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# The Mandelamide Keto−Enol System in Aqueous Solution. Generation of the Enol by Hydration of Phenylcarbamoylcarbene

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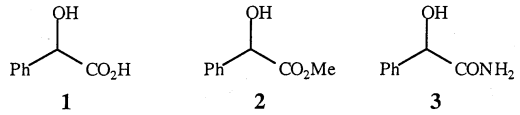
***Abstract:*** Flash photolysis of diazophenylacetamide in aqueous solution produced phenylcarbamoylcarbene, whose hydration generated a transient species that was identified as the enol isomer of mandelamide. This assignment is based on product identification and the shape of the rate profile for decay of the enol transient, through ketonization to its carbonyl isomer, as well as by the form of acid−base catalysis of and solvent isotope effects on the decay reaction. Rates of enolization of mandelamide were also determined, by monitoring hydrogen exchange at its benzylic position, and these, in combination with the ketonization rate measurements, gave the keto−enol equilibrium constant $pK_E = 15.88$, the acidity constant of the enol ionizing as an oxygen acid, $pQ_a^E = 8.40$, and the acidity constant of the amide ionizing as a carbon acid $pQ_a^K = 24.29$. (These acidity constants are *concentration quotients* applicable at ionic strength = 0.10 M.) These results show the enol content and carbon acid strength of mandelamide, like those of mandelic acid and methyl mandelate, to be orders of magnitude less than those of simple aldehydes and ketones; this difference can be attributed to resonance stabilization of the keto isomers of mandelic acid and its ester and amide derivatives, through electron delocalization into their carbonyl groups from the oxygen and nitrogen substituents adjacent to these groups. The enol of mandelamide, on the other hand, again like the enols of mandelic acid and methyl mandelate, is a substantially stronger acid than the enols of simple aldehydes and ketones. This difference can be attributed to the electronegative nature of the oxygen and nitrogen substituents geminal to the enol hydroxyl group in the enols of mandelic acid and its derivatives; in support of this, the acidity constants of these enols correlate well with field substituent constants of these geminal groups.

The enol isomers and enolate ions of simple carboxylic acids, esters, and amides play prominent roles in many important chemical and biological reactions. Such enols and enolate ions, however, are also very unstable, both kinetically and thermodynamically,[1] and relatively little directly obtained information about these elusive, short-lived substances has consequently become available. This stands in striking contrast to the remarkable expansion in the chemistry of enols and enolate ions of simple aldehydes and ketones that has taken place over the past two decades.[2] The difference is undoubtedly due to the much greater instability of carboxylic acid enols over the already quite unstable enols of simple aldehydes and ketones.

Flash photolytic fast reaction techniques have proven to be especially useful in studying unstable short-lived species, and we have employed such techniques to investigate the enol and enolate ions of mandelic acid, **1**,[3] and methyl mandelate, **2**.[4]




**1** **2** **3**

We now add to that a corresponding study of the mandelamide, **3**, keto−enol/enolate ion system.

We generated the enol of mandelamide by photolysis of diazophenylacetamide, **4**. Irradiation of a diazocarbonyl compound such as this generally gives a Wolff rearrangement producing a ketene, **5**, which, in aqueous solution, would become hydrated to a carboxylic acid, in the present case to phenylglycine, **6**, eq 1. However, when the migratory aptitude

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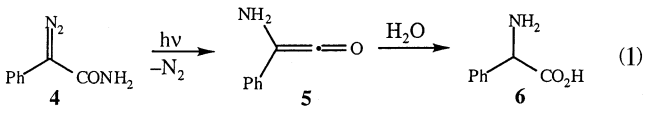
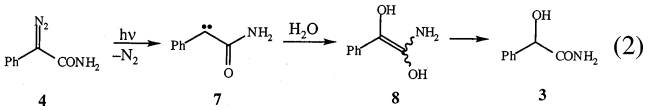
(1) Hegarty, A. F.; O'Neil, P. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990; Chapter 10. Kresge, A. J. *Chem. Soc. Rev.* **1996**, *25*, 275−280.
(2) See, for example: *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990.
(3) Chiang, Y.; Kresge, A. J.; Popik, V. V.; Schepp, N. P. *J. Am. Chem. Soc.* **1997**, *119*, 10203−10212.
(4) Chiang, Y.; Kresge, A. J.; Schepp, N. P.; Xie, R.-Q. *J. Org. Chem.* **2000**, *65*, 1175−1180.

of the potentially migrating group is poor, another process intervenes,[5] in which loss of nitrogen gives an α-carbonylcar-



(1)

bene, **7**, whose hydration provides an enol, **8**, that in this case would be the enol of mandelamide, **3**, eq 2. We have found



(2)

that mandelamide is in fact the major product formed by flash photolysis of diazophenylacetamide; some phenylglycine is produced as well, but this is made in very minor amounts.

## Experimental Section

**Materials.** Diazophenylacetamide (**4**) was prepared by a Bamford–Stevens reaction[6] on benzoylformamide[7] by converting the latter to its tosyl hydrazone and then cleaving the hydrazone with sodium hydroxide. The product, a bright yellow solid, mp = 129–130 °C, was obtained in 80% yield. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$/ppm = 7.46–7.24 (m, 5H), 5.41 (bs, 2H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$/ppm = 167.3, 129.8, 127.8, 127.4, 126.5, 64.7. HRMS: $m/e$ = 161.0603 (calcd), 161.0591 (found).

All other materials were best available commercial grades.

**Kinetics, Flash Photolysis.** Flash photolytic rate measurements were made using conventional (flash lamp)[8] and laser ($\lambda$ = 248 nm)[9] systems that have already been described.[8,9] Substrate concentrations in the solutions upon which the rate measurements were made were on the order of $10^{-4}$ M, and the temperature of these solutions during the rate measurements was controlled at 25.0 ± 0.05 °C. Reactions were monitored by following UV light absorbance changes, for the carbonylcarbene hydration reaction at $\lambda$ = 340 nm (absorbance decay in $HClO_4$ solutions and in $CH_3CO_2H$ and $H_2PO_4$ buffers; absorbance rise in $NH_4^+$ buffers and NaOH solutions) and for the enol ketonization reaction at $\lambda$ = 300–310 nm (absorbance decay in all solutions examined). Observed first-order rate constants were obtained by least-squares fitting of a single exponential function when rates of the carbonylcarbene hydration and enol ketonization reaction were sufficiently different, and by least-squares fitting of a double exponential function when they were not.

**Kinetics, Hydrogen Exchange.** Rates of deuterium incorporation from $D_2O$ solvent into the benzylic carbon–hydrogen bond of mandelamide were measured by monitoring the decrease in intensity of the benzylic $^1$H NMR signal of mandelamide at $\delta$ = 5.13 ppm. In the sodium hydroxide solutions used for this purpose, hydrolysis of the amide function of mandelamide also took place, and, to enable determination of hydrogen exchange rate constants from observed rate constants for loss of the mandelamide NMR signal, the $^1$H NMR signal of mandelate ion produced by hydrolysis at $\delta$ = 4.93 ppm was monitored as well. Measurements were made at 25 °C using a Varian Unity Inova 500 NMR spectrometer operating at 500 MHz. A relaxation delay between pulses of 57 s was used, which is 10-fold greater than the measured relaxation times of the benzylic protons of mandelamide and mandelate ion; 60 transients were usually collected. The baselines of the NMR spectra were subjected to a first-order drift correction before determination of integrated peak areas, and areas were measured relative to an internal tetramethylammonium ion standard.

The mandelamide hydrolysis reaction consumes hydroxide ion, and, to minimize the effect of this on hydroxide ion concentrations of the hydrogen exchange reaction mixtures, mandelamide substrate was always supplied at initial concentrations at least 10 times less than hydroxide ion concentrations. For sodium hydroxide concentrations of 0.08 M and greater, this was achieved by using an initial mandelamide concentration of 0.008 M and performing the NMR analysis directly on these reaction mixtures. For sodium hydroxide concentrations less than 0.08 M, reaction mixtures with initial mandelamide concentrations of 0.0008 M were used, and samples of these mixtures were concentrated before NMR spectra were taken. In applying this latter method, 5 mL aliquots of reaction mixture were withdrawn at appropriate reaction times, their pD was adjusted to ca. 6 with 2 M $CH_3CO_2D$ in $D_2O$ solution, and these samples were then concentrated under reduced pressure to a volume of ca. 0.7 mL. These concentrates were either subjected to NMR analysis directly or they were kept frozen until NMR analysis was performed a few days later. Control experiments showed that such frozen storage had no significant effect on the NMR analysis and also that the two kinetic methods produced identical results.

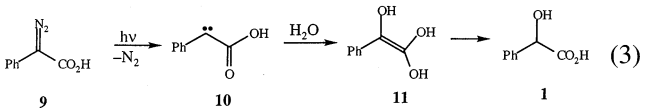
Observed first-order rate constants were determined from slopes of semilogarithmic plots of NMR peak area versus time; such plots were accurately linear for at least two reaction halftimes.

**Product Analysis.** Product analyses were conducted by HPLC using a Varian Vista 5500 instrument with a Novopak $C_{18}$ reverse-phase column and methanol–water (30/70 = v/v) as the eluent. Reaction solutions, containing diazophenylacetamide substrate at concentrations similar to those used for the rate measurements, were subjected to a single flash from our conventional flash photolysis system,[8] and products were identified by comparing retention times and UV spectra with those of authentic samples.

## Results

**Product Identification.** HPLC product analyses were conducted in wholly aqueous $1 \times 10^{-4}$ M $HClO_4$ and $1 \times 10^{-3}$ NaOH solutions and also in $H_2PO_4^-$ ($[H^+] = 2 \times 10^{-7}$ M) and $(CH_2OH)_3CNH_3^+$ ($[H^+] = 8 \times 10^{-9}$ M) buffers. These analyses showed that a single pulse from our conventional flash photolysis apparatus converted an average of 27% of the diazophenylacetamide substrate into products. Of the 27%, 25% was mandelamide (**3**) and 2% was phenylglycine (**6**); there were also trace amounts of other unidentified substances.

These results show that the major process by far occurring in the present flash photolysis study is that shown in eq 2, involving carbonylcarbene formation and hydration followed by enol ketonization. A very minor amount of the photo-Wolff reaction of eq 1, however, does take place as well. This is similar to the results obtained for flash photolysis of diazophenylacetic acid, **9**, where formation of phenylcarboxycarbene, **10**, and hydration of that to mandelic acid enol, **11**, followed by ketonization of the enol, eq 3, was found to be the principal reaction path, with only a minor amount of the corresponding photo-Wolff process taking place.[3] Flash pho-



(3)

tolysis of the methyl ester of diazophenylacetic acid, **12**, on the other hand, gave only the carbonylcarbene route leading to

(5) Chiang, Y.; Jefferson, E. A.; Kresge, A. J.; Popik, V. V.; Xie, R.-Q. *J. Phys. Org. Chem.* **1998**, *11*, 610–613.
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(8) Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000–4009.
(9) Andraos, J.; Chiang, Y.; Huang, C.-G.; Kresge, A. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1993**, *115*, 10605–10610.

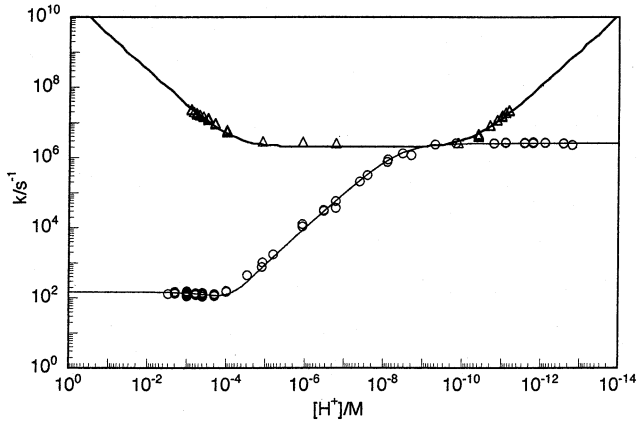
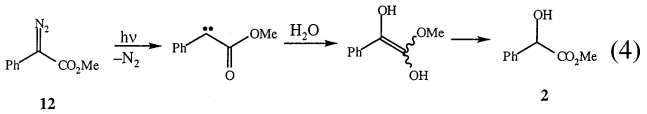



***Figure 1.*** Rate profiles for the hydration of phenylcarbamoylcarbene (Δ) and ketonization of mandelamide enol (O) in aqueous solution at 25 °C.

methyl mandelate (**2**) shown in eq 4, with no detectable amount of photo-Wolff reaction.[4]



**12** **2** (4)

**Carbonylcarbene Hydration.** Flash photolysis of diazophenylacetamide produced biphasic light absorbance changes, consistent with the presence of two reactive intermediates in the reaction scheme, eq 2, required by formation of mandelamide as the principal reaction product. The faster of these absorbance changes, with lifetimes in the submicrosecond range, may be assigned, in analogy to previous studies,[3,4] to hydration of phenylcarbomaylcarbene, **7**, itself formed within the laser pulse. This hydration produces mandelamide enol, **8**, whose ketonization gives the second somewhat slower absorbance change. Rates of the faster carbene hydration reaction were measured in wholly aqueous $HClO_4$ and NaOH solutions and in $CH_3CO_2H$, $H_2PO_4^-$ and $NH_4^+$ buffers. For each kind of solution, a range of concentrations was employed, and replicate measurements were made at each concentration; the ionic strength of all reaction solutions was maintained at 0.10 M by adding sodium perchlorate as required. These data are summarized in Tables S1−S3.[10]

The measurements in buffers were done in series of solutions of constant buffer ratio and constant ionic strength but varying total buffer concentration; the hydrogen ion concentrations along a given buffer series therefore remained constant. Observed first-order rate constants within a buffer series were found to increase linearly with increasing buffer concentration, and the data were therefore analyzed by least-squares fitting of the buffer dilution expression shown in eq 5. The zero-buffer-concentration intercepts obtained in this way, $k_{int}$, together with the rate

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

constants measured in $HClO_4$ and NaOH solutions, are displayed as the upper rate profile of Figure 1. Hydrogen ion concentrations of the buffer solutions needed for this purpose were obtained by calculation using literature values of the buffer acidity constants and activity coefficients recommended by Bates.[11]

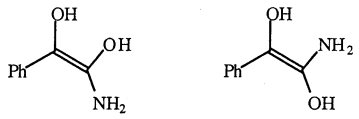
This rate profile, just as those for the hydration of carbonylcarbenes derived from diazophenylacetic acid, eq 3, and methyl diazophenylacetate, eq 4, shows acid-catalyzed, uncatalyzed, and base-catalyzed portions. It may therefore be analyzed using the simple rate law shown as eq 6. Least-squares fitting of this expression gave $k_{H^+} = (2.97 \pm 0.09) \times 10^{10}$ $M^{-1}$ $s^{-1}$,

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

$k_o = (2.11 \pm 0.13) \times 10^6$ $s^{-1}$, and $k_{HO^-} = (7.74 \pm 0.23) \times 10^9$ $M^{-1}$ $s^{-1}$. These results are numerically similar to those obtained for previous carbonylcarbene hydrations,[3,4] which reinforces assignment of the present process to the phenylcarbamoylcarbene hydration reaction.

**Enol Ketonization, Rate Profile.** Rates of the slower absorbance change produced by flash photolysis of diazophenylacetamide, attributable to ketonization of mandelamide enol (eq 2), were measured in wholly aqueous $HClO_4$ and NaOH solutions, as well as in $CH_3CO_2H$, $H_2PO_4^-$, $(CH_2OH)_3CNH_3^+$, and $NH_4^+$ buffers. A range of concentrations for each kind of solution was once again employed, replicate measurements were made, and the ionic strength was maintained constant at 0.10 M. These data are summarized in Tables S4−S6.[10]

Mandelamide enol can exist in two stereoisomeric forms as (*Z*)-1-amino-2-hydroxy-2-phenylethenol, **13**, or (*E*)-1-amino-2-hydroxy-2-phenylethenol, **14**. These two isomers would pre-



**13** **14**

sumably ketonize at somewhat different rates, leading to deviations from simple first-order enol decay. No such complications were observed, which suggests that only one enol stereoisomer was formed in the carbonylcarbene hydration reaction. We have no information, however, that allows us to decide which isomer that is.

The measurements in buffers were again done in series of solutions of constant buffer ratio but varying total buffer concentration, and observed first-order rate constants along a buffer series again increased linearly with increasing buffer concentration. The data were therefore once more analyzed by least-squares fitting of eq 5. The zero-buffer-concentration intercepts obtained by this treatment, together with the rate constants measured in $HClO_4$ and NaOH solutions, are displayed as the lower rate profile of Figure 1.

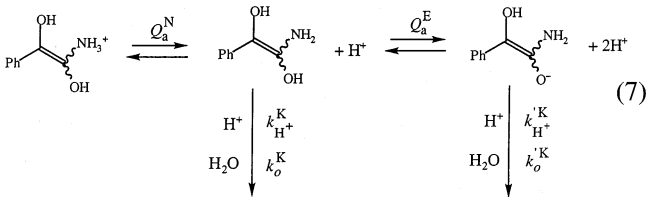
This rate profile is similar to those observed before for ketonization of the enols of mandelic acid[3] and methyl mandelate.[4] Like those rate profiles, it may be interpreted in terms of the known reaction mechanism for enol ketonization involving rate-determining proton transfer from any available acid to the $\beta$-carbon atom of the enol or its enolate ion.[12] Because this profile refers to reaction through solvent related species in aqueous solution, the available acids will be water and the

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

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

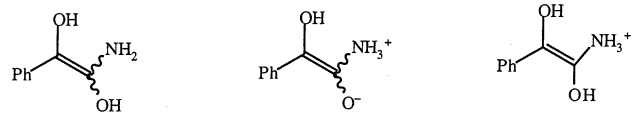
(12) Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990; Chapter 7.

hydronium ion, written here as $H^+$. The present enol, however, unlike those of mandelic acid and methyl mandelate, contains an amino group which might be protonated in acid solution, thus introducing another enol species. The resulting reaction scheme is shown in eq 7.



(7)

The presence of the amino group in the present enol also raises the question of whether the formally neutral enol form is the uncharged species **8** or the zwitterion **15**. Insight into this



**8** **15** **16**

matter can be obtained through knowledge of the relative acid strengths of the ammonio and hydroxyl groups in the fully protonated enol form, **16**: if the ammonio group is the stronger acid, its ionization will occur in preference to that of the hydroxyl group, and the neutral enol form **8** will predominate; if, on the other hand, the hydroxyl group is the stronger acid, its ionization will occur, and the zwitterionic form **15** will predominate. Simple ammonium ions with $pK_a \cong 10$ are considerably more acidic than simple alcohols with $pK_a \cong 16$. This difference, however, will not carry over intact to the ammonio and hydroxyl groups of **16** because each of these groups in **16** has a (different) geminal substituent that will modify its acid strength.

These acid strength modifying effects can be estimated using a Hammett-type $\sigma-\rho$ relationship. A critical analysis of the use of such relationships to correlate geminal substituent effects on the $pK_a$'s of simple ammonium ions and alcohols concluded that $\rho = 8.4$ for both kinds of acid and that inductive sigma constants, $\sigma_I$, work well for this purpose.[13] Using $\sigma_I(NH_3^+) = 0.60$ and $\sigma_I(OH) = 0.25$[14] then gives $\Delta pK_a = 5.0$ as the acid strengthening effect of the geminal ammonio group on the acidity of the hydroxyl group of **16** and $\Delta pK_a = 2.1$ as the acid strengthening effect of the geminal hydroxyl group on the acidity of the ammonio group of **16**. These modifying effects reduce the 6 p$K$ unit difference between the acid strength of simple ammonium ions and alcohols noted above, but they still leave the ammonio group of **16** a stronger acid than its hydroxyl group by 3 p$K$ units. This difference would seem to be large enough to compensate for any deficiency in the method used to estimate the modifying effects and to leave little doubt that the uncharged species **8** and not the zwitterion **15** is the predominant form of the neutral enol.

A $\sigma-\rho$ relationship that successfully correlates rates of protonation of a large number of carbon−carbon double bonds[15] predicts that $\beta$-carbon protonation of mandelamide enol by $H^+$ should occur with a rate constant $10^4$ times greater than that for the enol of mandelic acid. This gives the mandelamide enol reaction the rate constant $k^K_{H^+} = 9 \times 10^7\ M^{-1}\ s^{-1}$, which would provide the rate profile for this reaction with an acid-catalyzed component that should be clearly visible at acidities of $[H^+] = 10^{-5}$ M and higher. Figure 1 shows that no such component was observed, and that means that enol was being shifted from its reactive neutral form (**8**) into some unreactive species. A good candidate for this unreactive species is of course the amine-protonated form **16**. This interpretation then assigns the "uncatalyzed" reaction plateau observed in the acid region of the rate profile to ketonization beginning with amine-protonated enol as the initial state. This species first ionizes to give neutral enol and $H^+$, and that is then followed by rate-determining $\beta$-carbon of the enol by $H^+$. Because $H^+$ is first produced in a preequilibrium and is then used up in the rate-determining step, the overall process is independent of $[H^+]$ and has the appearance of an uncatalyzed reaction.

On the low acid side of this acid-region plateau, there is a diagonal rising section in which neutral enol is the initial state. Ketonization here occurs by equilibrium ionization of the hydroxyl group of the enol to give the much more reactive enolate ion,[16] followed by rate-determining $\beta$-carbon protonation of that by $H_2O$. Because the $H^+$ produced by the ionization is now not used up in the rate-determining step, the overall process is inversely proportional to $[H^+]$, giving an apparent hydroxide ion catalysis. Finally, at sufficiently low acidities, the position of the enol to enolate ionization equilibrium shifts to the ion side, and the advantage of converting a less reactive to a more reactive substrate species is lost. The result is simple protonation of the enolate ion by $H_2O$, giving the final horizontal profile segment.

The rate law that applies to this reaction scheme is shown in eq 8, whose rate and equilibrium constants are defined by eq 7.

$$k_{obs} = \frac{k^K_{H^+} Q^N_a [H^+]^2 + k'^K_o Q^N_a Q^E_a}{[H^+]^2 + Q^N_a [H^+] + Q^N_a Q^E_a} \qquad (8)$$

Least-squares fitting of this expression gave $k^K_{H^+} = (1.74 \pm 0.56) \times 10^6\ M^{-1}\ s^{-1}$, $k'^K_o = (2.56 \pm 0.06) \times 10^6\ s^{-1}$, $Q^N_a = (8.49 \pm 3.13) \times 10^{-5}$, $pQ^N_a = 4.07 \pm 0.16$,[17] and $Q^E_a = (3.95 \pm 0.18) \times 10^{-9}$ M, $pQ^E_a = 8.40 \pm 0.02$.[17] Because $k^K_{H^+}$ and $Q^N_a$ are somewhat correlated,[18] they are not well determined and have sizable associated uncertainties; $k'^K_o$ and $Q^E_a$, on the other hand, are well determined.

**Enol Ketonization, Buffer Catalysis.** The slopes of the buffer dilution plots $k_{buff}$, obtained by least-squares fitting of eq 5, were separated into their general acid, $k_{HA}$, and general base, $k_B$, components with the aid of eq 9, in which $f_A$ is the fraction of buffer present in the acid form.[19] Least-squares fitting

$$k_{buff} = k_B + (k_{HA} - k_B) f_A \qquad (9)$$

of this expression gave results that showed general base catalysis in the $CH_3CO_2H$, $H_2PO_4^-$, and $(CH_2OH)_3CNH_3^+$ buffers and

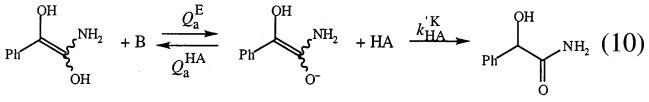
(13) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436−1449.
(14) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley-Interscience: New York, 1975; p 98.
(15) Csizmadia, V. M.; Koshy, K. M.; Lau, K. C. M.; McClelland, R. A.; Nowlan, V. J.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 974−979.
(16) Pruszynski, P.; Chiang, Y.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Phys. Chem.* **1986**, *90*, 3760−3766. Chiang, Y.; Kresge, A. J.; Santaballa, J. A.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 5506−5510.
(17) This is a concentration acidity constant applicable at ionic strength = 0.10 M.

***Table 1.*** General Acid Catalytic Coefficients for the Ketonization of Mandelamide Enol in Aqueous Solution at 25 °C[a]

| HA | $k'^{K}_{HA}/M^{-1}\,s^{-1}$ |
|---|---|
| $CH_3CO_2H$ | $7.10 \times 10^8$ |
| $H_2PO_4^-$ | $3.32 \times 10^8$ |
| $(CH_2OH)_3CNH_3^+$ | $1.40 \times 10^8$ |
| $NH_4^+$ | $4.37 \times 10^7$ |

[a] Ionic strength = 0.10 M.

general acid catalysis in the $NH_4^+$ buffers. These forms of buffer catalysis are consistent with the fact that the $H^+$ concentrations of the $CH_3CO_2H$, $H_2PO_4^-$, and $(CH_2OH)_3CNH_3^+$ buffers lay in the region of the ketonization rate profile showing apparent hydroxide ion catalysis, whereas those of the $NH_4^+$ buffers lay in the final plateau profile region. The general base catalytic coefficients may therefore be attributed to an analogue of the apparent hydroxide-ion-catalyzed process, that is, to general base-assisted ionization of the enol to enolate ion followed by rate-determining carbon protonation of enolate by the general base conjugate acid, eq 10. The general acid catalytic coefficient



(10)

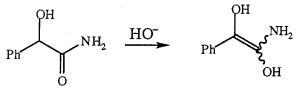
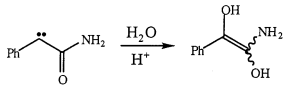
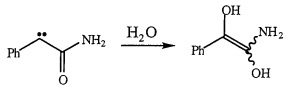
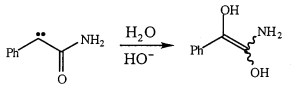
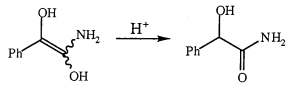
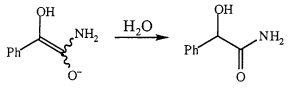
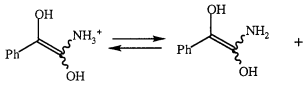
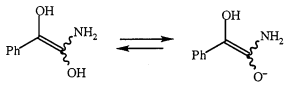
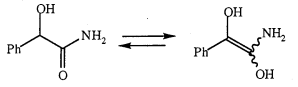
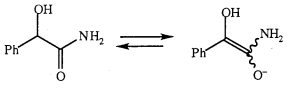
obtained from the $NH_4^+$ buffer data, on the other hand, may be attributed to direct carbon protonation of the enolate ion by $NH_4^+$.

The rate law for the reaction route of eq 10 leads to the relationship $k'^{K}_{HA} = k_B Q_a^{HA}/Q_a^E$, in which $k_B$ is the general base catalytic coefficient obtained by applying eq 9. Values of $k'^{K}_{HA}$ obtained in this way are summarized in Table 1. It may be seen that $k'^{K}_{HA}$ diminishes progressively with diminishing general acid strength, as is expected for a rate-determining proton transfer reaction. Although the acids are limited in number and of several different charge types, they nevertheless give a fairly good Brönsted relation with a low exponent, $\alpha = 0.33 \pm 0.04$, as is expected for such very fast reactions. This provides good support for the molecular interpretation of the experimental data given.

**Enol Ketonization, Isotope Effects.** Further support for this interpretation is given by solvent isotope effects on the ketonization reaction. These were provided by rate measurements made in the acidic and basic plateau regions of the ketonization rate profile using $D_2O$ solutions of $DClO_4$ and NaOD. These data are summarized in Tables S4 and S5.[10]

The measurements in basic solution gave the solvent isotope effect $k_{H_2O}/k_{D_2O} = 5.88 \pm 0.13$. This is similar to isotope effects in this profile region determined for the ketonization of mandelic acid enol ($k_{H_2O}/k_{D_2O} = 6.9$)[3] and methyl mandelate enol ($k_{H_2O}/k_{D_2O} = 7.7$).[4] The large values of these effects are as expected for the molecular mechanism assigned to this part of the rate profile, i.e., carbon protonation of an enolate ion by a water molecule. The primary kinetic isotope effect on such a process is augmented by a secondary effect in the normal ($k_H/k_D > 1$) direction, generated in the solvation shell of the hydroxide ion being formed by proton donation from a water molecule.[20]

***Table 2.*** Summary of Rate and Equilibrium Constants[a]

| Process | Constant |
|---|---|
|  | $k^E_{HO^-} = 8.32 \times 10^{-5}\ M^{-1}\,s^{-1}$ |
|  | $k_{H^+} = 2.97 \times 10^{10}\ M^{-1}\,s^{-1}$ |
|  | $k_o = 2.11 \times 10^6\ s^{-1}$ |
|  | $k_{HO^-} = 7.74 \times 10^9\ M^{-1}\,s^{-1}$ |
|  | $k^K_{H^+} = 1.7 \times 10^6\ M^{-1}\,s^{-1}$ |
|  | $k'^{K}_{o} = 2.56 \times 10^6\ s^{-1}$ |
|  | $Q_a^N = 8.5 \times 10^{-5}$ M, p$Q_a^N$ = 4.1 |
|  | $Q_a^E = 3.95 \times 10^{-9}$ M, p$Q_a^E$ = 8.40 |
|  | $K_E = 1.31 \times 10^{-16}$, p$K_E$ = 15.88 |
|  | $Q_a^K = 5.16 \times 10^{-25}$ M, p$Q_a^K$ = 24.29 |

[a] 25 °C; ionic strength = 0.10 M.

The measurements in acidic solutions gave the solvent isotope effect $k_{H_2O}/k_{D_2O} = 6.71 \pm 0.39$. The large value of this isotope effect is also consistent with the molecular mechanism assigned to this region of the rate profile, i.e., acid ionization of the amine-protonated enol followed by carbon protonation of the neutral enol by a hydronium ion. That makes this isotope effect a composite ratio consisting of an isotope effect on the acid ionization constant $Q_a^N$ times that on the rate constant $k^K_{H^+}$. Solvent isotope effects on the ionization of acids with acid strengths comparable to that of the present substance are on the order of 3,[21] and application of that to the observed ratio leaves $k^K_{H^+}/k^K_{D^+} = 2.2$. This is a reasonable value for such an

(18) The numerical value of the product $k^K_{H^+} Q_a^N$ is fixed by that of the acid-region rate profile plateau. Separation of this product into its constituent parts requires the acid-region plateau to be connected to the upward sloping diagonal which follows by another downward sloping diagonal segment, but such an additional diagonal segment can barely be discerned.

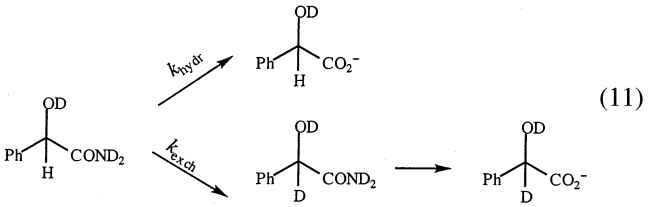
(19) Values of $k_{buff}$, before analysis by eq 9, were adjusted to reaction through either wholly ionized or wholly un-ionized enol, as required.

(20) Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, Chapter 4.

effect inasmuch as isotope effects on hydron transfer from the hydronium ion have an inverse secondary component and consequently are small.[22]

**Amide Enolization.** Rates of enolization of mandelamide were determined by measuring rates of hydrogen exchange at the benzylic position of the amide. This was done by monitoring the reduction of the $^1$H NMR signal of the mandelamide benzyl proton at $\delta = 5.13$ ppm as this proton was replaced by deuterium incorporated from a $D_2O$ solvent. Measurements were made in KOD solutions over the concentration range [KOD] = 0.01−0.08 M at a constant ionic strength of 0.10 M and at [KOD] = 0.08 and 0.20 at a constant ionic strength of 0.20 M. The data are summarized in Table S7.[10]

In the solutions used for these measurements, hydrolysis of the amide functional group of mandelamide also occurred, eq 11, at rates comparable to those of hydrogen exchange. This




(11)

produced mandelate ion, which gave a separate $^1$H NMR signal at $\delta = 4.93$ ppm. Observed rates of loss of the mandelamide signal at $\delta = 5.13$ ppm were therefore sums of rate constants for the hydrogen exchange and amide hydrolysis reactions: $k_{obs} = k_{exch} + k_{hydr}$. As the reaction scheme of eq 11 illustrates, both exchanged and unexchanged mandelamide eventually underwent complete hydrolysis, but, whereas the exchanged substrate gave mandelate ion with deuterium at the benzylic position, unexchanged substrate gave mandelate ion with protium at this position. The fraction of observed rates due to hydrolysis, $f_{hydr}$, could therefore be ascertained by determining the amount of protium remaining at the benzylic position of the mandelate ion hydrolysis product after hydrolysis was complete. This fraction could then be used to separate observed rate constants into their constituent hydrolysis and exchange parts: $k_{hydr} = f_{hydr}\,k_{obs}$ and $k_{exch} = (1 - f_{hydr})k_{obs}$.

Values of $f_{hydr}$ were obtained by comparing the areas of the benzylic, $A_{bz}$, and aromatic, $A_{ar}$, $^1$H NMR signals of mandelate ion obtained after 10 hydrolysis halftimes: $f_{hydr} = A_{bz}/(A_{ar}/5)$; the factor 5 accounts for the fact that there are 5 times as many aromatic as benzylic hydrogens. These data are also summarized in Table S7. Six determinations gave the average value $f_{hydr} = 0.500 \pm 0.005$.

Hydrogen exchange rate constants obtained in this way increased with increasing hydroxide ion concentration, as expected for exchange occurring through base-catalyzed enolization. As Figure 2 shows, however, the relationship between $k_{exch}$ and [$DO^-$] was not linear, but rather showed impending saturation of hydroxide ion catalysis at the higher values of [$DO^-$] employed.[23] Such behavior is consistent with a hydroxide-ion-assisted, rapid equilibrium ionization of a weakly acidic group of the substrate other than its benzylic hydrogen: such

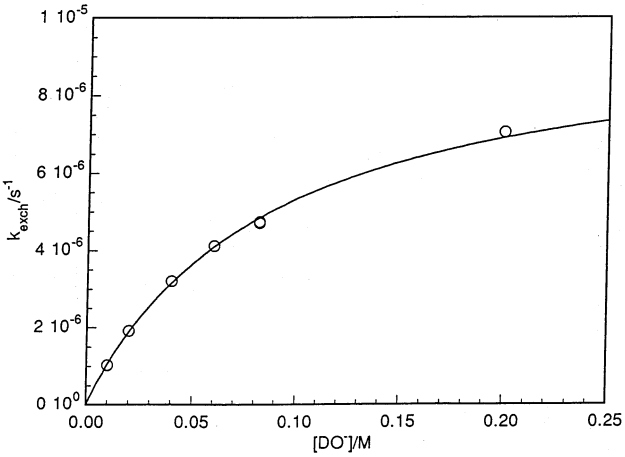



***Figure 2.*** Relationship between deuterioxide ion concentration and rates of incorporation of deuterium into the benzylic position of mandelamide in $D_2O$ solutions of KOD at 25 °C.

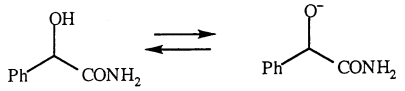
ionization would put negative charge on the substrate and thereby inhibit the negative-charge-forming enolization reaction. The reaction scheme that applies to such a situation is shown in eq 12, and its rate law is given by eq 13; $K_b$ is the basicity constant of this inhibiting group, and $k^E_{DO^-}$ is the deuterioxide

$$S^- + D_2O \overset{K_b}{\rightleftharpoons} SD + DO^- \xrightarrow{k^E_{DO^-}} \text{enol} \qquad (12)$$

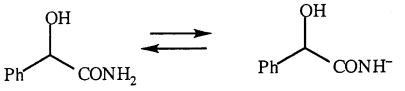
$$k_{exch} = k^E_{DO^-} K_b[DO^-]/(K_b + [DO^-]) \qquad (13)$$

ion catalytic coefficient for the enolization reaction. Least-squares fitting of this expression gave $K_b = (8.41 \pm 0.38) \times 10^{-2}$ M[24] and $k^E_{DO^-} = (1.17 \pm 0.02) \times 10^{-4}$ $M^{-1}$ $s^{-1}$. These parameters were used to draw the correlation line shown in Figure 2; it may be seen that the experimental data fit this reaction scheme well.

This inhibition of hydroxide-ion-catalyzed enolization could be produced by either ionization of the benzylic hydroxyl group of mandelamide, eq 14, or ionization of its amide group, eq 15.




(14)




(15)

Some insight into which of these it is can be obtained through estimates of the acidity constants of the two groups. Use of a $\sigma-\rho$ relationship that correlates acidity constants of secondary

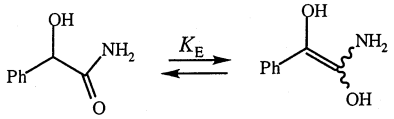
(21) Laughton, P. M.; Robertson, R. E. In *Solute−Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; M. Dekker: New York, 1969; Chapter 7.
(22) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228−7233.
(23) To better define this saturation, a set of measurements was made at [$DO^-$] = 0.20 M. This required an ionic strength, 0.20 M, greater than that, 0.10 M, of the more dilute KOD solutions employed, but control experiments, done at [$DO^-$] = 0.082 M with ionic strength = 0.10 and 0.20 M, showed that this difference had no significant effect on measured rate constants.
(24) This, strictly speaking, is a concentration quotient, $Q_b$. It is likely, however, that the activity coefficients of the $S^-$ and $DO^-$ species of eq 12 are similar, and, because these species appear on opposite sides of the equilibrium equation, their activity coefficients will cancel out of the expression for the thermodynamic basicity constant $K_b$; $Q_b$ is therefore likely to be a good surrogate for $K_b$.

alcohols[25] gives $pK_a = 12.5$ for the benzylic hydroxyl group. No such correlation appears to be available for the acidity constants of amide N−H bonds, but the $pK_a$ of acetamide is given as 15.1,[26] and, on the assumption that the difference between this value and that for mandelamide is the same as the $pK_a$ difference for the carboxylic acid groups of acetic acid and mandelic acid, $pK_a = 13.8$ may be estimated for the N−H bond of mandelamide.

These estimates predict that the alcoholic hydroxyl group of mandelamide is more acidic than is its amide N−H bond, which suggests that it is ionization of the hydroxyl group that produces inhibition of hydroxide-ion-catalyzed enolization of mandelamide. This conclusion is supported by reasonably good agreement between the predicted $pK_a$ of this group and the $pK_a$ that can be estimated from the basicity constant, $K_b$, obtained from the present experimental results for inhibition of the enolization reaction.

This basicity constant refers to the base ionization reaction in $D_2O$ solution, and it can be converted into an acidity constant in the same medium by applying the relationship $pK_a + pK_b = pK_w$, with $pK_w = 14.87$ as the autoprotolysis constant of $D_2O$.[27] Conversion of this to an acidity constant in $H_2O$ solution requires knowledge of the solvent isotope effect on the ionization of acids as weak as the present one. Two such values are available: $(K_a)_{H_2O}/(K_a)_{D_2O} = 4.5$ for $CF_3CH_2OH$ ($pK_a = 12.4$)[28] and $(K_a)_{H_2O}/(K_a)_{D_2O} = 4.8$ for $CH_2ClCH_2OH$ ($pK_a = 14.3$).[29] These isotope effects, however, are based on a value of $pK_w$ for $D_2O$ now known to be in error, and adjustment of the results using a value of $pK_w$ free of this error[27] gives isotope effects whose average is $(K_a)_{H_2O}/(K_a)_{D_2O} = 5.2$. Application of that to the present system then gives $pK_a = 13.1$ for ionization of the hydroxyl group of mandelamide in $H_2O$ solution. This result is gratifyingly consistent with the estimate $pK_a = 12.5$.

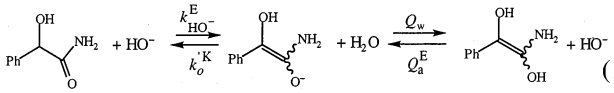
**Keto−Enol Equilibrium and Carbon Acid Acidity Constants.** The equilibrium constant, $K_E$, for mandelamide isomerizing to its enol in aqueous solution, eq 16, may be obtained from the presently determined rate constants for the enolization and ketonization reactions. To do this, the hydroxide ion



(16)

enolization catalytic coefficient must first be converted from a value for the $D_2O$ solvent in which it was measured to a value for the $H_2O$ solvent in which the ketonization rate measurements were made. Solvent isotope effects on hydroxide-ion-catalyzed reactions have no primary component, but they do have a secondary component produced by release of the water molecules solvating the hydroxide ion.[20] For the enolization of carbonyl compounds, this usually gives an inverse isotope effect of about 40%. For example, $k_{DO^-}/k_{HO^-} = 1.37$ for the enolization of acetaldehyde,[30] $k_{DO^-}/k_{HO^-} = 1.47$ for the enolization of acetone,[31] and $k_{DO^-}/k_{HO^-} = 1.39$ for the enolization of mandelate ion.[32] Application of the rounded average value $k_{DO^-}/k_{HO^-} = 1.4$ to $k^E_{DO^-} = (1.17 \pm 0.02) \times 10^{-4}\ M^{-1}\ s^{-1}$ then gives $k^E_{HO^-} = (8.32 \pm 0.16) \times 10^{-5}\ M^{-1}\ s^{-1}$ as the hydroxide ion catalytic coefficient for the enolization of mandelamide in $H_2O$ solution.

Keto−enol equilibration of mandelamide catalyzed by hydroxide ion may be formulated as shown in eq 17, and



(17)

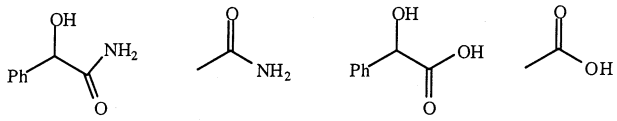
evaluation of the expression for its equilibrium constant, $K_E = (k^E_{HO^-}/k'^K_o)(Q_w/Q^E_a)$,[33] then gives $K_E = (1.31 \pm 0.07) \times 10^{-16}$, $pK_E = 15.88 \pm 0.02$.

The first part of the relationship of eq 17 includes the ionization of mandelamide as a carbon acid, and the equilibrium constant for this ionization can be evaluated as $Q^K_a = (k^E_{HO^-}/k'^K_o)Q_w = (5.16 \pm 0.17) \times 10^{-25}$ M, $pQ^K_a = 24.29 \pm 0.01$.[17]

## Discussion

The keto−enol equilibrium constant for mandelamide determined in the present study, $pK_E = 15.88$, is many orders of magnitude less than those for simple aldehydes and ketones, for example, $pK_E = 6.23$ for acetaldehyde,[8] $pK_E = 8.33$ for acetone,[34] and $pK_E = 7.96$ for acetophenone.[35] This striking difference may be attributed to resonance stabilization of the keto isomer in the amide system by interaction of its amino and carbonyl moieties; this interaction is lost in the enol isomer, and it consequently serves to increase the energy difference between the keto and enol forms making, $K_E$ as small as it is.

The keto−enol equilibrium constant for mandelamide, **3**, on the other hand, is some 3 orders of magnitude greater than that for its unsubstituted analogue, acetamide, **17**, for which the reliable estimate $pK_E = 19.2$ has recently been made.[36] This is



**3** **17** **1** **18**

similar to the difference in $K_E$ for mandelic acid, **1**, and acetic acid, **18**, noted before.[3] It can be attributed to the combined influence of the phenyl and hydroxyl groups in **3** and **1**, inasmuch as comparisons of the phenylacetaldehyde, **19**,[37] with acetaldehyde, **20**,[8] systems and the isochroman-4-one, **21**,[38] with

(25) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *$pK_a$ Predictions for Organic Acids and Bases*; Chapman and Hall: New York, 1981; p 127.
(26) Stewart, R. *The Proton: Applications to Organic Chemistry*; Academic Press: New York, 1985; p 71.
(27) Covington, A. K.; Robinson, R. A.; Bates, R. G. *J. Phys. Chem.* **1966**, *70*, 3820−3824. Gold, V.; Lowe, B. M. *J. Chem. Soc. A* **1967**, 936−943.
(28) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1959**, *81*, 1050−1053.
(29) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1959**, *81*, 2347−2352.
(30) Keeffe, J. R.; Kresge, A. J. *Can. J. Chem.* **1988**, *66*, 2440−2442.
(31) Pocker, Y. *Chem. Ind. (London)* **1959**, 1383.
(32) Pocker, Y. *Chem. Ind. (London)* **1958**, 1117−1118.
(33) $Q_w$ is the concentration quotient autoprotolysis constant of water at the ionic strength, 0.10 M, of the present measurements. It was evaluated as $Q_w = 1.59 \times 10^{-14}\ M^2$ using the thermodynamic value $K_w = 1.00 \times 10^{-14}\ M^2$ and activity coefficients recommended by Bates.[11]
(34) Chiang, Y.; Kresge, A. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1988**, *110*, 1, 3977−3980.
(35) Keeffe, J. R.; Kresge, A. J.; Toullec, J. *Can. J. Chem.* **1986**, *64*, 1224−1227.
(36) Richard, J. P.; Williams, G.; O'Donoghue, A. C.; Amyes, T. L. *J. Am. Chem. Soc.* **2002**, *124*, 2957−2968.
(37) Chiang, Y.; Kresge, A. J.; Yin, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 869−871.
(38) Chiang, Y.; Kresge, A. J.; Meng, Q.; More O'Ferrall, R. A.; Zhu, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11562−11569.

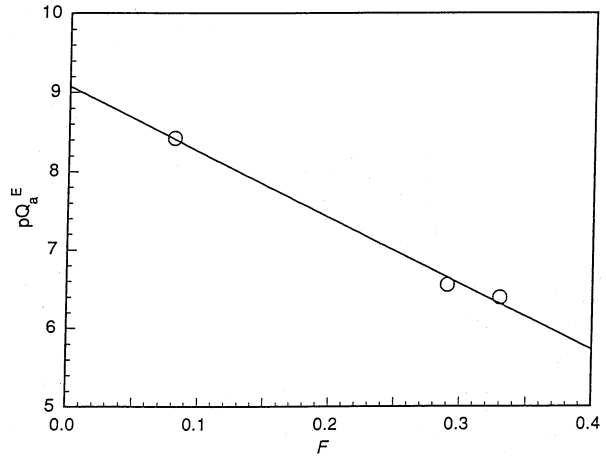
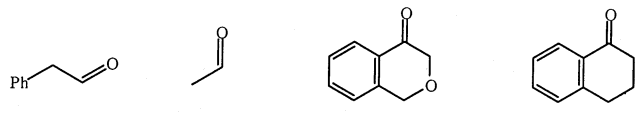



***Figure 3.*** Correlation of enol acidity constants for mandelic acid, methyl mandelate, and mandelamide using the field constant *F*.

tetralin, **22**,[38] systems show that both phenyl and oxygen substituents in the $\beta$-position raise keto−enol equilibrium constants.

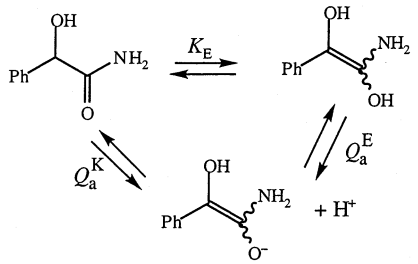



The acidity constant of mandelamide enol determined here, $pQ_a^E = 8.40$, on the other hand, is several orders of magnitude greater than those for the enols of simple aldehydes and ketones, for example, $pQ_a^E = 10.50$ for acetaldehyde enol,[8] $pQ_a^E = 10.94$ for acetone enol,[39] and $pQ_a^E = 10.40$ for acetophenone enol.[40] This difference may be attributed to the electronegative nature of the amino substituent in the mandelamide system, i.e., to its electron-withdrawing inductive or field effect: this will stabilize the negatively charged enolate ion, making the enol a stronger acid.

The hydroxyl and methoxyl substituents in the enols of mandelic acid and methyl mandelate also have electron-withdrawing inductive or field effects, and these enols are also more acidic than those of simple aldehydes and ketones. As Figure 3 shows, the acidity constants of all three of these more acidic enols are correlated well by the Swain−Lupton field constants *F* as modified by Hansch, Leo, and Taft.[41] Linear least-squares analysis gives the relationship $pQ_a^E = (9.08 \pm 0.17) - (8.38 \pm 0.66)F$.

A group of simple primary alcohols of structure $RCH_2OH$, whose $pK_a$'s were deemed to be reliable,[42] also gives a good correlation using these field constants: $pK_a = (15.68 \pm 0.19) - (8.92 \pm 1.00)F$. It is interesting that the sensitivity parameters obtained in these two correlations are not significantly different, which implies that substituent effects are transmitted as well through the $sp^2$ carbon center of enols as through the $sp^3$ carbon center of alcohols.

The acidity constant of mandelamide ionizing as a carbon acid determined here, $pQ_a^K = 24.29$, is less than those for simple aldehydes and ketones, for example, $pQ_a^K = 16.73$ for acetaldehyde,[8] $pQ_a^K = 19.27$ for acetone,[34,39] and $pQ_a^K = 18.36$ for acetophenone.[35,40] The direction of these differences is the same as that for the keto−enol equilibrium constants (vide supra), but their magnitude is smaller. This follows from the formulation of the carbon acid ionization reaction as the closing leg of a thermodynamic cycle, the other two legs of which are keto−enol equilibration and ionization of the enol as an oxygen acid, eq 18. The carbon acid ionization constant is therefore




(18)

equal to the product of keto−enol equilibrium and enol acidity constants, $Q_a^K = K_E\, Q_a^E$, and differences in $K_E\, Q_a^E$ will be equal to the product of differences in $K_E$ and $Q_a^K$. Because $K_E$ for mandelamide is less than $K_E$ for simple aldehydes and ketones by very large factors, while the differences in $Q_a^E$ are in the opposite direction by considerably smaller factors, the differences in $Q_a^K$ must be in the same direction as those for $K_E$ but by smaller though still quite large factors. This is, of course, is as observed.

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**Supporting Information Available:** Tables S1−S7 of rate data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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