

# The 2-Oxocyclopentanecarboxylic Acid Keto–Enol System in Aqueous Solution: Generation of the Enol by Hydration of an Acylketene

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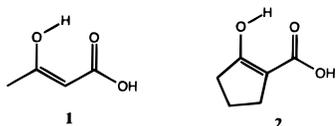
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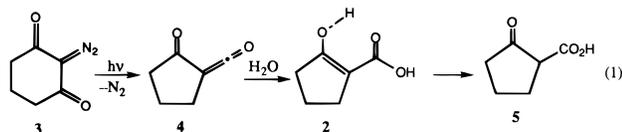
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**Abstract:** Flash photolysis of 2-diazocyclohexane-1,3-dione in aqueous solution produced 2-ketocyclopentylidene ketene, which hydrated to the enol of 2-oxocyclopentanecarboxylic acid, and the enol then isomerized to the keto form of the acid. This ketene proved to be a remarkably reactive substance, with an uncatalyzed hydration rate constant of  $k = 1.4 \times 10^6 \text{ s}^{-1}$  and a hydroxide-ion-catalyzed rate constant of  $7.5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ ; no acid catalysis of hydration was found. Ketonization of the enol was a slower process with rate constants in the millisecond to second range. The reaction shows a complex rate profile that could be interpreted in terms of rate-determining proton transfer to the  $\beta$ -carbon atom of successively ionized forms of the enol in successively more basic solutions. In concentrated acid solutions, the carboxylic acid group of the enol also underwent equilibrium protonation of its carbonyl group, with  $\text{p}K_{\text{SH}} = -3.86$ . Acidity constants of the carboxylic acid group of the enol,  $\text{p}Q_{\text{a,E}} = 4.16$ , and the hydroxyl group of the enol,  $\text{p}Q_{\text{a,E}} = 12.41$ , were also determined. (These acidity constants are concentration quotients applicable at an ionic strength of 0.10 M.) Rates of enolization of the keto form of the substrate were also measured by bromine scavenging, and these, in combination with ketonization rates, gave the keto–enol equilibrium constants  $\text{p}K_{\text{E}} = 2.51$  for the system in the un-ionized carboxylic acid form and  $\text{p}K'_{\text{E}} = 3.00$  for the ionized carboxylate form. The acidity constant of the carboxylic acid group of the keto form was determined as well:  $\text{p}Q_{\text{a,K}} = 3.67$ .

Although enols of  $\beta$ -keto esters have been investigated extensively for more than a century,<sup>1</sup> little attention has been paid to keto–enol isomerism in the  $\beta$ -keto acids themselves. We recently carried out a detailed study of the enol of acetoacetic acid, **1**,<sup>2</sup> and we now add to that a somewhat more extensive examination of the enol of 2-oxocyclopentanecarboxylic acid, **2**.



We generated this enol in aqueous solution by flash photolysis of 2-diazocyclohexane-1,3-dione, **3**. It was already known that irradiation of this substance gives a photo-Wolff reaction producing the acylketene 2-ketocyclopentylidene ketene, **4**, which, in the presence of water, undergoes hydration to 2-oxocyclopentanecarboxylic acid, **5**, through its enol **2**, eq 1.<sup>3</sup> We were able in the present study to monitor both the ketene hydration and the enol ketonization reactions.



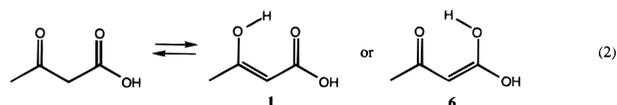
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(1) For reviews of the early work, see: Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1969; pp 794–837. Wheland, G. W. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons: New York, 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.

$\beta$ -Ketocarboxylic acids such as acetoacetic acid can, in principle, enolize to form either ketone enols **1** or carboxylic acid enols **6**, eq 2. Recent high-level *ab initio* calculations have



shown the ketone enol to be the more stable of these two isomers.<sup>4</sup> This is consistent with the fact that the remaining carbonyl group in the ketone enol has one direct and one vinylogous interaction with a hydroxyl group, whereas the carbonyl group in the acid enol has only two vinylogous hydroxyl group interactions: direct interactions can be expected to be stronger and therefore more stabilizing than vinylogous ones.

## Experimental Section

**Materials.** 2-Diazocyclohexane-1,3-dione was prepared from cyclohexane-1,3-dione by diazo transfer using *p*-acetoamidobenzene-sulfonyl azide as the diazo transfer reagent<sup>5</sup> and fluoride ion as the base. A mixture of 3.5 g of anhydrous KF and 1.38 g of cyclohexane-1,3-dione (Aldrich) dissolved in 50 mL of  $\text{CH}_2\text{Cl}_2$  was stirred at room temperature while a solution of 2.4 g of *p*-acetamidobenzene-sulfonyl azide (Aldrich) in 10 mL of  $\text{CH}_2\text{Cl}_2$  was added dropwise. The reaction mixture was then left at room temperature overnight, after which it was cooled to  $-10^\circ\text{C}$ , filtered through 4 cm of silica gel, washed with 0.1 M aqueous NaOH ( $2 \times 100 \text{ mL}$ ), and dried with  $\text{MgSO}_4$ . Removal of the solvent *in vacuo* and recrystallization of the residue from diethyl

(2) Chiang, Y.; Guo, H.-X.; Kresge, A. J.; Tee, O. S. *J. Am. Chem. Soc.* **1996**, *118*, 3386–3391.

(3) Korobitsyna, I. K.; Nikolaev, V. A. *J. Org. Chem. USSR (Engl. Transl.)* **1976**, *12*, 1245–1251.

(4) Hoz, S.; Kresge, A. J. *J. Phys. Org. Chem.* **1997**, *10*, 182–186.

(5) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709–1716.

ether gave 1.05 g of yellowish crystals, mp 48–49 °C (lit. mp 47–49 °C<sup>6</sup>) whose <sup>1</sup>H and <sup>13</sup>C NMR spectra agreed well with literature values.<sup>7</sup>

**2-Oxocyclopentanecarboxylic Acid.** This was prepared by hydrolysis of ethyl 2-oxocyclopentanecarboxylate (Aldrich). A solution of 1.2 g of the ester in 30 mL of 0.5 M aqueous NaOH was allowed to stand at room temperature for 3 days. The resulting yellow solution was then washed with five 15-mL portions of diethyl ether and cooled to 0 °C, and 3 mL of concentrated aqueous HCl was added. The resulting solution was extracted with five 20-mL portions of diethyl ether, and the combined ether extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and then concentrated to 15 mL. This produced 120 mg of a colorless crystalline byproduct of unknown constitution, which was removed by filtration. Cooling of the filtrate to –72 °C produced additional traces of this byproduct, which was also removed by filtration. Removal of the solvent from the filtrate gave 74 mg of 2-oxocyclopentanecarboxylic acid as a yellow oil whose <sup>1</sup>H NMR spectrum agreed with literature reports.<sup>3,8,9</sup>

All other materials were best available commercial grades.

**Kinetics.** Rates of hydration of 2-ketocyclopentylideneketene were measured with an excimer-laser flash photolysis system operating at  $\lambda = 248$  nm that has already been described,<sup>10</sup> and rates of ketonization of 2-oxocyclopentanecarboxylic acid enol were measured with a conventional flash photolysis system that has also been described.<sup>11</sup> The temperature of the reaction solutions was maintained at 25.0  $\pm$  0.1 °C, and the ionic strength was held constant at 0.10 M.

Rates of enolization of 2-oxocyclopentanecarboxylic acid were monitored by bromine scavenging under first-order reaction conditions with an excess of bromine over substrate. Bromine concentrations were in the range (4–40)  $\times 10^{-5}$  M and substrate concentrations, (1–15)  $\times 10^{-5}$  M. The reaction mixtures also contained bromide ion, supplied as the inert salt NaBr used to maintain the ionic strength at 0.10 M and also as the mineral acid HBr. Under these conditions, Br<sub>2</sub> is complexed as Br<sub>3</sub><sup>–</sup> and the reactions were followed by monitoring the decrease in absorbance of this ion at  $\lambda = 266$  or 310 nm. In sodium hydroxide solutions, Br<sub>2</sub> is converted to BrO<sup>–</sup> and the reactions here were followed by monitoring the decrease in absorbance of this ion at  $\lambda = 330$  nm. Measurements were made using either a Cary 2200 spectrometer or a Hi-Tech SF-S1 stopped-flow system; in both cases the temperature of reaction solutions was maintained at 25.0  $\pm$  0.05 °C.

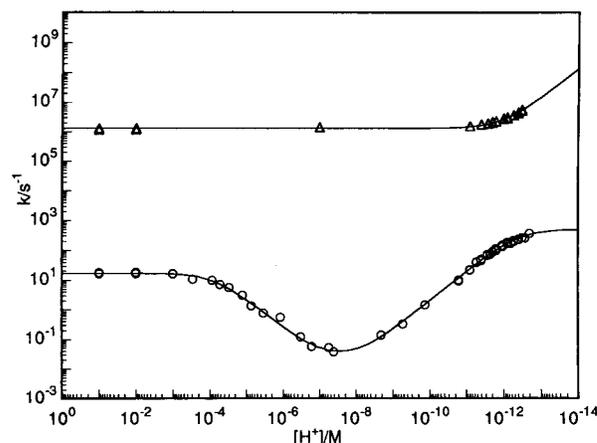
**pK<sub>a</sub> Determination.** The acidity constant of 2-oxocyclopentanecarboxylic acid was determined spectrophotometrically by using the difference in absorbance of the undissociated acid and its carboxylate anion at  $\lambda = 210$  nm. Absorbance measurements were made on solutions containing a fixed stoichiometric concentration of substrate (3.11  $\times 10^{-4}$  M) and varying hydrogen ion concentrations but fixed ionic strength (0.10 M). The data so obtained were analyzed by least-squares fitting of eq 3,

$$A = (A_{\text{HA}}[\text{H}^+] + A_{\text{A}}Q_{\text{a}})/(Q_{\text{a}} + [\text{H}^+]) \quad (3)$$

in which  $Q_{\text{a}}$  is the acid dissociation constant (concentration quotient at ionic strength = 0.10 M) of 2-oxocyclopentanecarboxylic acid,  $A_{\text{HA}}$  is the absorbance of un-ionized acid, and  $A_{\text{A}}$  is that of its carboxylate ion.

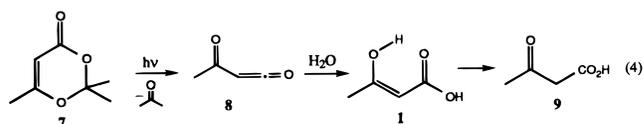
## Results and Discussion

Flash photolysis of aqueous solutions of 2-diazocyclohexane-1,3-dione produces a rapid rise in absorbance in the region  $\lambda = 250$ –300 nm followed by a much slower decay. These absorbance changes are very similar to those found in the generation of acetoacetic acid by flash photolysis of 2,2,6-



**Figure 1.** Rate profiles for the hydration of 2-ketocyclopentylideneketene ( $\Delta$ ) and the ketonization of 2-oxocyclopentanecarboxylic acid enol ( $\circ$ ) in aqueous solution at 25 °C.

trimethyl-4*H*-1,3-dioxin-4-one, **7**, where the absorbance rise was identified as the hydration of acetylketene, **8**, to the enol of acetoacetic acid, **1**, and the decay was identified as ketonization of this enol to the acid **9**, eq 4.<sup>2</sup> This similarity suggests that



an analogous assignment can be made in the present case, *i.e.*, that the rise in absorbance here can be attributed to the hydration of 2-ketocyclopentylideneketene, **4**, itself formed by photolysis of the diazo compound during the flash photolysis pulse, and that the absorbance decay can be attributed to ketonization of the enol of 2-oxocyclopentanecarboxylic acid, **2**, thus formed, according to eq 1. This conclusion is reinforced by the established photochemistry of 2-diazocyclohexane-1,3-dione, which is known to proceed according to eq 1, and also by the fact that the rate profiles produced by these absorbance changes (*vide infra*) are typical of ketene-hydration and enol-ketonization reactions.

**Ketene Hydration.** Rates of hydration of 2-ketocyclopentylideneketene 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 so obtained are summarized in Tables S1–S3<sup>12</sup> and are displayed as the upper rate profile of Figure 1.

These results show that the hydration of this ketene is not catalyzed by acids up to an acidity of  $[\text{H}^+] = 0.10$  M but is weakly catalyzed by hydroxide ion. Such behavior is characteristic of ketene hydration reactions, whose rate profiles commonly show large uncatalyzed regions with weak or nonexistent acid catalysis and somewhat stronger but still weak base catalysis.<sup>10,13</sup>

Least-squares analysis of the present data gives the following rate constants:  $k_0 = (1.40 \pm 0.01) \times 10^6 \text{ s}^{-1}$  for the uncatalyzed reaction and  $k_{\text{HO}^-} = (7.53 \pm 0.10) \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$  for the hydroxide-ion-catalyzed process. These results are similar to the rate constants found for the hydration of acetylketene (**8**; eq 4):  $k_0 = 1.54 \times 10^6 \text{ s}^{-1}$  and  $k_{\text{HO}^-} = 1.86 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ .<sup>2</sup>

(12) Supporting Information; see paragraph at the end of this paper regarding availability.

(13) (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.

(6) Stetter, H.; Kiehs, K. *Chem. Ber.* **1965**, *98*, 1181–1187.

(7) Leung-Toung, R.; Wenstrup, C. *J. Org. Chem.* **1992**, *57*, 4850–4858.

(8) Tirpack, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877–4879.

(9) <sup>13</sup>C NMR spectrum of the present preparation:  $\delta$  (CDCl<sub>3</sub>) = 213.01, 174.85, 55.03, 38.55, 27.63, 21.26.

(10) Andraos, J.; Chiang, Y.; Huang, C. G.; Kresge, A. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1993**, *115*, 10605–10610.

(11) Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000–4009.

They show that 2-ketocyclopentylideneketene, like acetylketene, is a very reactive substance, orders of magnitude more labile than ketene itself, for which  $k_o = 36.5 \text{ s}^{-1}$ .<sup>13b</sup> This is consistent with the mechanism of these reactions, which is known to involve nucleophilic attack of water or hydroxide ion on the carbon atom of the ketene carbonyl group: such attack generates a negative charge on the substrate that can be stabilized by delocalization into the additional carbonyl group of these acylketenes.

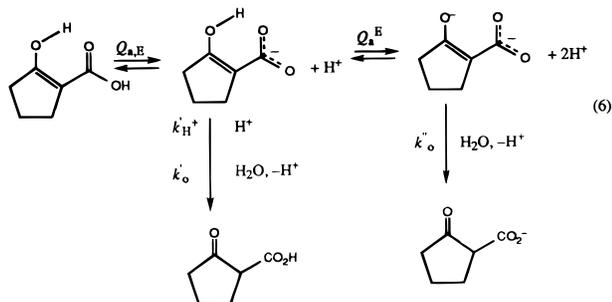
**Enol Ketonization.** Rates of ketonization of 2-oxocyclopentanecarboxylic acid enol were measured in aqueous perchloric acid and sodium hydroxide solutions and in aqueous formic acid, acetic acid, biphosphate ion, tris(hydroxymethyl)methylamine, and ammonia buffers. All measurements were made at a constant ionic strength of 0.10 M, except those in concentrated perchloric acid solutions where the ionic strength was equal to acid concentration. The data so obtained are summarized in Tables S4–S7.<sup>12</sup>

The measurements in buffers were carried out in series of solutions of constant buffer ratio and therefore constant hydrogen ion concentration. Strong buffer catalysis was observed, and the data conformed to the expected linear rate law of eq 5,

$$k_{\text{obs}} = k_s + k_{\text{buff}}[\text{buffer}] \quad (5)$$

in which  $k_s$  is the rate constant for reaction through catalysis by solvent-related species and  $k_{\text{buff}}$  is that for reaction via buffer. Least-squares fitting of the data using eq 5 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  $[\text{H}^+]$  in the buffer solutions needed for this purpose were obtained by calculation, using literature  $\text{p}K_a$ 's of the buffer acids and activity coefficients recommended by Bates.<sup>14</sup>

This rate profile is similar to that obtained for the ketonization of the enol of acetoacetic acid<sup>2</sup> and, like the latter, can be interpreted in terms of ketonization through rate-determining  $\beta$ -carbon protonation of the mono- and dianionic forms of the enol, eq 6. The bend in this rate profile at  $[\text{H}^+] \cong 10^{-4} \text{ M}$  then represents ionization of the carboxylic acid group of the substrate, and that at  $[\text{H}^+] \cong 10^{-12} \text{ M}$  represents ionization of its enolic hydroxyl group.



Because 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 substrate species. This will produce a horizontal "uncatalyzed" segment of the rate profile at acidities above the first bend, where reaction is through the monoanion but un-ionized enol is the major form of the substrate, and a diagonal segment of slope = -1 signifying acid catalysis at acidities below the first bend, where monoanion

is the major substrate form. At lower acidities, the dianion becomes the reacting form, but now  $[\text{H}^+]$  is so low that solvent water takes over the role of protonating species. This produces a diagonal segment of slope = +1, representing apparent hydroxide ion catalysis, at acidities above the second bend where monoanion is still the major substrate form, and a horizontal uncatalyzed portion at acidities below the second bend where dianion is the major substrate species.

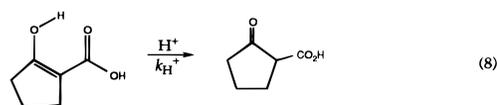
The rate law that corresponds to this reaction scheme is given as eq 7, whose rate and equilibrium constants are defined by

$$k_{\text{obs}} = \frac{k'_{\text{H}^+} Q_{\text{aE}} [\text{H}^+]}{Q_{\text{aE}} + [\text{H}^+]} + k'_o + \frac{k''_o Q_{\text{a}}^{\text{E}}}{Q_{\text{a}}^{\text{E}} + [\text{H}^+]} \quad (7)$$

eq 6. (Primed symbols are used for reactions of the monoanionic form of the substrate and double-primed symbols for the dianionic form.) Least-squares fitting of this expression gave the following results:  $k'_{\text{H}^+} = (2.41 \pm 0.13) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ ,  $k'_o = (2.57 \pm 0.30) \times 10^{-2} \text{ s}^{-1}$ ,  $k''_o = (4.84 \pm 0.28) \times 10^2 \text{ s}^{-1}$ ,  $Q_{\text{aE}} = (6.98 \pm 0.47) \times 10^{-5} \text{ M}$  ( $\text{p}Q_{\text{aE}} = 4.16 \pm 0.03$ ),<sup>15</sup>  $Q_{\text{a}}^{\text{E}} = (3.93 \pm 0.30) \times 10^{-13} \text{ M}$  ( $\text{p}Q_{\text{a}}^{\text{E}} = 12.41 \pm 0.03$ ).<sup>15</sup>

The reaction scheme of eq 6 interprets the narrow horizontal region at the bottom of the rate profile as reaction of the monoanionic form of the substrate with water as the proton donor. An alternative interpretation is reaction of the dianionic form of the substrate with hydrogen ion as the proton donor; the portion of the rate law representing this segment of the rate profile then becomes  $k''_{\text{H}^+} Q_{\text{a}}^{\text{E}}$ , where  $k''_{\text{H}^+}$  is the rate constant for  $\beta$ -carbon protonation of the substrate dianion. Such an interpretation was rejected in the case of acetoacetic acid enol because the data gave  $k''_{\text{H}^+} = 2.7 \times 10^{11} \text{ M}^{-1} \text{ s}^{-1}$ , which was regarded as improbably large. The present system gives the lower but perhaps still too large value  $k''_{\text{H}^+} = 6.5 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ .

Although the rate profile for ketonization of 2-oxocyclopentanecarboxylic acid enol up to an acidity of  $[\text{H}^+] = 0.10 \text{ M}$  (Figure 1) shows no evidence of further acid catalysis corresponding to rate-determining carbon protonation of the un-ionized form of the substrate, eq 8, such catalysis was found in



more concentrated acids. Rates of this further reaction were measured in aqueous perchloric acid solutions over the concentration range 6.7–9.9 M; the data so obtained are summarized in Table S7.<sup>12</sup>

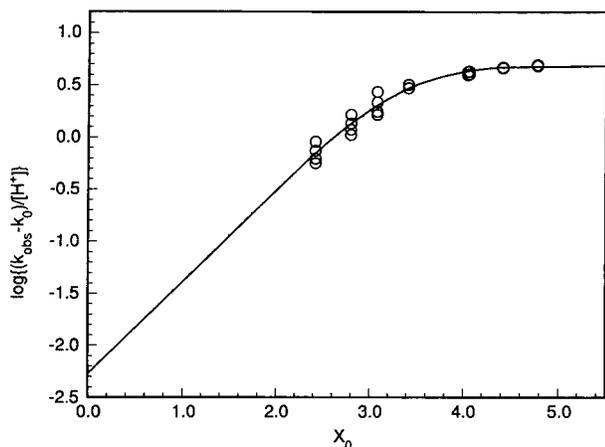
Observed first-order constants obtained in these concentrated acid solutions were found to increase with solution acidity more rapidly than in direct proportion to acid concentration. This is commonly the case for rate-determining carbon-protonation reactions, and the situation is generally handled by using an acidity function to correlate the data; the Cox–Yates  $X_o$  function<sup>16</sup> appears to be the best scale currently available for this purpose.<sup>17</sup> In the present case, allowance must be made for the background "uncatalyzed" reaction shown at the high acidity end of the rate profile of Figure 1, which actually represents hydrogen-ion catalysis of the anionic form of the substrate under conditions where the un-ionized form is the

(15) This is a concentration quotient applicable at ionic strength = 0.10 M.

(16) Cox, R. A.; Yates, K. *Can. J. Chem.* **1981**, *59*, 2116–2124.

(17) Kresge, A. J.; Chen, H. J.; Capen, G. L.; Powell, M. F. *Can. J. Chem.* **1983**, *61*, 249–256.

(14) Bates, R. G. *Determination of pH Theory and Practice*; Wiley: New York, 1973; p 49.



**Figure 2.** Correlation of rates of ketonization of 2-oxocyclopentanecarboxylic acid enol in concentrated aqueous perchloric acid solution at 25 °C. The line shown was drawn using parameters obtained by least-squares fitting of eq 10.

reaction's initial state; observed rate constants in this region are consequently equal to  $k'_{H^+}Q_{a,E}$ . The situation can be accommodated by adding this term to the standard expression generally used to correlate rate data with  $X_0$ ,<sup>18</sup> as shown in eq 9,

$$\log\{(k_{\text{obs}} - k'_{H^+}Q_{a,E})/[H^+]\} = \log k_{H^+} + m^{\ddagger}X_0 \quad (9)$$

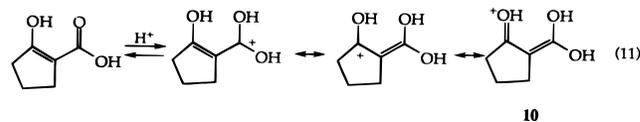
where  $k_{H^+}$  is the rate constant for the reaction of eq 8 and  $m^{\ddagger}$  is a slope parameter for the kinetic process. Such an expression has been used successfully to correlate rates of enol ketonization before,<sup>19</sup> and it did so here as well up to an acid concentration of 8.2 M. Beyond this point, however, observed rate constants were progressively smaller than required by this expression. Such deviations have been found for carbon-protonation reactions before and have been assigned to competitive protonation at another site which converts the substrate into a nonreactive form.<sup>20</sup> The further modification of the standard Cox–Yates expression that this nonproductive protonation requires is shown as eq 10,

$$\log\{(k_{\text{obs}} - k'_{H^+}Q_{a,E})/[H^+]\} = \log k_{H^+} + m^{\ddagger}X_0 + \log\left(\frac{K_{SH^+}}{K_{SH^+} + [H^+]10^{mX_0}}\right) \quad (10)$$

where  $K_{SH}$  is the acidity constant of the substrate protonated at the nonproductive site and  $m$  is a slope parameter for this equilibrium process. As Figure 2 shows, this expression correlates the present experimental data well. Least-squares fitting gave the results,  $k_{H^+} = (5.30 \pm 0.79) \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ ,  $k'_{H^+}Q_{a,E} = 17.4 \pm 0.9 \text{ s}^{-1}$ ,  $K_{SH} = (7.26 \pm 1.84) \times 10^3 \text{ M}$ ,  $\text{p}K_{SH} = -3.86 \pm 0.11$ ,  $m^{\ddagger} = 0.89 \pm 0.02$ , and  $m = 0.87 \pm 0.02$ . The value of  $k'_{H^+}Q_{a,E}$  obtained in this way agrees very well with that derived from least-squares fitting the rate profile of Figure 1:  $k'_{H^+}Q_{a,E} = 16.8 \pm 1.4 \text{ s}^{-1}$ .

There are two weakly basic sites in the present substrate whose protonation in concentrated acids would be expected to hinder ketonization and give rise to the observed nonproductive equilibrium effect. These sites are the enolic hydroxyl group

and the carboxylic acid carbonyl group. The fairly large slope parameter found for this protonation,  $m = 0.87$ , suggests that the nonproductive site is the carbonyl group, because  $m$  values for hydroxyl group protonation are usually much lower, *viz.*  $m = 0.13$  for the protonation of methanol and  $m = 0.14$  for that of ethanol, whereas  $m = 0.56$  for the protonation of benzoic acid.<sup>21</sup> The carboxylic acid group, moreover, might be expected to be the more basic site in the present substrate, for protonation of its carbonyl group produces a cation whose positive charge can be delocalized, as shown in eq 11, whereas protonation of



the enolic hydroxyl group gives a cation with a localized positive charge. This assignment of nonproductive protonation site is also consistent with the fact that the presently determined acidity constant,  $\text{p}K_{SH} = -3.86$ , makes the conjugate acid of the present substrate somewhat less acidic than protonated benzoic acid, for which  $\text{p}K_{SH} = -4.73$ ;<sup>21</sup> the extra delocalization of positive charge into the enolic hydroxyl group shown in structure **10** of eq 11 will make this substance more stable, and consequently a weaker acid, than protonated benzoic acid.

These considerations thus indicate that the progressive retardation of ketonization through carbon protonation of the un-ionized form of 2-oxocyclopentanecarboxylic acid enol, seen above  $[\text{HClO}_4] = 8.2 \text{ M}$  and illustrated in Figure 2, is caused by nonproductive protonation of the substrate's carboxylic acid group.

Further support for interpretation of the rate profile of Figure 1 in terms of the reaction scheme of eq 6 may be obtained from the form of acid–base catalysis shown by the ketonization reaction in buffer solutions. Buffer catalytic coefficients,  $k_{\text{cat}}$ , can be separated into their general acid,  $k_{\text{HA}}$ , and general base,  $k_{\text{B}}$ , components through the use of eq 12, in which  $f_A$  is the

$$k_{\text{cat}} = k_{\text{B}} + (k_{\text{HA}} - k_{\text{B}})f_A \quad (12)$$

fraction of buffer present in the acid form. Application of eq 12 requires data at several different buffer ratios to supply information at several different values of  $f_A$ , and this was available in the present case for acetic acid, biphosphate ion, and ammonium ion buffers. In the last two systems, hydrogen ion concentrations were such that the enol substrate was essentially completely in its monoanionic form, and slopes of buffer dilution plots,  $\Delta k_{\text{obs}}/\Delta[\text{buffer}]$ , could be equated with  $k_{\text{cat}}$ . In the acetic acid buffers, however, the substrate was present in both monoanionic and neutral forms, and  $\Delta k_{\text{obs}}/\Delta[\text{buffer}]$  had to be converted, through the use of eq 13, into  $k_{\text{cat}}$  for reaction

$$k_{\text{cat}} = \left(\frac{\Delta k_{\text{obs}}}{\Delta[\text{buffer}]}\right)\left(\frac{[H^+] + Q_{a,E}}{Q_{a,E}}\right)Q_{a,E} \quad (13)$$

beginning with monoanion only as the initial state.

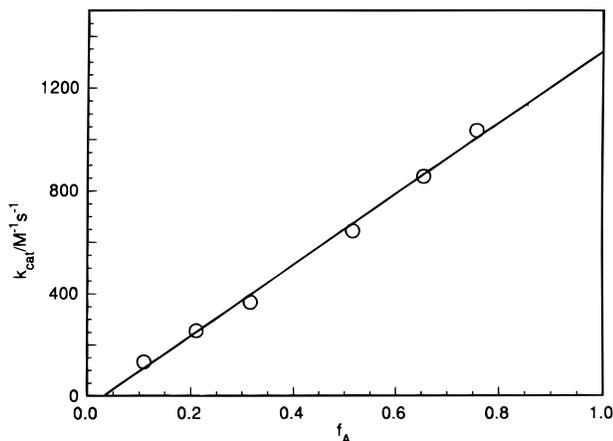
Catalysis in acetic acid buffers proved to be wholly of the general acid type. This is evident from Figure 3, where the ordinate at  $f_A = 0$  represents general base catalysis and that at  $f_A = 1$ , general acid catalysis, and also from least-squares analysis of the data, which gave  $k_{\text{HA}} = (1.34 \pm 0.03) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$  and  $k_{\text{B}} = -(4.42 \pm 2.44) \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$ . This result is consistent with the fact that the acetic acid buffers lie in a region of the rate profile where the ketonization mechanism

(18) Cox, R. A.; Yates, K. *Can. J. Chem.* **1979**, *57*, 2944–2951.

(19) Chiang, Y.; Kresge, A. J.; Krogh, E. T. *J. Am. Chem. Soc.* **1988**, *110*, 2600–2607. Chiang, Y.; Kresge, A. J.; Pruszyński, P. *J. Am. Chem. Soc.* **1992**, *114*, 3103–3107.

(20) Kresge, A. J.; Yin, Y. *J. Phys. Org. Chem.* **1989**, *2*, 43–50. Kresge, A. J.; Leibovitch, M. *J. Org. Chem.* **1990**, *55*, 5234–5236.

(21) Bagno, G.; Scorrano, G.; More O'Ferrall, R. A. *Rev. Chem. Intermediates* **1987**, *7*, 313–352.



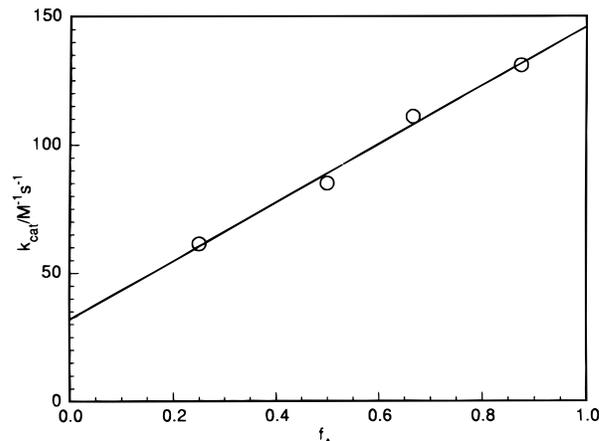
**Figure 3.** Relationship between buffer catalytic coefficients and the fraction of buffer present as acid for the ketonization of 2-oxocyclopentanecarboxylic acid enol in aqueous acetic acid buffer solutions at 25 °C.

assigned consists of rate-determining carbon protonation of the enol monoanion; such a reaction can be expected to show general acid catalysis. In biphosphate buffers, on the other hand, the reaction shows both general acid and general base catalysis (Figure 4); least-squares analysis gives  $k_{\text{HA}} = (1.46 \pm 0.04) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$  and  $k_{\text{B}} = (3.16 \pm 0.49) \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$ . This is consistent with the fact that these buffers lie in a region where rate-determining carbon protonation of the monoanion is beginning to give way to further ionization of this ion to the dianion followed by rate-determining carbon protonation of that species; the latter reaction with monoanion as the initial state will show an inverse rate dependence on hydrogen ion concentration for its prior equilibrium ionization step followed by general acid catalysis for the rate-determining carbon-protonation step, which is equivalent to general base catalysis. The ammonium ion buffers lie well into the region where ketonization occurs solely through the dianion with monoanion as the initial state, and consistent with this is the fact that only general base catalysis is observed here (Figure 5); least-squares analysis gives  $k_{\text{HA}} = -(9.08 \pm 7.23) \text{ M}^{-1} \text{ s}^{-1}$  and  $k_{\text{B}} = (1.45 \pm 0.07) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ .

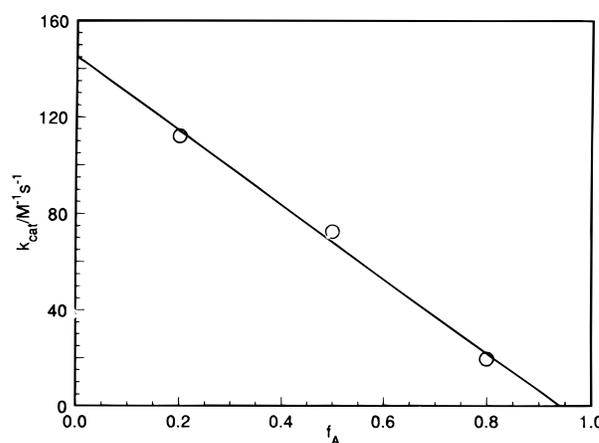
These general base catalytic coefficients are related to general acid catalytic coefficients for carbon protonation of the dianion,  $k''_{\text{HA}}$ , as shown in eq 14, where  $Q_{\text{a}}^{\text{BH}}$  is the acidity constant of

$$k_{\text{B}} = k''_{\text{HA}} Q_{\text{a}}^{\text{E}} / Q_{\text{a}}^{\text{BH}} \quad (14)$$

the buffer acid. Values of  $k''_{\text{HA}}$  obtained through this relationship, together with values of  $k_{\text{HA}}$  for carbon protonation of the monoanion, are listed in Table 1. It may be seen that both kinds of rate constants decrease with decreasing acidity of the catalyst, as expected, and also that the dianion is several orders of magnitude more reactive than the monoanion, again as expected and also as found before in comparisons of rates of reaction of enols and the corresponding enolate ions.<sup>22</sup> It is significant, however, that the increased reactivity of enolate over enol found here,  $k''_{\text{HA}}/k_{\text{HA}} = 9.2 \times 10^4$  for catalysis by  $\text{H}_2\text{PO}_4^-$ , is several orders of magnitude less than the factors of  $10^6$ – $10^8$  obtained before for simple enols without  $\beta$ -carboxylate groups,<sup>22</sup> inasmuch as the enol reaction here will be accelerated because the  $\beta$ -carboxylate group can act as an intramolecular general base catalyst in ketonization of the enol but not of the enolate ion; such intramolecular general base catalysis was noted before in



**Figure 4.** Relationship between buffer catalytic coefficients and the fraction of buffer present as acid for the ketonization of 2-oxocyclopentanecarboxylic acid enol in aqueous biphosphate ion buffer solutions at 25 °C.



**Figure 5.** Relationship between buffer catalytic coefficients and the fraction of buffer present as acid for the ketonization of 2-oxocyclopentanecarboxylic acid enol in aqueous ammonium ion buffer solutions at 25 °C.

**Table 1.** Catalytic Coefficients for the Ketonization of 2-Oxocyclopentanecarboxylic Acid Enol in Aqueous Solution at 25 °C<sup>a</sup>

catalyst	$k'_{\text{HA}} (\text{M}^{-1} \text{s}^{-1})^b$	$k''_{\text{HA}} (\text{M}^{-1} \text{s}^{-1})^b$
$\text{H}^+$	$2.41 \times 10^5$	
$\text{HCO}_2\text{H}$	$6.86 \times 10^3$	
$\text{CH}_3\text{CO}_2\text{H}$	$1.34 \times 10^3$	
$\text{H}_2\text{PO}_4^-$	$1.46 \times 10^2$	$1.34 \times 10^7$
$\text{NH}_4^+$		$1.89 \times 10^5$

<sup>a</sup> Ionic strength = 0.10 M. <sup>b</sup> Error limits are given in the text.

the acetoacetic acid system, where its rate acceleration was estimated to be approximately 2 orders of magnitude.<sup>2</sup>

The general magnitude of the ketonization rate constants obtained here is consistent with an earlier study which found rates of ketonization of this enol to be too fast to be measured by conventional techniques.<sup>23</sup>

**pK<sub>a</sub> Determination.** The acidity constant of 2-oxocyclopentanecarboxylic acid was determined by measuring the absorbance of solutions of the acid at a constant concentration in aqueous perchloric acid solutions and formic acid, acetic acid, and biphosphate ion buffers, all at a constant ionic strength of 0.10 M. As Figure 6, shows, the data so obtained (summarized

(22) Pruszyński, P.; Chiang, Y.; Kresge, A. J.; Schepp, N. P.; Walsh, P. A. *J. Phys. Chem.* **1986**, *90*, 3760–3766. Chiang, Y.; Kresge, A. J.; Santabella, J. A.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 5506–5510.

(23) Kirby, A. J.; Meyer, G. J. *Chem. Soc., Perkin Trans. II* **1972**, 1446–1451.

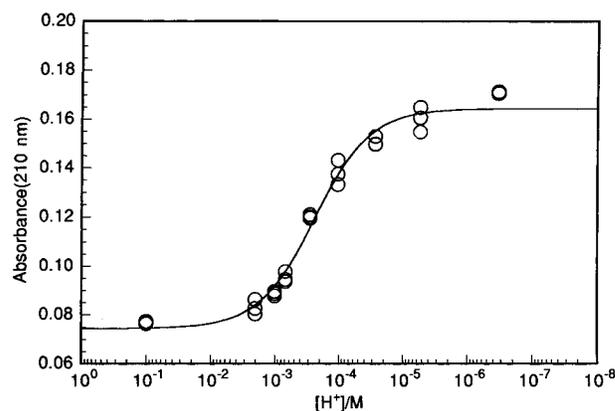
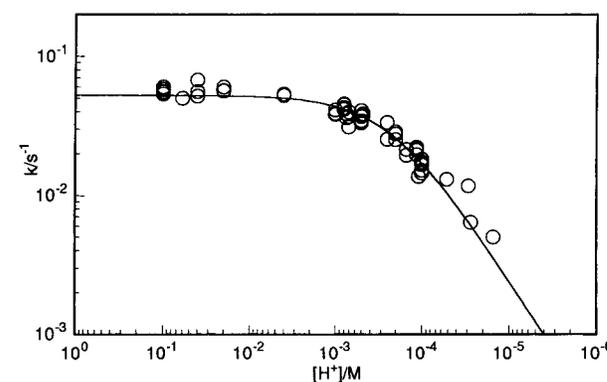
**Table 2.** Summary of Rate and Equilibrium Constants for the 2-Ketocyclopentylideneketene and 2-Oxocyclopentanecarboxylic Acid Systems<sup>a</sup>

Process	Constant <sup>b</sup>
	$k_o = 1.40 \times 10^6 \text{ s}^{-1}$
	$k_{HO^-} = 7.53 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$
	$k_o^E = 5.25 \times 10^{-2} \text{ s}^{-1}$
	$k_{HO^-}^E = 6.28 \text{ M}^{-1} \text{ s}^{-1}$
	$k_{H^+} = 5.30 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$
	$k_{H^+}^* = 2.41 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$
	$k_o = 2.57 \times 10^{-2} \text{ s}^{-1}$
	$k_o^* = 4.84 \times 10^2 \text{ s}^{-1}$
	$K_E = 3.07 \times 10^{-3}$ ; $pK_E = 2.51$
	$K_E = 1.00 \times 10^{-3}$ ; $pK_E = 3.00$
	$Q_{a,K} = 2.13 \times 10^{-4} \text{ M}$ ; $pQ_{a,K} = 3.67^c$
	$K_{SH} = 7.26 \times 10^3 \text{ M}$ ; $pK_{SH} = -3.86$
	$Q_{a,E} = 6.98 \times 10^{-5} \text{ M}$ ; $pQ_{a,E} = 4.16^c$
	$Q_a^E = 3.93 \times 10^{-13} \text{ M}$ ; $pQ_a^E = 12.41^c$

<sup>a</sup> Aqueous solution, 25 °C, ionic strength = 0.10 M. <sup>b</sup> Error limits are given in the text. <sup>c</sup> Concentration quotient at 0.10 M ionic strength.

in Table S8<sup>12</sup>) describe the expected sigmoid titration curve. Least-squares fitting of eq 3 gave the acidity constant  $Q_{a,K} = (2.37 \pm 0.26) \times 10^{-4} \text{ M}$ ,  $pQ_{a,K} = 3.63 \pm 0.05$ ;<sup>15</sup> this result agrees well with the acidity constant,  $pQ_{a,K} = 3.68 \pm 0.03$ , obtained from the rate profile of enolization of 2-oxocyclopentanecarboxylic acid (*vide infra*).

**Enolization.** Rates of enolization of 2-oxocyclopentanecarboxylic acid were determined by bromine scavenging of the enol as it formed. Measurements were made in hydrobromic acid and sodium hydroxide solutions and also in acetic acid buffers; the data obtained are summarized in Tables S9–S11.<sup>12</sup> In all cases, an initial consumption of 1 equiv of bromine was followed by a slower uptake of more halogen. In acidic solutions, the initial phase was faster than the subsequent one by well over an order of magnitude, and the two changes could be easily separated by fitting either a double-exponential expression or a single-exponential plus a straight line; good first-

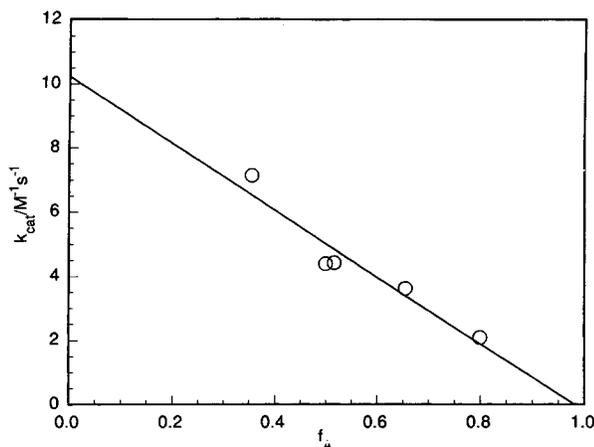
**Figure 6.** Spectrophotometric titration curve for the acid ionization of 2-oxocyclopentanecarboxylic acid in aqueous solution at 25 °C.**Figure 7.** Rate profile of the enolization of 2-oxocyclopentanecarboxylic acid in aqueous acid solutions at 25 °C.

order rate constants for the initial phase could consequently be obtained. In sodium hydroxide solutions, on the other hand, the initial phase was only about 5 times faster than the subsequent phase, and separation of the two changes was more difficult; first-order rate constants for the initial phase obtained in these solutions were therefore less accurate. Such consumption of additional amounts of halogen in enolization reaction studies has been observed before<sup>24</sup> and has been attributed to subsequent hydrolysis and oxidation reactions of the initial halogenated products;<sup>24a</sup> in the case of  $\beta$ -keto acids, such as the present substrate, decarboxylation followed by additional rapid halogenation is also known to occur.<sup>25</sup>

The enolization rate measurements in buffers, just like the ketonization rate measurements, were performed in series of solutions of constant buffer ratio but varying buffer concentration. Strong buffer catalysis was again found, with observed rate constants conforming well to the linear rate law of eq 5. Least-squares analysis gave intercepts of buffer dilution plots,  $k_s$ , which, together with the rate constants measured in hydrobromic acid solutions, are displayed in the rate profile of Figure 7.

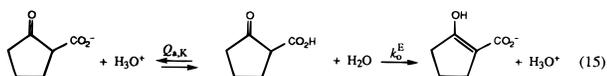
This enolization reaction can be expected to be the microscopic reverse of the ketonization of 2-oxocyclopentanecarboxylic acid enol, which was assigned a mechanism in the region of acidity of these enolization measurements involving rate-determining proton transfer from a hydronium ion to the  $\beta$ -carbon atom of the carboxylate-ion form of the enol, giving un-ionized 2-oxocyclopentanecarboxylic acid and a water molecule as reaction products (*vide supra*). Enolization will

(24) (a) Guthrie, J. P.; Cossar, J. *Can. J. Chem.* **1990**, *68*, 397–408. Guthrie, J. P.; Cossar, J.; Lu, J. *Can. J. Chem.* **1991**, *69*, 1904–1908. (b) Bell, R. P.; Page, M. I. *J. Chem. Soc., Perkin Trans. II* **1973**, 1681–1686. (25) Corey, E. J. *J. Am. Chem. Soc.* **1953**, *75*, 3297–3299.



**Figure 8.** Relationship between buffer catalytic coefficients and the fraction of buffer present as acid for the enolization of 2-oxocyclopentanecarboxylic acid in aqueous acetic acid buffer solutions at 25 °C.

therefore occur by rate-determining reaction of un-ionized 2-oxocyclopentanecarboxylic acid with a water molecule, giving the horizontal plateau seen at the high acidity end of the rate profile of Figure 7. The un-ionized acid, however, will also be in equilibrium with its carboxylate ion, as shown in eq 15, and



the need to convert this ion to un-ionized acid before enolization can take place will give the acid-catalyzed region seen at the low acidity end of the profile of Figure 7. The bend in the profile connecting these two regions, of course, corresponds to the ionization constant of the substrate acid.

The rate law that applies to this reaction scheme is shown in eq 16,

$$k_{\text{obs}} = \frac{k_o^E [\text{H}^+]}{Q_{a,K} + [\text{H}^+]} \quad (16)$$

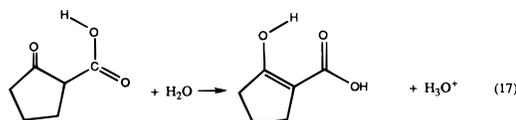
whose rate and equilibrium constants are defined in eq 15. Least-squares analysis of the data using this equation gave  $k_o^E = (5.25 \pm 0.14) \times 10^{-2} \text{ s}^{-1}$  and  $Q_{a,K} = (2.07 \pm 0.13) \times 10^{-4} \text{ M}$ ,  $pQ_{a,K} = 3.68 \pm 0.03$ .<sup>15</sup> These results are nicely consistent with determinations recently made in another laboratory,<sup>26</sup> and the rate constants also agree well with  $k = 5.2 \times 10^{-2} \text{ s}^{-1}$  reported before for the enolization of 2-oxocyclopentanecarboxylic acid on the basis of more limited measurements made in 0.1 and 0.01 M HCl.<sup>24b</sup> The equilibrium constant also agrees well with the acidity constant of 2-oxocyclopentanecarboxylic acid determined directly by spectrophotometric titration,  $pQ_{a,K} = 3.63 \pm 0.05$  (*vide supra*); the weighted average of these two results gives  $Q_{a,K} = (2.13 \pm 0.12) \times 10^{-4} \text{ M}$ ,  $pQ_{a,K} = 3.67 \pm 0.02$ ,<sup>15</sup> as the best value of this acidity constant.

The enolization rate measurements in acetic acid buffer solutions were performed at acidities where the substrate existed in both undissociated carboxylic-acid and dissociated carboxylate-ion forms, and slopes of buffer dilution plots were consequently converted to buffer catalytic coefficients for the undissociated carboxylic-acid form by applying the analog of eq 13. As Figure 8 demonstrates, the values of  $k_{\text{cat}}$  so obtained represent general base catalysis alone, with no contribution from general acid catalysis. This, of course, is the expected result

(26) Tee, O. S. Unpublished work.

because the microscopic reverse of this reaction, ketonization in acetic acid buffers, showed only general acid catalysis (*vide supra*). Least-squares analysis gave the results  $k_{\text{OAc}^-}^E = (1.02 \pm 0.10) \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$  and  $k_{\text{HOAc}}^E = -(1.94 \pm 7.89) \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ .

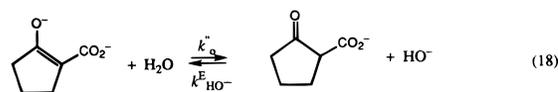
Several measurements of the rate of bromination of 2-oxocyclopentanecarboxylic acid were also made in D<sub>2</sub>O solutions of DBr at an acid concentration of 0.10 M. The results, summarized in Table S9,<sup>12</sup> when combined with rate constants obtained in H<sub>2</sub>O at the same acid concentration, give the isotope effect  $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.82 \pm 0.04$ . This isotope effect refers to an acid concentration where the substrate is in its undissociated carboxylic acid form and reaction occurs through proton removal by a water molecule. Such a process, eq 17, would be expected



to show a solvent isotope effect in the normal direction ( $k_{\text{H}}/k_{\text{D}} > 1$ ) as the hydrogens of the attacking water molecule are converted to the more loosely bound hydrogens of a hydronium ion,<sup>27</sup> and this isotope effect consequently offers additional support for the identification of this process as an enolization reaction.

Still further support is provided by a measurement of the rate of deuterium incorporation into the  $\alpha$ -position of 2-oxocyclopentanecarboxylic acid made in a D<sub>2</sub>O solution of 0.10 M DClO<sub>4</sub>. Loss of protium at this position was monitored by <sup>1</sup>H NMR using the six protons of the nonexchanging methylene groups of the substrate as an integration standard. The data so obtained conformed to the first-order rate law well, and least-squares fitting gave the rate constant  $k = (2.23 \pm 0.18) \times 10^{-2} \text{ s}^{-1}$ . This result is consistent with the bromination rate constant obtained in D<sub>2</sub>O solution at the same acid concentration,  $k = (3.13 \pm 0.02) \times 10^{-2} \text{ s}^{-1}$ , as it should inasmuch as enol formation will be the rate-controlling stage of both bromination and deuterium incorporation.

The less accurate rates of enolization measured in sodium hydroxide solutions showed this reaction to be catalyzed by hydroxide ion with rate constants a simple linear function of hydroxide ion concentration. This is the expected result on the basis of the mechanism assigned to the ketonization reaction in this region, which consists of carbon protonation of the dianionic form of the enol by solvent water, eq 18; the microscopic reverse



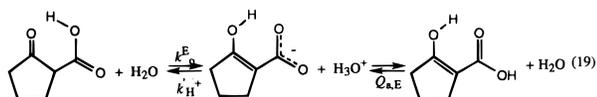
of this process is removal of a carbon-bound proton from the carboxylate form of the keto substrate by hydroxide ion, a process whose rate of reaction will be directly proportional to hydroxide ion concentration. Least-squares analysis of the data gave the hydroxide-ion catalytic coefficient  $k_{\text{HO}^-}^E = 6.28 \pm 0.28 \text{ M}^{-1} \text{ s}^{-1}$ .

**Keto–Enol Equilibria.** The enolization and ketonization rate constants determined here may be combined to provide values of keto–enol equilibrium constants for 2-oxocyclopentanecarboxylic acid. Because of the presence of the carboxylic acid group in this system, two such equilibrium constants can be defined, one,  $K_E$ , relating keto and enol forms with the

(27) Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncl, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, pp 177–273.

carboxylic acid group un-ionized and another,  $K'_E$ , with this group ionized.

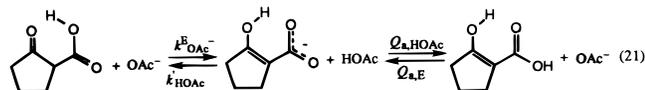
The first of these equilibria may be formulated as shown in eq 19, using hydronium ion and water as the catalysts to effect



the keto–enol isomerization. The equilibrium constant for this reaction may be expressed as shown in eq 20, and use of the

$$K_E = k_{o,E}^E / (k'_{H^+} Q_{a,E}) \quad (20)$$

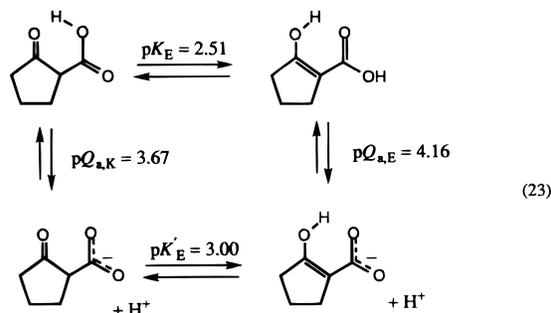
values of  $k_{o,E}^E$ ,  $k'_{H^+}$ , and  $Q_{a,E}$  determined here gives  $K_E = (3.13 \pm 0.28) \times 10^{-3}$ ,  $pK_E = 2.51 \pm 0.04$ . Another estimate of  $K_E$  may also be made using acetic acid and acetate ion to effect the interconversion, as shown in eqs 21 and 22,



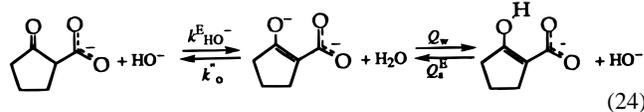
$$K_E = k_{OAc^-}^E Q_{a,HOAc} / (k'_{HOAc} Q_{a,E}) \quad (22)$$

and use of the appropriate data gives  $K_E = (2.98 \pm 0.36) \times 10^{-3}$ ,  $pK_E = 2.53 \pm 0.05$ , in very good agreement with the previous value. The weighted average of these two results gives  $K_E = (3.07 \pm 0.22) \times 10^{-3}$ ,  $pK_E = 2.51 \pm 0.03$ , as the best value of this keto–enol equilibrium constant.

Since the acidity constants of the carboxylic acid groups of the keto and enol isomers in this system have both been determined here, the thermodynamic cycle shown in eq 23 can



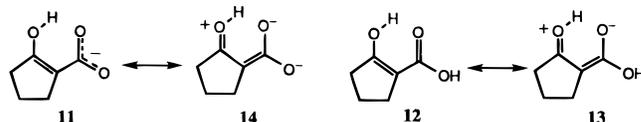
be set up and the relationship  $pK'_E = pK_E + pQ_{a,E} - pQ_{a,K}$  may be used to give  $K'_E = (1.00 \pm 0.11) \times 10^{-3}$ ,  $pK'_E = 3.00 \pm 0.05$ . Another estimate of this constant may also be obtained using kinetic data determined in basic solution where hydroxide ion and water are the keto–enol-interconverting catalytic pair. The equilibrium there may be formulated as shown in eqs 24 and 25,



$$K'_E = k_{HO^-}^E Q_w / (k'_{o,E} Q_{a,E}) \quad (25)$$

where  $Q_w$  is the acid ionization constant of water, and use of the relevant data gives  $K'_E = (5.24 \pm 0.56) \times 10^{-4}$ ,  $pK'_E = 3.28 \pm 0.05$ . This result is broadly consistent with the value obtained from the thermodynamic cycle. The fact that it is a factor of 2 less, however, reflects the difficulty of obtaining an accurate value of  $k_{HO^-}^E$  (*vide supra*), and the result from the thermodynamic cycle is consequently to be preferred.

These keto–enol equilibrium constants are much greater than those for most simple ketones without carboxylic acid or carboxylate ion substituents; for example,  $pK_E = 7.94$  for cyclopentanone itself.<sup>28</sup> The relatively high enol contents found here are in fact typical of  $\beta$ -dicarbonyl compounds in general, where their magnitude is usually attributed to stabilization of the enol isomer by intramolecular hydrogen bonding. A similar explanation may be applied here, but that cannot be the entire story because such an intramolecular hydrogen bond should be stronger and therefore more stabilizing in the carboxylate ion **11** than in the carboxylic acid **12**, and yet the enol content of



the carboxylate ion ( $pK'_E = 3.00$ ) is less than that of the carboxylic acid ( $pK_E = 2.51$ ). Some other effect must also be operating. A likely candidate is conjugative stabilization of the carboxylic acid enol by electron release from the hydroxyl group as shown in resonance structure **13**; the analogous structure in the case of the carboxylate ion enol **14** will be less stabilizing because it puts negative charge onto an already negatively charged group.

**Acknowledgment.** We are grateful to Professor O. S. Tee for communicating to us his unpublished data on the enolization of 2-oxocyclopentanecarboxylic acid and to the Natural Sciences and Engineering Research Council of Canada and the United States National Institutes of Health for financial support of this work.

**Supporting Information Available:** Tables S1–S11 of rate and equilibrium data (16 pages). See any current masthead page for ordering information and Internet access instructions.

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