Catalysis of Keto–Enol Tautomerism of Oxaloacetic Acid and Its Ions Studied by Proton Nuclear Magnetic Resonance[1]

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The proton nuclear magnetic resonance spectra of solutions of oxaloacetic acid (OA) have been measured at a number of pH values between 1 and 7 at 4 °C, and the line widths of the signals due to the enol, hydrate (*gem*-diol), and keto forms determined. The line width of the CH proton of the enol of OA is pH dependent, passing through a maximum at about pH 3. The pH dependence parallels that for the fraction of OA existing in the monoanion form. In contrast, the width of the signal due to the enol of 4-ethyl oxaloacetate exhibits only a monotonic change in the same pH region. The line broadening is attributed to keto–enol equilibration involving monofunctional general acid catalysis by the diacid of OA acting on the enol dianion. Involvement of one of the carboxyl groups of the enol in this catalytic process is possible.

Proton NMR spectra of solutions of oxaloacetic acid (OA) at pH 1–7 and 4 °C contain peaks assignable to enol, keto, and hydrate (gem-diol) forms. In the pH region 2 to 5, the line width for the signal due to the CH proton of the enol form passes through a maximum. Because of the small size of the enol peak and rapid decarboxylation, line width measurements are very difficult, but the enol line width is found to be proportional to the square of the monoanion concentration. This dependence along with the fact that the signal due to the enol of 4-ethyl oxaloocetate (the monoethyl ester group is β to the ketone carbonyl group) exhibits only a monotonic change between pH 2 and 5 is interpreted in terms of a catalytic mechanism in which the diacid of OA acts as a monofunctional general acid catalyst for the ketonization of the dianion of the enol of OA. The evidence does not appear to support a mechanism in which the monoanion of OA acts as a bifunctional catalyst for the ketonization of the enol monoanion in a manner analogous to the mechanisms suggested for the termolecular terms found for the enolization of acetone[2] and cyclohexanone[3] and as suggested[4] but disproven[5] for OA ketonization. But the results are consistent with intramolecular participation of a carboxylate group of the enol as in the case of catalysis of the enolization of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid[6] and as might be possible in the enzyme-catalyzed tautomerization.[7]

Experimental Section

Chemicals. Oxaloacetic acid was obtained from several sources: British Drug House (BDH), Nutritional Biochemicals, and Sigma Chemical Co. The material obtained from BDH was found to be 98.5% pure by means of equivalent weight determinations. 4-Ethyl oxaloacetate was obtained from Nutritional Biochemicals and was recrystallized from benzene and/or chloroform, mp 96–97 °C. This compound was also prepared by two different procedures from sodium diethyl oxaloacetate, which was obtained from Eastman. The first method involved direct saponification of the diester[8] and the second involved hydrolysis of a copper complex of the diester.[10] In each case the material was recrystallized from chloroform to yield products with melting points of 98–104 and 89–94 °C, respectively. Formic acid (Baker Chemical Co.), acetic acid (Baker Chemical Co.), malic acid (Eastman Chemical), succinic acid (Sigma), ethylenediaminetetraacetic acid EDTA (Sigma) and *tert*-butyl alcohol (Baker Chemical Co.) were used without further purification.

Solutions and NMR Spectra. To minimize the extent of decarboxylation, which is especially rapid with the monoanion form of OA, samples were prepared at 4 °C immediately before NMR measurements. The pH, which was measured using a Radiometer PHM or PH 26 meter, was adjusted by addition of either NaOH (for values above 1.2) or HCl. The ionic strength varied from 0.1 at pH 1.5 to 1.56 at pH 5.0 when only OA is present. When other carboxylic acids are also present the ionic strength is substantially higher.

All proton NMR spectra were measured at 4 ± 1 °C (determined using a thermometer and the chemical shift between the OH and the CH_3 proton resonance of methanol) to reduce bubbling, which results from the decarboxylation of OA. Most spectra were measured at 60 MHz using a Varian A-60A spectrometer; however, a Varian HA-100 spectrometer was used for the OA concentration study because of its better sensitivity. The A-60A, which uses an external lock, was more convenient to use than the HA 100 whose internal lock was affected by the build-up of bubbles. For each sample the line width at half-height of each signal was measured at least four times using a 100-Hz sweepwidth, and each measurement was alternated with the line width measurement for the CH_3 proton resonance of *tert*-butyl alcohol. When the width of the *tert*-butyl alcohol signal varied by more than 0.1 Hz from one measurement to the next, the data were rejected. This procedure avoided occasional spurious line width values caused by bubbles on the wall of the sample tube. To minimize the accumulation of bubbles on the wall, the tubes were washed several times with Decon 75 detergent (Decon Laboratories Ltd.). All solutions were prepared with distilled water, but to assure that the line width effects were not due to traces of paramagnetic metal ions several runs were made with 0.04 M EDTA present and with doubly distilled water.

Results

Line width data for the keto, hydrate, and enol CH proton resonances at 4 °C are reported in Table I as $\Delta = \Delta\nu_{OA} - \Delta\nu_{t\text{-BuOH}}$ in which $\Delta\nu$ is the line width at half-height in hertz. $\Delta\nu_{t\text{-BuOH}}$, which refers to the line width of *tert*-butyl alcohol CH_3 protons, is used to eliminate line width fluctuations caused by changes in the homogeneity of the magnetic field from one measurement to the next. In the pH range 2.0 to 4.0 the evolution of CO_2 due to decarboxylation of OA can cause additional line broadening, and $\Delta\nu_{t\text{-BuOH}}$ takes this effect into account also (see Experimental Section). The number of samples used at each pH is designated as n. For each sample, the line width for each signal is an average of four measurements, and the value given in the table along with its standard deviation is an average of all the samples. The signal intensities were measured at the beginning and completion of the line width measurements, and it was found that the concentration of OA decreased about 20% during the time of the measurements (about 30 min) in this pH region. Below pH 4, the pH increases about 0.1 to 0.2 of a unit during the time of the measurement and the final value is listed in the table. For 4-ethyl oxaloacetate, Δ values were also measured under the same pH and temperature conditions, and the value for its enol CH proton resonance increases in a monotonic manner as the pH decreases (see Figure 1). We did not attempt measurements on 1-ethyl oxaloacetate because the anion decarboxylates even more rapidly than the monoanion of oxaloacetic acid.[9] In addition Δ values for the CH proton of the enol of 4-ethyl oxaloacetate were measured for a number of solutions containing 1 M concentrations of acids having pK_a values close to pK_{a2} of OA, which is 4.37 at 25 °C,[11,12] i.e., formic ($pK_a = 3.76$)[13] at pH 3.70, acetic ($pK_a = 4.75$)[13] at pH

Table I. NMR Line Width Data for Oxaloacetic Acid in Aqueous Solution as a Function of pH at 4 °C [a]

pH	Δ_{enol},[b] Hz	Δ_{keto},[b] Hz	Δ_{Hyd},[b] Hz	n[c]
1.1 ± 0.1	0.76 ± 0.24	0.24 ± 0.07	0.48 ± 0.06	3
1.3 ± 0.1	0.41 ± 0.05	0.16 ± 0.02	0.49 ± 0.02	2
1.9 ± 0.1	0.27 ± 0.1	0.1 ± 0.1	0.27 ± 0.05	3
2.7	0.81	0.02	0.22	1
3.0	0.91 ± 0.15	0.16 ± 0.01	0.30 ± 0.1	3
3.7 ± 0.1	0.68 ± 0.25[d]	0.15	0.30	1
3.7 ± 0.1	0.37 ± 0.01[e]			2
3.8 ± 0.1	0.63 ± 0.15[f]			4
4.3 ± 0.1	0.19 ± 0.16	0.28 ± 0.23	0.21 ± 0.05	3
5.0	−0.02	0.04	0.27	1
6.0	−0.11	−0.08	0.11	1
7.1	−0.11	−0.04	0.17	1

[a] Concentration of OA is 0.85 M unless otherwise specified. [b] Enol CH, keto CH_2, and hydrate CH_2 proton resonances. Relative to the line width of the CH_3 proton resonance of *tert*-butyl alcohol; see text. [c] Number of samples. At least four measurements of each line width were made on each sample. [d] n = 4, measured using an A-60A and an HA-100 spectrometer. [e] [OA] = 0.40, measured using an HA-100 spectrometer. [f] [OA] = 1.0, measured using an HA-100 spectrometer.

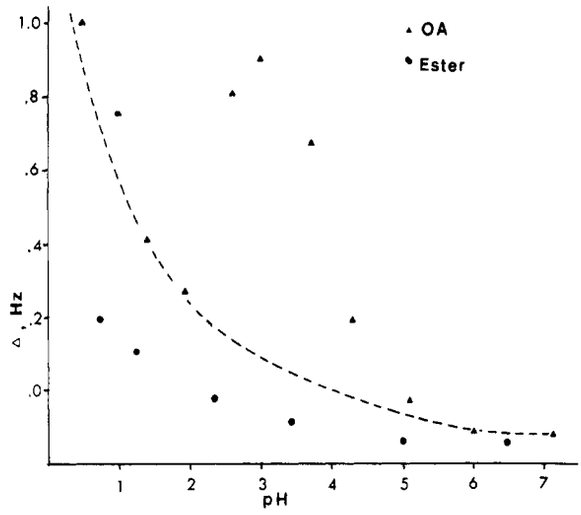
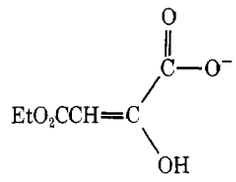


Figure 1. pH dependence for the NMR signal width due to the CH proton of the enol of OA and the monoethyl ester of OA in H_2O at 4 °C. $\Delta = \Delta\nu_{OA} - \Delta\nu_{t\text{-BuOH}}$, in which $\Delta\nu$ is the line width at half-height and $\Delta\nu_{t\text{-BuOH}}$ refers to the line width of the CH_3 proton of *tert*-butyl alcohol.

3.2, and malic acid (pK_{a_1} = 3.40 and pK_{a_2} = 5.11)[13] at pH 2.80 and 3.65. In the pH range employed the 4-ethyl oxaloacetate (pK_a = 2.74)[14] is mainly in the anionic form,



and the added acids are mainly in their acidic forms. The Δ values obtained under these conditions are within experimental error of those found for the monoester in the absence of added acid (see Figure 1), ranging from −0.03 Hz for malic to −0.10 Hz for acetic and formic acids.

Discussion

For the enol CH proton resonance of OA, Δ is pH dependent, and the form of this dependence is illustrated in Figure 1. As the pH is decreased from 7.1 to about 1.1, Δ passes through a maximum and a minimum, and this behavior is in contrast to that of the monotonic increase observed for the enol CH proton resonance of 4-ethyl oxaloacetate, which is illustrated in Figure 1, also, and was measured under identical conditions. Since effects due to fluctuation in field homogeneity have been removed, the variation in Δ is due to a variation in the proton exchange rate of a process involving the enol CH proton. We suggest that this process involves exchange between the enol CH proton and the keto and/or hydrate CH_2 protons. Proof for this exchange process involves detection of commensurate broadening of the CH_2 proton resonance of the keto and/or hydrate. The enol makes up only about 6% of the total OA concentration, while in the pH region at which Δ passes through a maximum, the keto and hydrate have comparable concentrations. Therefore, the broadening of the keto and hydrate signals is expected to be too small to be detected because the ratio of the line widths is inversely proportional to the ratio of the proton fractions when the signals are resolved.[15] That this is the case is indicated in Table I, which illustrates that the variation in Δ with pH is within the standard deviation for the keto and hydrate signal widths at pH values of 1.9 and above. Thus, while the broadening effects in this pH region are consistent with proton exchange between enol and keto and/or hydrate forms of OA (and similarly for the monoester), more accurate measurement would be needed to distinguish between these two processes. But the exchange process can be tentatively identified as an enol ⇌ keto tautomerization on the basis of experiments at 38 °C. At this temperature the enol signal for OA monoanion is too broad to be observed,[16,17] and although the keto/hydrate ratio ≃ 2.4, the width at half-height for the keto peak is twice that for the hydrate (1.8 vs. 0.9 Hz).[16]

The variation in Δ in the pH region 2 to 5 parallels that for the fraction of OA present as monoanion. To treat the data quantitatively, we have drawn a smooth curve through the points at low and high pH's and have calculated the difference (Δ_{dif}) between the experimental points and the dashed curve.[18] Values of Δ_{dif} along with the ionic strength are tabulated in Table II for various pH values. Also listed in Table II is the fraction of OA that exists as the monoanion calculated for each pH using the expression,[19]

$$f = ([H^+]/K_{a_1} + 1 + K_{a_2}/[H^+])^{-1}$$

in which $[H^+]$ = antilog [−pH]. The values for the macroscopic acid dissociation constants K_{a_1} and K_{a_2} for OA at 4 °C at zero ionic strength were obtained by extrapolation of values given at 25 and 37 °C[11] and differ only slightly from those at 25 °C. Since the ionic strength is not zero and varies with pH, values for K_{a_1} and K_{a_2} that are listed in Table II were calculated using the empirical expressions determined previously[11,12] at 25 °C, assuming that the ionic strength dependence at 4 °C is identical with that at 25 °C. The only modification of these equations involved substitution of the 4 °C values of K_{a_1} and K_{a_2} at zero ionic strength for the 25 °C values. This approach must be considered approximate for two reasons: (1) the empirical equations were developed from potentiometric data for solutions having ionic strengths up to 0.3 (NaCl)[11] whereas our solutions have substantially larger ionic strengths (see Table II); (2) the coefficients in these equations appear to be temperature dependent.[12] Consequently the analysis given below must be considered semiquantitative at best.

As indicated in Table II, the pH dependence of f parallels that for Δ_{dif} when the concentration of OA is constant. With these two parameters, it is possible to deduce a rate expression for exchange involving the enol proton in the following manner. Since the CH proton resonances of the keto, hydrate, and enol forms of OA are resolved, the average lifetime τ and rate for the enol CH proton can be calculated[15] using the expres-

Table II. Kinetic and Equilibrium Parameters for OA at 4 °C

pH	u[a]	$[OA]_t$,[b] M	pK_{a_1}	pK_{a_2}	f	Δ_{dif}, Hz	k_2', $M^{-1}\,s^{-1}$	k_2, $M^{-1}\,s^{-1}$
2.7	0.5	0.85	2.41	3.72	0.62	0.64	3.8[c]	6.2[d]
3.0	0.6		2.42	3.75	0.69	0.80	4.3	6.2
3.7	0.9		2.48	3.89	0.59	0.64	4.0	6.8
3.7	0.56	0.40	2.48	3.89	0.59	0.33	4.4	7.4
3.8	1.0	1.0	2.49	4.01	0.55	0.59	3.4	6.1
4.3	1.2	0.85	2.55	4.06	0.36	0.22	2.3	6.3
5.0	1.6		2.65	4.29	0.15	0.05	1.2	7.4

[a] Ionic strength, calculated assuming that OA^{2-} is equivalent to two monoanions. [b] Total concentration including all tautomeric forms and all degrees of protonation. [c] $k_2' = (\Delta_{dif}\pi)/(f[OA]_t)$. [d] $k_2 = (\Delta_{dif}\pi)/(f^2[OA]_t)$.

sions $1/\tau = \pi\Delta_{diff}$ and $1/\tau$ = rate/[enol]. Thus, rate = $\pi\Delta_{diff}$[enol], and the concentration dependence of the rate may be deduced from the pH and concentration data in Table II. A good fit is obtained using,

$$\text{rate} = k_2 f^2[\text{enol}]_t[OA]_t \quad (1)$$

in which $[OA]_t$ is the total concentration of OA, including all tautomeric forms and degrees of protonation, and $[enol]_t$ is the total enol concentration, including all degrees of protonation. The values of k_2 calculated according to eq 1 are listed in Table II. For comparison, the data also were fitted to the expression,

$$\text{rate} = k_2' f[\text{enol}]_t[OA]_t \quad (2)$$

and values of k_2' are listed in Table II. The data appear to fit eq 1 better than eq 2, although the very good fit obtained with eq 1 may be somewhat fortuitous in view of the precision of the line width measurements (see Table I) and the semiquantitative manner in which Δ_{dif} and the acid dissociation constants are determined. But eq 2 is unlikely to be correct. Let us consider eq 2 rewritten in two forms: rate = k_2'-$[EH^-][OA]_t$ and rate = $k_2'[\text{enol}]_t[OAH^-]$, in which EH^- is the monoanion of the enol and OAH^- is the monoanion of all tautomers of OA. The first form suggests that the catalytic power of an OA molecule is independent of its state of protonation, and the second suggests that the reactivity of an enol molecule is independent of its state of protonotion. Neither of these possibilities seems reasonable.

Furthermore, the magnitude of the broadening is too large to be explained on the basis of uncatalyzed or proton-catalyzed pathways.[20] The contribution from these pathways may be estimated from data of Banks[4] at 1.5 °C that indicate that the enol monoanion is more reactive than the dianion and from data of Leussing[21] at 25 °C which indicate that the enol monoanion is also more reactive than the diacid. Consequently, the pH rate profile for the enol would be bell shaped. However, the maximum contribution to the line width from this process is calculated to be only 0.35 Hz at 25 °C or 0.04 Hz to 1.5 °C. Thus this process cannot account for the maximum observed for Δ, which is 1.0 Hz larger at pH 3 than at pH 7, the pH at which the exchange has a negligible effect on the line width.

Therefore, to account for the additional line broadening, we have considered possible mechanisms of keto–enol tautomerisim that are consistent with eq 1. Equation 1 can be rewritten in at least three kinetically equivalent forms: (a) rate = $k_2[EH^-][OAH^-]$, (b) rate = $k_2(K_{a_1}/K_{a_2})[E^{2-}][OAH_2]$, and (c) rate = $k_2(K_{a_1}/K_{a_2})[EH_2][OA^{2-}]$. Form b can be interpreted mechanistically in terms of general acid catalysis and form c in terms of general base catalysis. Form a is consistent with either type of catalysis and with concerted general acid plus general base catalysis. We would like to identify the form that is kinetically most significant and to determine if there are any special bifunctional catalytic effects operating.

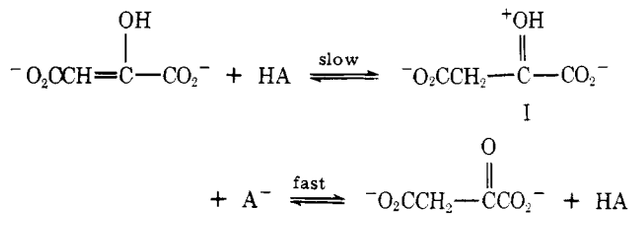
One approach to the detection of bifunctional catalysis is the comparison of the catalytic activities of monofunctional and bifunctional molecules using the Brönsted relationship. Unfortunately, experimentally determined Brönsted coefficients are not available, and it is necessary to estimate values for two of the possible five reaction pathways as discussed below.[22]

For a monofunctional acid such as acetic acid for which data are available, general acid catalysis of the reaction of the enol dianion (form b) and general base catalysis of the reaction of the enol monoanion (form a) are kinetically equivalent, and, therefore, if the Brönsted relations are obeyed, the coefficients are related by $\alpha + \beta = 1.0$. Scheme I shows the usual mechanisms for general acid and base catalysis of keto–enol tautomerization. Because of the kinetic equivalence it is impossible to know a priori which of the two slow steps is actually the rate-determining step. That is, in the absence of experimental Brönsted coefficients, any extrapolation from the observed catalytic coefficient of one catalyst to a predicted coefficient for some other catalyst must be done using the probable Brönsted coefficients for each of the pathways in Scheme I.

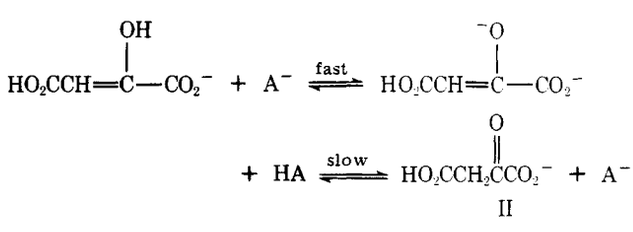
Our estimates of Brönsted coefficients are based on an observation by Bell[23] that the β for carboxylate ion catalyzed ionization of ketones is a function of the acidity of the ketone. Thus, for a general base-catalyzed reaction (involving the slow step of the lower pathway of Scheme I) we estimate $\beta = 0.52$, the value for the carboxylate-ion-catalyzed enolization of benzoylacetone, which has nearly the same pK_a as 4-ethyl oxaloacetate ion.[24] To estimate the Brönsted coefficient for a general acid-catalyzed reaction (involving the upper pathway of Scheme I) we make use of the fact that $\alpha' = 1 - \beta'$, in

Scheme I

General acid catalysis



General base catalysis



which β' is the Brönsted coefficient for the single step $^{-}O_2C$-$CH_2C(OH^+)CO_2^- + A^- \rightarrow {}^{-}O_2CCH{=}C(OH)CO_2^- + HA$. β' is expected to be smaller than β because the CH protons of the carbonyl-protonated oxaloacetate are much more acidic than those of carboxyl-protonated oxaloacetate. The difference, $\beta - \beta'$, for the oxaloacetate system is estimated to be 0.43, which is obtained from the values (0.88 and 0.45)[23,25] for the corresponding reactions for acetone. This approximation that $\beta - \beta'$ is the same for both acetone and oxaloacetate systems seems justified because the difference in acidity between the CH_2 protons in I and II is about the same as the corresponding difference between protonated acetone and acetone ($\Delta pK_a = -11$ and -14, respectively).[26] Thus, β' for oxaloacetate is the difference between 0.52 and 0.43, and α' is $1 - \beta'$ or 0.91.

With these values for α' and β, data for the catalysis of keto–enol tautomerization by acetic acid[4] can be used to estimate the effectiveness of other monofunctional catalysts. First consider kinetic form b, according to which OAH_2 acts as a general acid toward E^{2-}. For this form, a value of $k_2K_{a_1}/K_{a_2} = 150\ M^{-1}\ s^{-1}$ can be calculated using the average of the values of k_2 given in Table II and the values of K_{a_1} and K_{a_2} at pH 3.7. This can be compared to a value of $140\ M^{-1}\ s^{-1}$ obtained by extrapolation of Banks'[4] value of $1.2\ M^{-1}\ s^{-1}$ for acetic acid catalysis at 1.5 °C using the Brönsted relation and $\alpha' = 0.91$. According to this comparison, the observed catalysis is no greater than expected for *monofunctional* general acid catalysis by OAH_2.[30,31]

It is also possible to make the comparison in terms of the kinetically equivalent action of OAH^- or acetate ion on the (carboxyl protonated) enol monoanion. For form a, the average of the values of k_2 given in Table II is $6\ M^{-1}\ s^{-1}$, which can be compared to a value of $0.8\ M^{-1}\ s^{-1}$. The latter value was obtained by a Brönsted extrapolation of the corresponding rate constant ($12\ M^{-1}$) that was calculated from the data of Banks[4] for acetate catalysis on the enol monoanion using $\beta = 0.52$. Thus, *monofunctional* general base catalysis according to form a cannot account for the observed exchange rate. Allowing that 4-ethyl oxaloacetate anion is a good model for the principal protonated form of OAH^-, the line width for the ester in the presence of formic acid provides information that also appears to preclude this mechanism. Assuming that the exchange rate makes a negligible contribution to the line width for the ester enol CH proton resonance at pH 6.5, the excess line width at pH 3.72 in the presence of 1 M formic acid is 0.14 rad/s. Thus, the upper limit for the rate constant is calculated to be $0.28\ M^{-1}\ s^{-1}$ for formate ion catalysis of the ketonization of enol of the ester monoanion. Since the formate ion is a stronger base than OAH^-, this value is an upper limit for monofunctional general base catalysis by OAH^-. This limit is about 20 times smaller than k_2 (Table II), indicating that monofunctional general base catalysis cannot account for the exchange broadening.

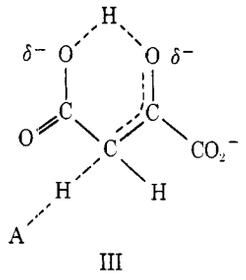
The ester results appear to rule out some of the other possible mechanisms also. Acid catalysis by formic acid for ketonization of the enol of the ester anion should be similar to monofunctional general acid catalysis according to form a. Based on the data in the preceding paragraph, the upper limit for the rate constant for formic acid catalysis of ketonization of the ester monoanion is $0.28\ M^{-1}\ s^{-1}$. Since the pK_a of formic acid is lower than pK_{a_2} for OA, this value would be an upper limit for general acid catalysis by OAH^- according to form a. This value is more than a factor of 20 smaller than k_2 in Table II; therefore, the contribution due general acid catalysis by OAH^- on EH^- appears to be negligible.

The relative importance of form c may also be ascertained by reference to the formic acid catalysis for the ester. Since the expression $k[E^-][HA]$ is kinetically equivalent to $k'\cdot[EH][A^-]$, in which HA is formic acid, an upper limit to k' can be obtained as $kK_{a(EH)}/K_{a(HA)}$, which has a value $2.8\ M^{-1}\ s^{-1}$. Assuming that the Brönsted relation applies, this value may be converted to one for the rate constant for general base catalysis by OA^{2-} according to form c. For this purpose, the difference between the pK_a for formic acid and that for OAH^- is assumed to be independent of ionic strength. Even if β were 1.0, the extrapolated value of the rate constant would be only $11\ M^{-1}\ s^{-1}$, which is over a factor of 10 smaller than the value for the experimental rate constant in terms of form c, $150\ M^{-1}\ s^{-1}$. Thus, the contribution to ketonization rate by form c appears small.

According to the discussion above then, general acid catalysis by OAH_2 of the ketonization of enol dianion (upper path of Scheme I) is the only *monofunctional* process that would be expected to be fast enough to explain the bell-shaped dependence observed for Δ for the enol in the pH range 2 to 5. However, none of the discussion presented above precludes the possibility of bifunctional catalysis by OAH^- in a general acid–general base fashion using the carboxyl and carboxylate groups on the OAH^- molecules.[32] If the monoanion of malic acid is used as a model for OAH^- then the line width data for the ester in the presence of 1 M malic acid indicate that this path is probably unimportant. At pH 3.65, the line width for the enol CH proton of the ester has the same value in the presence of either malic or formic acid. If the monoanion of malic acid were an effective bifunctional catalyst, its presence should result in a larger line width compared to formic acid. Thus general acid catalysis by OAH_2 appears to be the predominant pathway for the ketonization of the enol.

It is possible that this pathway is more complex than the process illustrated in Scheme I. The results for OA do not preclude the possibility of intramolecular assistance by one of the carboxylate groups. Bell suggests an intramolecular contribution in the enolization of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid catalyzed by acetate ions (or its kinetic equivalent, enolization of the carboxylate ion catalyzed by acetic acid)[6] in the enolization of 2-oxocyclopentanecarboxylic acid[6] and in the enolization of acetoacetic acid.[33] These suggestions are based on comparison of the reactivity of a keto acid with its corresponding ester, and the intramolecular contribution is pictured as an H-bonding or electrostatic stabilization of the transition state by the carboxyl group. The case for such participation may be stronger than previously suggested. The formulation of general acid catalysis in a mechanism like that in Scheme I is based on the observation that the general acid catalysis of ketonization of an enol and hydrolysis of its enol ether proceed with similar rates.[34] On the other hand, if protonation of the vinyl carbon is facilitated by intramolecular interaction between the OH of the enol and a carboxylate group, the enol should react considerably faster than the corresponding enol ether. In at least one case such a comparison is possible. Thus the "uncatalyzed" ketonization of the enol of cyclopentanone-2-carboxylic acid[6] is at least ten thousand times faster than the uncatalyzed hydrolysis of the corresponding enol ether.[35] For the purposes of this comparison, the rate constant for ketonization, k_{keto}, of the enol of 2-oxocyclopentanecarboxylic acid can be calculated using $k_{keto} = k_{enol}/K_{enol}$, in which k_{enol} is the experimental value of the enolization rate constant[6] and $K_{enol} = [enol]/[keto]$. Since the value of K_{enol} seems to be unreported, we have used $K_{enol} = 0.064$, which is the value for ethyl 2-oxocyclopentanecarboxylate in ethanol.[36] The ketonization rate constant obtained in this manner is probably too small, since we have probably overestimated K_{enol}, i.e., for ethyl acetoacetate, K_{enol} is reduced by a factor of about 30 when the solvent is changed from ethanol to water.[37] When the mechanism of OA enolization includes intramolecular participation of one of the carboxyl groups the distinction between general acid and base catalysis may vanish.[38] For example, if participation of the β-carboxyl

group is involved, then the mechanisms in Scheme I merge to one involving the transition state species III.



III

Registry No.—Oxaloacetic acid, 328-42-7; oxaloacetic acid enol, 7619-04-7; oxaloacetic acid hydrate (gem-diol), 60047-52-1; 4-ethyl oxaloacetate, 2401-96-9; 4-ethyl oxaloacetate enol, 63797-61-5.

References and Notes

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(18) This treatment is valid because the contribution to the line width is additive when several parallel processes are involved in the proton exchange. See, E. Grunwald and M. Cocivera, *Discuss. Faraday Soc.*, 105 (1965).
(19) Because the fraction of OA present as enol is relatively pH independent (ref 16), $f \simeq$ the fraction of the enol present as monoanion, and therefore use of microscopic acid dissociation constants is unnecessary to estimate this fraction. For this reason, eq 1 and 2 could also be written in terms of the square of the enol concentration.
(20) The increase in Δ at pH <2 may represent a previously unreported pathway of H^+-catalyzed reaction of the enol of fully protonated OA.
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(22) Data of Banks (ref 4) and Bruice (ref 5) are not sufficient to estimate α for general acid catalysis by carboxylic acids of the ketonization of the enol dianion.
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(26) The pK_a of the CH_2 protons of II should be about the same as that for the CH_2 protons of 4-ethyl oxaloacetate, which has a value of about 9.6 (ref 24). The value for the pK_a of the CH_2 protons of I is estimated to be about −1.1 in the following way. Since for OA^{2-} the value for $K_{enol} \simeq$ [enol]/[keto] is 0.08 (at 38 °C, ref 16), the CH_2 protons of I are 12 times less acidic than the OH proton. Assuming that the latter is as acidic as the corresponding OH in protonated acetone (i.e., $pK_a = -2.2$, ref 27) the pK_a for the CH_2 protons is obtained as $-2.2 + \log 12$. A similar approach can be applied to acetone using $K_{enol} = 1.5 \times 10^{-8}$ (ref 28), pK_a of protonated acetone given above, and $pK_a = 20$ for acetone (ref 29).
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(32) The fact that the experimental rate constant k_2 is considerably larger than an estimate obtained via a Brönsted relationship for general base catalysis in this case does *not* necessarily require that OAH^- is an exceptionally effective catalyst. It is a consequence of the kinetic equivalence of the mechanisms in Scheme I and their respective Brönsted coefficients that if an extrapolation (of data for acetic acid catalysis) in terms of the general acid-catalyzed pathway gives a rate constant near the experimental value, then the extrapolation via the general base-catalyzed pathway *must* give an estimated rate constant that appears to be too small. Nevertheless, this argument does not seem sufficient to preclude a process in which OAH^- acts as a bifunctional catalyst.
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(38) We are grateful to a referee for noting our failure to make this point.

Nucleophilic Aromatic Substitution Promoted by Cobalt(III) Trifluoroacetate[1]

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A series of aromatics was subjected to oxidation by cobalt(III) trifluoroacetate in the presence of a variety of nucleophiles. In this manner benzene was successfully halogenated with chloride, bromide, and iodide, and toluene, chlorobenzene, and benzotrifluoride were also chlorinated. Attempts to substitute fluoride, cyanide, and nitrate onto benzene were thwarted by solvent interference. Nitrite ion was oxidized to nitrogen dioxide and no substitution products were formed. A mechanism involving aromatic radical cations is most consistent for the aromatic–chloride–cobalt(III) reactions. However, with many of the other nucleophiles an alternate reaction pathway involving ligand oxidation by metal ion appears more likely.

An interesting type of nucleophilic aromatic substitution can be accomplished by reacting nucleophiles with aromatic radical cations produced by an appropriate oxidant (eq 1). Both electrochemical oxidation[2] and chemical oxidizing agents such as xenon difluoride,[3,4] peroxydisulfate,[5,6] manganese(III) acetate,[7,8] and cobalt(III) acetate[9] have been effectively used in this manner. One of the limitations of these reactions, however, is the need to use aromatics of somewhat lower ionization potential (i.e., more electron rich).[8] Substitution of trifluoroacetate for acetate ligands on the cobalt complex was found to enhance its oxidative powers,[9-11] thus allowing radical cations to be formed from benzene and deactivated