54*, 2843−2848. Allen, A. D.; Baigre, L. M.; Gong, L.; Tidwell, T. T. *Can. J. Chem.* **1991**, *69*, 138−145. Andraos, J.; Kresge, A. J.; Schepp, N. P. *Can. J. Chem.* **1995**, *73*, 539−543.

(12) Hine, J.; Skoglund, M. J. *J. Org. Chem.* **1982**, *47*, 4758−4766.

(13) (a) Tidwell, T. T. *Acc. Chem. Res.* **1990**, *23*, 273−279. (b) Allen, A. D.; Andraos, J.; Kresge, A. J.; McAllister, M. A.; Tidwell, T. T. *J. Am. Chem. Soc.* **1992**, *114*, 1878−1879. Andraos, J.; Kresge, A. J. *J. Am. Chem. Soc.* **1992**, *114*, 5643−5646.

$$\text{(5)}$$
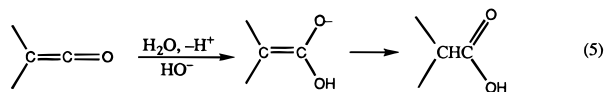
reactivity of hydroxide ion toward ketenes is not very much greater than that of water,[13a] and catalysis by hydroxide ion is consequently weak.

Least squares analysis of the data making up the rate profile shown in Figure 1 gives the following rate constants: $k = (1.54 \pm 0.07) \times 10^6$ s^{-1} for the uncatalyzed reaction and $k = (1.86 \pm 0.03) \times 10^8$ M^{-1} s^{-1} for the hydroxide-ion-catalyzed process. These results show acetylketene to be a remarkably reactive substance; its uncatalyzed reaction, for example, is 42 000 times more rapid than the uncatalyzed reaction of ketene itself, for which $k = 36.5$ s^{-1}.[10b] This enhanced reactivity may be attributed to the ability of the acetyl substituent to stabilize negative charge: in the reaction of ketenes with nucleophiles, the substrate takes on such charge which can then be delocalized into the acetyl group.

This enhanced reactivity of acylketenes has been noted before, and the suggestion has been advanced that it may be due to a carbonyl-assisted pathway in which the nucleophile experiences a stabilizing interaction with the acyl oxygen atom of the ketene.[14] Some support for this suggestion comes from an isotope effect determined in the present study. Rates of hydration of acetylketene were measured in acidic and basic D$_2$O solution, and the data, summarized in Tables S1 and S3,[9] when combined with results obtained in H$_2$O, provide the solvent isotope effects $k_H/k_D = 1.11 \pm 0.03$ on the uncatalyzed reaction and $k_H/k_D = 1.87 \pm 0.07$ on the hydroxide-ion-catalyzed process. The first of these isotope effects is unremarkable: it is similar to the small solvent isotope effects found on other uncatalyzed ketene hydrations,[8b,10] and it simply reinforces our conclusion that this process is a ketene-hydration reaction. The other isotope effect, however, that on the hydroxide-ion-catalyzed hydration, is unusual in that solvent isotope effects on hydroxide-ion-consuming processes such as this are generally inverse.[15] In the present case, this expected inverse component must be offset by a contribution in the normal ($k_H/k_D > 1$) direction, and that could be supplied by a carbonyl-assisted pathway. This assistance could take the form of strong hydrogen bond formation between the hydroxide ion and the carbonyl oxygen atom, as shown in eq 6, or it may even involve proton transfer down such a hydrogen bond while nucleophilic attack occurs.

$$\text{(6)}$$
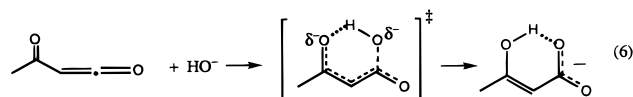
Enol Ketonization. Rates of ketonization of acetoacetic acid enol were measured in aqueous solutions of perchloric acid and sodium hydroxide as well as acetic acid, biphosphate ion, and tris(hydroxymethyl)methylammonium ion buffers. All measurements, except those in perchloric acid at $[HClO_4] = 0.20$, 2.4, and 3.2 M, were done at a constant ionic strength of 0.10 M. The data are summarized in Tables S4−S6.[9]

The measurements in buffers were carried out in series of solutions of constant buffer ratio and therefore constant hydrogen

(14) Allen, A. D.; McAllister, M. A.; Tidwell, T. T. *Tetrahedron Lett.* **1993**, *34*, 1095−1098.

(15) (a) Gold, V.; Grist, S. *J. Chem. Soc., Perkin Trans. 2* **1972**, 89−95. (b) Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, pp 177−273. (c) Washabaugh, M. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 683−692.
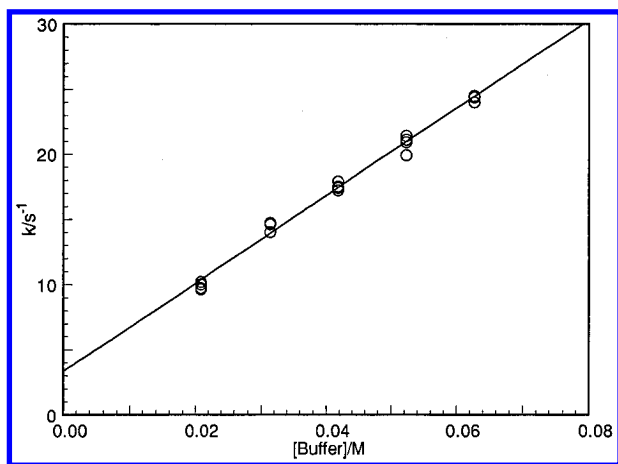
Figure 2. Relationship between buffer concentration and observed rate constants for ketonization of acetoacetic acid enol in aqueous acetic acid buffer solutions at 25 °C; buffer ratio = 1.09.

ion concentration. Strong buffer catalysis was observed, and as Figure 2 illustrates, the data obeyed the expected linear rate law of eq 7, in which k_{cat} is the buffer catalytic coefficient and

$$k_{obsd} = k_s + k_{cat}[buffer] \qquad (7)$$

k_s refers to reaction through solvent-related species. Least squares fitting of the data gave values of k_s, which, together with rate constants determined in perchloric acid and sodium hydroxide solutions, are displayed as the lower rate profile of Figure 1. Values of $[H^+]$ in the buffer solutions needed for this purpose were obtained by calculation, using literature values of the pK_a's of the buffer acids and activity coefficients recommended by Bates.[16]

This rate profile has two downward bends at $[H^+] \cong 10^{-4}$ M and $[H^+] \cong 10^{-13}$ M. A common cause of downward bends in rate profiles is a change in the state of ionization of acidic or basic groups in the substrate,[17] and the enol of acetoacetic acid does have two acidic groups. An interpretation of this rate profile may then be provided by the reaction scheme given in eq 8, with the first bend corresponding to ionization of the carboxylic acid group and the second corresponding to ionization of the enolic hydroxyl group.

$$(8)$$
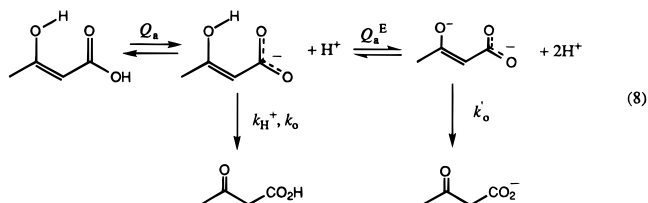
Since ketonization is an electrophilic addition reaction, successively ionized forms of the substrate will be more reactive than their precursors, and reaction will take place through them even when they are relatively minor species. This will produce a horizontal "uncatalyzed" segment of rate profile at acidities above the first bend, where reaction is through the monoanion but neutral enol is the major form of the substrate. This segment will give way to a diagonal portion of slope = −1, signifying acid catalysis, beyond the first bend where monoanion is the major form of substrate. At lower acidities, the dianion becomes the reacting form, but now, $[H^+]$ is so low that solvent water takes over the role of protonating species. This will produce a

(16) Bates, R. G. *Determination of pH Theory and Practice*; Wiley: New York, 1973, p 49.
(17) Loudon, G. M. *J. Chem. Educ.* **1991**, *68*, 973−984.

diagonal segment of slope +1, representing apparent hydroxide ion catalysis, at acidities before the second bend where monoanion is still the major substrate form. This segment will finally give way to another horizontal, uncatalyzed portion beyond the second bend where dianion becomes the major substrate form.

The rate law that corresponds to this reaction scheme is given by eq 9, whose rate and equilibrium constants are defined by eq 8. The rate constants k_o and k'_o signify reaction through water

$$k_{obsd} = \frac{k_{H^+}Q_a[H^+]}{Q_a + [H^+]} + k_o + \frac{k'_o Q_a^E}{Q_a^E + [H^+]} \qquad (9)$$

as the proton donor, and the equilibrium constants Q_a and Q_a^E are concentration quotients applicable at an ionic strength of 0.10 M. Least squares fitting of this expression gave the following parameters: $k_{H^+} = (1.28 \pm 0.07) \times 10^5$ M^{-1} s^{-1}, $k_o = (1.80 \pm 0.18) \times 10^{-2}$ s^{-1}, $k'_o = (9.06 \pm 1.29) \times 10^2$ s^{-1}, $Q_a = (8.93 \pm 0.51) \times 10^{-5}$ M, $pQ_a = 4.05 \pm 0.02$, and $Q_a^E = (6.63 \pm 1.04) \times 10^{-14}$ M, $pQ_a^E = 13.18 \pm 0.07$. The line shown in Figure 1 was drawn using these parameters; it may be seen that they represent the data well.

The reaction scheme of eq 8 interprets the narrow horizontal region at the bottom of the rate profile as ketonization of the monoanionic form of the enol with water acting as the proton donor. An alternative interpretation is reaction of the dianionic form with hydrogen ion as the proton donor, but that seems unlikely because then k_o must be replaced by $k'_{H^+}Q_a^E$ and the value of k'_{H^+} required by the data is the improbably large rate constant $k'_{H^+} = (2.72 \pm 0.51) \times 10^{11}$ M^{-1} s^{-1}.

Additional support for the reaction scheme of eq 8, and for our conclusion that the process being studied is the ketonization of acetoacetic acid enol, comes from solvent isotope effects. Rate measurements were made in acidic and basic D$_2$O solutions, and the data, summarized in Tables S4 and S5, when combined with their H$_2$O counterparts, provide the solvent isotope effects $k_H/k_D = 8.93 \pm 0.23$ on the reaction occurring in the first plateau region at high acidity, and $k_H/k_D = 29.2 \pm 1.2$ on the reaction in the region of apparent hydroxide ion catalysis.[18] The portion of the rate law of eq 9 that applies in the first plateau region of the rate profile is $k_{obsd} = k_{H^+}Q_a$, and the isotope effect here is consequently the product of isotope effects on the rate constant for carbon protonation of the substrate and on the acid dissociation constant of the carboxylic acid group of the substrate. Solvent isotope effects on the acid dissociation constants of carboxylic acids are commonly on the order of $K_H/K_D = 3$,[20] and division of the observed effect by this value leaves $k_H/k_D = 3.0$ for the isotope effect on the rate constant. This is a reasonable value for hydron transfer to carbon[15b] and is similar to isotope effects found for the ketonization of other enols.[21]

The rate law that applies to ketonization in the region of apparent hydroxide ion catalysis is $k_{obsd} = k'_o Q_a^E/[H^+]$, and the observed isotope effect is once again the product of isotope effects on rate and equilibrium constants. The equilibrium

(18) These isotope effects compare rates at the same hydrogen ion concentration, *i.e.* at $[H^+] = [D^+]$; where required, values of $[D^+]$ were calculated from $[DO^-]$ using the isotope effect on the auto protolysis constant of water, $K_H/K_D = 7.34$.[19]
(19) Covington, A. K.; Robinson, R. A.; Bates, R. G. *J. Phys. Chem.* **1966**, *70*, 3820−3824. Gold, V.; Lowe, B. M. *J. Chem. Soc. (A)* **1967**, 936−943.
(20) Laughton, P. M.; Robertson, R. E. In *Solute-Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; pp 399−538.
(21) Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990; pp 399−480.
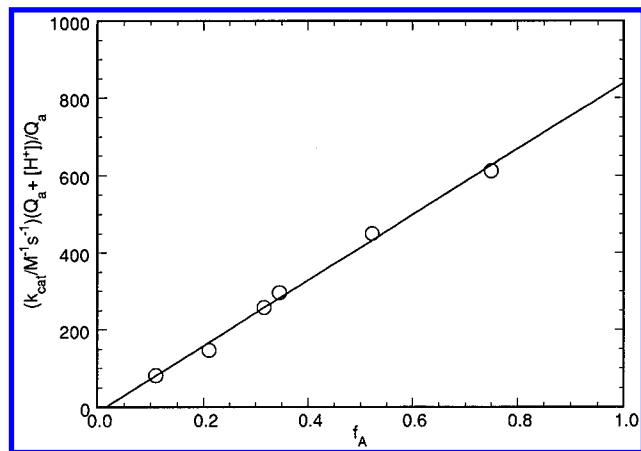
Figure 3. Relationship between buffer catalytic coefficients and the fraction of buffer present as acid for the ketonization of acetoacetic acid enol in aqueous acetic acid buffer solutions at 25 °C.

constant this time refers to the acid ionization of an enol, for which a solvent isotope effect of $K_H/K_D = 6$ may be estimated on the basis of the value $K_H/K_D = 5.88 \pm 0.32$ that has been determined for the ionization of isobutyrophenone enol.[22] This leaves $k_H/k_D = 5$ for the rate process, which again is a reasonable value for hydron transfer from a water molecule to carbon.[15b]

Still further support for the identification of the present process as an enol–ketonization reaction comes from the form of buffer catalysis. Buffer catalytic coefficients, k_{cat}, can be separated into their general acid, k_{HA}, and general base, k_B, constituents through the use of eq 10, in which f_A is the fraction

$$k_{cat} = k_B + (k_{HA} - k_B)f_A \qquad (10)$$

of buffer present in the acidic form. Application of this expression to the data obtained in acetic acid buffers, illustrated in Figure 3, gives $k_B = -13.6 \pm 14.1$ M^{-1} s^{-1} and $k_{HA} = 851 \pm 33$ M^{-1} s^{-1}. This shows that the buffer catalysis is completely of the general acid type, as expected for a rate-determining proton transfer to carbon such as this ketonization reaction.

Keto–Enol Equilibrium. An estimate of the keto–enol equilibrium constant for acetoacetic acid may be made by combining the present results with information about the enolization reaction reported in the literature.[2a] In that previous study, rates of enolization were measured in dilute hydrochloric acid solutions using bromine to scavenge the enolate as it formed. The rate of enolization was found to be independent of acid concentration, which is consistent with our observation that ketonization is also independent of acid concentration in this region plus the requirement that the form of catalysis of a chemical reaction be the same in the forward and reverse directions. Keto–enol equilibration of the acetoacetic acid system in these solutions may then be formulated as shown in eq 11, with a water molecule serving as the base removing a
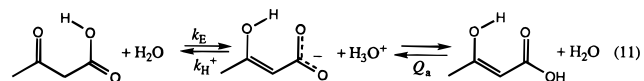
proton from carbon in the enolization direction, and the keto–enol equilibrium constant, K_E, may be expressed as shown in eq 12.

$$K_E = k_E/k_{H^+}Q_a \qquad (12)$$

(22) Chiang, Y.; Kresge, A. J.; Walsh, P. A. *Z. Naturforsch.* **1989**, *44a*, 406–412.

The enolization rate measurements reported in the literature were made at 0° and 18 °C. Extrapolation of these data to 25 °C gives $k_E = 6.42 \times 10^{-2}$ s^{-1}, and combination of that with the values of k_{H^+} and Q_a determined here gives $K_E = 5.62 \times 10^{-3}$ and p$K_E = 2.25$. This result is nicely consistent with an estimate, $K_E = 0.007$, made on the basis of an initial rapid uptake of bromine that was observed in the earlier enolization study and was attributed to the reaction of bromine with enol present at equilibrium.

Discussion

Equilibria. The results obtained here show the carboxylic acid group of the enol of acetoacetic acid, with p$Q_a = 4.05$, to be considerably more acidic than the prediction of p$Q_a = 5.67$ that can be made using a correlation of acidity constants for substituted acrylic acids.[23] The difference between these two values may be attributed to the hydrogen bond formed between the hydroxyl group of the enol and the carbonyl group of the acid (eq 13), which is not taken into account by the correlation. This hydrogen bond will become much stronger as the acid ionizes, thus stabilizing the ionized state.
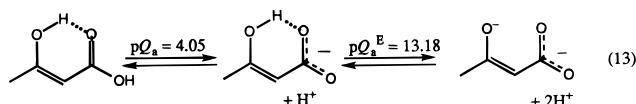

This same strong hydrogen bond should stabilize the initial state of the second ionization shown in eq 13, that of the enol hydroxyl group, thus making the enol a weaker acid. In fact this enol is unusually weakly acidic (p$Q_a^E = 13.18$): the enol group in the corresponding methyl ester, for example, has p$Q_a^E = 9.48$ (eq 14).[24] Another factor contributing to the weak
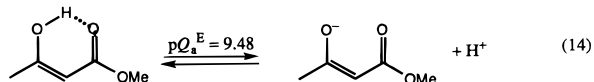
acidity of the enol group in the acetoacetic acid system is electrostatic repulsion between the two negative charges in the dianionic product.

The enol content of acetoacetic acid is also less than that of its methyl ester,[24] which likewise may be attributed to hydrogen bonding. In both cases, as shown in eqs 15 and 16, hydrogen
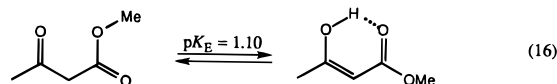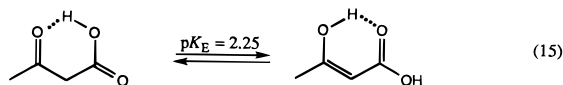

bonds will be formed in the enol products, and these bonds should be of comparable strength in the two enols. In the acid system, however, another hydrogen bond is formed in the keto initial state, but no counterpart exists in the keto form of the ester. Thus, there is a greater energy gap between initial and final states for the acid system than for the ester system, producing a smaller keto–enol equilibrium constant for the former than for the latter.

(23) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pKa Predictions for Organic Acids and Bases*; Chapman and Hall: New York, 1981; p 127. The pKa provided by this correlation was converted to a pQa using activity coefficients as recommended by Bates.[16]

(24) Bunting, J. W.; Kanter, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 11705–11715.

A keto−enol equilibrium constant for the acetoacetate anion may also be obtained by making use of the thermodynamic cycle shown in eq 17. Values of equilibrium constants for two legs
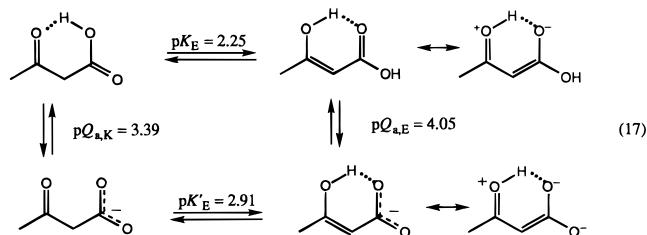
of this cycle, $pK_E = 2.25$ and $pQ_{a,E} = 4.05$, are available from the present study. A third, $pQ_{a,K} = 3.39$, may be estimated by extrapolating to 25 °C values of the pK_a of acetoacetic acid determined at 0 and 18 °C[25] and then converting that result into a pQ_a using activity coefficients recommended by Bates.[16] The equilibrium constant for the fourth leg, the enolization of acetoacetate ion, may then be obtained by combining the other three values: $pK'_E = pK_E + pQ_{a,E} − pQ_{a,K} = 2.91$.

The keto−enol equilibrium constant of the acetoacetate ion is about 5 times less than that of the unionized acid. At first glance this might seem odd because the enol isomer in the acetoacetate ion system would be expected to have a stronger hydrogen bond than the enol isomer of the unionized acid. That will be offset, however, by electron delocalization from the enol group into the carboxylate or carboxylic acid function, as shown by the resonance forms in eq 17, and such delocalization will be stronger into the neutral carboxylic acid group than into the negatively charged carboxylate ion. In addition, there will be an initial state polar interaction between the negatively charged carboxylate group and the positive end of the keto carbonyl-group dipole that will stabilize the keto isomer in this system. Apparently the combined influence of these resonance and polar effects is strong enough to overcome the hydrogen-bonding influence.

Kinetics. The acid-catalyzed ketonization of enols is similar to the acid-catalyzed hydrolysis of vinyl ethers in that both reactions occur by rate-determining proton transfer to a vinyl carbon (eq 18).[21,26] The rates of these two reactions for
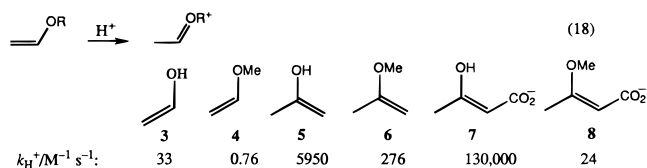

substrates of equivalent structure are therefore similar, with a small difference of 1−2 orders of magnitude favoring enols over

(25) Pedersen, K. J. *J. Phys. Chem.* **1934**, *38*, 993−998.
(26) For a brief review of the evidence regarding vinyl ether hydrolysis, see: Kresge, A. J. *Acc. Chem. Res.* **1987**, *20*, 364−370.

methyl vinyl ethers.[21] For example, vinyl alcohol (**3**)[8a] is 43 times more reactive than methyl vinyl ether (**4**),[27] and the enol of acetone (**5**)[5] is 22 times more reactive than methyl isopropenyl ether (**6**).[28] The enol of acetoacetate ion (**7**), however, is more reactive than the corresponding methyl vinyl ether (**8**)[28] by a much greater margin, a factor of 5400, which suggests that in this case ketonization and vinyl ether hydrolysis may not be occurring by the same reaction mechanism.

The preceding suggestion can be accommodated by a mechanism for ketonization in which the reaction is assisted by a transition state interaction between the enol hydroxyl and carboxylate groups. Conceivably, the interaction could be formation of a strong hydrogen bond, as shown in **9**, or it could involve actual proton transfer, as shown in **10**.[29] In either case, some transition state stabilization would be achieved and a faster rate would result.
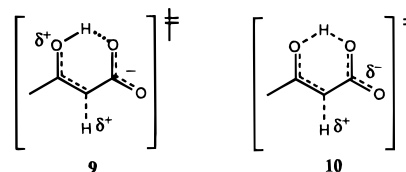
Ketonization through **9** or **10** can be described as intramolecular general base catalysis, and such catalysis has been found before in the ketonization of the enol of the 2-ketocyclohexane-1-carboxylate ion.[2b] The equivalent of this interaction in the reverse enolization direction would amount to intramolecular general acid catalysis, and such catalysis has also been described in the enolization of some cyclic β-ketocarboxylate ions.[2c]

Supporting Information Available: Tables S1−S6 of rate data (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

(27) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228−7233.
(28) Kresge, A. J.; Ubysz, D. *J. Phys. Org. Chem.* **1994**, *7*, 316−322.
(29) In water, bromine attack on the salicylate (*o*-hydroxybenzoate) anion is 380 times faster than that on the *o*-anisate (*o*-methoxybenzoate) anion, whereas phenol is only 12 times as reactive as anisole. For this and other reasons, it has been argued that electrophilic attack on salicylate anions is assisted by intramolecular proton transfer,[30] analogous to that depicted in structure **10**. Correspondingly, the debromination and enolization of related cyclohexadienones exhibit intramolecular general acid catalysis.[30,31]
(30) Tee, O. S.; Iyengar, N. R. *J. Org. Chem.* **1985**, *50*, 4468−4473.
(31) (a) Tee, O. S.; Iyengar, N. R.; Bennett, J. M. *J. Org. Chem.* **1986**, *51* 2585−2589. (b) Tee, O. S.; Iyengar, N. R. *Can. J. Chem.* **1987**, *65*, 1714−1718.