The α-Cyano-α-phenylacetic Acid Keto–Enol System. Flash Photolytic Generation of the Enol in Aqueous Solution and Determination of the Keto–Enol Equilibrium Constants and Acid Dissociation Constants Interrelating All Keto and Enol Forms in That Medium

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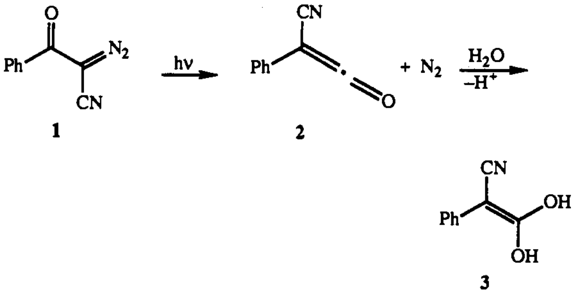
Abstract: The enol of α-cyano-α-phenylacetic acid was observed as a short-lived transient species formed upon flash photolytic generation of phenylcyanoketene by a photo-Wolff reaction of α-cyano-α-diazoacetophenone followed by hydration of the ketene. Rates of ketonization of the enol were measured in dilute hydrochloric acid solutions and acetic acid, biphosphate ion, tris(hydroxymethyl)methylamine, and ammonia buffers; this gave a rate profile with turning points from which the first and second acid ionization constants of the enol were determined: $pK_1 = 0.99$ and $pK_2 = 8.70$. Rates of enolization of the keto tautomer were also determined by bromine scavenging, and combination of these with rates of ketonization of the enol gave the keto–enol equilibrium constant $pK_E = 7.22$, relating the un-ionized carboxylic acid to the un-ionized enol, and the additional keto–enol equilibrium constant $pK'_E = 6.49$, relating the carboxylate ion to the enolate monoanion. The results also provided the acidity constants $pK_a = 1.68$ for the carboxylic acid ionizing as an oxygen acid to give the carboxylate ion, $pK_a^K = 8.22$ for the carboxylic acid ionization as a carbon acid to give the enolate monoanion, and $pK'^K_a = 15.19$ for the carboxylate ion ionizing as a carbon acid to give the enolate dianion; the latter agrees well with $pK_a^K = 15.25$ obtained directly by monitoring the extent of carbon acid ionization of the carboxylate ion in concentrated potassium hydroxide solutions. The magnitudes of these equilibrium constants are discussed, and comparisons with other keto–enol systems are made.

Many reactions of carbonyl compounds occur through their enol isomers, and enols are therefore important reaction intermediates. During the past decade there has been a remarkable development of methods for generating enols of simple aldehydes and ketones in solution and observing their reactions directly, and as a result much is now known about the chemistry of these unstable substances.[1] Very much less, however, is known about the enol isomers of carboxylic acids, undoubtedly because they are much less stable, and only a few studies of their behavior in solution have been reported so far. In one of these, stability was conferred on carboxylic acid enols by placing bulky substituents in the β-position.[2] Investigations of much less stable and much more reactive carboxylic acid enols have also been reported, namely that of cyclopentadienecarboxylic acid[3] and that of mandelic acid[4] as well as those of some indenecarboxylic acids derived from diazonaphthoquinones;[5] the latter, however, have only recently been identified as carboxylic acid enols.[6]

To this limited amount of information we now add some chemistry of the enol of α-cyano-α-phenylacetic acid, **3**. We generated this enol by hydration of cyanophenylketene, **2**, formed by flash photolytic Wolff rearrangement of α-cyanodiazoacetophenone, **1**, eq 1. By measuring rates of ketonization of this enol in acidic and basic solutions, we were able to determine both its first and second acidity constants, K_a^E and K'^E_a, and these results, in combination with rates of enolization of the keto form of the acid (**4**), then allowed us to determine all of the equilibrium constants shown in the scheme of eq 2. (In this scheme and



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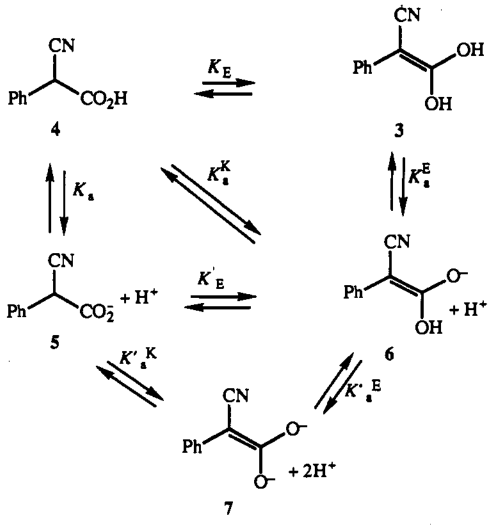

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[●] Abstract published in *Advance ACS Abstracts*, December 1, 1993.

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throughout this paper we used unprimed symbols to designate reactions of neutral species, primed symbols for monoanions, and double primed symbols for dianions.)

Experimental Section

Materials. α-Cyano-α-diazoacetophenone was prepared by diazo transfer from 2-azido-3-ethylbenzothiazolium tetrafluoroborate (Aldrich) to α-cyanoacetophenone (Aldrich).[7] α-Cyano-α-phenylacetic acid was made by saponification of its ethyl ester, which in turn was obtained by treating the sodium salt of benzyl cyanide with diethyl carbonate,[8] and the acid was also made by reaction of carbon dioxide with the organolithium reagent formed from benzyl cyanide and butyllithium;[9] the two samples gave identical results. These substances had NMR spectra consistent with their structures and physical properties consistent with literature values.

All other reagents were best available reagent grades and were used as received.

Kinetics, Ketonization. Rates of ketonization of the enol of α-cyano-α-phenylacetic acid were measured spectroscopically by monitoring decay of the strong absorbance of the enol at λ = 300 nm. Reactions were initiated flash photolytically using a conventional flash-lamp system[10] and a laser system[6b] at the University of Toronto and another laser system at the University of Basel.[11] Excitation in the laser systems was provided by excimer lasers operating at λ = 248 nm. Reaction mixtures were thermostatted at 25.0 ± 0.05 °C in the Toronto systems. The Basel system had no direct temperature control, but the room in which the apparatus was housed was maintained at 25 ± 1°. Concordant results were obtained with all systems. Substrate concentrations in the reaction mixtures were *ca.* 1×10^{-4} M.

The transient signal decays conformed to the first-order rate law well, and observed first-order rate constants were obtained by least-squares fitting to an exponential function.

Kinetics, Enolization. Rates of enolization of α-cyano-α-phenylacetic acid were determined by bromine scavenging under first-order conditions with bromine in large excess: cyanophenylacetic acid concentrations were *ca.* 1×10^{-5} M and bromine concentrations were in the range $1\text{–}6 \times 10^{-3}$ M. Measurements were made with a Cary Model 2200 spectrometer whose cell compartment was thermostatted at 25.0 ± 0.05 °C.

Two series of determinations were made, one in perchloric acid and another in acetic acid buffer solutions. The reactions in perchloric acid were monitored by following either the decrease in Br_2 absorbance at λ = 395 nm or the increase in Br_3^- absorbance at λ = 266 nm. The latter ion was formed in the reaction mixtures by a rapidly established equilibrium between Br_2 and Br^- produced by the bromination reaction, eq 3; under the conditions employed Br_3^- concentrations were directly proportional to Br^- concentrations and thus provided an accurate measure of the extent of reaction. In some of these experiments it was necessary to know that exact concentration of Br_2 (*vide infra*); this was estimated either from the absorbance of Br_2 at λ = 395 nm, using a molar extinction coefficient from the literature,[12] or from the absorbance of Br_3^- at λ = 266 nm, using practical extinction coefficients determined here appropriate to the experimental conditions employed. The data obtained by monitoring Br_2 absorbance fit the first-order rate law and observed first-order rate constants were calculated by least-squares fitting to a single-exponential function. The data obtained by monitoring Br_3^- absorbance, on the other hand, showed a slow upward drift after 5–8 half-lives. This problem was handled by least-squares fitting to a double-exponential function and discarding the second, slower rate constant; the first, more rapid rate constants obtained in this way were consistent with bromination rate constants determined by monitoring Br_2 decrease.

(3)

$$Br^- + Br_2 \rightleftharpoons Br_3^-$$

The measurements in acetic acid buffer solutions were also monitored by following changes in Br_3^- absorbance, this time at λ = 317 nm. These experiments were done in the presence of a large excess of deliberately added Br^- (0.0143 M), and the absorbance due to Br_3^- therefore fell as Br_2 was depleted during the course of a reaction; the conditions were such that this absorbance decrease was once again accurately proportional to the extent of reaction. Absorbances at the end of the bromination reactions again showed a slow drift, and this was handled, as for the perchloric acid runs, by fitting the data to a double-exponential equation.

pK_a Determination. The acidity constant of α-cyano-α-phenylacetate ion ionizing as a carbon acid was determined by measuring the absorbance of the dianion at its maximum, λ_{max} = 297 nm, where the monoanion does not absorb. Measurements were made at constant stoichiometric substrate concentrations (6×10^{-5} M) in concentrated aqueous potassium hydroxide solutions. The dianion is oxidized rapidly by dissolved oxygen in these media, but this problem was overcome by purging all solutions with argon, protecting the UV-cuvettes in which the measurements were made with serum-cap stoppers, and extrapolating absorbance readings to the time of adding substrate to potassium hydroxide solutions. Measurements were made with a Cary Model 2200 spectrometer with cell compartment thermostatted at 25.0 ± 0.05 °C.

Results

Substrate Stability. The UV spectrum of α-cyano-α-diazoacetophenone, with λ_{max} = 260 and 285 nm, does not change with time in neutral and in 1 M $HClO_4$ aqueous solution. In basic solution, on the other hand, these absorptions decrease rapidly with a half-life of *ca.* 5 min in 0.001 M NaOH and *ca.* 1 h in 1:1 boric acid buffer, both at room temperature. This substrate is therefore stable in acid and neutral solution but is unstable in base.

Product Analysis. When α-cyano-α-diazoacetophenone in dilute (10^{-4} M) neutral or acidic aqueous solution is irradiated by several successive flash photolysis pulses, its UV spectrum changes into that of α-cyano-α-phenylacetic acid, with λ_{max} = 258 nm. When the diazoketone is flashed in a 1:1 boric acid buffer (pC_{H^+} = 9; $pC_{H^+} = -\log[H^+]$), on the other hand, this spectral change is accompanied by appearance of an additional absorption band at λ = 350 nm. Irradiation of the diazoketone dissolved in a 9:1 boric acid buffer (pC_{H^+} = 8) also produces this additional band, but its intensity is considerably less than that obtained in the 1:1 buffer.

This UV spectral examination of solutions subjected to flash photolysis was augmented by HPLC analysis of somewhat more concentrated solutions of α-cyano-α-diazoacetophenone (4×10^{-3} M) subjected to continuous irradiation in a Rayonet Photochemical Reactor for 30 min at λ = 300 nm. The HPLC trace of an irradiated solution of diazoketone dissolved in neutral water showed only two major peaks, which were identified by addition of authentic samples as α-cyano-α-phenylacetic acid and benzyl cyanide; the latter is presumably a secondary, nonphotochemical product formed by the known[13] ready decarboxylation of the primary carboxylic acid product. Analysis of an irradiated solution of diazoketone dissolved in a 1:1 boric acid buffer, on the other hand, showed the presence of additional substances.

These observations indicate that irradiation of α-cyano-α-diazoacetophenone in dilute acidic or neutral solution results in the clean formation of α-cyano-α-phenylacetic acid, as expected on the basis of the well-known photo-Wolff reaction[14] illustrated in eq 1. In basic solution, on the other hand, other, as yet unidentified, processes intervene.

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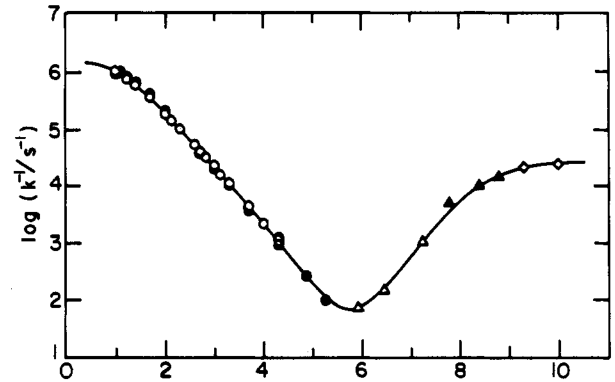
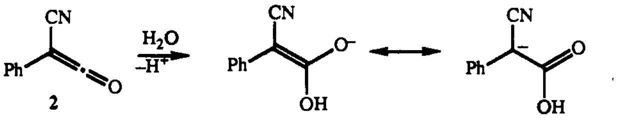


Figure 1. Rate profile for the ketonization of the enol of α-cyano-α-phenylacetic acid in aqueous solution at 25 °C, ionic strength = 0.10 M; (○) hydrochloric acid solutions, (●) acetic acid buffers, (△) biphosphate buffers, (▲) TRIS buffers, and (◇) ammonium ion buffers.

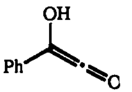
Ketonization. Flash photolysis of acidic or neutral solutions of α-cyano-α-diazoacetophenone produces a short-lived transient species which absorbs strongly near λ = 300 nm, as expected for an enol with a styryl chromophore such as that of α-cyano-α-phenylacetic acid, 3. This transient absorbance is generated within the pulse of our laser systems (*ca.* 50 ns), and it then decays more slowly at rates that are not affected by degassing but that do respond to the acid–base properties of the solution in a way characteristic of the ketonization of an enol.

Enol intermediates in the photo-Wolff reaction are preceded by ketenes, eq 1, but the ketene precursor could not be observed in the present case. This is not unexpected, for the present ketene, cyanophenylketene, **2**, should be very reactive. The hydration of ketenes to carboxylic acid enols occurs by nucleophilic attack of water at carbonyl carbon, eq 4,[15] which gives a carbanion whose



(4)

negative charge is delocalized onto the β-carbon atom; electron-withdrawing groups at this position stabilize this charge and accelerate the hydration reaction.[16] The lifetime of hydroxyphenylketene, **8**, the analog of the present ketene with –OH



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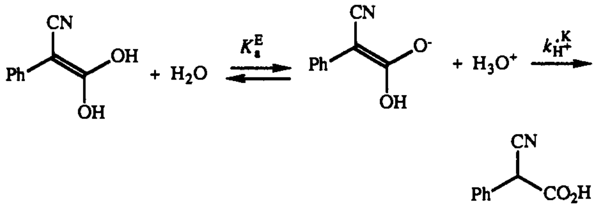
replacing the –CN group, is only 1.5 μs in aqueous solution,[4] and the much stronger electron-withdrawing effect of –CN should easily reduce this lifetime to a value shorter than the resolving time of our laser flash systems (~50 ns).

We measured the rate of ketonization of α-cyano-α-phenylacetic acid enol in dilute aqueous hydrochloric acid solutions over the concentration range pC_{H^+} = 1–4. The data are summarized in Table S1[17] and are displayed as open circles in the rate profile of Figure 1. It may be seen that the ketonization is catalyzed by acid, with observed first-order rate constants directly proportional to acid concentration at pC_{H^+} = 2–4, but that this catalysis begins to show saturation at acidities above pC_{H^+} = 2. This is the behavior expected of an enol that exists in both un-ionized and ionized (enolate) forms under the reaction conditions, with ketonization occurring only through the enolate form, eq 5,[18] and that in turn is consistent with the standard



(5)

mechanism for enol ketonization by rate-determining protonation on β-carbon[20] and the known much greater reactivity of enolate ions over enols.[21]

The rate law that applies to the reaction scheme of eq 5 is shown in eq 6

$$k_{\mathrm{obs}} = k_{\mathrm{H}^+}^{\prime\mathrm{K}} K_{\mathrm{a}}^{\mathrm{E}}/(K_{\mathrm{a}}^{\mathrm{E}} + [\mathrm{H}^+]) \qquad (6)$$

Least squares fitting of the data to this expression gave K_a^E = (1.01 ± 0.05) × 10^{-1} M, pK_a^E = 0.99 ± 0.02, for the acidity constant of α-cyano-α-phenylacetic acid enol[22] and $k_{H^+}^{\prime K}$ = (2.09 ± 0.02) × 10^7 M^{-1} s^{-1} as the hydronium ion catalytic coefficient for ketonization of this enol by carbon protonation of the enolate ion. This acidity constant is in the range of pK_a^E = 0.4–1.3 reported for the enols of cyclopentadienecarboxylic acid[3] and several indenecarboxylic acids,[6b] but it is greater than that reported for the enol of mandelic acid ($pK_a{}^E$ = 6.6);[4] the latter difference, however, is consistent with the greater electron-withdrawing effect and acidifying influence of a cyano over a hydroxy substituent. The present hydronium ion catalytic coefficient is also consistent with $k_{H^+}^{\prime K}$ = 10^6–10^7 M^{-1} s^{-1} found for cyclopentadiene- and indenecarboxylic acid enols.[3,6b]

We also determined solvent isotope effects on the ketonization of α-cyano-α-phenylacetic acid enol catalyzed by the hydronium ion. Replicate rate measurements were made in H_2O and in D_2O at two different acid concentrations; the data, summarized in Table S2,[17] provide the observed isotope effects k_H/k_D = 2.23 ± 0.08 at 0.005 M acid and k_H/k_D = 5.38 ± 0.27 at 0.33 M acid.

Such variation in observed isotope effect is to be expected for the reaction scheme of eq 5 and the rate law of eq 6, and it provides good evidence for the essential correctness of this scheme. At low acidity the position of the equilibrium in the first step of eq 5 will lie to the right; the enolate ion will therefore be the initial state of the observed reaction, and the observed isotope effect will be that on the rate constant $k_{H^+}^{\prime K}$. At high acidities, on the other hand, the equilibrium will shift to the left, the enol will then be the initial state, and the observed isotope effect will be that on the rate constant times that on the equilibrium constant K_a^E.

It is possible to extract isotope effects on each of these two constants from observed isotope effects determined at the two different acidities and the known value of K_a^E in H_2O, by setting up and solving two simultaneous equations based on the two sets of experimental conditions. This treatment gives $k_{H^+}^{\prime K}/k_{D^+}^{\prime K}$ = 2.0 and $(K_a^E)_H/(K_a^E)_D$ = 3.2. The first of these, though small, is a reasonable value for the present reaction, inasmuch as such

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[17] Supplementary material; see paragraph at the end of this paper regarding availability.

[18] We do not know which of the hydroxyl groups of the enol ionizes in this reaction, but we have arbitrarily chosen the one *trans* to phenyl because the *trans*-enol of phenylacetaldehyde is more acidic than the *cis*-enol.[19]

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[22] This is a concentration dissociation constant that applies at the ionic strength of the measurements (0.10 M).

isotope effects pass through maxima and can be expected to reach fairly low values for reactions as fast as the present one;[23] the corresponding isotope effect for the enol of isobutyrophenone, for which $k_{H^+}^{'K} = 3 \times 10^8$ M^{-1} s^{-1},[21] for example, is actually unity.[24] The isotope effect on K_a^E is also consistent with expectation, for acids are generally less completely ionized in D_2O than in H_2O and the isotope effect on the acidity constant for carboxylic acids is often in the vicinity of 3.[25]

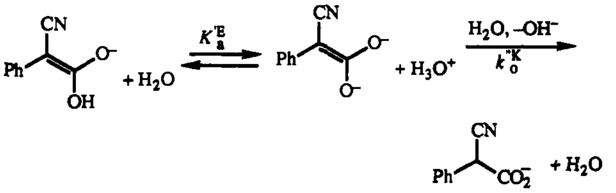
Rates of ketonization of α-cyano-α-phenylacetic acid enol were also measured in aqueous acetic acid, biphosphate ion, TRIS {tris(hydroxymethyl)methylamine}, and ammonia buffer solutions. Series of solutions of constant buffer ratio and constant ionic strength (0.10 M), and therefore constant hydrogen ion concentration, but varying buffer concentration were used. Four to five buffer concentrations spanning a 5-fold range were generally employed within a series, and replicate measurements were made at each concentration. The data are summarized in Table S3.[17]

Observed rate constants within each buffer series proved to be accurately proportional to buffer concentration, and the data were therefore fitted to the rate law of eq 7 by linear least-squares analysis. This provided a number of extrapolated, buffer-independent rate constants, k_x^K, at different values of pC_{H^+} which were used to complete the rate profile of Figure 1.[26]

$$k_{obs} = k_x^K + k_{cat}^K[\text{buffer}] \qquad (7)$$

It may be seen that the data obtained in acetic acid buffers continue the downward leg of the rate profile established in hydrochloric acid solutions. Beyond this, however, there is a turning point, and the data from biphosphate buffers begin a new upward leg of inverse dependence of rate on hydronium ion concentration or apparent hydroxide ion catalysis. This catalysis is continued by the first data point obtained from TRIS buffers, but beyond that, in the remaining TRIS buffers and the ammonia buffers, this catalysis becomes saturated.

Such apparent hydroxide ion catalysis is commonly found in enol ketonization.[20] It is produced by ionization of the enol, in the present case further ionization to the dianion, followed by β-carbon protonation of that species by water, eq 8. Hydroxide ion catalysis occurs when the acidity is still sufficiently high to make monoenolate ion the initial state; the equilibrium ionization then produces a hydronium ion which is not used up in the subsequent slow step, and the overall reaction rate is inversely proportional to [H⁺] or directly proportional to [HO⁻]. When the acidity drops to the point where the dianion becomes the initial state, the prior equilibrium no longer plays a role, and the hydroxide ion catalysis becomes saturated.



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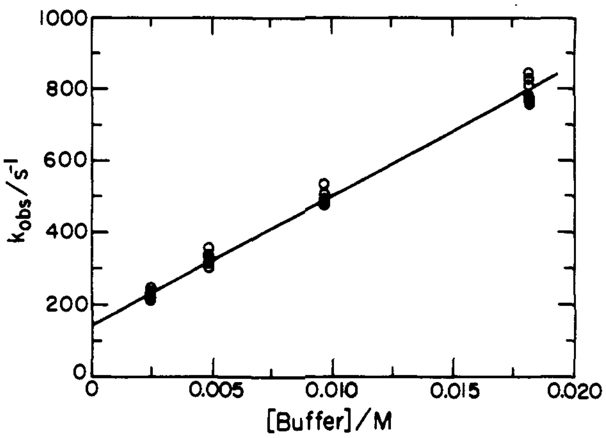


Figure 2. Buffer catalysis of the ketonization of α-cyano-α-phenylacetic acid enol in aqueous phosphate buffers; $[H_2PO_4^-]/[HPO_4^{=}] = 2.0$, ionic strength = 0.10 M, 25 °C.

$$k_{obs} = k_0^{''K}K_a^{'E}/(K_a^{'E} + [H^+]) \qquad (9)$$

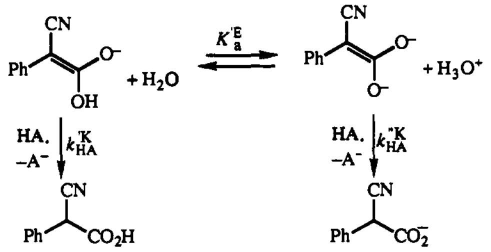
The rate law that applies to this reaction scheme is shown in eq 9. Least-squares fitting of the data from biphosphate ion, TRIS, and ammonia buffers to this expression gave $k_0^{''K} = (2.53 \pm 0.36) \times 10^4$ s^{-1} and $K_a^{'E} = (2.44 \pm 0.47) \times 10^{-9}$ M, $pK_a^{'E} = 8.61 \pm 0.08$.[22] These parameters, together with those obtained for the acidic portion of the rate profile using eq 6, were used to calculate the line drawn in Figure 1. It may be seen that they reproduce the experimental data well.

The ketonization of enols, being a rate-determining proton-transfer reaction, should be subject to buffer catalysis, and the present example conforms to this expectation. As Figure 2 shows, observed rate constants determined in phosphate buffers depend strongly on buffer concentration. Equally marked dependences were found for all of the other buffers examined.

Measurements made at different buffer ratios showed that the buffer catalysis in acetic acid buffers was purely of the general acid type, whereas in biphosphate buffers both general acid and general base catalysis were operating; in TRIS and ammonia buffers, the situation was complicated by the second ionization of the enol. This behavior can be understood in terms of reaction of the buffer acid with either one or both of the ionized forms of the enol, as shown in the scheme of eq 10. The rate law that applies to this scheme is given in eq 11; it consists of expressions

$$k_{obs} = k_{HA}^{'K}[HA]\left(\frac{[H^+]}{K_a^{'E} + [H^+]}\right) + k_{HA}^{''K}[HA]\left(\frac{K_a^{'E}}{K_a^{'E} + [H^+]}\right) \qquad (11)$$

for reaction of the two enol forms each multiplied by fractions that express the relative amount of enol in that form.



(10)

In acetic acid and biphosphate ion buffers, $[H^+] > K_a^{'E}$ ($pC_{H^+} = 4.9$–7.3, $pK_a^{'E} = 8.6$), and this rate law simplifies to the expression shown in eq 12. Since $[HA]/[H^+] = [A^-]/K_a^{HA}$ where A^- represents the conjugate base of the buffer acid and K_a^{HA} is its acidity constant, this expression is equivalent to eq 13. The first

$$k_{obs} = k_{HA}^{'K}[HA] + k_{HA}^{''K}K_a^{'E}[HA]/[H^+] \qquad (12)$$

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(23) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228–233.

(24) Chiang, Y.; Kresge, A. J.; Walsh, P. A. *Z. Naturforsch* **1989**, *44a*, 406–412.

(25) Laughton, P. M.; Robertson, R. E. In *Solute-Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; Chapter 7. Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; *Secondary and Solvent Isotope Effects*; Buncel, E., Lee, C. C., Eds.; Elsevier: New York; 1987; Vol. 7, Chapter 4.

(26) Values of [H⁺] of the buffer solutions required for this purpose were obtained by calculation using thermodynamic acidity constants from the literature and activity coefficients recommended by Bates.[27]

$$k_{\mathrm{obs}} = k^{\prime\mathrm{K}}_{\mathrm{HA}}[\mathrm{HA}] + k^{\prime\prime\mathrm{K}}_{\mathrm{A}}K^{\prime\mathrm{E}}_{\mathrm{a}}[\mathrm{A}^-]/K_{\mathrm{a}} \qquad (13)$$

term of this rate law, with its dependence on [HA], denotes general acid catalysis, whereas the second term, because it contains [A^-], denotes general base catlaysis. In acetic acid buffers the relative concentration of enolate dianion was too low to allow a significant amount of reaction through this species; the second term of the rate law therefore made no contribution, and only general acid catalysis was observed. In biphosphate buffers, on the other hand, reaction occurred through both enolate forms and both general acid and general base catalysis were found. Analysis of the data for both buffers using eq 13 produced the catalytic coefficients listed in Table 2.

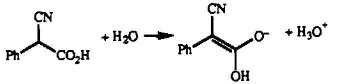
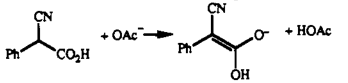
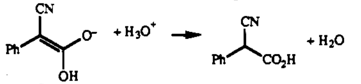
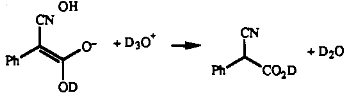
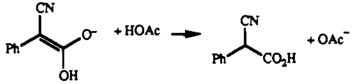
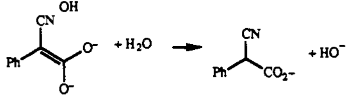
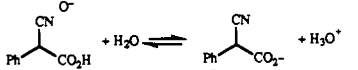
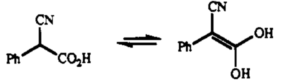
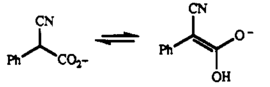
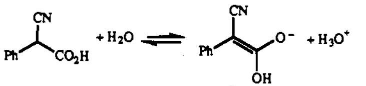
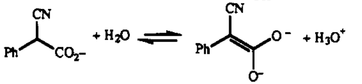
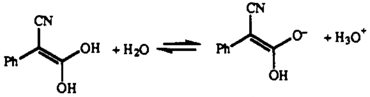
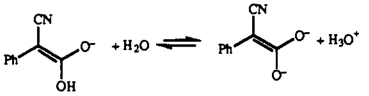
In TRIS and ammonia buffers, [H^+] was no longer substantially greater than $K^{\mathrm{E}}_{\mathrm{a}}$ (pC_{H^+} = 7.8–10.0, p$K^{\mathrm{E}}_{\mathrm{a}}$ = 8.6) and the simplified rate law of eqs 12 and 13 therefore did not apply. On the other hand, fitting the data for TRIS buffers to the full rate law of eq 11 produced a small negative value of $k^{\prime\mathrm{K}}_{\mathrm{HA}}$, indicating that no significant amount of reaction had occurred through the enolate monoanion. The first term of eq 11 was therefore dropped, and the data were fitted to an expression consisting of the second term only. This treatment gave the catalytic coefficients listed in Table 2 and two values of the enol acidity constant: $K^{\prime\mathrm{E}}_{\mathrm{a}}$ = (1.76 ± 0.05) × 10^{-9} M, p$K^{\prime\mathrm{E}}_{\mathrm{a}}$ = 8.76 ± 0.01[22] (from TRIS buffers) and $K^{\prime\mathrm{E}}_{\mathrm{a}}$ = 1.81 × 10^{-9} M, p$K^{\prime\mathrm{E}}_{\mathrm{a}}$ = 8.74[22] (from NH_3 buffers).[28] These acidity constants agree well with one another and are consistent with the value obtained from the rate profile, p$K^{\prime\mathrm{E}}_{\mathrm{a}}$ = 8.61. This agreement provides good support for the essential correctness of the data treatment employed.

Further verification comes from the fact that the catalytic coefficients obtained (summarized in Table 2) form a sensible pattern. The value of $k^{\prime\mathrm{K}}_{\mathrm{HA}}$ for CH_3CO_2H, for example, is greater than that for the weaker acid $H_2PO_4^-$, as is $k^{\prime\prime\mathrm{K}}_{\mathrm{HA}}$ for TRIS·H$^+$ compared to that for the weaker acid NH_4^+; this is expected on the basis of the Bronsted relation, which requires the stronger acid to be the better catalyst. The value of $k^{\prime\prime\mathrm{K}}_{\mathrm{HA}}$ for $H_2PO_4^-$ is also greater than $k^{\prime\mathrm{K}}_{\mathrm{HA}}$ for this acid, consistent with the expected greater reactivity of the dianion toward electrophilic reagents. An inversion of the expected relationship between rate constant and acid strength appears in the values of $k^{\prime\prime\mathrm{K}}_{\mathrm{HA}}$ for $H_2PO_4^-$ and TRIS·H$^+$, but these acids are of different charge type and different coulombic effects will operate in the two transition states. Specifically, charge repulsion between $H_2PO_4^-$ and the dianionic substrate will destabilize the transition state for that reaction, whereas an attractive interaction between TRIS·H$^+$ and the dianion will stabilize that transition state,[29] and these effects will retard the $H_2PO_4^-$ reaction and accelerate the TRIS·H$^+$ reaction to an extent that overcomes the expected relationship between rate and catalyst acidity.

Enolization. Rates of enolization of α-cyano-α-phenylacetic acid were determined by bromine scavenging of the enol as it formed in aqueous perchloric acid solutions and acetic acid buffers. This method requires the scavenging reaction to be much faster than reketonization of the enol, for only then is enolization rate-determining and are observed rate constants a true measure of the enolization process. This condition may not always be fulfilled, especially in strongly acidic solutions, for reketonization is an acid-catalyzed process, whereas reaction of the enol with bromine is not.[30]

In situations where scavenging is not sufficiently fast, observed rate constants become dependent on scavenger concentration.[31] We found this to be the case in the present study at the higher acidities used ([H^+] = 0.01–0.10 M). This is illustrated in Figure 3, where a decrease in observed rate constant with decreasing bromine concentration may clearly be seen.

Table 1. Summary of Rate and Equilibrium Constants for the α-Cyano-α-phenylacetic Acid Keto–Enol System at 25 °C[a]

Process	Constant
	$k^{\mathrm{E}}_{\mathrm{o}}$ = 1.27×10^{-1} s^{-1}
	$k^{\mathrm{E}}_{\mathrm{B}}$ = 5.84×10^{1} M^{-1} s^{-1}
	$k^{\prime\mathrm{K}}_{\mathrm{H}^+}$ = 2.09×10^{7} M^{-1} s^{-1}
	$k^{\prime\mathrm{K}}_{\mathrm{D}^+}$ = 1.04×10^{7} M^{-1} s^{-1}
	$k^{\prime\mathrm{K}}_{\mathrm{HA}}$ = 2.27×10^{5} M^{-1} s^{-1}
	$k^{\prime\prime\mathrm{K}}_{\mathrm{o}}$ = 2.53×10^{4} s^{-1}
	K_{a} = 2.10×10^{-2} M; pK_{a} = 1.68
	K_{E} = 5.98×10^{-8}; pK_{E} = 7.22
	K'_{E} = 3.23×10^{-7}; pK'_{E} = 6.49
	$K^{\mathrm{K}}_{\mathrm{a}}$ = 6.06×10^{-9} M; p$K^{\mathrm{K}}_{\mathrm{a}}$ = 8.22
	$K'^{\mathrm{K}}_{\mathrm{a}}$ = 6.46×10^{-16} M; p$K'^{\mathrm{K}}_{\mathrm{a}}$ = 15.19
	$K^{\mathrm{E}}_{\mathrm{a}}$ = 1.01×10^{-1} M; p$K^{\mathrm{E}}_{\mathrm{a}}$ = 0.99
	$K^{\prime\mathrm{E}}_{\mathrm{a}}$ = 2.00×10^{-9} M; p$K^{\prime\mathrm{E}}_{\mathrm{a}}$ = 8.70

[a] Ionic strength = 0.10 M; equilibrium constants are concentration quotients appropriate to that ionic strength.

Table 2. Catalytic Coefficients for Ketonization of α-Cyano-α-phenylacetic Acid Enol in Aqueous Buffer Solutions at 25 °C[a]

catalyst	pK_{a}	$k^{\prime\mathrm{K}}_{\mathrm{HA}}$, 10^6 M^{-1} s^{-1} [b]	$k^{\prime\prime\mathrm{K}}_{\mathrm{HA}}$, 10^6 M^{-1} s^{-1} [c]
CH_3CO_2H	4.76	0.212	
$H_2PO_4^-$	7.20	0.020	5.91
TRIS·H$^+$	8.07		10.1
NH_4^+	9.25		1.66

[a] Ionic strength = 0.10 M. [b] Reaction of enolate monoanion. [c] Reaction of enolate dianion.

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

(28) No uncertainty is given for this value because measurements in NH_3 buffers were made at only two buffer ratios; only two data points were therefore available for fitting to the rate law, and since no parameters had to be determined, no estimate of the goodness of fit could be made.

(29) Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* **1973**, *95*, 803–806. Chwang, W. K.; Eliason, R.; Kresge, A. J. *J. Am. Chem. Soc.* **1977**, *99*, 805–808. Dahlberg, D. B.; Kuzemko, M. A.; Chiang, Y.; Kresge, A. J.; Powell, M. R. *J. Am. Chem. Soc.* **1983**, *105*, 5387–5390.

(30) Chiang, Y.; Kresge, A. J.; More O'Ferall, R. A.; Murray, B. A.; Schepp, N. P.; Wirz, J. *Can. J. Chem.* **1990**, *68*, 1653–1656.

(31) Chiang, Y.; Kresge, A. J.; Morimoto, H.; Williams, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 3981–3982.

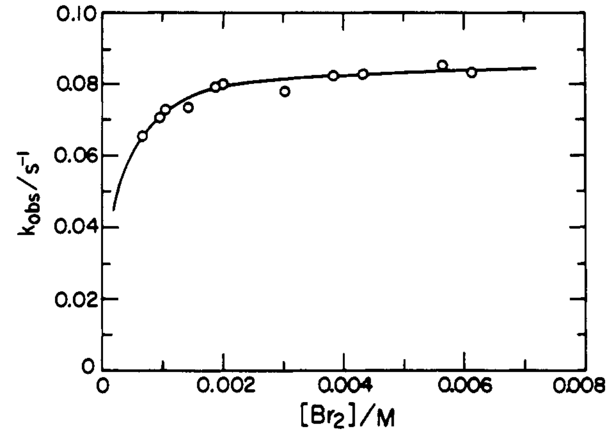
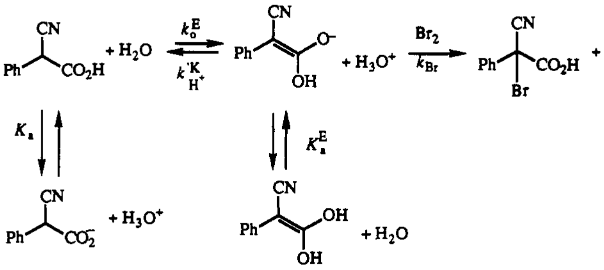


Figure 3. Relationship between bromine concentration and observed rates of bromination of α-cyano-α-phenylacetic acid in 0.05 M aqueous perchloric acid solution at 25 °C.

The data were therefore treated according to a reaction scheme that takes reketonization into account. This scheme, shown in eq 14,[32] also allows for the fact that the enol, with $pK_a^E = 0.99$ (*vide supra*) as well as the substrate acid for which $pK_a = 1.88$,[33] exist in both ionized and un-ionized forms at the acidities employed. The rate law that applies to this reaction scheme is shown in eq 15; it consists of rate constants for the enolization

$$k_{obs} = \frac{k_0^E\left\{\frac{[H^+]}{K_a + [H^+]}\right\}k_{Br}[Br_2]}{k_{H^+}^{'K}[H^+]\left\{\frac{K_a^E}{K_a^E + [H^+]}\right\} + k_{Br}[Br_2]} \tag{15}$$

(k_0^E) and reketonization ($k_{H^+}^{'K}$) steps, each multiplied by a fraction that expresses the position of the relevant acid ionization equilibrium, plus a rate constant for bromination of the enol (k_{Br}).



(14)

Rates of bromination of α-cyano-α-phenylacetic acid were measured in series of perchloric acid solutions over the concentration range 0.01–0.1 M, with bromine concentrations in each series varied from 0.001 to 0.006 M. These data are summarized in Table S4.[17] Observed first-order rate constants for each series were then fitted to eq 15 in the abbreviated form shown as eq 16,

$$k_{obs} = \frac{k_{extrp}[Br_2]}{a + [Br_2]} \tag{16}$$

in which k_{extrp} is the enolization rate constant at a given $[H^+]$ corrected for insufficiently fast scavenging by extrapolation to "infinite" $[Br_2]$, eq 17, and a is the quantity defined by eq 18. This treatment produced a number of values of a at different (known) $[H^+]$, from which, with the aid of $k_{H^+}^{'K}$ ($=2.09 \times 10^7$ M^{-1} s^{-1}) and

$$k_{extrp} = k_0^E\left\{\frac{[H^+]}{K_a + [H^+]}\right\} \tag{17}$$

$$a = k_{H^+}^{'K}[H^+]\left\{\frac{K_a^E}{K_a^E + [H^+]}\right\}/k_{Br} \tag{18}$$

K_a^E ($= 1.01 \times 10^{-1}$ M (determined by the ketonization studies described above, k_{Br} could be evaluated. The result, $k_{Br} = (2.34 \pm 0.37) \times 10^9$ M^{-1} s^{-1}, shows that the bromination of this enol is a very fast, nearly diffusion-controlled reaction, consistent with the bromination of other enols.[31,34]

Knowledge of this bromination rate constant allowed direct comparison of rates of bromination with rates of reketonization, which showed that, at the bromine concentrations used, bromination becomes two orders of magnitude faster than reketonization at $[H^+] = 0.005$ M; bromine was therefore an adequate scavenger at this and lower acidities. Further bromination rate measurements were consequently made at a single bromine concentration (0.002 M) over the perchloric acid concentration range 0.002–0.005 M. These data are also summarized in Table S4.[17]

Rates of bromination of α-cyano-α-phenylacetic acid were also measured in acetic acid buffer solutions. Just as in the ketonization studies, series of solutions of constant buffer ratio and constant ionic strength but varying buffer concentration were used. This served to hold $[H^+]$ constant along a given buffer series. The data are summarized in Table S5.[17]

Observed first-order rate constants of enolization, just as those for ketonization, proved to be accurately proportional to buffer concentration in each buffer series. The data were therefore fitted to the enolization analog of eq 7, shown as eq 19, by linear least-squares analysis. This gave a series of extrapolated buffer-independent enolization rate constants, k_x^E, at different values of $[H^+]$. These rate constants, together with those measured in 0.001–0.005 M perchloric acid plus values of k_{extrp} determined in 0.01–0.1 M perchloric acid, were then fitted to eq 17. Figure 4 shows that these data obeyed that relationship quite well; least-squares analysis produced $k_0^E = (1.27 \pm 0.01) \times 10^{-1}$ s^{-1}, as the rate constant for enolization of α-cyano-α-phenylacetic acid through the proton transfer to a water molecule (eq 14), and $K_a = (2.10 \pm 0.06) \times 10^{-2}$ M, $pK_a = 1.68 \pm 0.01$, as the acidity constant of the carboxylic acid group in α-cyano-α-phenylacetic acid. The latter is a concentration quotient that applies at the ionic strength (0.10 M) of the present measurements; it agrees well with $pK_a = 1.70$ which can be estimated from the thermodynamic acidity constant of α-cyano-α-phenylacetic acid, $pK_a = 1.88$,[33] with the aid of appropriate activity coefficients.[27]

$$k_{obs}^E = k_x^E + k_{cat}^E[\text{buffer}] \tag{19}$$

These rate measurements in acetic acid buffer solutions also provided rate constants for catalysis of the enolization reaction by the buffer, k_{cat}^E (eq 19). Comparison of results for different buffer ratios showed this catalysis to be solely of the general acid type, consistent with the exclusive general acid catalysis found for ketonization of the enol of α-cyano-α-phenylacetic acid in acetic acid buffers. The data were analyzed according to eq 20,

$$k_{cat}^E = k_B^E + (k_{HA}^E - k_B^E)f_A \tag{20}$$

in which k_{HA}^E and k_B^E are general acid and general base catalytic coefficients and f_A is the fraction of buffer present in the acid form. Figure 5 shows that the data obeyed this relationship well; least-squares analysis gave $k_B^E = -(2.86 \pm 1.96) \times 10^{-3}$ M^{-1} s^{-1} and $k_{HA}^E = (7.56 \pm 0.17) \times 10^{-2}$ M^{-1} s^{-1}. The latter is the rate

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[32] Enolization is shown here as an "uncatalyzed" process in which the base that removes the proton from the α-carbon atom of the acid is a solvent water molecule, in accordance with the requirement that this must be the microscopic reverse of ketonization which is established by the present study as occurring through carbon protonation of the enolate by hydronium ion.

[33] Widequist, A. *Arkiv Kemi* **1952**, *3*, 281–288.

[34] Hochstrasser, R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 7875–7876.

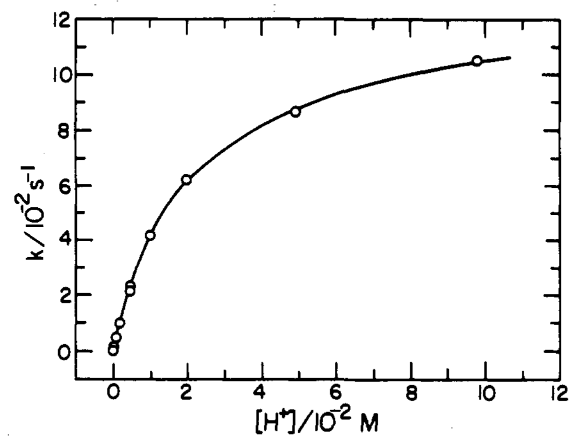


Figure 4. First-order rate constants for enolization of α-cyano-α-phenylacetic acid in aqueous perchloric and solutions and acetic acid buffers at 25 °C plotted according to eq 16.

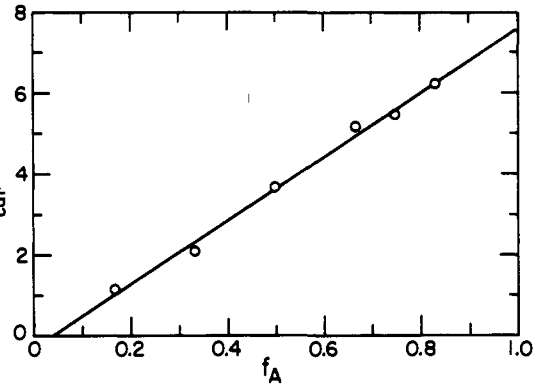
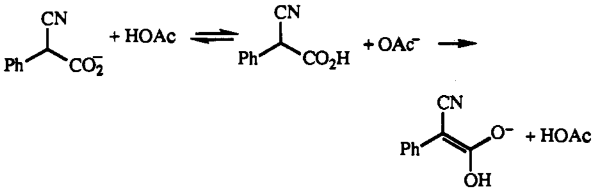


Figure 5. Relationship between buffer catalytic coefficients and fraction of buffer present as acid for the enolization of α-cyano-α-phenylacetic acid in aqueous acetic acid buffer solutions at 25 °C.

constant for enolization of α-cyano-α-phenylacetate ion, which is the predominant form of the substrate in acetic acid buffers, through protonation of its carboxylate group by acetic acid followed by proton transfer from α-carbon to acetate ion, eq 21;



(21)

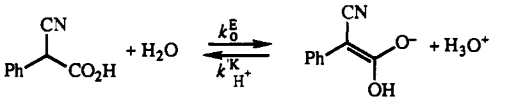
this is the microscopic reverse of the enol ketonization reaction, which, as was shown above, occurs in acetic acid buffers through carbon protonation of the enolate ion by acetic acid.

pK_a Determination. The extent of ionization of α-cyano-α-phenylacetate ion as a carbon acid was determined by measuring the absorbance of the dianion product in a series of aqueous potassium hydroxide solutions over the concentration range [KOH] = 0.4–10 M. The data so obtained were transformed into values of I (=[dianion]/[monoanion]), and the fit of log I to different basicity functions was examined. Three functions were tried: an H_- scale based on neutral indole indicators,[35] an $H_=$ scale based on indoles bearing carboxylate groups,[35] and an $H_=$ scale based on aromatic amines bearing carboxylate and sulfonate groups.[36] The $H_=$ scale based on indoles was found to be the most appropriate; it gave a plot of log I vs $H_=$ whose slope was essentially unity (1.022 ± 0.015), whereas the other basicity functions produced slopes significantly different from unity (1.112 ± 0.022 and 1.273 ± 0.015). The data were therefore fitted to a titration curve using this indole-based $H_=$ scale as a measure of the basic strength of the solutions employed; this produced the acidity constant pK_a = 15.251 ± 0.021.

Discussion

Equilibria Involving Neutral and Singly Ionized Species. The reaction scheme describing the α-cyano-α-phenylacetic acid system shown as eq 2 contains two neutral species, the carboxylic acid (**4**) and the enol (**3**), and two singly ionized species, the carboxylate ion (**5**) and the enolate monoanion (**6**). These substances are interconnected by the equilibria that make up the upper, square part of this scheme.

Two of the equilibrium constants of this scheme have been determined from turning points in the acidity dependence of rate constants measured here: K_a from rates of enolization and K_a^E from rates of ketonization. A third equilibrium constant, K_a^K can be determined as the ratio of two rate constants, that for the limiting rate of enolization in acid solutions, k_o^E, which represents proton removal from β-carbon by a water molecule, and that, $k_{H^+}^{\prime K}$, for ketonization through carbon protonation of the enolate ion by hydronium ion, eq 22: $K_a^K = k_o^E/k_{H^+}^{\prime K} = (1.27 \pm 0.15) \times 10^{-1}/(2.09 \pm 0.02) \times 10^7 = (6.06 \pm 0.09) \times 10^{-9}$ M, $pK_a^K = 8.22 \pm 0.01$.



(22)

Knowledge of K_a^K then allows K_E to be determined from the relationship $K_E = K_a^K/K_a^E$, which applies to the thermodynamic cycle that makes up the triangle of reactions in the upper right corner of the scheme of eq 2; this gives $K_E = (6.06 \pm 0.09) \times 10^{-9}/(1.01 \pm 0.05) \times 10^{-1} = (5.98 \pm 0.28) \times 10^{-8}$, $pK_E = 7.22 \pm 0.02$. A similar relationship involving K_a^K applies to the triangle of reactions in the lower left corner of the square part of this scheme, and that allows K'_E to be determined as the ratio K_a^K/K_a:$K'_E = (6.06 \pm 0.09) \times 10^{-9}/(2.10 \pm 0.06) \times 10^{-2} = (2.88 \pm 0.10) \times 10^{-7}$, $pK'_E = 6.54 \pm 0.01$.

The latter equilibrium constant relates the keto and enol forms of α-cyano-α-phenylacetic acid when both exist as monoanionic species. This is the situation in the acetic acid buffers examined here, eq 23, and K'_E may consequently also be evaluated as the

(23)

ratio of rate constants for acetic acid catalyzed enolization and ketonization: $K'_E = k_{HA}^{\prime E}/k_{HA}^{\prime E} = (7.56 \pm 0.17) \times 10^{-2}/(2.12 \pm 0.05) \times 10^5 = (3.57 \pm 0.11) \times 10^{-7}$, $pK'_E = 6.45 \pm 0.01$. This result is consistent with the value obtained from the thermodynamic cycle. The best value of this constant may then be taken as the average of the two results, $K'_E = (3.23 \pm 0.35) \times 10^{-7}$, $pK'_E = 6.49 \pm 0.05$.

Equilibria Involving the Doubly Ionized Enolate Dianion. This species is formed to an appreciable extent only in the more basic solutions examined here above pC_{H^+} = 8, where our product analysis indicates processes other than ketonization of α-cyano-α-phenylacetic acid are occurring. This raises the question of whether or not the phenomenon observed by flash photolysis in this region is in fact ketonization of the enol, and, in particular, whether the turning point in the rate profile at pC_{H^+} = 8.7 used to determine the second ionization constant of the enol, K_a^E, is produced by this ionization. The fact that analysis of buffer catalysis in TRIS and ammonia buffers gives ionization constants

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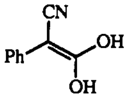
[35] Yagil, G. *J. Phys. Chem.* **1967**, *71*, 1034–1044.

[36] Halle, J.-C.; Terrier, F.; Schaal, R. *Bull. Soc. Chim. Fr.* **1969**, 4569–4575.

(TRIS: p$K_a^{\prime E}$ = 8.76, NH_3: p$K_a^{\prime E}$ = 8.74) consistent with that obtained from the rate profile (p$K_a^{\prime E}$ = 8.61) suggests that, despite the occurrence of secondary reactions, the phenomenon being monitored flash photolytically is enol ketonization. This conclusion is reinforced by the fact that these values of $K_a^{\prime E}$, when combined with K'_E according to a relationship dictated by the triangular thermodynamic cycle at the bottom of the scheme of eq 2, gives a value of $K_a^{\prime K}$ consistent with a direct determination of this quantity in concentrated potassium hydroxide solutions (*vide infra*). It would therefore seem reasonable to assume that ketonization is indeed still the process being observed flash photolytically in these basic solutions.

These three determinations of $K_a^{\prime E}$, from the rate profile and from buffer catalysis in TRIS and ammonia buffers, then lead to the average value, $K_a^{\prime E} = (2.00 \pm 0.22) \times 10^{-9}$ M, p$K_a^{\prime E}$ = 8.70 ± 0.05, for the second acidity constant of the enol of α-cyano-α-phenylacetic acid. The thermodynamic cycle at the bottom of the scheme of eq 2 provides the relationship $K_a^{\prime K} = K'_E K_a^{\prime E}$, and that gives $K_a^{\prime K} = \{(3.23 \pm 0.34) \times 10^{-7}\}\{(2.00 \pm 0.22) \times 10^{-9}\} = (6.46 \pm 0.99) \times 10^{-16}$, p$K_a^{\prime K}$ = 15.19 ± 0.07 for the acidity constant of α-cyano-α-phenylacetate ion ionizing as a carbon acid. This quantity was also determined directly in the present study by measuring the extent of ionization in concentrated potassium hydroxide solutions and extrapolating the results down an appropriate basicity function. That method presumably gives a thermodynamic acidity constant, referred to an infinitely dilute standard state, whereas the result obtained from kinetic measurements as described above refers to the ionic strength, 0.10 M, at which these measurements were made; comparison of the two values therefore requires application of activity coefficients. These are not known for the α-cyano-α-phenylacetate ion and the enolate dianion, but use of recommended values for benzoate and carbonate ions[27] as surrogates, together with a recommended value for the hydronium ion,[27] converts the thermodynamic p$K_a^{\prime K}$ (= 15.25) into the concentration quotient applicable at 0.10 M ionic strength, p$K_a^{\prime K}$ = 14.83. This agrees reasonably well with the value obtained from the thermodynamic cycle described above, p$K_a^{\prime K}$ = 15.19. It is likely, however, that carbonate ion is a poor model for the enolate dianion, for the charge in the latter is certainly much more delocalized, and making allowance for this difference pushes the estimate, p$K_a^{\prime K}$ = 14.83, closer to p$K_a^{\prime K}$ = 15.19. The agreement of the two values must therefore be considered to be quite good, and that in turn provides good evidence that the flash photolytic measurements made in basic solutions do refer to the ketonization reaction.

Comparison with Other Systems. The present results show the enol of α-cyano-α-phenylacetic acid to be a remarkably strong acid: with pK_a^E = 0.99 it is more acidic than most carboxylic acids, and it is in fact more acidic than the carboxylic acid group of its keto isomer, for which pK_a = 1.68. This great acid strength is due, of course, to the acidifying effect of the α-hydroxyl, β-phenyl, and β-cyano groups in this substance. The total influence of these groups can be estimated at 9.5 pK units by comparing this enol, **3**, with that of acetaldehyde, **9**, for which pK_a^E = 10.50.[10] Further comparison of acetaldehyde enol (**9**) with that of phenylacetaldehyde, **10** (pK_a^E = 9.46),[19] implies that only 1.0 pK unit of this difference is due to the phenyl group. Assessing the effect of the α-hydroxyl group is more difficult, but comparison of the acid strengths of several alcohols with the corresponding *gem*-diols suggests that this contributes *ca.* 2 pK units.[37] That leaves 6.5 pK units for the acidifying effect of the β-cyano group.



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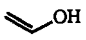

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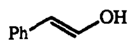

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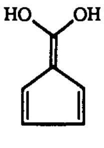
The enol of cyclopentadienecarboxylic acid (**11**) has also been found to be a strong acid, with pK_a^E = 1.3,[3] as have the enols of several indenecarboxylic acids (**12**,**13**; R = SO_3^-, SO_3Ph) with pK_a^E = 0.4–1.3.[6b] The acidity of these substances can be attributed to delocalization of the enolate negative charge into the cyclopentadienyl ring, which gives this ring aromatic character. The enol of mandelic acid (**14**) with pK_a^E = 6.62[4] is also considerably more acidic than the enol of acetaldehyde or phenylacetaldehyde, but it is not as acidic as the enol of α-cyano-α-phenylacetic acid; the latter difference is consistent with the expected greater acidifying effect of a cyano over a hydroxyl group, as shown, for example, in the greater acidity of cyano-substituted over hydroxy-substituted phenols.[38]



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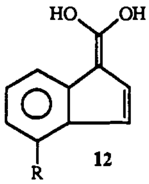

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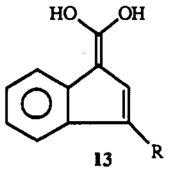

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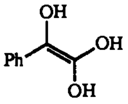

14

The strong acidifying effect of a cyano group is also apparent in the second ionization of the enol of α-cyano-α-phenylacetic acid; with p$K_a^{\prime E}$ = 8.70 it is still somewhat more acidic than the enol of phenylacetaldehyde. The difference between the first and second pK_a's of α-cyano-α-phenylacetic acid enol, ΔpK_a = 7.7, is similar to that for the enol of cyclopentadienecarboxylic acid, for which ΔpK_a = 9.1,[3] and is also not unlike that for carbonic acid, with ΔpK_a = 6.4.[38]

The present results also show the keto–enol equilibrium constant for α-cyano-α-phenylacetic acid to be remarkably high. Keto–enol equilibrium constants for simple carboxylic acids with no enol stabilizing substituents are expected to be much smaller than those for simple aldehydes and ketones, because of stabilization of the keto isomer through interaction of the carbonyl and hydroxyl groups of the carboxylic acid function. No direct measurements have so far been made, but a recent estimate of the free energy of formation of the enol of acetic acid leads to pK_E = 21 for the enolization of this acid, eq 24, in aqueous solution.[39] This is 14 pK units more than the presently obtained result for α-cyano-α-phenylacetic acid: pK_E = 7.22.

(24)

A similarly large keto–enol equilibrium constant has been reported for cyclopentadienecarboxylic acid, pK_E = 6.7,[3] whose enolization benefits from the production of an enol with a fulvenoid structure (**11**). The enol content of mandelic acid is considerably less, but at pK_E = 15.4[4] it is still considerably greater than the estimate of pK_E = 21 for acetic acid; this, of course, is due to the considerable double-bond stabilizing effects of the β-phenyl and β-hydroxyl groups in mandelic acid enol (**14**). The double bond stabilizing effect of the cyano group, D_{CN} = 2.8 kcal mol^{-1},[40] is considerably less than that of the hydroxyl group, D_{OH} = 5.4 kcal mol^{-1},[41] and on this basis the enol content of α-cyano-α-phenylacetic acid would be expected to be less than that of mandelic acid. There is, however, a large difference in the opposite direction, and this may be attributed to strong interaction of the

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(37) Stewart, R. *The Proton: Applications to Organic Chemistry*; Academic Press: New York, 1985; p 44.

(38) Jencks, W. P.; Regenstein, J. *Ionization Constants of Acids and Bases.* In *Handbook of Biochemistry Selected Data for Molecular Biology*, 2nd ed.; Sober, H. A. Ed.; Chemical Rubber Co.: Cleveland, OH, 1970; pp (J-187)–(J-226).

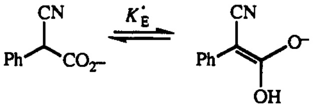
(39) Guthrie, J. P., submitted to *Can. J. Chem.*

(40) Hine, J.; Skoglund, M. J. *J. Org. Chem.* **1982**, *47*, 4766–4770.

(41) Keeffe, J. R.; Kresge, A. J. *J. Phys. Org. Chem.* **1992**, *5*, 575–580.

electron-withdrawing cyano group with the electron-supplying enolic hydroxyl groups across the double bond, which stabilizes the enol.

The keto–enol equilibrium involving singly ionized species, eq 25, with pK'_E =6.49, is somewhat more favorable toward enol

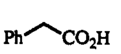


(25)

than is the equilibrium involving neutral species (pK_E = 7.22). A somewhat larger difference in the same direction has been reported for the cyclopentadienecarboxylic acid system: pK'_E = 3.3 and pK_E = 6.7.[3] As the scheme of eq 2 shows, these two equilibria are related by the acid dissociations of the carboxylic acid and enol, and pK'_E = pK_E − pK_a + pK_a^E. The more favorable keto–enol equilibrium involving the charged species is thus a direct consequence of the fact that the enol is a stronger acid than the carboxylic acid.

In the mandelic acid system, the enol, with pK_a^E = 6.62, is a weaker acid than the carboxylic acid (pK_a = 3.41),[38] and the keto–enol equilibrium involving charged species is consequently less favorable toward enol than is the equilibrium involving neutral species. This difference between the mandelic acid and α-cyano-α-phenylacetic acid systems may be understood in terms of the differential effects of the hydroxyl and cyano groups on the various species involved in these equilibria. The effects will be stronger in the charged system than in the neutral system, and in the charged system they will be stronger in the enolate ion, where the groups interact with the negative charge through a double bond, than in the carboxylate ion, where the interaction is through a single bond. Then, because the hydroxyl group is electron donating, it will destabilize the enolate ion making the keto–enol equilibrium less favorable in the charged system than in the neutral system, whereas the cyano group, because it is electron-withdrawing will have the opposite effect. The difference in the cyclopentadienecarboxylic acid system will parallel that for α-cyano-α-phenylacetic acid because the cyclopentadienyl group is electron-stabilizing as well.

The present results also show the α-cyano-α-phenylacetate ion to be an unusually strong carbon acid. The acidity constant determined here, p$K_a^{\prime K}$ = 15.19, is 15 pK units less than p$K_a^{\prime K}$ = 30.2 reportedfor α-phenylacetate ion, **14**, the analog without a cyano group, in a solvent consisting of 20% hexamethylphosphoramide and 80% tetrahydrofuran.[42] This difference again attests to the remarkably strong acid strengthening effect of a cyano group. A similar difference of 14.5 pK units exists between the acidity constants of acetophenone, **15** (pK_a = 24.7), and α-cyanoacetopheone, **16** (pK_a = 10.2), in dimethyl sulfoxide solution.[43]



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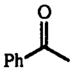

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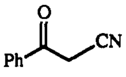

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Supplementary Material Available: Tables S1–S5 of rate data (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(42) Renaud, P.; Fox, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 5705–5709.
(43) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.