q, 1, J = 10, 0.5 Hz), 9.85 (br, 1), 1.2 to 2.2 (br m, 4); uv max (95% EtOH) 236 nm (ε 22,800); mass spectrum (70 eV) *m/e* 221 (M^+).

Anal. Calcd for $C_{14}H_{23}NO$: C, 76.02; H, 10.41; N, 6.33. Found: C, 75.87; H, 10.69; N, 6.04.

Isoxazole 3d. Following the procedure outlined for the synthesis of **1a**, this isoxazole was prepared from oxime **2d** in 57% yield: bp 72–74° (0.04 mm); ir ($CHCl_3$) 2910, 1620, 1440, 1414 cm^{-1}; nmr ($CDCl_3$) δ 0.72 (s, 3), 1.00 (s, 3), 1.50 (m, 3), 1.90 (s, 3), 2.14 (s, 3), 2.96 (br s, 1), 5.63 (m, 1), 1.2 to 2.2 (br m, 4); uv max (95% EtOH) 225 nm (ε 8150); mass spectrum (70 eV) *m/e* 219 (M^+).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.71; H, 9.59; N, 6.39. Found: C, 76.43; H, 9.60; N, 6.22.

Vinylogous Amide 6d. When the isoxazole **3d** was reduced with a limited amount of sodium (see preparation of **3c**), the enamino ketone **6d** was obtained in 81% yield: mp 93–94° after recrystallization from acetone: ir ($CHCl_3$) 3485, 1605, 1575, 1480 cm^{-1}; nmr ($CDCl_3$) δ 0.86 (s, 3), 0.92 (s, 3), 1.2 to 1.6 (br m, 2), 1.59 (m, 3), 1.97 (s, 3), 2.01 (s, 3), 2.0–2.3 (br m, 2), 3.25 (br s, 1), 5.66 (m, 1); uv max (95% EtOH) 318 nm (ε 11,500); mass spectrum (70 eV) *m/e* 221 (M^+).

Anal. Calcd for $C_{14}H_{23}NO$: C, 76.02; H, 10.41; N, 6.33. Found: C, 75.76; H, 10.12; N, 6.30.

Methyl-α-damascone (4d). The crude β-amino ketone **5d** obtained by reduction of isoxazole **3d** with sodium, as described for the preparation of **1a** and **1b**, was dissolved in toluene and the solution passed down a Pyrex column (13 mm × 150 mm) packed with glass helices ($^3/_{32}$ in.) kept at 230–250° while a slow stream of argon was passed through the system. Work-up and distillation gave methyl-α-damascone (**4d**) (59%): bp 70–71° (0.05 mm); ir ($CHCl_3$) 2920, 1655, 1640 cm^{-1}; nmr ($CDCl_3$) δ 0.80 (s, 3), 0.97 (s, 3), 1.56 (m, 3), 1.86 (br s, 3), 2.00 (m, 3), 3.54 (br s, 1), 5.63 (m, 1), 6.85 (br q, 1, J = 6.5 Hz), 1.2 to 2.2 (br m, 4); uv max (95% EtOH) 233 nm (ε 12,600); mass spectrum (70 eV) *m/e* 206 (M^+).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.55; H, 10.68. Found: C, 81.67; H, 10.69.

Isopropenyl Ethyl Ketone (1e). Diethyl ketone and formaldehyde were condensed by the method of Colonge and Cumet[21] to form isopropenyl ethyl ketone (**1e**): bp 116–118° (lit.[21] bp 117–119°).

(21) J. Colonge and L. Cumet, *Bull. Soc. Chim. Fr.*, 838 (1947).

Isopropenyl Ethyl Ketoxime (2e). This oxime was prepared in 89% yield following the procedure described for the preparation of **2c**: bp 30–32° (10 mm); ir ($CHCl_3$) 3575, 3270, 2970, 960, 900 cm^{-1}; nmr ($CDCl_3$) δ 1.13 (t, 3, J = 7 Hz), 2.00 (br s, 3), 2.64 (q, 2, J = 7 Hz), 5.36 (br s, 1), 5.48 (br s, 1); uv max (95% EtOH) 227 nm (ε 7500); mass spectrum (70 eV) *m/e* 113 (M^+).

3-Ethyl-4-methylisoxazole (3e). Oxidation of oxime **2e** with triiodide as described above, followed by evaporation of the solvents at atmospheric pressure and distillation, gave isoxazole **3e** in 55% yield: bp 75–77° (50 mm); ir ($CHCl_3$) 2960, 1615, 1455, 1120 cm^{-1}; nmr ($CDCl_3$) δ 1.30 (t, 3, J = 7 Hz), 2.02 (s, 3), 2.67 (q, 2, J = 7 Hz), 8.17 (br s, 1); uv max (95% EtOH) 217 nm (ε 4520); mass spectrum (70 eV) *m/e* 111 (M^+).

Anal. Calcd for C_6H_9NO: C, 64.86; H, 8.11; N, 12.61. Found: C, 65.15; H, 8.22; N, 12.74.

2-Methylpent-2-enal (4e). Sodium was added to a stirred mixture of liquid ammonia (100 ml), THF (30 ml), *tert*-butyl alcohol (0.210 g), and 3-ethyl-4-methylisoxazole (**3e**) (1.041 g, 9.35 mmol) until the solution remained dark blue. The reaction was stirred for 15 min, decolorized with solid ammonium chloride, and treated with dry ether (50 ml). After evaporation of the ammonia with a stream of nitrogen, the material was cooled to 0°, and dry HCl was bubbled in rapidly. The precipitate was filtered, washed with ether (25 ml) and pentane (25 ml), and stored over potassium hydroxide overnight. A portion amounting to 35% of the total precipitate was pyrolyzed in a short-path distillation apparatus at 100° (130 mm) to yield 0.235 g (72%) of 2-methylpent-2-enal (**4e**): ir ($CHCl_3$) 2965, 1675, 1635 cm^{-1}; nmr ($CDCl_3$) δ 1.16 (t, 3, J = 7 Hz), 1.73 (br s, 3), 2.41 (d of q, 2, J = 7, 7.5 Hz), 6.43 (t of q, J = 7, 0.5 Hz), identical with that reported in ref 22.

Acknowedgments. We are indebted to Firmenich et Cie., Geneva, for generous financial support and to Professor K. B. Sharpless, Massachusetts Institute of Technology, for a stimulating discussion.

(22) K. Mori, S. K. Roy, and D. M. S. Wheeler, *J. Chem. Soc.*, 5815 (1964).

Enamine Formation and Hydrolysis. Ethyl β-Cyanomethylaminocrotonate[1]

J. Peter Guthrie*[2] and Frank Jordan[3]

Contribution from the James Bryant Conant Laboratory of the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138.
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Abstract: Rate constants for the hydrolysis of the enamine ethyl β-cyanomethylaminocrotonate (**1**) have been studied as a function of pH and buffer concentration. At high buffer concentration, from pH 4 to pH 7, the rate-determining step is the acid-catalyzed addition of water to the imine tautomer. At very low buffer concentrations, tautomerization is rate determining. Equilibrium constants have been measured as a function of pH, so that rate constants for enamine formation may be calculated. The equilibrium constant for the formation of **1** from free aminoacetonitrile and ethyl acetoacetate is 0.94 M^{-1}.

As part of an investigation[4,5] of the amine-catalyzed decarboxylation of acetoacetic acid, the reaction of aminoacetonitrile (AAN) with ethyl acetoacetate (EAA) was studied. It was hoped that this reaction, leading to reversible formation of the enamine ethyl β-cyanomethylaminocrotonate (ECC), would serve as a model for the reaction of aminoacetonitrile with acetoacetic acid, without the complication of irreversible decarboxylation. The immediate purpose was to evaluate rate constants for imine formation from EAA and AAN for comparison with the rate constants for the AAN-catalyzed decarboxylation of acetoacetic acid. This proved to be more difficult than was an-

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(2) National Research Council of Canada Special Scholarship; address correspondence to Department of Chemistry, University of Western Ontario, London, Canada.

(3) NIH Postdoctoral Fellow.

(4) J. P. Guthrie and F. H. Westheimer, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 26, 562 (1967).

(5) J. P. Guthrie and F. Jordan, *J. Amer. Chem. Soc.*, **94**, 9136 (1972).

Table I. Rate Constants for the Hydrolysis of Enamines[a]

Ethyl β-cyanomethylamino-crotonate in H_2O[b]			Ethyl β-cyanomethylamino-crotonate in D_2O[b]			Ethyl β-anilino-crotonate in H_2O[c]		
pH	Buffer, *M*	k_{obsd}, sec^{-1}	pD[f]	Buffer, *M*	k_{obsd}, sec^{-1}	pH	Buffer *M*	k_{obsd}, sec^{-1}
3.97	0.556[d,i]	0.44	4.36	0.566[d]	0.293	4.01	0.556[d]	1.13
	0.222[d]	0.39		0.111[d]	0.178		0.222[d]	1.02
	0.111[d]	0.33		0.0278[d]	0.0883		0.111[d]	0.92
	0.0556[d]	0.26		0.00556[d]	0.0409		0.0556[d]	0.91
	0.0111[d]	0.129					0.0278[d]	0.85
	0.00556[d]	0.092					0.0111[d]	0.73
							0.00556[d]	0.64
5.00	0.145[d]	0.049	5.36	0.142[d]	0.0345	5.03	0.426[d]	0.151
	0.0435[d]	0.039		0.0284[d]	0.0179		0.213[d]	0.143
	0.00870[d]	0.022		0.00710[d]	0.00821		0.0852[d]	0.126
	0.00435[d]	0.020		0.00142[d]	0.00378		0.0426[d]	0.119
5.98	0.0808[e]	0.00691	6.50	0.0813[e]	0.00385		0.0170[d]	0.108
	0.0323[e]	0.00580		0.0162[e]	0.00240		0.0085[d]	0.095
	0.0162[e]	0.00492		0.00406[e,g]	0.00103			
				0.000513[e,h]	0.00035			

[a] Temperature = 30.0 ± 0.1°. [b] Rate constants corrected to zero acetonitrile concentration; μ = 0.1 (KCl). [c] μ = 1.0 (KCl); 1% (v/v) acetonitrile. [d] Acetate buffer. [e] Phosphate buffer. [f] pD = pH (meter reading) + 0.41. [g] Final pD was 6.57. [h] Final pD was 6.77. [i] The effect of acetonitrile concentration was small but significant, *e.g.*, for this point; [acetonitrile] (*M*), k_{obsd} (sec^{-1}): 0.194, 0.408; 0.318, 0.386.

ticipated because of the surprising complexity of the kinetics. The hydrolysis of ECC involves three steps: tautomerization to the imine, addition of water to give a carbinolamine, and finally loss of amine. It appears that under suitable conditions any of these steps may be rate limiting.

Our conclusions concerning the rate-determining step in the hydrolysis of conjugated enamines are at variance with those of a recent study of related compounds.[6] It appears that the hydrolytic chemistry of these relatively stable enamines may be both more complicated and more interesting than had at first appeared.

Experimental Section

Materials and Methods. Aminoacetonitrile sulfate was purified as described previously,[7] starting with the commercial "bisulfate"; ethyl β-anilinocrotonate and ethyl acetoacetate were redistilled *in vacuo* shortly before use for kinetics; chemicals for buffers were of reagent grade and were used without further purification. Nmr spectra were recorded on a Varian A-60; pH values were measured with a Radiometer pH meter 4. For solutions in D_2O, pD was calculated by adding 0.41 to the pH meter reading.[8] Acetonitrile was spectroscopic grade and was used without further purification.

Ethyl β-Cyanomethylaminocrotonate (ECC). Aminoacetonitrile "bisulfate" (20 g, 0.13 mol) was neutralized (to pH 6) with saturated barium hydroxide solution and filtered; to the filtrate was added ethyl acetoacetate (40 ml, 0.31 mol). After stirring 5.5 hr at room temperature, the mixture was cooled (ice bath) and filtered, giving 14.3 g of solid (0.085 mol, 65%, mp 101–103°) which was recrystallized from 1-propanol (mp 103–104°).

Anal. Calcd for $C_8H_{12}N_2O_2$: C 57.13, H 7.19, N 16.66. Found: C 57.37, H 7.23, N 16.80. Nmr, $CDCl_3$, δ 1.27 (t, *J* = 7 Hz, OCH_2CH_3), 2.07 (s, CH_3—C=), 4.17 (q,d, both with *J* = 7 Hz, OCH_2CH_3, $NHCH_2CN$), 4.77 (s, C=CHCO), 8.75 (broad, NH); CD_3OD, δ 1.22 (t, *J* = 7 Hz, OCH_2CH_3), 2.03 (s, CH_3C=), 4.07 (q, *J* = 7 Hz, OCH_2CH_3), 4.37 (d, *J* = 7 Hz, $NHCH_2CN$), 4.65 (s, C=CHCO–); uv spectra: solvent, λ_{max} (nm), ϵ_{max}; acetonitrile, 275, 19,000; methanol, 276, 19,200.

Kinetic Methods. Reactions were followed spectrophotometrically, using a Cary 15 at 275 nm for ECC and at 296 nm for ethyl β-anilinocrotonate. Hydrolysis reactions were initiated by adding a known amount of an acetonitrile solution of enamine to a 3-ml cuvette containing buffer equilibrated at 30.0 ± 0.1°. For the faster reactions, the enamine solution was placed on the flattened end of a glass stirring rod and added to the cell with the recorder running. Mixing could be achieved within 2 or 3 sec, and the data gave good first-order plots for at least two and usually three half-lives. Formation kinetics were initiated by adding 50–100 μl of an aqueous solution of EAA to an AAN solution.

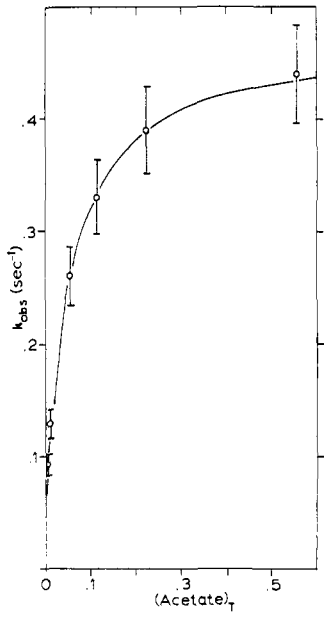


Figure 1. Rate of hydrolysis of ECC as a function of acetate buffer concentration in water at 30.0 ± 0.1°, μ = 0.1 *M* (KCl). The line is calculated using the parameters from Table II.

Results

Hydrolysis of ECC. The rate of hydrolysis was found to be affected by the concentration of acetonitrile present in the reaction mixture. In Table I are rate constants for hydrolysis in H_2O and D_2O extrapolated to zero acetonitrile concentration. As Figure 1 shows, the rate constants are strikingly dependent upon the concentration of buffer, *but* become insensitive to it at high buffer concentrations. This can arise if the hydrolysis has two kinetically significant steps, one of

(6) J. K. Coward and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 5329 (1969).
(7) J. P. Guthrie, *ibid.*, **94**, 7024 (1972).
(8) A. K. Corington, M. Paabo, R. A. Robinson, and R. G. Bates, *Anal. Chem.*, **40**, 700 (1968).

Table II. Buffer Effects on Rate Constants for Enamine Hydrolysis[a]

pH (pD)	Buffer	a^b	b^b	$c \times 10^{-3}$ [b]	k^0 [f]	$k^0_{H^+}$ [g]	k^∞ [h]	$k^\infty_{H^+}$ [i]
				a. Ethyl β-cyanomethylaminocrotonate				
3.97	c	132 ± 20	16 ± 1	0.28 ± 0.05	0.068 ± 0.0002	(6.3 ± 0.02) × 10^2	0.48 ± 0.003	(4.5 ± 0.3) × 10^3
5.00	c	95 ± 61	67 ± 13	1.6 ± 1.2	0.015 ± 0.003	(1.5 ± 0.3) × 10^3	0.06 ± 0.04	(6 ± 4) × 10^3
5.98	d	98 ± 47	340 ± 57	11.8 ± 4.6	0.0030 ± 0.0005	(2.9 ± 0.5) × 10^3	0.008 ± 0.004	(7 ± 4) × 10^3
4.36[e]	c	108 ± 11	37 ± 2	0.309 ± 0.037	0.027 ± 0.001	(6.2 ± 0.2) × 10^2	0.35 ± 0.04	(8.0 ± 0.9) × 10^3
5.36[e]	c	360 ± 44	386 ± 25	8.0 ± 1.3	0.0026 ± 0.0001	(6.0 ± 0.3) × 10^2	0.045 ± 0.007	(1.0 ± 0.2) × 10^4
6.50[e]	d	1260 ± 260	4660 ± 720	270 ± 60	0.00021 ± 0.00003	(6.7 ± 1.0) × 10^2	0.0047 ± 0.0010	(1.5 ± 0.3) × 10^4
				b. Ethyl β-anilinocrotonate				
4.01	c	62 ± 36	1.7 ± 0.2	0.057 ± 0.035	0.59 ± 0.06	(5.9 ± 0.6) × 10^3	1.1 ± 0.7	(1.1 ± 0.7) × 10^4
5.03	c	32 ± 13	11 ± 0.7	0.200 ± 0.093	0.091 ± 0.005	(9.2 ± 0.5) × 10^3	0.16 ± 0.07	(1.7 ± 0.7) × 10^4

[a] In water, or D_2O, at 30.0 ± 0.1°. μ is 0.1 *M* (ECC) or 1.0 *M* (ethyl β-anilinocrotonate); dimensions are sec^{-1} or M^{-1} sec^{-1}. [b] Defined in the text. [c] Acetate buffer. [d] Phosphate buffer. [e] In D_2O. [f] Pseudo-first-order rate constant at zero buffer concentration; $k^0 = 1/b$. [g] $k^0_{H^+} = k^0/[H^+]$. [h] Pseudo-first-order rate constant at infinite buffer concentration; $k^\infty = a/c$. [i] $k^\infty_{H^+} = k^\infty/[H^+]$.

which is sensitive to buffer catalysis, so that the rate-determining step changes as the buffer concentration is increased; *i.e.*

$$\text{enamine} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \text{X} \xrightarrow{k_2} \text{prod.}$$

Whichever step is sensitive to buffer catalysis, the equation relating the observed rate constants to the buffer concentration will be of the form

$$k_{obsd} = (1 + a[\text{buffer}])/(b + c[\text{buffer}])$$

where *a*, *b* and *c* are adjustable parameters whose significance depends upon the mechanism. Values of these parameters, evaluated by the method of least squares, are given in Table II. At high buffer concentration, where the rate of hydrolysis is insensitive to buffer concentration, the reaction is clearly catalyzed by hydrogen ion. Furthermore, under these conditions there is an inverse solvent isotope effect with $k^\infty_{H^+} = 4.5 \times 10^3\ M^{-1}\ sec^{-1}$, $k^\infty_{D^+} = 1.0 \times 10^4\ M^{-1}\ sec^{-1}$, and $k^\infty_{H^+}/k^\infty_{D^+} = 0.45$. This requires specific acid catalysis.[9]

The rate constants at zero buffer concentration are more difficult to determine because of the extrapolation involved: see Figure 1. Phosphate at pH 6 does not provide adequate buffer capacity at the low concentrations required to specify k^0, so that k^0 is imprecise at pH 6, though it is clear that there is a change in rate-determining step and that k^0 is about ten times less than at pH 5. In D_2O, $k^0_{D^+} = 6.0 \times 10^2\ M^{-1}\ sec^{-1}$; in H_2O $k^0_{H^+}$ calculated from the value at pH 5 is 1.5×10^3, so that $k^0_{H^+}/k^0_{D^+} = 2.3$. This requires that the reaction involves proton transfer from H_3O^+ or D_3O^+ in the transition state.[10]

Extrapolation of the absorbance *vs.* time curves for the hydrolysis of ECC to $t = 0$ permitted calculation of an extinction coefficient for ECC in water. At pH 6 the hydrolysis was slow enough to permit accurate extrapolation, leading to $\epsilon_{270} = 17{,}100 \pm 700$.

Formation of ECC. The rate of increase in absorbance when AAN and EAA were mixed was measured as a function of [AAN]. The final absorbance increased linearly with [AAN], showing that only a small portion of the EAA was converted to ECC under the conditions used; see Table III. The slope of a graph of ϵ^∞ *vs.* [AAN] at fixed pH will then be $K(\epsilon_{ECC} - \epsilon_{EAA})$, where *K* is the equilibrium constant for enamine formation. From the known extinction coefficients for ECC and EAA, 17,100 and 27, respectively, values of *K* may be calculated as listed in Table III. Values of k_{obsd} at pH 5 or 6 increase linearly with AAN concentration; the best lines have slope = 0.217 ± 0.017 M^{-1} sec^{-1}, intercept = 0.0203 ± 0.0007 sec^{-1} at pH 5.0, and slope = 0.0276 ± 0.0031 M^{-1} sec^{-1}, intercept = 0.00273 ± 0.00012 sec^{-1} at pH 6.0. The observed pseudo-first-order rate constant for approach to equilibrium is the sum of the rate constants for formation and hydrolysis of the enamine. However, calculation of the pseudo-first-order rate constant for enamine formation from the known rates of hydrolysis and the equilibrium constant shows that the rate constant for formation makes a negligible contribution to k_{obsd}.

(9) F. A, Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).
(10) C. A, Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, **83**, 3214 (1961).

Table III. Rate and Equilibrium Constants for the Formation of ECC[a]

pH	Buffer,[b] M	AAN,[c] M	ϵ^{∞},[d] M^{-1} cm^{-1}	k_{obsd}, sec^{-1}	$K\epsilon$, M^{-2} cm^{-1}	K, M^{-1}
4.05		0.0754	85.4	0.187		
3.96	0.215	0.0388	62.7	*e*	823 ± 30	0.048 ± 0.003
3.96	0.215	0.0258	51.8	*e*		
3.96	0.215	0.0129	39.9	*e*		
3.96	0.323	0.0258	49.9	*e*		
3.96	0.108	0.0258	52.4	*e*		
4.99		0.0673	364	0.0379		
5.04		0.0656	400	0.0347	5,700 ± 100	0.33 ± 0.02
5.00		0.0258	174	0.0253		
5.01		0.0129	101	0.0234		
6.03		0.0647	1047	0.00442	16,100 ± 300	0.94 ± 0.04
6.00		0.0259	442	0.00353		
6.01		0.0129	232	0.00301		
7.15		0.0665	1100	0.000500	16,100 ± 300	0.94 ± 0.04

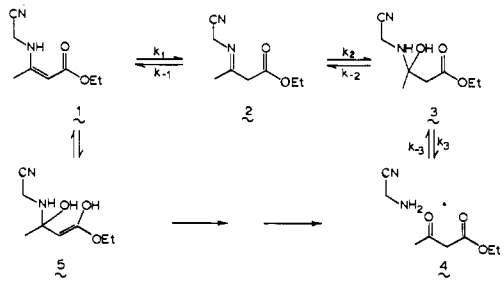
[a] Aqueous solution 30.0 ± 0.1°, μ = 0.1 (KCl). [b] Acetate buffer. [c] Total amine concentration. [d] Apparent extinction coefficient at equilibrium: final absorbance, divided by initial ethyl acetoacetate concentration. [e] Too rapid to measure.

The slope of the plots of k_{obsd} *vs.* [AAN] represents general acid catalysis by the conjugate acid of AAN of the hydrolysis reaction. The rate constants for ECC hydrolysis at zero buffer obtained in these formation experiments are consistent with those measured directly.

Discussion

There are two paths by which ECC might hydrolyze, as indicated in Scheme I: (a) by tautomerization to

Scheme I



the imine **2**, followed by addition of water to give the carbinolamine **3**, and finally loss of amine to give ethyl acetoacetate; (b) by acid-catalyzed addition of water to give the enol carbinolamine **5** which could then decompose in a variety of ways. The hydrolysis of 4-methoxy-3-buten-2-one (**6**) has been shown[11] to involve a path analogous to (b). However, path b should be more difficult for ECC than for **6** because of the greater stability of the conjugated system. ECC is a vinylogous urethan while **6** is a vinylogous ester; they may be compared to CH_3CH_2–O–CO–NH_2 and CH_3–O–CO–CH_3, for which the rate constants for acid-catalyzed hydrolysis at 37° are 5.07 × 10^{-8} M^{-1} sec^{-1} [12] and 2.2 × 10^{-4} M^{-1} sec^{-1},[13] respectively. Although vinylogy may be an imperfect guide, these values do suggest that ECC should be expected to react more slowly than **6** by path b. However, the rate constant for the acid-catalyzed hydrolysis of ECC is 1.5 × 10^3 M^{-1} sec^{-1} at zero buffer concentration and is 4.5 × 10^3 M^{-1} sec^{-1} at high buffer concentration, in either case much *larger* than that for **6**, which is[11] 0.5 M^{-1} sec^{-1}. Thus path b may be ruled out for ECC. It is reasonable that ECC should undergo C-protonation much more readily than **6** because of the greater basicity of nitrogen than oxygen.

The hydrolytic behavior of the imine **2** can be predicted, with some precision, on the basis of the many[14] studies of imine formation and hydrolysis which have been carried out in simpler systems. The most closely analogous cases which have been reported are *p*-chlorobenzylideneaniline[15] (**7**) and *N*-isobutylidinetrifluoroethylamine[16] (**8**). The hydrolysis of **7** shows a change in the rate-determining step near pH 5, with acid-catalyzed hydration of the imine being rate determining above this pH. The acid catalysis is associated with a Brønsted α near 1, that is, general acid catalysis by buffer species causes only a modest increase in rate. At lower pH carbinolamine deamination is rate determining; this step is general acid catalyzed with α = 0.25. Since the rate of formation of **8** has been studied between pH 5.5 and 12.5, and the equilibrium constant for imine formation is known, rate constants for hydrolysis may be calculated. For these conditions the rate-determining step for imine formation is the acid catalyzed (pH 5.5–10) or uncatalyzed (pH greater than 10) dehydration of the carbinolamine. General acid catalysis was not detectable. Therefore, the rate-determining step for hydrolysis of **8** is the addition of water, with carbinolamine deamination a fast process.

Studies of simple, nonconjugated enamines such as 1-*N*-morpholino-1-isobutene[17,18] (**9**) showed that above pH 4 the rate-determining step was general acid catalyzed (α = 0.3)[19] C-protonation with an isotope effect, $k_{H_3O^+}/k_{D_3O^+}$ = 2.5 ± 0.7. From pH 4 to pH 0 hydration of the iminium ion was rate determining, and for $H_0 < 0$ carbinolamine deamination became rate limiting. Sollenberger and Martin studied[20] the hydrolysis of the morpholine enamine of propiophenone (**11**) and found

(11) L. R. Fedor and J. McLaughlan, *J. Amer. Chem. Soc.*, **91**, 3594 (1969).
(12) K. J. Pedersen, *Acta Chem. Scand.*, **14**, 1448 (1960).
(13) J. C. Hornel and J. A. V. Butler, *J. Chem. Soc.*, 1361 (1936).
(14) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1968, pp 490–496; W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964); and references contained therein.
(15) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 832 (1962).
(16) J. Hine and F. A. Via, *ibid.*, **94**, 190 (1972).
(17) E. J. Stamhuis and W. Maas, *J. Org. Chem.*, **30**, 2156 (1965).
(18) W. Maas, M. J. Janssen, E. J. Stamhuis, and H. Wynberg, *ibid.*, **32**, 1111 (1967).
(19) Calculated from data in ref 17.
(20) P. Y. Sollenberger and R. B. Martin, *J. Amer. Chem. Soc.*, **92**, 4261 (1970).

that above pH 5 C-protonation was rate limiting. This step was sensitive to general acid catalysis with $\alpha = 0.50$. On considering the results obtained for ECC, it is clear that the rate-determining step at high buffer concentration, where the observed rate constant increased with increasing hydrogen ion concentration from pH 7 to pH 4 and had a solvent isotope effect consistent with specific acid catalysis, must be hydration of the imine.

The rate-determining step at zero buffer concentration is subject to general acid–base catalysis, as is shown by its sensitivity to buffer concentration, and the solvent isotope effect. Both C-protonation of the enamine and loss of amine from the carbinolamine are subject to general acid catalysis. However, the process at zero buffer concentration is still decreasing in rate with decreasing hydrogen ion concentration at pH 6, so that the uncatalyzed rate is less than 0.003 min^{-1}; the equilibrium constant for enamine formation at pH 6 is 0.94 M^{-1}, so that if this process were loss of amine from the carbinolamine, the rate constant for uncatalyzed formation of the carbinolamine would have to be less than 0.003 M^{-1} min^{-1}; this is contrary to what is found in related systems,[16] where carbinolamine formation is fast as long as the amine is free to react. Therefore the rate-determining step at zero buffer concentration at pH 5 and 6 cannot be loss of amine from the carbinolamine and must be C-protonation of the enamine. The decrease in rate constant at pH 4, though small, is outside experimental error; this may represent a change to partly rate limiting loss of amine from 3. Loss of amine from the carbinolamine is expected[14,15] to become rate limiting at a pH around 4.[21]

In a recent study[6] of the hydrolysis of a variety of conjugated enamines, Bruice and Coward proposed that C-protonation of the enamine was rate determining in all cases which they studied, for pH >2. One of the compounds included in their study was ethyl β-anilinocrotonate which is closely similar to ECC. To confirm the generality of our observations, the effect of buffer concentration on the rate of hydrolysis of ethyl anilinocrotonate was investigated. The results (Tables I and II) clearly show that for this compound as well there is a nonlinear dependence of k_{obsd} on buffer concentration. By analogy with ECC we propose that the rate-determining step at high buffer concentration is hydration of the imine tautomer, and that C-protonation of the enamine becomes rate limiting at low buffer concentration. For ethyl anilinocrotonate, at least, our conclusions differ from those of Bruice and Coward.[22]

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(21) Analysis of the kinetics of the AAN-catalyzed decarboxylation of acetoacetate[5] led to rate constants for imine formation, and for the imine–enamine tautomerization. Imine formation was catalyzed by H^+ but insensitive to buffer concentration; imine–enamine tautomerization showed a large buffer catalysis term.

(22) Bruice and Coward observed only modest catalysis by buffer for any of the compounds they studied, which were mostly conjugated cyano enamines. This is quite different from the behavior observed for C-protonation of the enamines ECC or ethyl anilinocrotonate, as well as simpler enamines,[11,20] but similar to the behavior expected for rate limiting imine hydration.

Amine-Catalyzed Decarboxylation of Acetoacetic Acid. The Rate Constant for Decarboxylation of a β-Imino Acid[1]

J. Peter Guthrie*[2] and Frank Jordan[3]

Contribution from the James Bryant Conant Laboratory of the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138.
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Abstract: Aminoacetonitrile (AAN) is the most powerful catalyst for the decarboxylation of acetoacetic acid out of a series of primary amines of widely varying pK_a. The rate constants for AAN-catalyzed decarboxylation are closely similar to those for imine formation from AAN and ethyl acetoacetate. Spectrophotometric study of AAN-catalyzed decarboxylation revealed three successive kinetic processes characterized by three pseudo-first-order rate constants. The imine from AAN and acetoacetate could be trapped by cyanoborohydride. Analysis of the kinetics led to rate constants for imine formation and hydrolysis and for interconversion of imine and enamine, as well as for the decarboxylation of the imine. This latter rate constant, 10 sec^{-1}, is 300,000 times faster than that for the decarboxylation of acetoacetic acid itself.

The spontaneous thermal decarboxylation of acetoacetic acid and related compounds is a well-understood reaction.[4-10] The amine-catalyzed decarboxylation of acetoacetic acid, though it has been known for a

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(3) NIH Postdoctoral Fellow.
(4) E. M. P. Widmark, *Acta Med. Scand. Suppl.*, 53, 393 (1920); *Chem. Zentralbl.*, (I) **92**, 9 (1921).
(5) G. Ljunggren, Dissertation, Lund, 1925; results quoted by K. J. Pedersen, *J. Amer. Chem. Soc.*, **51**, 2098 (1929).
(6) H. von Euler and A. O. Lander, *Z. Anorg. Allg. Chem.*, **147**, 295 (1925).
(7) E. M. P. Widmark and C. C. Jeppson, *Skand. Arch. Physiol.*, **42**, 43 (1922); *Chem. Zentralbl.*, (I) **93**, 526 (1922).
(8) J. Bredt, *Ann. Acad. Sci. Fenn., Ser. A*, **29**, No. 2 (1927); *Chem. Zentralbl.*, (II) **98**, 2298 (1927); *Chem. Abstr.*, 1152 (1928).
(9) K. J. Pedersen, *J. Amer. Chem. Soc.*, 51, 2098 (1929); **58**, 240 (1936).
(10) F. H. Westheimer and W. A. Jones, *ibid.*, 63, 3283 (1941).