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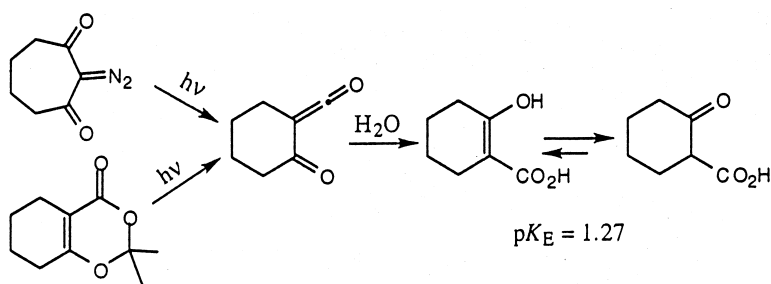
The 2-Oxocyclohexanecarboxylic Acid Keto–Enol System in Aqueous Solution

J. A. Chang, A. J. Kresge, V. A. Nikolaev, and V. V. Popik

$$pK_E = 1.27$$

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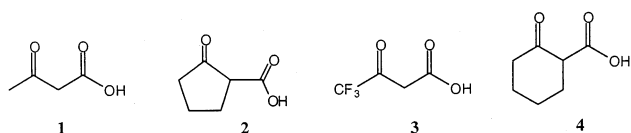# The 2-Oxocyclohexanecarboxylic Acid Keto−Enol System in Aqueous Solution

J. A. Chang,[†] A. J. Kresge,*,[†] V. A. Nikolaev,[‡] and V. V. Popik[†]

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Abstract: Flash photolysis of 2-diazocycloheptane-1,3-dione or 2,2-dimethyl-5,6,7,8-tetrahydrobenzo-4*H*-1,3-dioxin-4-one in aqueous solution produced 2-oxocyclohexylideneketene, which underwent hydration to the enol of 2-oxocyclohexanecarboxylic acid, and the enol then isomerized to the keto form of the acid. Isomerization of the enol to keto forms was also observed using solid enol, a substance heretofore commonly believed to be the keto acid. Rates of ketonization were measured in perchloric acid, sodium hydroxide, and buffer solutions, and a ketonization rate profile was constructed. Rates of enolization of the keto acid were also measured using bromine to scavenge the enol as it formed. Rates of enolization and ketonization were then combined to provide the keto−enol equilibrium constant pK_E = 1.27. This and some of the other results obtained are different from the corresponding quantities for the 2-oxocyclopentanecarboxylic acid keto−enol system. These differences are discussed.

In striking contrast to β-keto esters, whose keto−enol tautomerism has been investigated over the course of more than a century and about which there is consequently an impressively large body of information,[1] little attention has been paid to keto−enol tautomerism of the parent β-keto acids themselves. We have recently reported detailed studies of the acetoacetic acid (**1**),[2] 2-oxocyclopentanecarboxylic acid (**2**),[3] and 4,4,4-trifluoroacetoacetic acid (**3**)[4] keto−enol systems, and we now add to that an examination of the 2-oxocyclohexanecarboxylic acid (**4**) system. Our previous work showed strong similarities between


keto−enol tautomerism of acetoacetic acid and 2-oxocyclopentanecarboxylic acid, but we now find interesting differences between those systems and that of 2-oxocyclohexanecarboxylic acid.
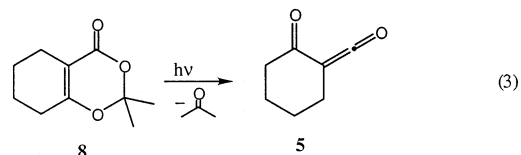

[†] University of Toronto.
[‡] St. Petersburg State University.

(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) Chiang, Y.; Guo, H.-X.; Kresge, A. J.; Tee, O. S. *J. Am. Chem. Soc.* **1996**, *118*, 3386−3391.
(3) Chiang, Y.; Kresge, A. J.; Nikolaev, V. A.; Popik, V. V. *J. Am. Chem. Soc.* **1997**, *119*, 11183−11190.
(4) Chiang, Y.; Kresge, A. J.; Meng, Q.; Morita, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 8345−8351.

We began the present study by generating the enol, **6**, as we had before,[2−4] through hydration of the corresponding ketocarbene, **5**, eq 1, itself produced either by a photo-Wolff reaction
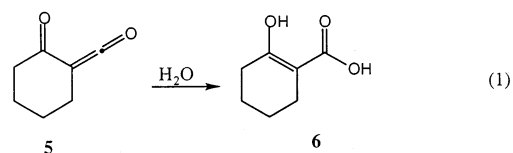
of 2-diazocycloheptane-1,3-dione, **7**, eq 2, or by a photolytic
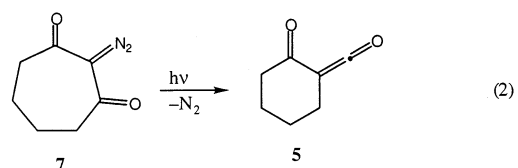
retro-[2+4]-cycloaddition reaction of 2,2-dimethyl-5,6,7,8-tetrahydrobenzo-4*H*-1,3-dioxin-4-one, **8**, eq 3. Our initial work,

however, raised the possibility that the solid material commonly believed to be 2-oxocyclohexanecarboxylic acid is actually the enol isomer. We therefore performed an X-ray diffraction

analysis on the solid and found that it is in fact the enol.[5] We consequently used this material directly for most of our subsequent work.

Experimental Section

Materials. 2-Diazocycloheptane-1,3-dione (**7**) was prepared by diazo group transfer from tosyl azide to cycloheptane-1,3-dione.[6] A material at first believed to be 2-oxocyclohexanecarboxylic acid (**4**) was prepared by base-catalyzed hydrolysis of ethyl 2-oxocyclohexanecarboxylate; this produced a solid, mp 82–83°, whose X-ray analysis showed it to be the enol isomer (**6**) of 2-oxocyclohexanecarboxylic acid.[5] 2,2-Dimethyl-5,6,7,8-tetrahydrobenzo-4*H*-1,3-dion-4-one (**8**) was prepared from this enol plus acetone.[7] All other materials were best available commercial grades.

pK_a Determination. The acidity constant of 2-oxocyclohexanecarboxylate ion ionizing further as a carbon acid was determined by monitoring the reversible absorbance change at $\lambda = 276$ nm that took place as this reaction occurred. Absorbance measurements were made using a Carey 2200 spectrometer whose cell compartment was thermostated at 25.0 ± 0.05 °C.
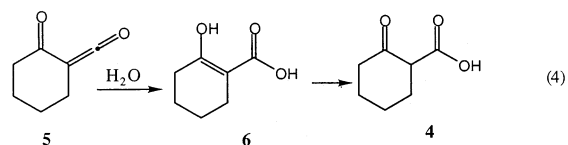
Kinetics. Rates of hydration of 2-oxocyclohexylideneketene (**5**) were measured using a nanosecond excimer laser flash photolysis system operating at $\lambda = 248$ nm that has already been described,[8] and rates of ketonization of the 2-oxocyclohexanecarboxylic acid enol (**6**) thus produced were measured with a conventional microsecond (flash lamp) flash photolysis system that has also already been described.[9] The temperature of the reacting solutions was maintained at 25.0 ± 0.05 °C, and photolysis substrate concentrations were of the order of 3×10^{-5} M. Reactions were followed by monitoring absorbance changes at $\lambda = 270–290$ nm, and observed first-order rate constants were calculated for the most part by least-squares fitting of an exponential function. In some of the slower runs, however, instability of the monitoring light source produced an absorbance drift, and a linear term was consequently added to the exponential function. Rates of the very slow reactions were measured by first generating the enol with a single pulse from the conventional flash system and then quickly transferring the ketonizing solution to a Cary 2200 spectrometer for reaction monitoring with that instrument. Once again, the temperature of reacting solutions was maintained at 25.0 ± 0.0 °C.

Rates of ketonization in solutions prepared using solid enol were also measured using the Cary spectrometer. Stock solutions of enol in acetonitrile were prepared, and ketonizations were then initiated by injecting a few microliters of these stock solutions into 3.0 mL of wholly aqueous reaction mixtures. Some ketonization took place slowly in these acetonitrile stock solutions, but useful amounts of enol still remained even 1 day after preparation.

Rates of enolization were measured by bromine scavenging of the enol as it formed. Bromine concentrations were in the range $(4–100) \times 10^{-5}$ M, and substrate concentrations were in the range $(3.5–12) \times 10^{-5}$ M, with bromine always in excess. The ionic strength of these solutions was maintained at 0.10 M through the addition of sodium bromide, and reactions were followed by monitoring the absorbance change of tribromide ion at $\lambda = 310$ nm. The temperature of reacting solutions was again maintained at 25.0 ± 0.05 °C, and observed first-order rate constants were calculated by least-squares fitting of an exponential function.

(5) Lough, A. J.; Kresge, A. J.; Zhu, Y. *Acta Crystallogr.* **2003**, *E59*, σ344–σ346.

(6) Cossy, J.; Belotti, D.; Thellend, A.; Pete, J. P. *Synthesis* **1988**, 720–721. Regitz, M.; Maas, G. *Diazo Compounds Properties and Synthesis*; Academic Press: New York, 1986; Chapter 13.

(7) Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896–1901.

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

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

Results and Discussion

Reaction Identification. Flash photolysis of aqueous solutions of 2-diazocycloheptane-1,3-dione (**7**) or 2,2-dimethyl-5,6,7,8-tetrahydrobenzo-4*H*-1,3-dioxin-4-one (**8**) produced a rapid rise in absorbance in the region $\lambda = 270–290$ nm followed by a much slower decay. These absorbance changes are similar to those found in our previous studies of β-oxocarboxylic keto–enol systems[2–4] and, by analogy with the previous work, may be assigned to hydration of 2-oxocyclohexylideneketene (**5**), giving the enol of 2-oxocyclohexanecarboxylic acid (**6**), followed by ketonization of this enol to the acid itself, **4**, eq 4.

This assignment is supported by the response of these absorbance changes to acid–base catalysis (vide infra).

Ketene Hydration. Rates of hydration of 2-oxocyclohexylideneketene, **5**, were measured in dilute aqueous perchloric acid and sodium hydroxide solutions and in biphosphate ion, tris-(hydroxymethyl)methylammonium ion, and ammonium ion buffers. The ionic strength of these solutions was maintained at 0.10 M through addition of sodium perchlorate as required. The ketene was generated by photo-Wolff reaction of diazo compound **7** in the perchloric acid and buffer solutions. This substrate, however, was unstable in sodium hydroxide solutions, undergoing base-catalyzed ring cleavage,[10] and dioxinone **8** was therefore used as the flash photolytic substrate here instead. Concordant results were obtained with the two substrates. The data are summarized in Tables S1–S3.[11]

The rate measurements in buffers were performed in series of solutions of constant buffer ratio and, because the ionic strength was constant, also constant hydronium ion concentration, but varying buffer concentration. Observed first-order rate constants proved to be linearly proportional to buffer concentration, and the data were therefore analyzed by linear least-squares fitting of the buffer dilution expression shown as eq 5. The zero-buffer-concentration intercepts, k_{int}, obtained in this way,

$$k_{obs} = k_{int} + k_{buff}[\text{buffer}] \tag{5}$$

together with the rate constants determined in perchloric acid and sodium hydroxide solutions, are displayed as the upper rate profile shown in Figure 1. Hydronium ion concentrations of the buffer solutions needed for this purpose were obtained by calculation using literature values of the buffer acid acidity constants and activity coefficients recommended by Bates.[12]

This rate profile shows no acid catalysis, a long uncatalyzed portion, and weak hydroxide-ion catalysis. Such behavior is typical of ketene hydration reactions, which commonly show

(10) Regitz, M.; Maas, G. *Diazo Compounds Properties and Synthesis*; Academic Press: New York, 1986; pp 511–512. Chiang, Y.; Kresge, A. J.; Zhu, Y. *ARKIVOC* **2001**, *2*, 108–115.

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

(12) Bates, R. G. *Determination of pH Theory and Practice*; Wiley: New York, 1973; p 49.
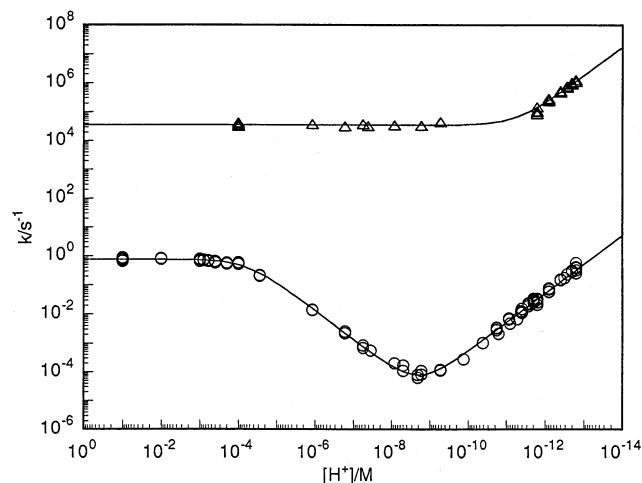
Figure 1. Rate profiles for the hydration of 2-oxocyclohexylideneketene (△) and the ketonization of 2-oxocyclohexanecarboxylic acid enol (○) in aqueous solution at 25 °C.

large uncatalyzed regions with weak or nonexistent hydronium-ion catalysis and somewhat stronger but still weak hydroxide-ion catalysis.[13] The present rate profile is similar to those found before for ketenes whose hydrations produced the enols of acetoacetic acid[2] and 2-oxocyclopentanecarboxylic acid.[3]

Least-squares analysis using the simple rate law shown in eq 6 gave $k_o = (3.45 \pm 0.15) \times 10^4$ s^{-1} and $k_{HO^-} = (1.08 \pm$

$$k_{obs} = k_o + k_{HO^-}[HO^-] \qquad (6)$$

$0.03) \times 10^7$ M^{-1} s^{-1}. These results show that the present ketene is a rather reactive substance, consistent with the nucleophilic nature of this reaction[14] and the ability of the ketene's β-carbonyl group to stabilize the negative charge being generated on the substrate in the reaction's transition state.

Enol Ketonization. Rates of decay of 2-oxocyclohexane-carboxylic acid enol, **6**, were measured in dilute aqueous perchloric acid and sodium hydroxide solutions and in acetic acid, biphosphate ion, *tert*-butylhydrogenphosphonate ion, tris-(hydroxymethyl)methylammonium ion, ammonium ion, and hydrogencarbonate ion buffers. The measurements in perchloric acid were made using diazo compound and enol as the substrate, those in sodium hydroxide using dioxinone and enol as the substrate, and those in buffer using all three substrates. Concordant results were once again obtained with different substrates. The ionic strength of all solutions was maintained at 0.10 M through the addition of sodium perchlorate as required. The data thus obtained are summarized in Tables S4−S6.[11]

The measurements in buffers were performed in series of solutions of constant buffer ratio, and therefore constant hydronium ion concentration, but varying total buffer concentration. Observed first-order rate constants were again linearly dependent on buffer concentration, and the data were therefore again analyzed by least-squares fitting of eq 5. The zero-buffer-concentration intercepts obtained in this way, together with the rate constants measured in perchloric acid and sodium hydroxide

solutions, are displayed as the lower rate profile of Figure 1. Hydronium ion concentrations needed for this purpose were again obtained by calculation using buffer acid acidity constants from the literature and activity coefficients recommended by Bates.[12]

This rate profile, like those for the ketonization of enols of other β-oxocarboxylic acids,[2−4] can be interpreted in terms of the accepted reaction mechanism for enol ketonization involving rate-determining protonation of the substrate on its β-carbon atom.[15] Because this profile refers to reaction through solvent-related species, protonation will be either by the hydronium ion, written here as H$^+$, or by a water molecule, and, over the acidity range represented by this profile, the enol will react through either its monoanionic or its dianionic form, as shown in eq 7.

(7)
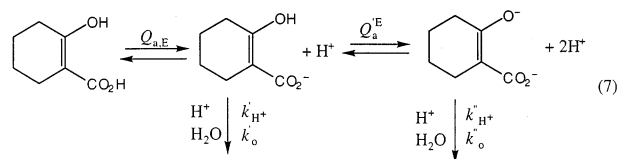
Because ketonization is an electrophilic addition reaction, successively ionized forms of the enol will be more reactive than their precursors, and ketonization will take place through them even when they are relatively minor substrate species. This produces a horizontal "uncatalyzed" rate profile segment at the high acid end where reaction is through carbon protonation of the enol carboxylate ion by H$^+$, while un-ionized enol is still the major substrate species. Such a reaction produces H$^+$ in a rapidly established preequilibrium and then uses it up in the rate-determining step, giving an overall process independent of H$^+$ concentration.

As the acidity is lowered, this uncatalyzed ketonization gives way to a reaction where H$^+$ is still the protonating agent but now the enol exists principally in its carboxylate ion form. This produces a downward bend in the profile, corresponding to the acid ionization constant $Q_{a,E}$ and leading to a diagonal acid-catalyzed segment of slope = −1. At sufficiently low acidity, this acid catalysis gives way to a narrow second horizontal plateau, whose origin, discussed below, is uncertain. Beyond this plateau, ketonization takes place through the dianionic form of the enol while its monoanion is still the dominant substrate form, with water as the carbon-protonating agent. This gives a preequilibrium which produces H$^+$ that is now not used up in the rate-determining step, giving a process whose rate is inversely proportional to H$^+$ concentration and having the appearance of hydroxide-ion catalysis.

In the rate profiles for ketonization of the enols of the previous β-oxocarboxylic acids that we investigated, this apparent hydroxide-ion catalysis became saturated and gave way to a third horizontal plateau as the fully ionized enol became the dominant substrate species.[2−4] This did not happen in the present case because the acidity constant of this enol, pQ_a^E = 14.53 (vide infra) is well beyond the rate profile limit, p[H$^+$] = 12.80, imposed by the requirement to keep ionic strength constant at 0.10 M.

(13) See, for example: Chiang, Y.; Kresge, A. J.; Popik, V. V. *J. Am. Chem. Soc.* **1995**, *117*, 9165−9171.

(14) Tidwell, T. T. *Acc. Chem. Res.* **1990**, *23*, 273−279. Tidwell, T. T. *Ketenes*; Wiley: New York, 1995; pp 576−585. Andraos, J.; Kresge, A. J. *Can. J. Chem.* **2000**, *78*, 508−515.

(15) Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990; Chapter 7.

The rate law that corresponds to the reaction scheme of eq 7 is given as eq 8, with k_{uc} as the rate constant for the process of

$$k_{obs} = \frac{k'_{H^+} Q_{a,E}[H^+]}{Q_{a,E} + [H^+]} + k'_{uc} + k'_{HO^-}[HO^-] \qquad (8)$$

uncertain origin responsible for the horizontal plateau at the center of the rate profile, k'_{HO^-} as the rate constant for the apparent hydroxide-ion catalysis, and the other constants defined by eq 7. Least-squares fitting of this expression gave $k'_{H^+} = (1.35 \pm 0.08) \times 10^4$ M^{-1} s^{-1}, $Q_{a,E} = (5.55 \pm 0.39) \times 10^{-5}$ M, $pQ_{a,E} = 4.26 \pm 0.03$,[16] $k_{uc} = (2.32 \pm 0.60) \times 10^{-5}$ s^{-1}, and k'_{HO^-} (3.31 ± 0.07) M^{-1} s^{-1}.

It was pointed out above that the origin of the rate profile plateau with rate constant k_{uc} is uncertain. This is because it could be due to ketonization of the monoanionic form of the enol through carbon protonation by a water molecule or to equilibrium ionization of the monoanion to dianion followed by carbon protonation of that by H$^+$. In the latter case, k_{uc} would be equal to $k''_{H^+} Q'^E_a$, and it is sometimes possible to rule out this interpretation because the value of k''_{H^+} required by this relationship is impossibly large. That, however, is not the case here, for use of the estimate $pQ'^E_a = 14.53$ (vide infra) leads to $k''_{H^+} = 7.9 \times 10^9$ M^{-1} s^{-1}. This is a large rate constant, but its value does not exceed the encounter-controlled limit.
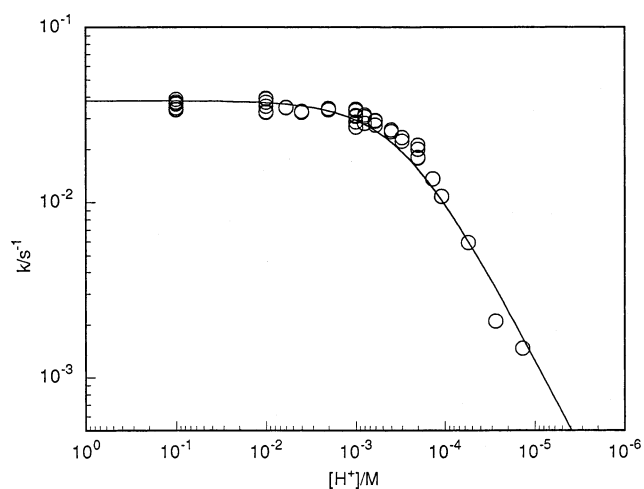
Enolization. Rates of enolization of 2-oxocylcohexanecarboxylic acid were measured by bromine scavenging in aqueous hydrobromic acid solutions and in acetic acid buffers. The ionic strength of all solutions was maintained at 0.10 M through the addition of sodium bromide as required. The data thus obtained are summarized in Tables S7 and S8.[11]

The measurements in buffers were again made in series of solutions of constant buffer ratio, and therefore constant H$^+$ concentration, and observed first-order rate constants were found to be linearly dependent upon buffer concentration. The data were therefore analyzed by least-squares fitting of eq 5. The buffer-independent rate constants, k_{int}, thus obtained, together with the rate constants measured in hydrobromic acid solution, are displayed as the rate profile shown in Figure 2.

This enolization reaction is the microscopic reverse of the ketonization of 2-oxocyclohexanecarboxylic acid enol, which was assigned a reaction mechansim in the region of acidity of these enolization rate measurements involving rate-determining carbon protonation of the carboxylate-ion form of the enol by H$^+$, giving un-ionized 2-oxocyclohexanecarboxylic acid and a water molecule as reaction products (vide supra). Enolization will therefore occur by the rate-determining reaction of un-ionized 2-oxoclohexanecarboxylic acid with a water molecule, giving the horizontal "uncatalyzed" region seen at the high acidity end of the rate profile of Figure 2. The un-ionized acid, however, will also be in equilibrium with its carboxylate ion, as shown in eq 9, and the need to convert this ion to un-ionized
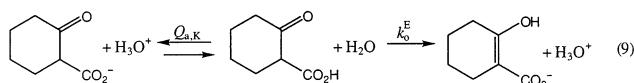
(16) This is a *concentration* dissociation constant, applicable at ionic strength = 0.10 M.

Figure 2. Rate profile for the enolization of 2-oxocyclohexanecarboxylic acid in aqueous solution at 25 °C.

acid before enolization can take place will give the acid-catalyzed profile region seen at the lower acidity end of the profile of Figure 2. The bend in the profile connecting these two regions, of course, corresponds to the ionization constant of the substrate acid.

The rate law that fits this reaction scheme is shown in eq 10, whose rate and equilibrium constants are defined in eq 9. Least-

$$k_{obs} = k^E_o[H^+]/([H^+] + Q_{a,K}) \qquad (10)$$

squares analysis of the data using this expression gave $k^E_o = (3.79 \pm 0.10) \times 10^{-2}$ s^{-1} and $Q_{a,K} = (2.91 \pm 0.20) \times 10^{-4}$ M, $pQ_{a,K} = 3.54 \pm 0.03$.[16] This rate constant is consistent with $k^E_o = 1.34 \times 10^{-2}$ M^{-1} s^{-1} reported for this reaction at 10 °C,[17] and the acidity constant is in reasonable agreement with the estimate $pQ_{a,K} = 3.24$ that can be made using a $\sigma-\rho$ correlation.[18]

Keto−Enol Equilibria. The enolization and ketonization rate constants determined here can be combined to provide keto−enol equilibrium constants for the 2-oxocyclohexanecarboxylic acid system (Table 1). Two such equilibrium constants may be defined: one, K_E, relating keto and enol isomers with the carboxylic acid group in its un-ionized form and another, K'_E, with this group in its carboxylate ion form.

The first of these equilibria can be formulated as the ratio of enolization to ketonization rate constants, as shown in eq 11, using rate constants that refer to enolization in the "uncatalyzed"
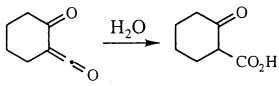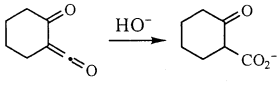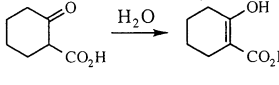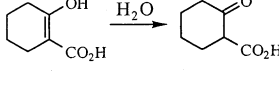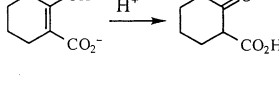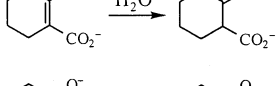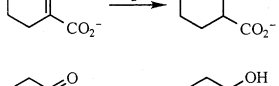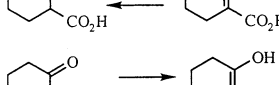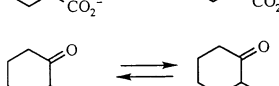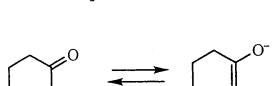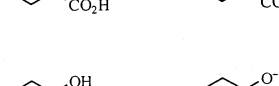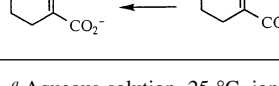
$$K_E = k^E_o/k^K_o \qquad (11)$$

reaction region of the rate profile shown in Figure 2 and ketonization in the corresponding region of the rate profile of Figure 1. The rate profile of Figure 1, however, was constructed using rates of decay of enol, which, because ketonization is slightly reversible ($K_E = 0.05$; vide infra), are actually rates of approach to equilibrium and contain a small (5%) enolization component. The quantity $k'_{H^+} Q_{a,E}$ that represents the acid-region plateau of the profile in Figure 1 must therefore be

(17) Cox, B. G.; Hutchinson, R. E. J. *J. Chem. Soc., Perkin Trans. 2* **1974**, 613−616.
(18) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK$_a$ Predictions for Organic Acids and Bases*; Chapman and Hall: New York, 1981; p 127.

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

| Process	Constant
	$k_o = 3.45 \times 10^4 \text{ s}^{-1}$
	$k_{HO^-} = 1.08 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$
	$k_o^E = 3.79 \times 10^{-2} \text{ s}^{-1}$
	$k_o^K = 7.09 \times 10^{-1} \text{ s}^{-1}$
	$k_{H^+}' = 1.35 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$
	$k_{HO^-}' = 3.31 \text{ M}^{-1} \text{ s}^{-1}$
	$k_o'' = 1.80 \times 10^1 \text{ s}^{-1}$
	$K_E = 5.34 \times 10^{-2}$ $pK_E = 1.27$
	$K_E' = 1.02 \times 10^{-2}$ $pK_E' = 1.99$
	$Q_{a,K} = 2.91 \times 10^{-4} \text{ M}$ $pQ_{a,K} = 3.54$
	$Q_a'^K = 2.98 \times 10^{-17} \text{ M}$ $pQ_a'^K = 16.53$
	$Q_{a,E} = 5.55 \times 10^{-5} \text{ M}$ $pQ_{a,E} = 4.26$
	$Q_a'^E = 2.92 \times 10^{-15} \text{ M}$ $pQ_a'^E = 14.53$

[a] Aqueous solution, 25 °C, ionic strength = 0.10 M.

corrected by subtracting k_o^E to convert it into a pure ketonization rate constant: $k_o^K = k_{H^+}' Q_{a,E} - k_o^E$. Rates of enolization, of course, require no correction because they were determined by bromine scavenging under nonreversible conditions. The rate and equilibrium constants determined here applied in this way then lead to $K_E = (5.34 \pm 0.23) \times 10^{-2}$, $pK_E = 1.27 \pm 0.02$.

The second keto–enol equilibrium constant, K_E', involving carboxylate ion species, can be derived from K_E using the thermodynamic cycle shown in eq 12. The relationship $K_E' =$

(12)
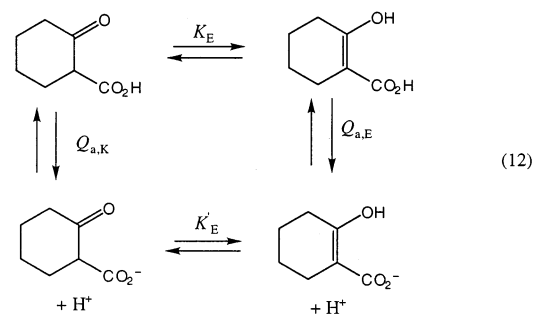
$K_E Q_{a,E}/Q_{a,K}$, with values of $Q_{a,E}$ and $Q_{a,K}$ obtained from rate profile fittings, then leads to $K_E' = (1.02 \pm 0.11) \times 10^{-2}$, $pK_E' = 1.99 \pm 0.05$.

pK_a Determination. The acidity constant of 2-oxocyclohexanecarboxylate ion ionizing further as a carbon acid, eq 13, was

(13)
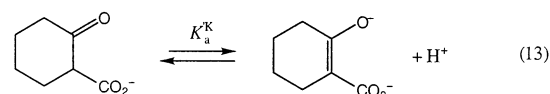
determined spectrophotometrically by monitoring the reversible UV absorbance change that accompanies this reaction. Measurements were made in concentrated potassium hydroxide solutions over the concentration range 1.5−17.3 M. The data thus obtained are summarized in Table S9.[11]

These data were transformed into values of I (=[basic form]/[acidic form]), and the fit of log I to different basicity functions was examined. Three functions were tried: an H_- scale based on neutral indole indicators,[19] an $H_=$ scale based on indoles bearing carboxylate groups,[19] and an $H_=$ scale based on aromatic amines bearing carboxylate and sulfonate groups.[20] The H_- scale based on indoles proved to be the most appropriate: it gave a plot of log I versus H_- whose slope was unity (0.96 ± 0.04), whereas the other basicity functions produced slopes significantly different from unity (0.85 ± 0.04 and 0.86 ± 0.04). The data were therefore analyzed using the H_- scale with the titration curve expression of eq 14, in which $10^{(-H_-)}$ serves as a measure of the basic strength of the solutions employed. Figure 3 shows

$$A = (A_{AH} 10^{(-H_-)} + A_B K_a'^K)/(10^{(-H_-)} + K_a'^K) \quad (14)$$

that the data conformed to this relationship well. Least-squares analysis produced the result $K_a'^K = (1.15 \pm 0.08) \times 10^{-17}$, $pK_a'^K = 16.94 \pm 0.03$.

Basicity functions such as the H_- scale used here are anchored to an infinitely dilute standard state, and the acidity constant determined here is therefore a thermodynamic value applicable at zero ionic strength. It may be converted into a concentration dissociation constant appropriate to the ionic strength, 0.10 M, used for the other measurements made here by application of activity coefficients. Employment of $f = 0.83^{12}$ for the hydrogen ion plus the acetate ($f = 0.775$)[12] and hydrogencitrate ($f = 0.36$)[12] values as surrogates for the mono- and dianions of eq 13 then gives $Q_a'^K = (2.98 \pm 0.21) \times 10^{-17}$, $pQ_a'^K = 16.53 \pm 0.03$.[16]
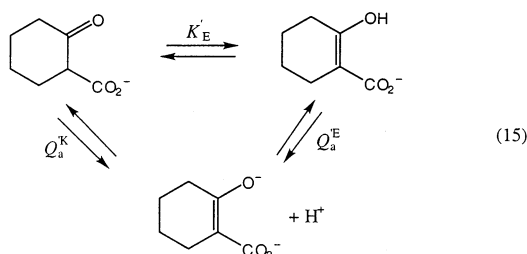
(19) Yagil, G. *J. Phys. Chem.* **1967**, *71*, 1034−1044.
(20) Halle, J.-C.; Terrier, F.; Schall, R. *Bull. Soc. Chim. Fr.* **1969**, 4569−4575.
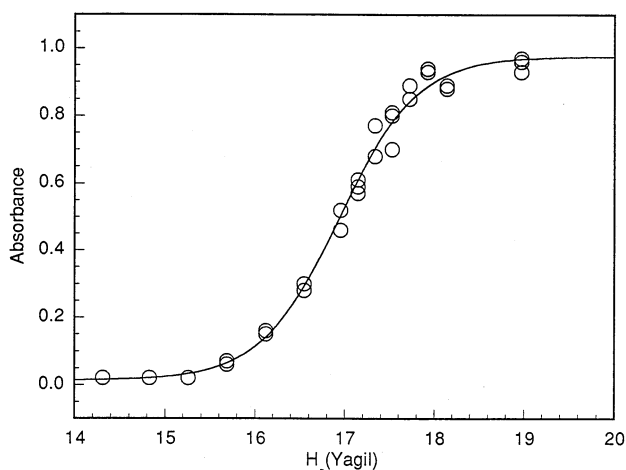
Figure 3. Spectrophotometric titration curve for the carbon-acid ionization of 2-oxocyclohexanecarboxylate ion in aqueous solution at 25 °C.

p$Q_a^{\prime K}$ and $k_o^{\prime\prime}$ Determination. The thermodynamic cycle given in eq 15 shows that $Q_a^{\prime K} = K_E^{\prime} Q_a^{\prime E}$. This relationship then

$$(15)$$

allows the enol acidity constant $Q_a^{\prime E}$ to be determined from the now known values of $K_E^{\prime}$ and $Q_a^{\prime K}$: $Q_a^{\prime E} = Q_a^{\prime K}/K_E^{\prime} = (2.92 \pm 0.38) \times 10^{-15}$ M, p$Q_a^{\prime E} = 14.53 \pm 0.06$.[16]

It was pointed out above that values of this enol acidity constant were obtained for other β-oxocarboxylic acid systems from bends at the low acidity ends of their rate profiles. The very low value of this acidity constant determined here for the present system shows why such a rate-profile-derived determination could not be made in this case: the relevant bend would have come well beyond the lowest acidity available, $[H^+] = 10^{-13}$ M, consistent with maintaining an ionic strength of 0.10 M.

This presently determined value of $Q_a^{\prime E}$ for the 2-oxocyclohexanecarboxylic acid system can in turn be used to obtain a value of the rate constant $k_o^{\prime\prime}$ for ketonization by the "uncatalyzed" route beyond the unobserved rate profile bend, that is, through carbon protonation of the enol dianion by a water molecule, as shown in eq 16. This rate constant is related to


$$(16)$$
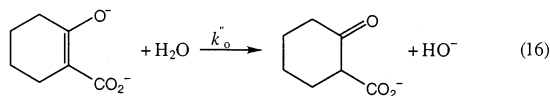
the hydroxide-ion catalytic coefficient of eq 8, $k_{HO^-}^{\prime}$: $k_{HO^-}^{\prime} = k_o^{\prime\prime} Q_a^{\prime E}/Q_w$, and insertion of the known values of $Q_a^{\prime E}$ and the autoprotolysis constant of water, Q_w, gives $k_o^{\prime\prime} = (1.80 \pm 0.23) \times 10^1$ s^{-1}. This result is considerably above the largest rate constant measured at the low acidity end of the rate profile of Figure 1, $k_{obs} = 5 \times 10^{-1}$ s^{-1}, which again points to the

incompatibility of making measurements in this profile region while maintaining an ionic strength of 0.10 M.

Comparison of Cyclohexyl and Cyclopentyl Systems. The rates of hydration of 2-oxocyclohexylideneketene measured here show this reaction to be significantly slower than hydration of 2-oxocyclopentylideneketene, by a factor of 41 for the uncatalyzed reaction and by a factor of 7 for the hydroxide-ion-catalyzed process. This difference is consistent with the nucleophilic character of these reactions, which occur by attack of the nucleophile on the ketene carbonyl-group carbon atom through approach in the ketene molecular plane:[14] such an approach is hindered in the cyclohexyl system but less so in the cyclopentyl case. Cyclic ketenes can be expected to be structurally similar to cyclic ketones, inasmuch as both have exocyclic double bonds. In the most stable, chair conformation of cyclohexanone, this double bond is eclipsed on both sides by immediately adjacent carbon–hydrogen bonds,[21] which interfere with the in-plane approach of an external reagent to the analogous ketene. In the favored half-chair conformation of cyclopentanone, on the other hand, this eclipsing interaction gives way to a more staggered arrangement,[22] and an in-plane approach to the analogous ketene is facilitated. It is significant, moreover, that the difference between the cyclohexyl and cyclopentyl system is greater for the slower uncatalyzed hydration than for the faster hydroxide-ion-catalyzed process, in keeping with the reactivity–selectivity principle.

The present results also show the keto–enol equilibrium constants for the 2-oxocyclohexanecarboxylic acid system to be greater than those for 2-oxocyclopentanecarboxylic acid, by a factor of 17 for the reaction with the carboxylic acid groups in their un-ionized form and by a factor of 10 for these groups in their ionized carboxylate form. The direction of this difference is the same as for the simple, uncarboxylated keto–enol systems, where K_E for cyclohexanone is 36 times that for cyclopentanone.[23] A ring-size effect in the same direction has also been found for the keto–enol equilibria of 2-carbomethoxycycloalkanones.[24]

Another interesting comparison for the 2-oxocyclohexanecarboxylic acid and 2-oxocyclopentanecarboxylic acid systems is provided by the acidity constants of the enol hydroxy groups of the carboxylate ion forms of the substance, eq 17. These

$$(17)$$
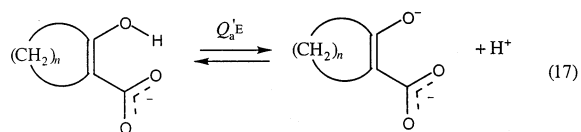
acidity constants, with p$Q_a^{\prime E} = 12.41$ for $n = 3$[3] and p$Q_a^{\prime E} = 14.53$ for $n = 4$, differ by more than two pQ units. Both acids are also considerably weaker than enols of simple monofunctional aldehydes and ketenes, whose acidity constants tend to lie in the range p$Q_a^E = 10-11$.[25] This acid weakness may be attributed to formation of a good hydrogen bond between the hydroxyl and carboxylate groups in the initial state of the

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ionization reaction and electrostatic repulsion between the two negative charges in the final state of this reaction; these effects will stabilize the initial state and destabilize the final state, increasing the energy difference between them and making the acid weaker. The fact that the cyclohexyl enol is a weaker acid than the cyclopentyl enol means that these effects must be stronger in the cyclohexyl system than in the cyclopentyl system. This is consistent with the fact that the exocyclic olefinic bonds in cyclohexene[26] are somewhat less splayed out than are the corresponding bonds in cyclopentene.[27] As a result, the hydrogen

bonding groups and the electrostatically repelling groups are somewhat closer in the cyclohexyl system than in the cyclopentyl system, giving cyclohexyl more initial state stabilization and also more final state destabilization. The result is a considerably less acidic cyclohexyl enol, as was observed.

Supporting Information Available: Tables S1−S9 of rate and equilibrium data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA030054J

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