The 2-Oxocyclobutanecarboxylic Acid Keto−Enol System in Aqueous Solution: A Remarkable Acid-Strengthening Effect of the Cyclobutane Ring

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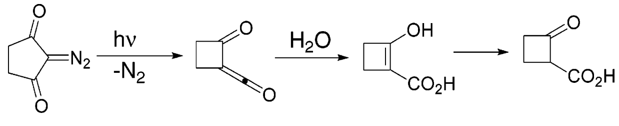
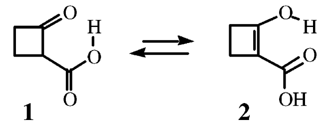


Enol is unusually strong acid.

Flash photolysis of 2-diazocyclopentane-1,3-dione in aqueous solution produced 2-oxocyclobutylideneketene, which underwent hydration to the enol of 2-oxocyclobutanecarboxylic acid; the enol then isomerized to the keto form of this acid. Rates of the ketene and enol reactions were measured in acid, base, and buffer solutions across the acidity range $[H^+] = 10^{-1} - 10^{-13}$ M, and analysis of these data, together with rates of enolization of the keto form of 2-oxocyclobutanecarboxylic acid determined by bromine scavenging, gave keto−enol equilibrium constants as well as acidity constants of the keto and enol forms. The keto−enol equilibrum constants proved to be 2 orders of magnitude less than those reported previously for the next higher homolog, 2-oxocyclopentanecarboxylic acid, reflecting the difficulty of inserting a carbon−carbon double bond into a small, strained carbocyclic ring. The acidity constant of the enol group of 2-oxocyclobutanecarboxylate ion, on the other hand, is greater, by 4 orders of magnitude, than that of the corresponding enol in the cyclopentyl system. This remarkable increase in acidity with diminishing ring size is consistent with the enhanced s character of the orbitals used to make the exocyclic bonds of the smaller cyclobutane ring.

In striking contrast to keto−enol tautomerism of β-ketoesters, which has been investigated extensively for more than a century,[1] little attention has been paid to such tautomerism of β-ketoacids themselves. We recently carried out detailed studies of keto−enol interconversion of acetoacetic acid,[2] 2-oxocyclopentanecarboxylic acid,[3] 4,4,4-trifluoroacetoacetic acid,[4] 2-oxocyclohexanecarboxylic acid,[5] and 2-oxo-3,3,5,5-tetramethylcyclopentanecarboxylic acid;[6] and we now add to that an examination of the 2-oxocyclobutanecarboxylic acid keto (**1**)−enol (**2**) system, eq 1. Our investigation has shown that enol **2** is an unexpectedly strong acid, a phenomenon that may be attributed to a remarkable acid-strengthening effect of the cyclobutane ring.



1 **2** (1)

We generated the enol of 2-oxocyclobutanecarboxylic acid in aqueous solution, as we did the enols of the other β-ketoacids

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(1) For reviews of 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.

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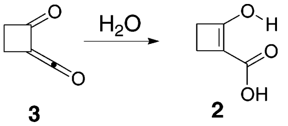
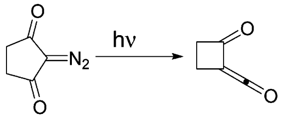
that we have studied,[2−6] by hydration of the corresponding acylketene (**3**), eq 2. The ketene, in turn, was produced by a photo-Wolff reaction of 2-diazocyclopentane-1,3-dione (**4**) eq 3. The reactions involved in these transformations are fast, and flash photolytic methods were therefore used to monitor their progress.

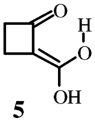


3 **2** (2)



4 **3** (3)

β-Ketocarboxylic acids, such as that investigated here, can, in principle, form either ketone enols, such as that shown in eqs 1 and 2, or carboxylic acid enols, such as **5**. High-level ab initio calculations have shown, however, that ketone enols are considerably more stable than the corresponding carboxylic acid enols,[7] in keeping with much greater enol content of acetone (pK_E = 8)[8] than that of acetic acid (pK_E = 20).[9] It seems safe to conclude, therefore, that the substance studied here is the ketone enol, as shown in eq 1.



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Experimental Section

Materials. 2-Diazocyclopentane-1,3-dione was prepared from cyclopenetane-1,3-dione by diazo transfer, using tosyl azide as the diazo transfer agent and triethylamine as the base.[10]

2-Oxocyclobutanecarboxylic acid was prepared by photolyzing 2-diazocyclopentane-1,3-dione in the presence of water. A solution of 300 mg of the diazo compound in 15 mL of acetonitrile to which 500 μL of water had been added was irradiated with 254 nm Hg-lamps (Rayonet) in a quartz test tube for 1 h. The reaction mixture was then dried over magnesium sulfate and the solvent was removed in vacuuo to provide 240 mg (87% yield) of 2-oxocyclobutanecarboxylic acid, whose ^{1}H NMR spectrum agreed with a published report.[11]

All other materials were best available commercial grades.

Kinetics. Rates of ketene hydration and enol ketonization were measured with microsecond[12] and nanosecond[13] (eximer laser operating at $\lambda = 248$ nm) flash photolysis systems that have already been described.[12,13] With both systems, the temperature of the reacting solutions was controlled at 25.0 ± 0.05 °C, and reactions were followed by monitoring changes in UV absorption in the region 265−290 nm. Most of the kinetic data obtained conformed to the first-order rate law well, and observed first-order rate constants were calculated by least-squares fitting of a single-exponential function. In some of the ketene hydrations, however, a minor amount of a competing reaction, perhaps hydration of a ketocarbene intermediate,[14] appeared to be taking place. This additional reaction produced minor deviations from first-order behavior, and in these cases the fitting was done by using either a single-exponential plus linear expression or a double exponential function.

Rates of enolization of 2-oxocyclobutanecarboxylic acid were measured by bromine scavenging under first-order conditions, using an excess of bromine in HBr and NaOH solutions. The measurements in HBr were done in the presence of NaBr where bromine is complexed as the Br_3^- ion, and the reaction was followed by monitoring the absorbance of this ion at $\lambda = 268$ nm. A Cary 2200 spectrometer, whose cell compartment was thermostated at 25.0 ± 0.05 °C, was used for this purpose. The measurements in NaOH solutions were done under conditions where bromine exists as the OBr^- ion, and these reactions were followed by monitoring the absorbance of this ion at $\lambda = 330$ nm. A stopped-flow spectrometer operating at 25.0 ± 0.05 °C was used for this purpose.

Rates of hydrolysis of 2-oxocyclobutanecarboxylic acid were also measured spectrophotometrically, again with the Cary spectrometer operating at 25.0 ± 0.05 °C. The reactions were followed by monitoring decay of the absorbance of this acid at $\lambda = 200$ nm.

Acidity Constant Determination. The acid ionization constant of the carboxylic acid group of 2-oxocyclobutanecarboxylic acid was determined spectrophotometrically by monitoring the increase in absorbance at $\lambda = 210$ nm, which occurred as this acid ionized. The data so obtained were analyzed by using the titration curve expression shown in eq 4, in which Q_{aK} is the acid ionization

$$A = \frac{A_{HA}[H^+] + A_B Q_{aK}}{[H^+] + Q_{aK}} \tag{4}$$

constant at the ionic strength of the measurement (0.10 M), A_{HA} and A_B are the limiting absorbances of the acidic and basic forms of the substrate, respectively, and A is the absorbance of a solution in which both forms of the substrate are present.

Results

Reaction Identification. Irradiation of 2-diazo-1,3-diketones is known to give a photo-Wolff reaction producing acylketenes, which, in the presence of water, undergo hydration to 2-oxo-carboxylic acids.[2−6,15] This was verified in the present case by showing that irradiation of 2-diazocyclopentane-1,3-dione in acetonitrile solution containing 3% water produced a 90% yield of 2-oxocyclobutanecarboxylic acid, whose ^{1}H NMR spectrum agreed with a published report.[11]

Flash photolysis of aqueous solutions of 2-diazocyclopentane-1,3-dione produced a rapid, microsecond rise in absorbance at λ = 260−300 nm followed by a much slower decay. These changes were assigned, on the basis of the above-described product study, as well as by analogy with the behavior of our previously examined 2-diazo-1,3-diketone systems,[3,5,6] to hydration of 2-oxocyclobutylideneketene, itself formed within the time of the laser pulse; this gave the enol of 2-oxocyclobutanecarboxylic acid (eq 2), followed by ketonization of the enol to

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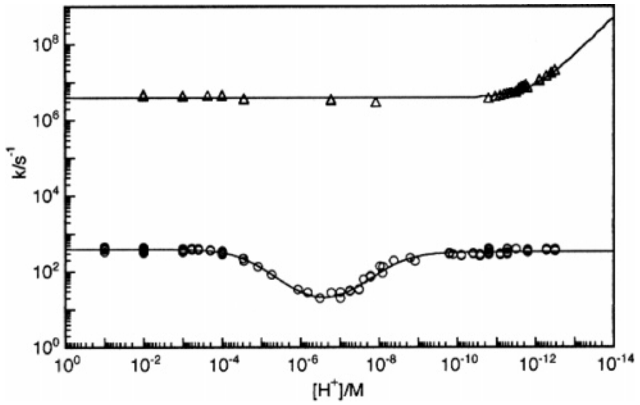

FIGURE 1. Rate profiles for the hydration of 2-oxocyclobutylideneketene (△) and the ketonization of 2-oxocyclobutanecarboxylic acid enol (○) in aqueous solution at 25 °C.

ketoacid product (reverse of eq 1). This assignment is supported by the response of these absorbance changes to acid−base catalysis as well as by the solvent isotope effects that they gave (vide infra).

Ketene Hydration. Rates of hydration of 2-oxocyclobutylideneketene were measured in dilute aqueous perchloric acid and sodium hydroxide solutions and in formic acid, acetic acid, biphosphate ion, and monohydrogen-*tert*-butylphosphonate ion buffers. The ionic strength of the reacting solutions was maintained at 0.10 M through the addition of sodium perchlorate as required. The data so obtained are summarized in Tables S1−S3.[16]

The measurements in buffers were made in a series of solutions of constant buffer ratio, and therefore constant hydrogen ion concentration, but differing buffer concentrations. Observed first-order rate constants were found to increase linearly with increasing buffer concentration, and the data were therefore analyzed by using the linear buffer dilution expression shown as eq 5 . In this expression, k_{cat} is the buffer catalytic

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

coefficient and k_s represents reaction through solvent-related species. Least-squares fitting of the data gave values of k_s, which, together with the rate constants determined in perchloric acid and sodium hydroxide solutions, are displayed as the upper rate profile of Figure 1. Values of $[H^+]$ needed for this purpose were evaluated by calculation, using literature values of the pK_a's of the buffer acids and activity coefficients recommended by Bates.[17]

This rate profile is characteristic of ketene hydration reactions, which typically show extensive uncatalyzed regions, weak hydroxide ion catalysis, and even weaker or, more commonly, no hydrogen ion catalysis.[2−6,13,18]

Least-squares fitting of the profile data gave $k_o = (4.05 \pm 0.06) \times 10^6\ s^{-1}$ for the uncatalyzed ketene hydration reaction and $k_{HO^-} = (3.40 \pm 0.0.08) \times 10^8\ M^{-1}\ s^{-1}$ for the hydroxide ion catalyzed process. (These and subsequently determined numerical results are summarized in Table 1.) These rate constants are large, and they show that this ketene is quite reactive, just like the other acyl ketenes that we have examined. This of course is consistent with the nucleophilic nature of these reactions and the ability of the acyl group to stabilize the negative charge being put on the ketene as it reacts with nucleophiles.

The present results agree well with a remarkably good correlation of uncatalyzed and hydroxide ion catalyzed rate constants for the hydration of some 30 ketenes, which spans 10 orders of magnitude in reactivity and gives k_o with a root-mean-square deviation of 1.9.[19] This correlation predicts $k_o = 3.3 \times 10^6\ s^{-1}$ for the present system, a result that is nicely consistent with the observed value $k_o = 4.1 \times 10^6\ s^{-1}$.

Uncatalyzed ketene hydrations typically give weak solvent isotope effects in the normal direction ($k_H/k_D > 1$),[19] as expected for a reaction that occurs by nucleophilic attack of water on the ketene carbonyl carbon atom, in a process that involves no making or breaking of bonds to hydrogen but does require the attacking water molecule to take on positive charge.[20] Rates of the present reaction were therefore also measured in D_2O solutions of perchloric acid, and the results, summarized in Table S1,[16] when combined with their H_2O counterparts, give the isotope effect $k_{H_2O}/k_{D_2O} = 1.35 \pm 0.02$. This result is entirely consistent with expectation, and it further supports identification of the reaction as hydration of 2-oxocyclobutylideneketene.

Enol Ketonization. Rates of ketonization of 2-oxocyclobutanecarboxylic acid enol were measured in dilute aqueous perchloric acid and sodium hydroxide solutions and in acetic acid, biphosphate ion, tris(hydroxymethyl)methylammonium ion, and monohydrogen-*tert*-butylphosphonate ion buffers. The ionic strength of these solutions was again maintained at 0.10 M ($NaClO_4$). The data so obtained are summarized in Tables S4−S6.[16]

The measurements in buffers were again made in a series of solutions of constant buffer ratio, and linear buffer catalysis was again found. The data were therefore once more analyzed with use of eq 5. Values of k_s obtained in this way, together with the rate constants determined in perchloric acid and sodium hydroxide solutions, are displayed as the lower rate profile of Figure 1.

This rate profile is similar in shape to those found for the ketonization of the enols of the other β-ketoacids that we have studied.[2−6] It may therefore be interpreted in the same way as those rate profiles were, in terms of rate-determining carbon protonation of successively ionized forms of the substrate, either by the hydronium ion, written here as H^+, or by H_2O, eq 6. This interpretation is consistent with the accepted general mechanism for enol ketonization, which involves rate-determining β-carbon protonation by any available acid,[21] and it is also consistent with the fact that ketonization is an electrophilic addition reaction, expected to occur more rapidly with successively ionized forms of the substrate even when they are relatively minor species.

The plateau at the high acidity end of this rate profile then

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[16] Supporting Information; see the paragraph at the end of this paper regarding availability.

[17] Bates, R. G. *Determination of pH Theory and Practice*; Wiley: New York 1973; p 49.

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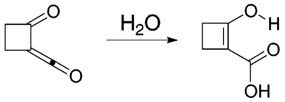
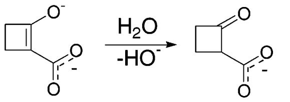
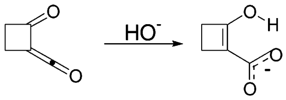
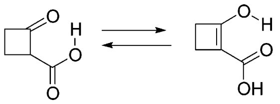
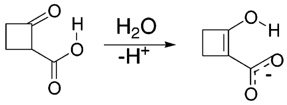
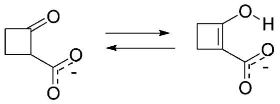
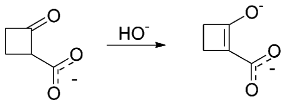
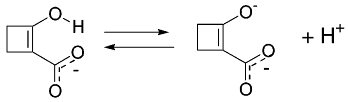
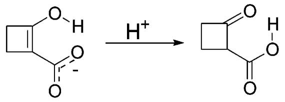
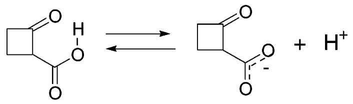
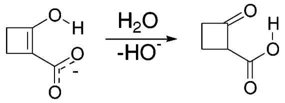
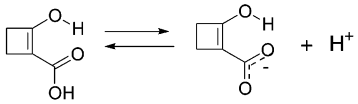
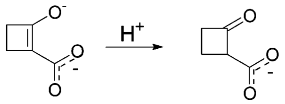
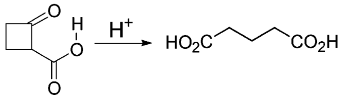
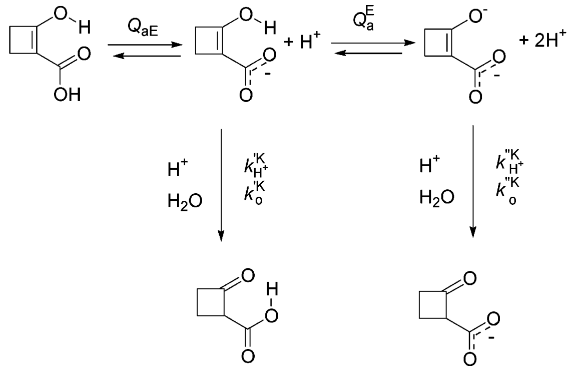
TABLE 1. Summary of Rate and Equilibrium Constants for the 2-Oxocyclobutylideneketene and 2-Oxocyclobutanecarboxylic Acid System[a]

Process	Constant	Process	Constant
	$k_o = 4.05\times10^{6}\ s^{-1}$		$k_o^{''K} = 3.19\times10^{2}\ s^{-1}$
	$k_{HO^-} = 3.40\times10^{8}\ M^{-1}\ s^{-1}$		$K_E = 1.45\times10^{-5}$; $pK_E = 4.84$
	$k_o^E = 5.47\times10^{-3}\ s^{-1}$		$K'_E = 1.07\times10^{-6}$; $pK'_E = 5.97$
	$k_{HO^-}^E = 1.20\times10^{2}\ M^{-1}\ s^{-1}$		$Q_a^E = 3.39\times10^{-9}\ M$; $pQ_a^E = 8.47$
	$k_{H^+}^{'K} = 1.59\times10^{7}\ M^{-1}\ s^{-1}$		$Q_{aK} = 3.21\times10^{-4}\ M$; $pQ_{aK} = 3.49$
	$k_o^{'K} = 1.28\times10^{1}\ s^{-1}$		$Q_{aE} = 2.37\times10^{-5}\ M$; $pQ_{aE} = 4.63$
	$k_{H^+}^{''K} = 3.95\times10^{9}\ M^{-1}\ s^{-1}$		$k_{H^+}^h = 1.42\times10^{-2}\ M^{-1}\ s^{-1}$

[a] Aqueous solution, 25 °C, ionic strength = 0.10 M. Acidity constants are concentration quotients applicable at 0.10 M ionic strength.



(6)

represents rate-determining carbon protonation of the enol carboxylate ion by H^+, under conditions where most of the enol is still in its un-ionized carboxylic acid form; ionization of the acid to its reactive form produces H^+, but H^+ is then used in the subsequent step, giving an overall reaction independent of $[H^+]$. At lower acidities where most of the enol exists in its carboxylate form, prior substrate ionization no longer takes place and cancellation of H^+ concentrations no longer occurs; the reaction then becomes first order in $[H^+]$ giving the diagonal profile segment immediately following the high-acidity plateau.

This diagonal section is followed by another, quite short uncatalyzed portion, which could be due either to carbon protonation of the carboxylate form of the substrate by H_2O or to protonation of the doubly ionized but still minor carboxylate−enolate form by H^+; in the latter case H^+ is produced in a prior equilibrium but is used up in the rate-determining step, again leading to $[H^+]$ cancellation and a profile section independent of $[H^+]$. It is sometimes possible to rule out the first of these interpretations because such a mechanism gives rate constants too similar in value for reactions catalyzed by acids as different in strength as H^+ and H_2O.[22] It is likewise sometimes possible to rule out the second of these interpretations because that gives an impossibly large value to the rate constant for reaction catalyzed by H^+.[2,6] Neither of these situations, however, applies here (vide infra), and a choice between the two alternatives cannot be made on the basis of the available information.

At acidities just below those of this short second plateau, the carboxylate−enolate dianion is still a minor substrate form, but reaction nevertheless occurs through it, this time through carbon protonation by H_2O. Formation of the substrate reactive form then produces H^+, but since H^+ is not used in the subsequent step, the rate of the overall process is inversely proportional to $[H^+]$; this gives the second diagonal profile segment, which has the appearance of hydroxide ion catalysis. At sufficiently low $[H^+]$, the dianion becomes the major substrate form, and carbon protonation of it by H_2O then gives the last $[H^+]$-independent profile section.

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[22] (a) Chiang, Y.; Eustace, S. E.; Jefferson, E. A.; Kresge, A. J.; Popik, V. V.; Xie, R.-Q. *J. Phys. Org. Chem.* **2000**, 461−467. (b) Chiang, Y.; Kresge, A. J.; Schepp, N. P.; Xie, R.-Q. *J. Org. Chem.* **2000**, *65*, 1175−1180.

These assignments of the reactions producing the ketonization rate profile lead to two somewhat different rate laws, eqs 7 and 8, corresponding to the two different interpretations of

$$k_{obs} = \frac{k'^{K}_{H^+} Q_{aE}[H^+]}{Q_{aE} + [H^+]} + k'^{K}_{o} + \frac{k''^{K}_{o} Q^{E}_{a}}{Q^{E}_{a} + [H^+]} \qquad (7)$$

$$k_{obs} = \frac{k'^{K}_{H^+} Q_{aE}[H^+]}{Q_{aE} + [H^+]} + \frac{(k''^{K}_{H^+}[H^+] + k''^{K}_{o}) Q^{E}_{a}}{Q^{E}_{a} + [H^+]} \qquad (8)$$

the central horizontal profile segment. Least-squares fitting of these two expressions, nevertheless, produced the same values of the two equilibrium constants, $Q_{aE} = (2.37 \pm 0.27) \times 10^{-5}$ M, $pQ_{aE} = 4.63 \pm 0.05$,[23] and $Q^{E}_{a} = (3.24 \pm 0.29) \times 10^{-9}$ M, $pQ^{E}_{a} = 8.49 \pm 0.04$,[23] and also the same value of the rate constant for carbon protonation of the monoanion by H^+, $k'^{K}_{H^+} = (1.59 \pm 0.17) \times 10^{7}\ M^{-1}\ s^{-1}$. The two equations, however, did give slightly different values of the rate constant, k''^{K}_{o}, for carbon protonation of the dianionic form of the substrate by H_2O, but the difference is not statistically significant: $k''^{K}_{o} = (3.13 \pm 0.06) \times 10^{2}\ s^{-1}$ (eq 7) and $k''^{K}_{o} = (3.25 \pm 0.06) \times 10^{2}\ s^{-1}$ (eq 8). The weighted average of these two values is $(3.19 \pm 0.04) \times 10^{2}\ s^{-1}$. Equation 7 also gave $k'^{K}_{o} = (1.28 \pm 0.17) \times 10^{1}\ s^{-1}$ as the rate constant for carbon protonation of the monoanionic form of the substrates by H_2O, and eq 8 gave $k''^{K}_{H^+} = (3.95 \pm 0.80) \times 10^{9}\ M^{-1}\ s^{-1}$ as the rate constant for carbon protonation of the dianionic form of the substrate by H^+.

The last of these rate constants is large, but not impossibly so, i.e., it does not exceed the encounter-controlled limit. It cannot therefore, as noted above, be used to rule out interpretation of the central horizontal segment of the rate profile as representing carbon protonation of the dianionic form of the substrate by H^+. The alternative interpretation, carbon protonation of the monoanionic formed by H_2O, likewise, cannot be ruled out, inasmuch as the rate constant for this process obtained from eq 7, $k'^{K}_{o} = 1.28 \times 10^{1}\ s^{-1}$, is sufficiently less than $k'^{K}_{H^+} = 1.59 \times 10^{7}\ M^{-1}\ s^{-1}$ to fit the expectation for protonation of the same substrate by two acids of such widely disparate strengths as H_2O and H^+.

Some measurements of enol ketonization were also made in 0.01M solutions of perchloric acid in D_2O and 0.001 M solutions of sodium hydroxide in D_2O. These data are summarized in Tables S-4 and S-5.[16] When combined with their H_2O counterparts, they give the isotope effects $k_{H_2O}/k_{D_2O} = 8.13 \pm 0.22$ (acid solutions) and $k_{H_2O}/k_{D_2O} = 9.51 \pm 0.42$ (base solutions). These isotope effects provide good support for the interpretation of the ketonization rate profile detailed above.

The isotope effect measured in acid solutions refers to a region where the rate laws of eqs 7 and 8 reduce to $k_{obs} = k'^{K}_{H^+} Q_{aE}$, and this isotope effect is therefore the product of effects on a rate constant and an equilibrium constant. The equilibrium constant is the acid dissociation constant of a carboxylic acid, which is a process that normally shows solvent isotope effects in the region $K_{H_2O}/K_{D_2O} = 3-4$.[24] That leaves a factor of 2−3 for the isotope effect on the rate constant, which is a reasonable value for a reaction such as this involving rate-determining proton transfer from the solvated hydronium ion to a substrate: in such a process there is a primary isotope effect, but this is accompanied by an inverse ($k_H/k_D < 1$) secondary component that reduces the overall effect, and a factor of 2−3 is in fact a good value for such a solvent isotope effect.[25]

The isotope effect measured in basic solutions refers to a region of the rate profile where the rate laws of eqs 7 and 8 reduce to $k_{obs} = k''^{K}_{o}$, and the process under observation is carbon protonation of the substrate by water. The primary isotope effect here is also accompanied by a secondary effect, but now the secondary effect is in the normal direction ($k_H/k_D > 1$).[20] The result is an overall effect that is quite large, similar to the strong effect observed here, and isotope effects of this magnitude have in fact been found on the ketonization of other enols effected by carbon protonation through proton transfer from water.[22b,26]

2-Oxocyclobutanecarboxylic Acid Hydrolysis. It was found that the 2-oxocyclobutanecarboxylic acid product of enol ketonization is unstable in aqueous solution and is hydrolyzed to glutaric acid in an acid-catalyzed process. Rates of this reaction were measured in dilute aqueous perchloric acid solutions whose ionic strength was maintained at 0.10 M by the addition of sodium perchlorate. The data so obtained are summarized in Table S7.[16]

Observed first-order rate constants for this reaction increased linearly with increasing acid concentration, and linear least-squares analysis produced the hydrogen ion catalytic coefficient $k^{h}_{H^+} = (1.42 \pm 0.01) \times 10^{-2}\ M^{-1}\ s^{-1}$.

Acidity Constant Determination. The acid ionization constant for 2-oxocyclobutanecarboxylic acid was determined by monitoring the change in its UV absorption at 210 nm in perchloric acid solutions and also in formic acid, acetic acid, and biphosphate ion buffers at a constant ionic strength of 0.10 M. These solutions covered the acidity region $[H^+] = 1 \times 10^{-1}$ to 4×10^{-8} M. The data so obtained, summarized in Table S8,[16] conformed well to the titration curve expression of eq 4, and least-squares analysis gave the acidity constant $Q_{aK} = (3.36 \pm 0.33) \times 10^{-4}$ M; $pQ_{aK} = 3.47 \pm 0.04$.[23]

Ketone Enolization. Rates of enolization of the ketone group of 2-oxocyclobutanecarboxylic acid were measured by bromine scavenging under first-order conditions in hydrobromic acid solutions over the concentration range [HBr] = 0.0001 to 0.4 M. The ionic strength of these solutions was maintained at 0.10 M through the addition of sodium bromide as required, except at [HBr] > 0.10 M where the ionic strength was equal to [HBr]. These data are summarized in Table S9[16] and are displayed as the rate profile of Figure 2.

This rate profile shows a nearly horizontal "uncatalyzed" segment at moderate acidities followed by a diagonal section signifying an acid-catalyzed reaction at lower acidities. This suggests that enolization occurs, as required, by a route that is the microscopic reverse of the mechanism, eq 6, established above for enol ketonization in acidic solutions, i.e., enolization through proton removal by H_2O from the α-keto C−H bond of the more reactive, un-ionized carboxylic acid form of the substrate under conditions where both this and the carboxylate

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[23] This is a *concentration* equilibrium constant, applicable at the ionic strength, 0.10 M, at which it was determined.

[24] Laughton, P. M.; Robertson, R. E. In *Solute−Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; M. Dekker: New York; 1969, Chapter 7.

[25] Kresge, A. J.; Sagatys D. S.; Chen, H.-L. *J. Am. Chem. Soc.* **1977**, *99*, 7228−7233.

[26] Chiang, Y.; Kresge, A. J.; Walsh, P. A. *Z. Naturforsch.* **1988**, *44a*, 406−412.

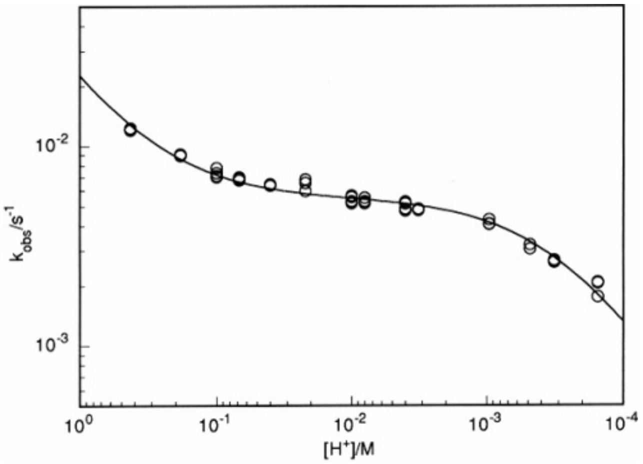
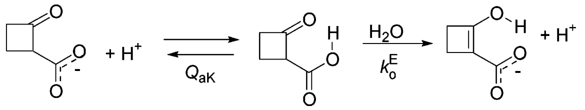


FIGURE 2. Rate profile for the enolization and hydrolysis of 2-oxocyclobutanecarboxylic acid in aqueous hydrobromic acid solutions at 25 °C.

form exist in rapid equilibrium, eq 9. The rate profile, however, also shows a second acid-catalyzed segment at higher acidities that has no counterpart in the ketonization direction and is not required by the principle of microscopic reversibility. This region of acidity, however, is where 2-oxocyclobutanecarboxylic acid undergoes acid-catalyzed hydrolysis to glutaric acid (vide supra), and that suggests that this second acid-catalyzed profile segment is due to that hydrolysis reaction.



(9)

Such a hydrolysis reaction would create an additional route for consumption of 2-oxocyclobutanecarboxylic acid, and the process would become a system of two parallel reactions. In such a kinetic scheme the two parallel reactions proceed at a common rate, and increasing the rate of one, e.g., by acid catalysis, increases the rate of the other.[27] The rate law for this reaction scheme is given by eq 10, in which $k^h_{H^+}$ is the rate constant for the acid-catalyzed hydrolysis reaction, k_o^E is the

$$k_{obs} = (k^h_{H^+}[H^+] + k_o^E)[H^+]/(Q_{aK} + [H^+]) \qquad (10)$$

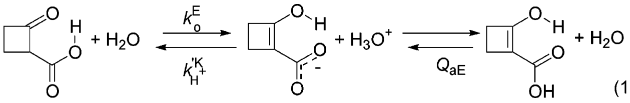
rate constant for water-catalyzed enolization, and Q_{aK} is the acidity constant of the carboxylic acid group of 2-oxocyclobutanecarboxylic acid. Least-squares analysis of the experimental data gave $k_o^E = (5.47 \pm 0.08) \times 10^{-3}$ s^{-1}, $k^h_{H^+} = (1.72 \pm 0.09) \times 10^{-2}$ M^{-1} s^{-1}, and $Q_{aK} = (3.17 \pm 0.16) \times 10^{-4}$ M, pQ_{aK} = 3.50 ± 0.02.[23] These last two quantities are consistent with $k^h_{H^+} = 1.42 \times 10^{-2}$ M^{-1} s^{-1} and pQ_{aK} = 3.47 measured directly, which validates this interpretation of the experimental data. The weighted averages of the two determinations of each of these constants give $k^h_{H^+} = (1.42 \pm 0.01) \times 10^{-2}$ M^{-1} s^{-1} and $Q_{aK} = (3.21 \pm 0.14) \times 10^{-4}$ M, pQ_{aK} = 3.49 ± 0.02[23] as their best values.

Rates of enolization of the ketone group of 2-oxocyclobutanecarboxylate acid were also measured by bromine scavenging under first-order conditions in sodium hydroxide solutions. Determinations were made over the concentration range [NaOH] = 0.01 to 0.05 M at a constant ionic strength of 0.10 M maintained by the addition of sodium perchlorate. These data are summarized in Table S10.[16] Observed first-order rate constants increased linearly with [NaOH], and linear least-squares analysis gave the hydroxide ion catalytic coefficient $k^E_{HO^-} = (1.20 \pm 0.01) \times 10^2$ M^{-1} s^{-1}.

Discussion

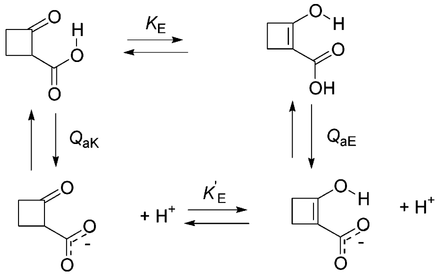
Keto−Enol Equilibria. The enolization and ketonization rate constants and related equilibrium constants determined here may be combined to provide values of keto−enol equilibrium constants for 2-oxocyclobutanecarboxylic acid. Because of the presence of the carboxylic acid group in this system, two such equilibrium constants can be defined, one relating keto and enol isomers with the carboxylic acid group un-ionized, K_E, and another with this group ionized, K'_E.

The first of these equilibria may be formulated as shown in eq 11, using water and hydronium ion as the agents effecting keto−enol isomerization. The equilibrium constant for this process may then be expressed as $K_E = k_o^E/(k'^K_{H^+}Q_{aE})$, and use of the values of k_o^E, $k'^K_{H^+}$, and Q_{aE} determined here gives $K_E = (1.45 \pm 0.23) \times 10^{-5}$, p$K_E$ = 4.84 ± 0.07.



(11)

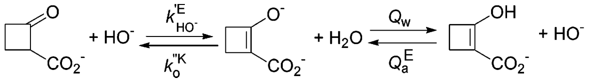
This keto−enol equilibrium involving un-ionized carboxylic acid species can be related to its ionized, carboxylate ion counterpart through the thermodynamic cycle show in eq 12.



(12)

The keto−enol equilibrium involving ionized carboxylate species may then be expressed as $K'_E = K_EQ_{aE}/Q_{aK}$, and use of the values of K_E, Q_{aE}, and Q_{aK} determined here gives $K'_E = (1.07 \pm 0.21) \times 10^{-6}$, $pK'_E = 5.97 \pm 0.09$.

The keto−enol equilibrium involving ionized carboxylic acid species may also be expressed by using hydroxide ion and water to effect the keto−enol isomerization, as shown in eq 13. The equilibrium constant expression for this process is given as eq 14, and rearrangement of that then provides an expression, eq 15, from which an estimate of the acid ionization constant of the enol hydroxyl group of the carboxylate ion, Q_a^E, in addition



(13)

$$K'_E = k^E_{HO^-}Q_w/k''^K_oQ^E_a \qquad (14)$$

$$Q^E_a = k^E_{HO^-}Q_w/k''^K_oK'_E \qquad (15)$$

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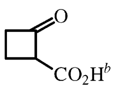
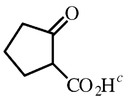
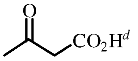
(27) Espenson, J. H. *Chemical Kinetics and Reaction Mechanism*, 2nd ed.; McGraw-Hill: New York, 1995; pp 58−61.

TABLE 2. Comparison of 2-Oxocyclobutanecarboyxlic Acid with Other β-Ketoacid Keto−Enol Systems

Constant[a]			
pQ_{aK}	3.49	3.67	3.39
pQ_{aE}	4.63	4.16	4.05
pK_E	4.84	2.51	2.25
pK'_E	5.97	3.00	2.91
pQ_a^E	8.47	12.41	13.18

[a] Aqueous solution; 25 °C; ionic strength = 0.10M. Acidity constants are concentration quotients applicable at 0.10 M ionic strength. [b] Present work. [c] Reference 3. [d] Reference 2.

to the one based on the rate profile of Figure 1 (vide supra), may be obtained. Insertion of the appropriate numerical values into eq 15 then gives $Q_a^E = (5.57 \pm 1.11) \times 10^{-9}$ M, $pQ_a^E = 8.25 \pm 0.09$,[23] which is consistent with the more accurate value, $pQ_a^E = 8.49 \pm 0.04$, provided by the rate profile. This corroboration is especially valuable because this enol has been found to be an unexpectedly strong acid (vide infra). The weighted average of the two values gives $Q_a^E = (3.39 \pm 0.028) \times 10^{-9}$ M, $pQ_a^E = 8.47 \pm 0.04$[23] as the best value of this quantity.

Comparison with Other Systems. Equilibrium constants determined here for the 2-oxocyclobutanecarboxylic acid keto−enol system are compared in Table 2 with their counterparts for the next larger cyclic β-ketoacid, 2-oxocyclopentanecarboxylic acid, and its acylic analogue, acetoacetic acid. It may be seen that the acidity constants of the carboxylic acid groups of the keto isomers (Q_{aK}) in all three systems are much the same, and that is also true of the acidity constants of the carboxylic acid groups of the enol isomers (Q_{aE}). The keto−enol equilibrium constants of the cyclobutyl system, however, are strikingly less than those for the other two systems: that for the equilibrium with un-ionized carboxylic acid groups (K_E) by some two and one-half orders of magnitude and that of the equilibrium with ionized carboxylate groups (K'_E) by 3 orders of magnitude. These lower keto−enol equilibrium constants are reflected in lower rates of enolization and higher rates of ketonization. For example, the value of k_o^E for the cyclobutyl system is an order of magnitude less than those for the cyclopentyl and acyclic systems and the value of $k'^K_{H^+}$ for the cyclobutyl enol is 2 orders of magnitude greater than those for the cyclopentyl and acyclic enols.

The low enol content of 2-oxocyclobutanecarboxylic acid undoubtedly reflects the difficulty of introducing a carbon−carbon double bond into a four-membered ring: the small endocyclic angles required by such a ring are at odds with the significantly greater bond angles required by the sp^2 double-bonded framework. It is likely, however, that another factor is operating as well: enols of β-ketocarbonyl compounds are stabilized by intramolecular hydrogen bonding between their carbonyl and enol hydroxyl groups, and such a hydrogen bond in the cyclobutyl system with its splayed out exocyclic bonds will have to span a greater distance and will therefore be less strong and less stabilizing than the hydrogen bonds allowed by the geometry of the cyclopentyl and acyclic systems.

The comparisons of Table 2 also show that the acidity constant of the enol group of 2-oxocyclobutanecarboxylate ion, Q_a^E, differs from those of the cyclopentyl and acyclic systems by an even greater amount than the differences between the K_E and K'_E values, with the cyclobutyl enol now being the stronger acid by some 4 to 5 orders of magnitude. The enols of 2-oxocyclopentanecarboxylate ion and acetoacetate ion are significantly weaker acids than are simple enols without adjacent carboxylate groups; the enol of acetone, for example, with $pQ_a^E = 10.94$,[21] is a stronger acid by some 2 orders of magnitude. This difference has been attributed to two effects:[2] (1) formation of a strong intramolecular hydrogen bond between the enol hydroxyl group and the adjacent carboxylate ion in the un-ionized enol and (2) electrostatic repulsion between the negative charge of the enolate ion and the negative charge of the carboxylate group in the ionized enol. The first of these effects stabilizes the initial state of the ionization process and the second destabilizes its final state, and since the ionization is an uphill process, this makes the energy difference between initial and final states greater, and the acid consequently weaker, than it would otherwise be.

Each of these effects will be weakened by the splayed out exocyclic bonds of the cyclobutyl system: the first because the hydrogen bond will now have to span a greater distance and the second because the negative charges will now be farther apart. This will reduce the energy difference between the initial and final states of the ionization reaction, and that will make the cyclobutyl enol a stronger acid than the cyclopentyl and acyclic enols.

This reduction of the acid weakening effects, however, should not make the cyclobutyl enol a stronger acid than the enol of acetone. The acid-weakening effects, though reduced, are still present in modified form in the cyclobutyl system, and that should make the cyclobutyl enol a weaker acid than acetone enol, where the acid-weakening effects are completely eliminated. Since the cyclobutyl enol is a stronger acid than acetone enol by some two and one-half orders of magnitude, an additional acid-strengthening effect must be operating.

This additional effect might be the enhanced s-character of the orbitals used to construct the exocyclic bonds of cyclobutyl rings. To accommodate the small internal bond angles required by small carbocyclic rings, the endocyclic bonds in such rings are made of orbitals with more p-character than those used in larger rings and acyclic systems, and that leaves more s-character for the orbitals of exocyclic bonds of small rings. More s-character is of course associated with increased acidity, as evidenced for example by the enhanced acid strength of acetylenic carbon−hydrogen bonds. An example of this phenomenon with particular relevance to the present situation is provided by acidity constants recently determined for a series of protonated primary amines by a new method that measures pK_a differences with unusual precision.[28] These measurements show the cyclopropylammonium ion to be more acidic than the cyclopentylammonium ion by 1.559 ± 0.011 pK units and the cyclobutylammonium ion to be more acidic than the cyclopentylammonium ion by 0.596 ± 0.004 units.

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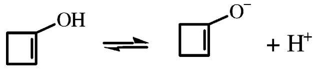
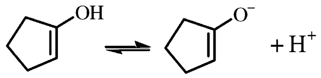
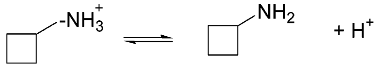
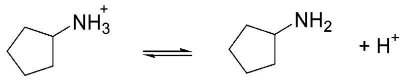
(28) Perrin, C. L.; Fabian, M. A.; Rivero, I. A. *Tetrahedron* **1999**, *55*, 5773−5780.

TABLE 3. Calculated (MP2/6-31+G*) Energy Differences for the Ionization of Enols and Ammonium Ions in the Gas Phase[a]

Reaction	ΔH/kcal mol^{-1}
	342.7
	346.2
	216.8
	219.1

[a] Corrected for zero-point vibrational energy contributions calculated at the HF/6-31+G* level.

This difference between cyclobutyl and cyclopentyl ammonium ion pK_a values is considerably less than the pK_a enhancement required by the present results, which must be somewhat greater than the two and one-half pK unit difference between the acidity constants of acetone enol and the enol of 2-oxocyclobutanecarboxylic acid. It is possible, however, that the s-character stabilization of the full negative charge on an enolate ion would be stronger than its stabilization of an unshared electron pair in a neutral amine, and the acid strengthening effect would consequently be greater on enol ionization than on ammonium ion ionization. Some support for this idea comes from the results of ab initio calculations summarized in Table 3, which compare gas phase energies of ionization of enols and ammonium ions of cyclobutyl and cyclopentyl substrates. In both series the cyclobutyl derivatives are the stronger acids, as observed experimentally in aqueous solution. The difference between the cyclobutyl and cyclopentyl systems, moreover, is greater for the enol ionization reactions, $\delta\Delta H = 3.5$ kcal mol^{-1}, than that for the ammonium ion ionizations, $\delta\Delta H = 2.3$ kcal mol^{-1}.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support of this work.

Supporting Information Available: Tables S1−S10 of rate and equilibrium data. This material is available free of charge via the Internet at http://pubs.acs.org.

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