

# The 4,4,4-Trifluoroacetoacetic Acid Keto–Enol System in Aqueous Solution. Generation of the Enol by Hydration of Trifluoroacetylketene

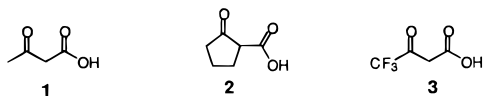
Y. Chiang,<sup>†</sup> A. J. Kresge,<sup>\*,†</sup> Q. Meng,<sup>†</sup> Y. Morita,<sup>‡</sup> and Y. Yamamoto<sup>‡</sup>

Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada, and The Tohoku College of Pharmacy, Sendai 981, Japan

Received May 10, 1999. Revised Manuscript Received July 6, 1999

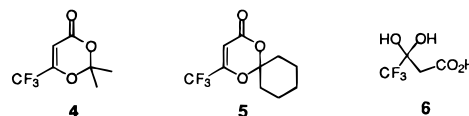
**Abstract:** Trifluoroacetylketene was generated in aqueous solution by flash photolysis of 2,2-dimethyl-6-trifluoromethyl-4H-1,3-dioxin-4-one and its spiro analogue, 4-trifluoromethyl-1,5-dioxaspiro[5.5]undec-3-en-2-one, and rates of hydration of the ketene to 4,4,4-trifluoroacetoacetic acid enol as well as subsequent ketonization of the enol were measured in this solvent across the acidity range  $[H^+] = 10^{-1}–10^{-12}$  M. Analysis of the rate profile produced by these data provides the acidity constants  $pQ_{a,E} = 1.85$  for the carboxylic acid group of the enol and  $pQ_a^E = 9.95$  for its enolic hydroxyl group, which make these groups 2 and 3 orders of magnitude more acidic, respectively, than the corresponding groups in the parent unfluorinated acetoacetic acid enol. Rates of enolization of the keto group of 4,4,4-trifluoroacetoacetic acid were also measured, by bromine scavenging, and these, together with a value of the equilibrium constant for hydration of the keto group to its *gem*-diol derivative based upon a free energy relationship,  $K_h = 2900$ , provide an estimate of the keto–enol equilibrium constant for this system:  $pK_E = 0.28$ . This is greater, by 2 orders of magnitude, than the keto–enol equilibrium constant for the unfluorinated acetoacetic acid.

There is a large body of information on keto–enol tautomerism of  $\beta$ -ketoesters, gathered over the course of more than a century.<sup>1</sup> In striking contrast, few investigations of tautomerism of  $\beta$ -ketoacids have been performed. We recently carried out detailed studies of the acetoacetic acid (**1**)<sup>2</sup> and the 2-oxocyclopentanecarboxylic acid (**2**)<sup>3</sup> keto–enol systems, and we now add to that an examination of the enol of 4,4,4-trifluoroacetoacetic acid (**3**).



We generated this enol, as we did the enol of acetoacetic acid,<sup>2</sup> by flash photolytic retro-[2 + 4]-cycloaddition of appropriate dioxinones, using in this case 2,2-dimethyl-6-trifluoromethyl-4H-1,3-dioxin-4-one (**4**) and its spiro analogue, 4-trifluoromethyl-1,5-dioxaspiro[5.5]undec-3-en-2-one (**5**) as the photolysis substrates. Photocleavage of dioxinones is known to produce acylketenes,<sup>4</sup> which, in aqueous solution, are rapidly hydrated to enols. We also found that, whereas 4,4,4-trifluoro-

acetoacetic acid exists as the ketone hydrate, **6**, in aqueous solution, the anhydrous acid tautomerizes to substantial amounts of enol in organic solvents such as acetonitrile or tetrahydrofuran; we consequently used such solutions as sources of the enol as well.



Whereas our earlier work showed that rate and equilibrium constants for interconversion of the various species involved were much the same for the acetoacetic acid and 2-oxocyclopentanecarboxylic acid systems, introduction of a trifluoromethyl group has now provided some interesting differences. The rate and equilibrium constants are summarized in Table 1.

## Experimental Section

**Materials.** 4,4,4-Trifluoroacetoacetic acid was prepared by acid-catalyzed hydrolysis of the ethyl ester;<sup>5</sup> this produced the hydrate, which was converted to anhydrous trifluoroacetoacetic acid by sublimation under reduced pressure. 2,2-Dimethyl-6-trifluoromethyl-4H-1,3-dioxin-4-one was a sample prepared in a previous study,<sup>6</sup> and 4-trifluoromethyl-1,5-dioxaspiro[5.5]undec-3-en-2-one was made by an analogous method; its properties were consistent with a literature description.<sup>7</sup> All other materials were best available commercial grades.

**Kinetics.** Flash photolytic rate measurements were made using conventional flash lamp and laser systems ( $\lambda_{exc} = 248$  nm) that have already been described.<sup>8</sup> Substrate concentrations were of the order of

(5) Swarts, F. *Bull. Sci. Acad. R. Belg.* **1926**, *12*, 721–725.

(6) Morita, Y.; Kamakura, R.; Takeda, M.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1997**, 359–360.

(7) Iwaoka, T.; Murohashi, T.; Sato, M.; Kaneko, C. *Synthesis* **1992**, 977–981.

<sup>†</sup> University of Toronto.

<sup>‡</sup> Tohoku College of Pharmacy.

(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: Toulecc, 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) Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, 1219–1248. Tidwell, T. T. *Ketenes*; John Wiley & Sons: New York, 1995; pp 125–128.

**Table 1.** Summary of Rate and Equilibrium Constants<sup>a</sup>

Process	Constant	Ratio <sup>b</sup>
	$k_o = 1.75 \times 10^6 \text{ s}^{-1}$	1.14
	$k_{o,h}^E = 1.91 \times 10^3 \text{ s}^{-1}$	-
	$k_{H^+}^K = 7.44 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$	1/172
	$k_{H^+}^{K'} = 1.88 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$	-
	$k_o^{K'} = 3.20 \times 10^2 \text{ s}^{-1}$	1/28,000
	$Q_{a,h} = 3.51 \times 10^{-4} \text{ M}$ $pQ_{a,h} = 3.45$	-
	$Q_{a,E} = 1.42 \times 10^{-2} \text{ M}$ $pQ_{a,E} = 1.85$	159
	$Q_a^E = 1.13 \times 10^{-10} \text{ M}$ $pQ_a^E = 9.95$	1,700
	$K_{E,h} = 1.81 \times 10^{-4}$ $pK_{E,h} = 3.74$	-
	$K_{E,h}^1 = 7.31 \times 10^{-3}$ $pK_{E,h}^1 = 2.14$	-
	$(K_a = 2.90 \times 10^3)$	-
	$(K_h^1 = 3.35 \times 10^1)$	-
	$(k_o^E = 5.54 \text{ s}^{-1})$	(86)
	$(Q_{a,K} = 3.04 \times 10^{-2} \text{ M})$ $(pQ_{a,K} = 1.52)$	(75)
	$(K_E = 5.24 \times 10^{-1})$ $(pK_E = 0.28)$	(93)
	$(K_E^1 = 2.45 \times 10^{-1})$ $(pK_E^1 = 0.61)$	(201)

<sup>a</sup> Aqueous solution, 25 °C, ionic strength = 0.10 M. Values in parentheses are estimates based upon hydration equilibrium constants,  $K_h$  and  $K_h^1$ , obtained using a free energy relationship; see text for details. Acidity constants are concentration quotients at ionic strength = 0.10 M. <sup>b</sup> Ratio of constant for 4,4,4-trifluoroacetic acid system to that for acetoacetic acid system.

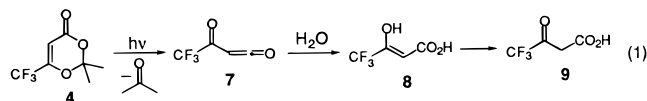
$6 \times 10^{-5} \text{ M}$ , and reactions were monitored by following the rise and decay of enol absorbance at  $\lambda = 260\text{--}270 \text{ nm}$ . Some reaction rates were too slow to be determined well in even the conventional flash photolysis system, and these measurements were consequently made with a Cary 2200 spectrometer, using reaction mixtures in which dioxinones had been activated by a single flash from the conventional system, or reaction mixtures in which enol was supplied from a tetrahydrofuran stock solution made using anhydrous trifluoroacetoacetic acid.

Rates of enolization of trifluoroacetoacetic acid were determined using bromine to scavenge the enol as it formed. These measurements were made in hydrobromic acid solutions, where bromine exists as the tribromide ion, and reactions were followed by monitoring the absorbance of this ion at  $\lambda = 310 \text{ nm}$ . Stoichiometric bromine concentrations in the reaction mixtures were ca.  $1 \times 10^{-4} \text{ M}$ , and trifluoroacetoacetic acid concentrations were ca.  $8 \times 10^{-5} \text{ M}$ .

The temperature of all reaction mixtures used for rate measurements was controlled at  $25.0 \pm 0.05 \text{ °C}$ . The rate data conformed to the first-order rate law well, and observed rate constants were obtained by least-squares fitting of exponential functions.

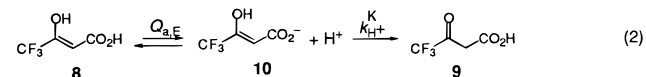
## Results

Flash photolysis of the dioxinone substrates **4** and **5** in aqueous solution produced a rapid, microsecond rise in absorbance at  $\lambda = 260\text{--}270 \text{ nm}$ , followed by a much slower decay. These changes were assigned, on the basis of analogy with the acetoacetic acid system where similar absorbance changes were observed,<sup>2</sup> to formation of trifluoroacetoacetic acid enol (**8**) by hydration of trifluoroacetylketene (**7**), itself formed within the time of the laser flash; this was then followed by subsequent ketonization of the enol to trifluoroacetoacetic acid (**9**), eq 1.



This assignment is also supported by the response of these absorbance changes to acid–base catalysis and to changes in the isotopic composition of the solvent (vide infra).

Rates of decay of the enol were the same for this species produced from the dimethyldioxinone **4** as for that produced from the spirodioxinone **5**. This is illustrated in Figure 1, where rates of ketonization in perchloric acid solution are compared. At these acidities, the enol exists in both un-ionized carboxylic acid (**8**) and ionized carboxylate ion (**10**) forms, eq 2, but



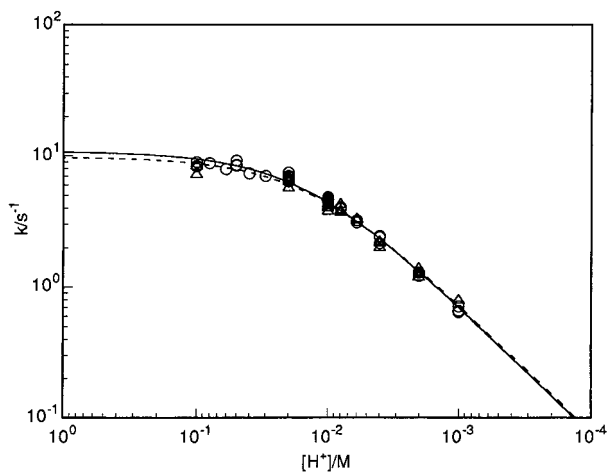
ketonization occurs through the more reactive carboxylate form. The rate law that applies to this reaction scheme is shown in eq 3, where  $Q_{a,E}$  is the ionization constant of the carboxylic acid group and  $k_{H^+}^K$  is the rate constant for ketonization of the carboxylate form catalyzed by the hydronium ion.

$$k_{\text{obs}} = k_{H^+}^K Q_{a,E} [\text{H}^+] / (Q_{a,E} + [\text{H}^+]) \quad (3)$$

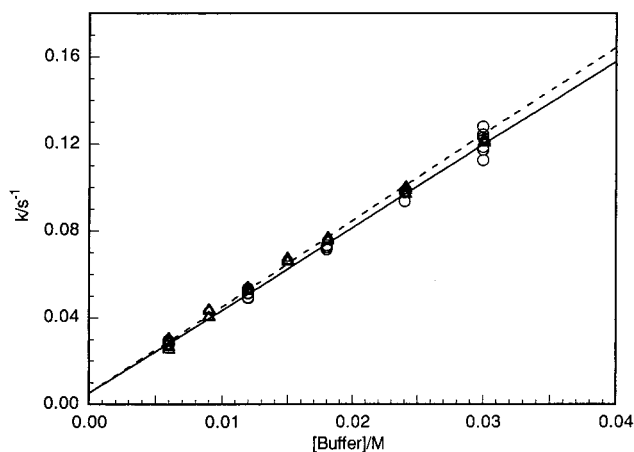
Least-squares fitting of this expression gave  $k_{H^+}^K = (7.42 \pm 0.16) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ ,  $Q_{a,E} = (1.46 \pm 0.06) \times 10^{-2} \text{ M}^9$  for enol produced from the dimethyldioxinone and  $k_{H^+}^K = (7.72 \pm$

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

(9) This is a concentration ionization constant applicable at the ionic strength (0.10 M) at which it was determined.



**Figure 1.** Comparison of rates of ketonization of 4,4,4-trifluoroacetoacetic acid enol produced from dimethyldioxinone **4** (O and solid line) and from spirodioxinone **5** (Δ and broken line) in aqueous perchloric acid solution at 25 °C.



**Figure 2.** Comparison of rates of ketonization of 4,4,4-trifluoroacetoacetic acid enol derived from dimethyldioxinone **4** (O and solid line) and from the anhydrous acid (Δ and broken line) in aqueous  $(\text{CH}_2\text{OH})_3\text{CNH}_3^+$  buffer solutions at 25 °C.

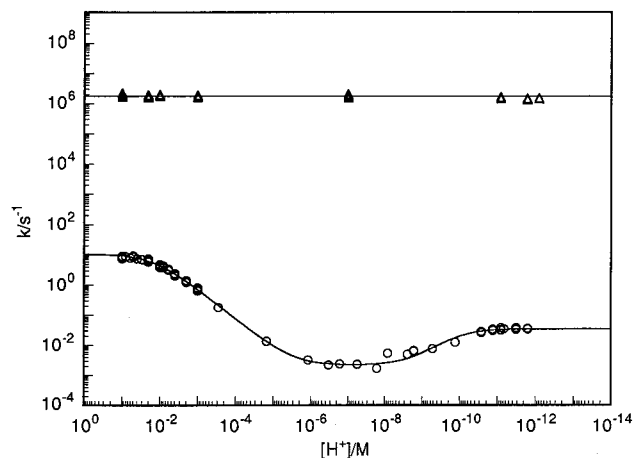
$0.23) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ ,  $Q_{a,E} = (1.27 \pm 0.09) \times 10^{-2} \text{ M}^9$  for enol produced from the spirodioxinone.

Rates of ketonization of enol produced by photolysis of the dioxinones were also the same as those for enol obtained from an equilibrated tetrahydrofuran stock solution made using anhydrous trifluoroacetoacetic acid. This is illustrated in Figure 2, where rates measured in  $(\text{CH}_2\text{OH})_3\text{CNH}_3^+$  buffers are compared. Linear least-squares analysis of these data gave  $k_{\text{obs}}/\text{s}^{-1} = (4.92 \pm 0.68) \times 10^{-3} + (3.82 \pm 0.06)[\text{buffer}]$  for enol from the dimethyldioxinone and  $k_{\text{obs}}/\text{s}^{-1} = (5.03 \pm 0.85) \times 10^{-3} + (3.98 \pm 0.08)[\text{buffer}]$  for enol from the acid.

**Ketene Hydration.** Rates of hydration of trifluoroacetylketene 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,  $[\text{HClO}_4] = 0.001\text{--}0.1 \text{ M}$  and  $[\text{NaOH}] = 0.002\text{--}0.02 \text{ M}$ , and replicate measurements were made at each concentration. The ionic strength was held constant at 0.10 M. The data so obtained are summarized in Tables S1–S3<sup>10</sup> and are also displayed as the upper rate profile of Figure 3.

It may be seen that the rates measured remain constant throughout the range of acidity examined,  $[\text{H}^+] = 10^{-1}\text{--}10^{-12}$

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



**Figure 3.** Rate profiles for the hydration of trifluoroacetylketene (Δ) and ketonization of 4,4,4-trifluoroacetoacetic acid enol (O).

M. This is characteristic of ketene hydration reactions, whose rate profiles typically show extensive uncatalyzed regions: acid catalysis is only rarely present, and base catalysis is usually weak.<sup>2,3,8b,11</sup> In the present case, the dioxinone substrates were unstable in base and decomposed rapidly in sodium hydroxide solutions more concentrated than ca. 0.01 M, further precluding observation of base catalysis. Some measurements of ketene hydration were also made in  $\text{D}_2\text{O}$  solutions of perchloric acid and in  $\text{D}_2\text{O}$  with no acid or base added as well. These data are summarized in Tables S1 and S3.<sup>10</sup> The average value of the rate constants so obtained, when combined with the  $\text{H}_2\text{O}$  counterpart,  $k = (1.75 \pm 0.30) \times 10^6 \text{ s}^{-1}$ , gives the isotope effect  $k(\text{H}_2\text{O})/k(\text{D}_2\text{O}) = 0.88 \pm 0.02$ . Near-unity values of isotope effects such as this are also characteristic of uncatalyzed ketene hydrations,<sup>2,3,8b,11</sup> 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.<sup>12</sup>

**Enol Ketonization.** Rates of ketonization of 4,4,4-trifluoroacetoacetic acid enol were measured in aqueous perchloric acid and sodium hydroxide solutions. Acid and base concentrations were varied,  $[\text{HClO}_4] = 0.001\text{--}0.1 \text{ M}$  and  $[\text{NaOH}] = 0.0006\text{--}0.01 \text{ M}$ , and replicate measurements were made at each concentration; ionic strength was maintained constant at 0.10 M. The data so obtained are summarized in Tables S4 and S5.<sup>10</sup>

Rate measurements were also made in aqueous  $\text{HCO}_2\text{H}$ ,  $\text{CH}_3\text{CO}_2\text{H}$ ,  $\text{H}_2\text{PO}_4^-$ ,  $(\text{CH}_2\text{OH})_3\text{CNH}_3^+$ , and  $\text{NH}_4^+$  buffers. Series of buffer solutions of constant buffer ratio and constant ionic strength (0.10 M) but varying total buffer concentration were used. These data are summarized in Table S6.<sup>10</sup>

Strong buffer catalysis was found, with observed rate constants increasing in the expected linear fashion with increasing buffer concentration. The data were therefore analyzed by least-squares fitting of eq 4. The zero-buffer-concentration intercepts,  $k_0$ , obtained in this way, together with rate constants measured in perchloric acid and sodium hydroxide solutions,

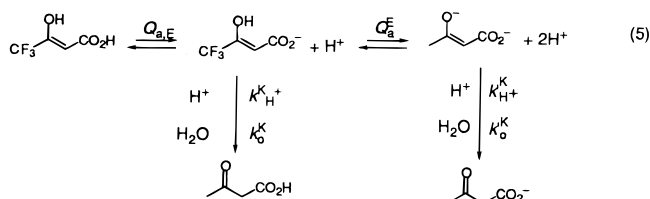
(11) (a) Allen, A. D.; Kresge, A. J.; Schepp, N. P.; Tidwell, T. T. *Can. J. Chem.* **1987**, *65*, 1719. Allen, A. D.; Stevenson, A.; Tidwell, T. T. *J. Org. Chem.* **1989**, *54*, 2843–2848. Tidwell, T. T. *Acc. Chem. Res.* **1990**, *23*, 273–279. Allen, A. D.; Baigre, L. M.; Gong, L.; Tidwell, T. T. *Can. J. Chem.* **1991**, *69*, 138–145. (b) Andraos, J.; Kresge, A. J. *J. Photochem. Photobiol. A* **1991**, *57*, 165–173. (c) Andraos, J.; Kresge, A. J.; Schepp, N. P. *Can. J. Chem.* **1995**, *75*, 539–543. Chiang, Y.; Kresge, A. J.; Popik, V. V. *J. Am. Chem. Soc.* **1995**, *117*, 9165–9171.

(12) 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.

$$k_{\text{obs}} = k_{\text{o}} + k_{\text{buff}}[\text{buffer}] \quad (4)$$

were used to construct the lower rate profile shown in Figure 3. Hydronium ion concentrations of the buffer solutions needed for this purpose were obtained by calculation, using literature  $pK_{\text{a}}$ 's of the buffer acids and activity coefficients recommended by Bates.<sup>13</sup>

This rate profile is similar to those found for ketonization of the enols of acetoacetic acid<sup>2</sup> and 2-oxocyclopentanecarboxylic acid,<sup>3</sup> and it may be interpreted in the same way as those rate profiles were, using the reaction scheme of eq 5. Downward



bends in rate profiles such as those found here at  $[\text{H}^+] \cong 10^{-2}$  and  $[\text{H}^+] \cong 10^{-10}$  M are commonly produced by ionization of acidic groups in the substrate,<sup>14</sup> and the present bends may be attributed to ionization of the carboxylic acid and enolic hydroxyl groups of the enol. Ketonization of enols is known to occur by rate-determining protonation of the enol on its  $\beta$ -carbon atom,<sup>15</sup> and, since this profile represents reaction through solvent-related species, protonation will take place by proton transfer either from the hydronium ion, represented here by  $\text{H}^+$ , or from  $\text{H}_2\text{O}$ . Moreover, since ketonization is an electrophilic addition reaction, successively ionized forms of the substrate will be more reactive than their precursors, and reaction will take place through them even when they are relatively minor forms. The short horizontal, "uncatalyzed" portion of this rate profile at acidities above the first bend then represents ketonization through protonation on carbon by  $\text{H}^+$  of the ionized carboxylate form of the substrate, when un-ionized carboxylic acid is still the dominant substrate form: this reaction first generates  $\text{H}^+$  in a fast equilibrium ionization and then uses it up in the rate-determining step, producing an overall process whose rate is independent of  $[\text{H}^+]$ . At acidities below the first bend, on the other hand, carboxylate ion is the principal substrate form, and carbon protonation of this substance by  $\text{H}^+$  becomes an acid-catalyzed process with rate proportional to  $[\text{H}^+]$ , which produces a diagonal rate profile segment with slope = -1.

At lower acidities, with  $[\text{H}^+] < 10^{-8}$  M, the dianion becomes the reactive form, but now  $[\text{H}^+]$  is too low for  $\text{H}^+$  to be an effective protonating agent, and  $\text{H}_2\text{O}$  takes over the role of proton donor. This produces a diagonal segment with slope = +1 at acidities above the second bend, where the monoanion is still the dominant substrate form: equilibrium ionization of the second acidic (enolic) group to provide the reactive dianion generates  $\text{H}^+$ ; this, however, is not used up in the rate-determining step, and that gives an overall process whose rate is inversely proportional to  $[\text{H}^+]$ , or directly proportional to  $[\text{HO}^-]$ , producing an apparent hydroxide ion catalysis. At acidities below the second bend, the dianion is the principal substrate form, and reaction of this with  $\text{H}_2\text{O}$  gives another horizontal "uncatalyzed" profile segment.

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

(14) Loudon, G. M. *J. Chem. Educ.* **1991**, 68, 973–984.

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

The two diagonal parts of this rate profile are connected by another horizontal segment whose molecular interpretation is less straightforward: this portion could be due to reaction of the monoanion with  $\text{H}_2\text{O}$ , or it could be caused by ionization of the monoanion to dianion followed by reaction of that with  $\text{H}^+$ . An argument suggesting a choice between these possibilities is presented below.

The rate law that applies to this reaction scheme is shown in eq 6, in which  $k_{\text{uc}}$  represents the mechanistically ambiguous

$$k_{\text{obs}} = \frac{k_{\text{H}^+}^{\text{K}} Q_{\text{a,E}} [\text{H}^+]}{Q_{\text{a,E}} + [\text{H}^+]} + k_{\text{uc}} + \frac{k_{\text{o}}^{\text{K}} Q_{\text{a}}^{\text{E}}}{Q_{\text{a}}^{\text{E}} + [\text{H}^+]} \quad (6)$$

middle portion of the rate profile and the other constants are as defined by eq 5. Least-squares fitting of this expression produced the following results:  $k_{\text{H}^+}^{\text{K}} = (7.44 \pm 0.20) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ ,  $k_{\text{uc}} = (2.12 \pm 0.12) \times 10^{-3} \text{ s}^{-1}$ ,  $k_{\text{o}}^{\text{K}} = (3.20 \pm 0.12) \times 10^{-2} \text{ s}^{-1}$ ,  $Q_{\text{a,E}} = (1.42 \pm 0.08) \times 10^{-2} \text{ M}$ ,  $pQ_{\text{a,E}} = 1.85 \pm 0.02$ ,<sup>9</sup> and  $Q_{\text{a}}^{\text{E}} = (1.13 \pm 0.16) \times 10^{-10} \text{ M}$ ,  $pQ_{\text{a}}^{\text{E}} = 9.95 \pm 0.06$ .<sup>9</sup>

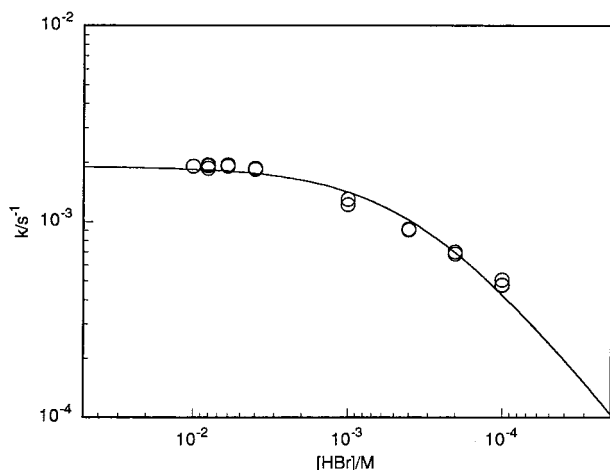
Interpretation of the horizontal middle portion of the rate profile as representing ionization of monoanion to dianion followed by reaction of the latter with  $\text{H}^+$  requires  $k_{\text{uc}}$  to be equal to  $k_{\text{H}^+}^{\text{K}} Q_{\text{a}}^{\text{E}}$ , and  $k_{\text{H}^+}^{\text{K}}$  can consequently be evaluated as  $k_{\text{uc}}/Q_{\text{a}}^{\text{E}}$ . In the case of acetoacetic acid enol, that gave the improbably large rate constant  $k_{\text{H}^+}^{\text{K}} = 3 \times 10^{11} \text{ M}^{-1} \text{ s}^{-1}$ ,<sup>2</sup> and this molecular interpretation was consequently rejected. The present results, on the other hand, give the perfectly acceptable value  $k_{\text{H}^+}^{\text{K}} = (1.88 \pm 0.29) \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ , and a mechanistic choice can therefore not be made here on the basis of the magnitude of this rate constant. The alternative explanation, however, i.e., carbon protonation of the monoanionic form of the substrate by  $\text{H}_2\text{O}$  with  $k_{\text{uc}} = k_{\text{o}}^{\text{K}}$ , leads to the improbably low rate ratio,  $k_{\text{o}}^{\text{K}}/k_{\text{H}^+}^{\text{K}} = (3.20 \times 10^{-2})/(2.12 \times 10^{-3}) = 15.1$ , for protonation of enolate ion and enol by  $\text{H}_2\text{O}$ . In a number of simple enol systems, ionization of the enol to enolate ion was found to increase the rate of ketonization catalyzed by the same acid by many orders of magnitude.<sup>16</sup> For acetoacetic acid enol, for example, this ratio is  $k_{\text{o}}^{\text{K}}/k_{\text{H}^+}^{\text{K}} = 5 \times 10^4$ , and the reactivity–selectivity principle leads to the expectation that this ratio should be even greater for the present considerably less reactive system (vide infra). Its small value thus suggests that this mechanistic interpretation is not correct and that the other assignment, i.e., ionization of monoanion to dianion followed by protonation of that by  $\text{H}^+$ , is to be preferred. Such a stepwise mechanism has, in fact, been assigned to this part of the rate profile for the ketonization of simple enols on the basis of other evidence.<sup>16b</sup>

Additional support for the interpretation of the present rate profile in terms of the ketonization reaction scheme of eq 5 comes from the form of buffer catalysis of these reactions. The buffer catalytic coefficients,  $k_{\text{buff}}$ , of eq 4 can be separated into their general acid,  $k_{\text{HA}}$ , and general base,  $k_{\text{B}}$ , components with the aid of eq 7, in which  $f_{\text{A}}$  is the fraction of buffer present in the acid form. Application of this relationship gave  $k_{\text{HA}} = (3.53$

$$k_{\text{buff}} = k_{\text{B}} + (k_{\text{HA}} - k_{\text{B}})f_{\text{A}} \quad (7)$$

$\pm 0.60) \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$  and  $k_{\text{B}} = (1.20 \pm 0.08) \text{ M}^{-1} \text{ s}^{-1}$  for  $\text{H}_2\text{PO}_4^-$  buffers and  $k_{\text{HA}} = (3.14 \pm 4.95) \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$  and  $k_{\text{B}} = (4.96 \pm 0.29) \text{ M}^{-1} \text{ s}^{-1}$  for  $(\text{CH}_2\text{OH})_3\text{CNH}_3^+$  buffers, showing both general acid and general base catalysis in the more acidic  $\text{H}_2\text{PO}_4^-$  buffer solutions but only general base catalysis

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



**Figure 4.** Rate profile for the enolization of 4,4,4-trifluoroacetoacetic acid in aqueous HBr solutions at 25 °C.

in the more basic  $(\text{CH}_2\text{OH})_3\text{CNH}_3^+$  solutions. Ketonization, being a reaction that occurs by rate-determining proton transfer from catalyst to substrate, should, of course, show general acid catalysis. In situations where the rate-determining step is preceded by acid ionization of the substrate, however, such as the present conversion of monoanionic to dianionic substrate forms, the prior acid–base equilibrium will convert the general acid catalysis of the rate-determining step into overall general base catalysis. It is significant, therefore, that both general acid and general base catalysis was observed in the more acidic buffers, where our mechanistic interpretation has ketonization occurring by rate-determining carbon protonation of the monoanion (general acid catalysis) plus ionization of that anion to dianion, followed by rate-determining carbon protonation of that species (general base catalysis), whereas only general base catalysis was observed in the more basic buffers, where our interpretation has only the latter mechanism operating.

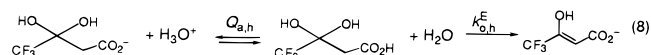
**Ketone Enolization.** Rates of enolization of 4,4,4-trifluoroacetoacetic acid, monitored by bromine scavenging, were measured in hydrobromic acid solutions over the concentration range  $[\text{HBr}] = 0.0001\text{--}0.01\text{ M}$ . A number of acid concentrations were used, and replicate measurements were made at most concentrations. The ionic strength of the reaction mixtures was maintained at 0.10 M through the addition of NaBr. These data are summarized in Table S7<sup>10</sup> and are displayed as the rate profile of Figure 4.

This rate profile has a downward bend, which suggests that the substrate is undergoing acid ionization in the range of acidity used for these rate measurements. Since enolization, being a proton removal process, puts negative charge on the substrate, the ionized and already negatively charged form of the substrate will be less reactive than the neutral un-ionized form. Enolization, moreover, must be the microscopic reverse of ketonization, which was assigned a mechanism in this range of acidity consisting of rate-determining proton transfer from hydronium ion to substrate, giving a water molecule as the conjugate base reaction product; water will, therefore, be the proton removing agent in the enolization process.

At acidities above the bend in this rate profile, where the substrate exists in its reactive un-ionized form, enolization will consequently be a simple “uncatalyzed” reaction of substrate with water, producing a horizontal profile segment. At acidities below the bend, on the other hand, where the substrate is in its less reactive ionized form, conversion of that to un-ionized acid will first take place; this requires a proton, and the reaction thus

becomes an acid-catalyzed process with rate proportional to  $[\text{H}^+]$ , giving a diagonal profile segment of slope =  $-1$ .

Although enolization involves proton removal from the keto isomer, it is unlikely that the initial state of the enolization process is free ketoacid. Ketones with strongly electron-withdrawing substituents, such as trifluoromethyl, are known to form *gem*-diol hydrates,<sup>17</sup> and trifluoroacetoacetic acid is a deliquescent substance with a strong tendency to form a solid hydrate.<sup>5</sup> Ethyl trifluoroacetate exists mainly, and sometimes even completely, as the hydrate in water–organic solvent mixtures,<sup>18</sup> and there is evidence that the hydration equilibrium is set up rapidly relative to the rate of enolization.<sup>18a</sup> This suggests that 4,4,4-trifluoroacetoacetic acid in aqueous solution will exist in mobile equilibrium with its *gem*-diol hydrate and that the latter will be the major species present. The enolization process may, therefore, be formulated as shown in eq 8. The

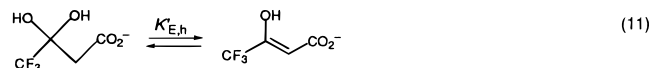
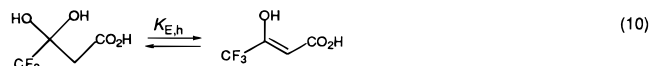


rate law that applies to this reaction scheme is shown in eq 9. Least-squares fitting of this expression gave  $k_{o,h}^E = (1.91 \pm 0.06) \times 10^{-3}\text{ s}^{-1}$  and  $Q_{a,h} = (3.51 \pm 0.28) \times 10^{-4}\text{ M}$ ,  $pQ_{a,h} = 3.45 \pm 0.04$ .<sup>9</sup>

$$k_{\text{obs}} = k_{o,h}^E[\text{H}^+]/(Q_{a,h} + [\text{H}^+]) \quad (9)$$

## Discussion

**Equilibria.** Keto–enol equilibrium constants can be evaluated as ratios of enolization to ketonization rate constants:  $K_E = k_E/k_K$ , and we have employed this method to obtain values of  $K_E$  for the acetoacetic acid<sup>2</sup> and 2-oxocyclopentanecarboxylic acid<sup>3</sup> systems. In the present case, because the rates of enolization measured refer not to free ketone but rather to a *gem*-diol hydrate initial state (vide supra), this technique leads to hydrate–enol rather than keto–enol equilibrium constants. Two such constants may be evaluated:  $K_{E,h}$  for the equilibrium involving un-ionized carboxylic acid groups shown in eq 10 and  $K'_{E,h}$  for the equilibrium involving carboxylate ions shown in eq 11. The first of these constants applies to the region of



acidity represented by the first horizontal segments of the rate profiles of Figures 3 and 4 and may be evaluated from data obtained in this region as  $K_{E,h} = k_{o,h}^E/(k_{H^+}^K Q_{a,E}) = (1.81 \pm 0.09) \times 10^{-4}$ , and the second applies to the region of acidity represented by the diagonal segments immediately following these horizontal portions and may be evaluated as  $K'_{E,h} = k_{o,h}^E/(Q_{a,h} k_{H^+}^K) = (7.31 \pm 0.47) \times 10^{-3}$ .

Both of these constants are small, and they indicate that enol is only a minor species present to an extent of less than 1% in aqueous solutions of 4,4,4-trifluoroacetoacetic acid. This may appear to be at variance with reports that much greater amounts of enol are found in equilibrated solutions of ethyl trifluoro-

(17) Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1–29.

(18) (a) Camps, F.; Coll, J.; Messeguer, A.; Roca, A. *Tetrahedron* **1977**, *33*, 1637–1640. (b) Fomin, A. N. J.; Saloutin, V. I.; Pashkevich, K. I.; Bazhenov, D. V.; Grishin, Y. K.; Ustyuyuk, Y. A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* (Engl. Transl.) **1983**, *32*, 2361–2364.

acetoacetate in organic solvents.<sup>18a,19</sup> These seemingly disparate observations are reconcilable, however, if most of the system in aqueous solution exists as hydrate, with both keto and enol isomers only minor forms.

Information regarding this question may be obtained by converting the hydrate–enol equilibrium constants into keto–enol equilibrium constants according to the relationships  $K_E = K_{E,h}K_h$ . The required hydration equilibrium constants,  $K_h$ , have not been measured, but reliable estimates may be made using the free energy relationship of eq 12,<sup>20</sup> with values of  $\sigma^*$  from the compilation by Perrin, Dempsey, and Serjeant.<sup>21</sup> This free

$$pK_h = 2.81 - 1.70\sum\sigma^* \quad (12)$$

energy relationship, for example, predicts  $K_h = 42$  for 1,1,1-trifluoroacetone, which agrees well with the measured value  $K_h = 35$ .<sup>22</sup> Use of this relationship provides  $K_h = 2900$  for 4,4,4-trifluoroacetoacetic acid and  $K'_h = 34$  for its carboxylate ion, and application of these results to the hydrate–enol equilibrium constants gives  $K_E = 0.52$  for the unionized acid and  $K'_E = 0.25$  for the carboxylate ion.

The near-unit values of these keto–enol equilibrium constants indicate that the keto and enol isomers of 4,4,4-trifluoroacetoacetic acid are, indeed, of comparable stability in aqueous solution, consistent with observations made for organic solvents.<sup>18a,19</sup> These results are also consistent with the fact that, in the kinetics studies described above, we were able to make stock solutions containing considerable amounts of enol by dissolving the anhydrous acid in tetrahydrofuran.

Comparison of these results with those for the acetoacetic acid system<sup>2</sup> shows that the trifluoromethyl group increases enol content appreciably, by a factor of 90 for the un-ionized acids and by a factor of 200 for the carboxylate ions. These effects are consistent with the strongly electron-withdrawing nature of the trifluoromethyl groups, which will produce an unfavorable interaction with the adjacent positive end of the carbonyl group dipole of the keto isomer, destabilizing this form and thereby bringing its energy closer to that of the enol isomer.

The trifluoromethyl substituent also has a strong effect on the ionization of various acidic groups in the present system. Comparison of the present results with those for the enol of acetoacetic acid<sup>2</sup> shows that trifluoromethyl increases the acidity constant of the carboxylic acid group of the enol ( $Q_{a,E}$ ) by a factor of 160 and that it increases the acidity constant of the enolic hydroxyl group ( $Q_a^E$ ) by a factor of 1700. Both of these effects are in the expected direction, inasmuch as the electron-withdrawing ability of trifluoromethyl will stabilize the anionic products of these acid ionization reactions. Neither effect, on the other hand, is as great as the factor of 37 000 provided by comparison of the acidity constant of trifluoroacetic acid (**11**,  $pK_a = 0.19$ )<sup>23</sup> with that of acetic acid (**12**,  $pK_a = 4.76$ ).<sup>24</sup> In



(19) Filler, R.; Naqvi, S. M. *J. Org. Chem.* **1961**, *26*, 2571–2573. Burdett, J. L.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 2105–2109; *J. Phys. Chem.* **1966**, *70*, 939–941.

(20) Greenzaid, P.; Luz, Z.; Samuel, D. *J. Am. Chem. Soc.* **1967**, *89*, 749–756.

(21) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK<sub>a</sub> Predictions for Organic Acids and Bases*; Chapman and Hall: New York, 1981; pp 109–126.

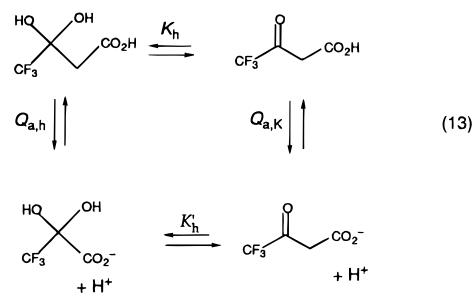
(22) Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898–906.

(23) Milne, J. B.; Parker, T. J. *J. Soln. Chem.* **1981**, *10*, 479–487.

(24) Harned, H. S.; Ehlers, R. W. *J. Am. Chem. Soc.* **1933**, *55*, 652–656.

the present system, however, the trifluoromethyl group is two carbon atoms farther away from the carboxylic acid group than it is in trifluoroacetic acid, and this will attenuate its acid-strengthening influence on this group. The spatial relationship of trifluoromethyl to enolic hydroxyl group, on the other hand, is the same as it is to the hydroxyl group of trifluoroacetic acid, but ionization of the enol puts negative charge into an already negatively charged group, and that will oppose the acidifying effect of trifluoromethyl and attenuate it once again.

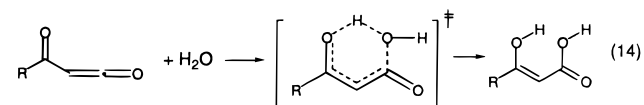
An acidity constant for the carboxylic acid group of the keto form of trifluoroacetoacetic acid,  $Q_{a,K}$ , may be obtained through the thermodynamic cycle shown in eq 13, where  $Q_{a,K} = Q_{a,h}K_h/K'_h = 3.04 \times 10^{-2}$  M,  $pQ_{a,K} = 1.52$ .<sup>9</sup> This value is 75



times greater than  $Q_{a,K}$  for acetoacetic acid,<sup>2</sup> which is less than the factor of 160 obtained above for the effect of trifluoromethyl on the acidity of the carboxylic acid group of the enol ( $Q_{a,E}$ ). This difference shows that the vinyl group separating trifluoromethyl and carboxyl in the enol is a better transmitter of electrical effects than is the carbonyl plus methylene entity of the keto form.

**Kinetics.** Acyl substituents increase the reactivity of ketenes markedly. For example, the uncatalyzed hydration of acetylketene in aqueous solution is 42 000 times faster than the corresponding reaction of ketene itself.<sup>2,11b</sup> This enhanced reactivity has been explained in terms of a reaction mechanism involving nucleophilic attack of water on the carbon atom of the ketene carbonyl group, which generates a negative charge on the substrate that can be stabilized by an acyl substituent. This explanation, however, is inconsistent with the present results for trifluoroacetylketene. A trifluoroacetyl group, because of the additional electron-withdrawing effect of trifluoromethyl, should be substantially better than an acetyl group at stabilizing such negative charge being generated on the substrate, but the present results give a rate constant for reaction of trifluoroacetylketene with water that is virtually the same as that for reaction of acetylketene with water:  $k_o(\text{CF}_3\text{COC}=\text{C}=\text{O})/k_o(\text{CH}_3\text{COC}=\text{C}=\text{O}) = 1.14$ .

The present results, on the other hand, may not be inconsistent with another reaction mechanism, eq 14, involving a cyclic transition state, in which proton transfer from water to the acyl oxygen atom occurs at the same time as nucleophilic attack on the ketene carbonyl atom is taking place. If proton transfer



offsets negative charge generation in such a transition state, then trifluoroacetylketene and acetylketene might show similar reaction rates. There is some additional evidence from theoretical calculations,<sup>25</sup> relative reactivities,<sup>26</sup> and isotope effects<sup>2</sup> to

(25) Birney, D. M.; Wagenseller, P. E. *J. Am. Chem. Soc.* **1994**, *116*, 6262–6270.

support such a cyclic reaction mechanism. It is not clear, however, that such a cyclic mechanism would give the weakly inverse solvent isotope effect found for this reaction in this case (vide supra).

In contrast to its negligible effect on the rate of ketene hydration, trifluoromethyl does influence rates of enolization and ketonization. The rate of enolization by proton transfer from the keto form to a water molecule,  $k_{\text{o}}^{\text{E}}$ , is 86 times greater for trifluoroacetoacetic acid than for acetoacetic acid, in keeping with the electron-withdrawing and acid-strengthening effect of trifluoromethyl. Rates of ketonization, on the other hand, are lowered by the trifluoromethyl group: by a factor of 170 for proton transfer from the hydronium ion to  $\beta$ -carbon of the enol

in its carboxylate form ( $k_{\text{H}^+}^{\text{K}}$  ratio) and by a factor of 28 000 for proton transfer from a water molecule to  $\beta$ -carbon of the doubly ionized enolate–carboxylate ion ( $k_{\text{o}}^{\text{K}}$  ratio); these rate retardations are also in keeping with the electron-withdrawing nature of trifluoromethyl, which lowers the electron density of the enolic vinyl group and makes it less susceptible to electrophilic attack by acids.

**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–S7 of rate data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

(26) Leung-Toung, R.; Wentrup, C. *Tetrahedron* **1992**, *36*, 7641–7654. Allen, A. D.; McAllister, M. A.; Tidwell, T. T. *Tetrahedron Lett.* **1993**, *34*, 1095–1096. Birney, D. M.; Xu, X.; Ham, S.; Huang, X. *J. Org. Chem.* **1997**, *62*, 7114–7120.