Flash Photolytic Generation and Study of the Enol of 2-Hydroxy-2-cyano-*N*-methylacetamide in Aqueous Solution, Leading to an Empirically-Based Estimate of the Keto−Enol Equilibrium Constant for the Parent Unsubstituted Acetamide in That Medium

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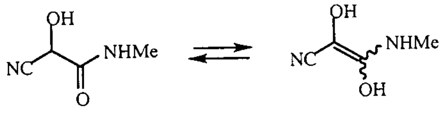
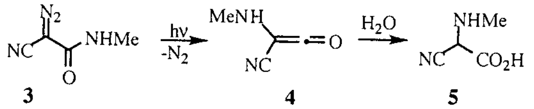
Enols of simple carboxylic acids and their ester and amide derivatives are very unstable, both kinetically and thermodynamically,[1] and little direct information on their chemistry is consequently available. Some studies have been made using very bulky[2,3] or strongly electron-withdrawing substituents[4,5] in the β-position to stabilize the enols, and a few less stable enols have been examined using fast-reaction flash photolytic techniques.[6−8] Carbon-acid ionization constants for enolate ion formation from some acetic acid esters and amino acids have also been determined by combining very slow rates of enolization with estimates of rate constants for the reverse reaction.[9] The knowledge obtained in this way, however, is still very much less than the large body of information now available on the chemistry of enol isomers of simple aldehyde and ketones.[10]

To this relatively meager knowledge we now add a study of the 2-hydroxy-2-cyano-*N*-methylacetamide, **1**, keto−enol system, eq 1. Our experimental results, coupled with data from the literature, enable us to estimate the keto−enol equilibrium constant for the parent acetamide itself and thereby supply the first empirically based evaluation of this quantity for a simple unsubstituted carboxylic acid amide.

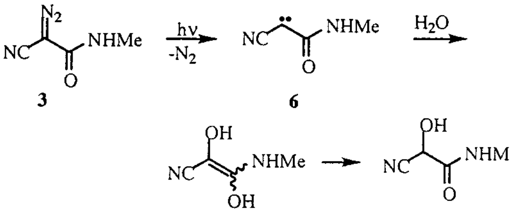


1 **2** (1)

We generated enol **2** in aqueous solution by photolysis of 2-diazo-2-cyano-*N*-methylacetamide, **3**. Irradiation of diazo compounds such as this generally results in a Wolff rearrangement producing a ketene, **4**, which in aqueous solution would be hydrated to a carboxylic acid, **5**, eq 2. When the migratory aptitude of the potentially migrating group is poor, however, another process intervenes, in which loss of nitrogen gives an α-carbonylcarbene, **6**, whose hydration provides an enol, **2**,[11] and ketonization of that produces a hydroxyamide, **1**, as the ultimate product, eq 3. These two reactions give different final products, and they can be distinguished on that basis. We found that irradiation of 2-diazo-2-cyano-*N*-methylacetamide produced a single substance whose ^{1}H- and ^{13}C NMR spectra were identical with those of an authentic sample of 2-hydroxy-2-cyano-*N*-methylacetamide that had been characterized by X-ray crystallography.[12] This showed that the process under investigation was the α-carbonylcarbene formation and hydration reaction of eq 3.



3 **4** **5** (2)



3 **6** **2** **1** (3)

Laser flash photolysis of 2-diazo-2-cyano-*N*-methylacetamide using a $\lambda = 248$ nm excitation pulse produced a transient absorbance whose decay was monitored at $\lambda = 280$ nm. This decay proved to be biexponential, in keeping with the nature of the process of eq 3, which contains two transient species. The more rapid of these decays was assigned to hydration of α-carbonylcarbene **6** to enol **2** and was not investigated in detail. The slower decay, on the other hand, was monitored in perchloric acid solution and in acetic acid, biphosphate ion, tris-(hydroxymethyl)methylammonium ion, and ammonium ion buffers. The measurements in buffers were conducted in series of solutions of constant buffer ratio and constant ionic strength (0.10 M), and

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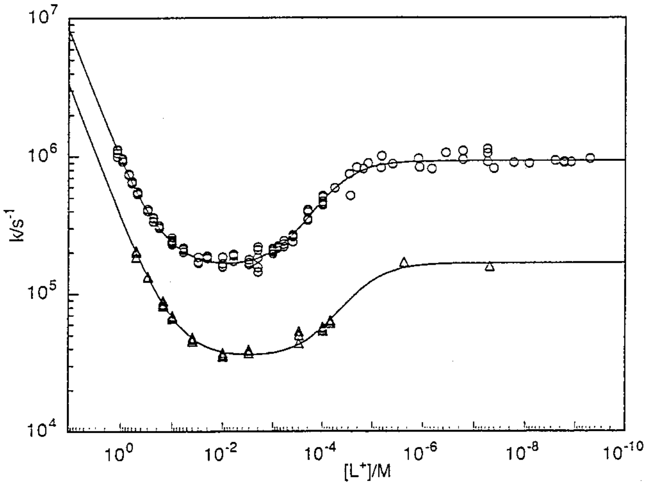
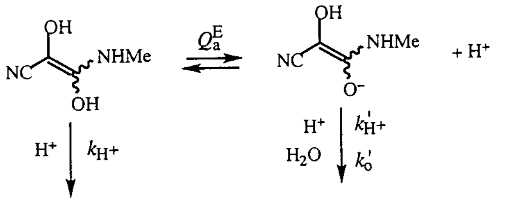


Figure 1. Rate profile for the ketonization of the enol of 2-hydroxy-2-cyano-*N*-methylacetamide in H_2O(O) and D_2O (Δ) solution at 25 °C.

extrapolation of these data to zero buffer concentration gave intercepts, which, together with the perchloric acid data, were used to construct the upper rate profile shown in Figure 1. Some measurements were also made in D_2O solution, and these provided the lower rate profile of Figure 1.

These rate profiles are typical of enol ketonization reactions. Ketonization is known to occur through rate-determining β-carbon protonation of either the enol or enolate ion,[13] as illustrated for the present system by eq 4. The acid-catalyzed portion of such



(4)

rate profiles at high acidity then represents carbon protonation of the enol by H^+. As $[H^+]$ drops, this reaction soon gives way to carbon protonation of the much more reactive enolate ion by H^+, and, with un-ionized enol as the initial state, this produces the lower "uncatalyzed" portion of the rate profile. At still lower $[H^+]$, carbon protonation of the enolate by H_2O takes over, and with un-ionized enol still as the initial state, this gives a region of apparent hydroxide-ion catalysis. Eventually, at low enough $[H^+]$, enolate ion becomes the initial state, and protonation of that by H_2O produces the second "uncatalyzed" reaction plateau.

The rate law that applies to this reaction scheme is shown as eq 5 whose rate and equilibrium constants are defined by eq 4.

$$k_{\mathrm{obs}} = k_{\mathrm{H^+}}[\mathrm{H^+}] + (k'_{\mathrm{H^+}}[\mathrm{H^+}] + k'_o)Q_a^E/(Q_a^E + [\mathrm{H^+}]) \qquad (5)$$

Least-squares fitting produced the following results: $k_{\mathrm{H^+}} = (8.35 \pm 0.15) \times 10^5\ \mathrm{M^{-1}\ s^{-1}}$, $k_{\mathrm{H^+}}/k_{\mathrm{D^+}} = 2.48 \pm 0.06$, $k'_{\mathrm{H^+}} = (2.18 \pm 0.13) \times 10^9\ \mathrm{M^{-1}\ s^{-1}}$, $k'_{\mathrm{H^+}}/k'_{\mathrm{D^+}} = 1.28 \pm 0.14$, $(k'_o)_{\mathrm{H_2O}} = (9.27 \pm 0.15) \times 10^5\ \mathrm{s^{-1}}$, $(k'_o)_{\mathrm{H_2O}}/(k'_o)_{\mathrm{D_2O}} = 5.57 \pm 0.24$, $(Q_a^E)_{\mathrm{H_2O}} = (7.00 \pm 0.34) \times 10^{-5}$ M, $\mathrm{p}(Q_a^E)_{\mathrm{H_2O}} = 4.15 \pm 0.02$, $(Q_a^E)_{\mathrm{H_2O}}/(Q_a^E)_{\mathrm{D_2O}} = 3.47 \pm 0.33$.

The isotope effects provided by these measurements support identification of the system under observation as the enol ketonization process of eq 4. In particular, the normal ($k_H/k_D > 1$) effects on $k_{\mathrm{H^+}}$ and $k'_{\mathrm{H^+}}$ are as expected for rate-determining carbon protonation by H^+, with the modest magnitude of $k_{\mathrm{H^+}}/k_{\mathrm{D^+}}$ consistent with the known inverse ($k_H/k_D < 1$) secondary component inherent in this isotope effect,[14] and the near-unity value of $k'_{\mathrm{H^+}}/k'_{\mathrm{D^+}}$ consistent with the very fast, perhaps partly diffusion-controlled, nature of that reaction. The isotope effect on k'_o is large because the secondary component here operates in the normal ($k_H/k_D > 1$) direction,[14] and the isotope effect on Q_a^E agrees well with equilibrium isotope effects on the ionization of other oxygen acids.[15]

We also measured rates of enolization of 2-hydroxy-2-cyano-*N*-methylacetamide by monitoring loss of the ^{1}H NMR signal from its β-proton in D_2O solutions of DCl. Adjustment of these data to H_2O solution[16] and combination of the results with ketonization rate constants at the same acidity, then gave the keto−enol equilibrium constant $K_E = (8.38 \pm 0.61) \times 10^{-13}$, $\mathrm{p}K_E = 12.08 \pm 0.03$. This result can be combined with the enol acidity constant Q_a^E according to the relationship $K_E Q_a^E = Q_a^K$ to give $Q_a^K = (5.87 \pm 0.51) \times 10^{-17}$ M, $\mathrm{p}Q_a^K = 16.23 \pm 0.04$, as the acidity constant of 2-hydroxy-2-cyano-*N*-methylacetamide ionizing as a carbon acid.

The value of $\mathrm{p}K_E$ for 2-hydroxy-2-cyano-*N*-methylacetamide determined here may be used to estimate $\mathrm{p}K_E$ for the parent *N*-methylacetamide by making allowance for the effects of its hydroxyl and cyano groups. The effect of hydroxyl can be estimated from $\Delta pK_E = 3.7$ as the combined effect of hydroxyl and phenyl, based upon $\mathrm{p}K_E = 16.2$ for mandelic acid[6d] and $\mathrm{p}K_E = 19.9$ for acetic acid,[17] modified by $\Delta pK_E = 3.3$ for phenyl, based upon $\mathrm{p}K_E = 2.9$ for phenylacetaldehyde[18] and $\mathrm{p}K_E = 6.2$ for acetaldehyde;[19] this gives $\Delta pK_E = 0.4$ for the hydroxyl group alone. The effect of cyano can be estimated in a similar manner from $\Delta pK_E = 12.7$ for the combined effect of cyano and phenyl, based upon $\mathrm{p}K_E = 7.2$ for cyanophenylacetic acid,[6b] and the value cited above for acetic acid, again modified by the phenyl effect of $\Delta pK_E = 3.3$; this gives $\Delta pK_E = 9.4$ for the cyano group alone. This cyano group effect agrees well with another estimate, $\Delta pK_E = 9.0$, based upon $\mathrm{p}K_E = 9.6$ for ethyl cyanoacetate,[5b] and $\mathrm{p}K_E = 18.6$ for ethyl acetate.[9b] The average of these two cyano group effects, plus the hydroxyl group effect, applied to $\mathrm{p}K_E = 12.1$ then leads to $\mathrm{p}K_E = 21.7$ for unsubstituted *N*-methylacetamide.

This is a sensible result, in that, coupled with $\mathrm{p}K_E = 18.6$ for ethyl acetate and $\mathrm{p}K_E = 19.9$ for acetic acid, it gives a series of regularily decreasing enol content. The enol contents of carboxylic acids and their esters and amides are very low because the keto isomers are stabilized by conjugation of their carbonyl groups with the electron-donating oxygen and nitrogen moieties directly attached. Since electron-donating ability increases as this moiety changes from ethoxyl in ethyl acetate to hydroxyl in acetic acid to methylamino in *N*-methylacetamide, as evidenced for example by the R^+ resonance parameters: −1.07 for OEt, −1.25 for OH, and −1.78 for NHMe,[20] keto-isomer stabilization should increase, and enol contents consequently should decrease, along this series.

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Supporting Information Available: Details of conversion of enolization rate constants measured in D_2O solution to the corresponding H_2O values (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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