Organic and Biological Chemistry

Mechanism of Enamine Hydrolysis[1]

Paula Y. Sollenberger and R. Bruce Martin

Contribution from the Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901. *Received October 14, 1969*

Abstract: The rates of hydrolysis of the morpholine, dimethylamine, piperidine, and pyrrolidine enamines of propiophenone have been investigated in the pH range −3 to 14 at 25°. Hammett $\sigma\rho$ correlations were obtained at pH 10.4, 4.7, and 1.1 and at $H_0 = -2.3$ and −3.3 for *para*-substituted derivatives of the morpholine enamine. In neutral and basic solutions the rate-limiting step is either general acid catalyzed protonation of the β-carbon atom of the free base or carbinolamine formation *via* uncatalyzed attack of water and/or hydroxide ion on the immonium ion, the reactivity being determined by the inductive effect of the amino group and the relative ease of formation of the exocyclic double bond and its consequent stability. Monobasic phosphate and bicarbonate ions exhibit unusually large catalytic effects on the rate of immonium ion formation. In weakly acidic solutions (pH 1–6), carbinolamine formation *via* uncatalyzed attack of water is rate limiting. Thermodynamic parameters were determined in this pH region where reactivity is influenced by the inductive effect of the amino group and the stability of the carbon–nitrogen double bond. Below pH 1 an increase in acidity decreases the rate of hydrolysis because of the combined effects of acid inhibition of carbinolamine zwitterion formation and the departure of the activity of water from unity. In solutions in which $H_0 < -1.3$, decomposition of the carbinolamine zwitterion to propiophenone and amine is rate limiting.

Enamines, α,β-unsaturated amines, have been proposed as intermediates in both nonenzymatic and enzyme catalyzed reactions. Several aldol condensation reactions have been shown to be more effectively catalyzed by primary and secondary amines than by tertiary amines.[2] This result suggests the possibility of enamine intermediates. An enamine intermediate has been established in the enzyme catalyzed decarboxylation of acetoacetic acid.[3] Other instances also appear in the literature.[4]

The relative stability of many enamines provides an opportunity to study directly the reactivity of these significant reaction intermediates. Enamines with a phenyl group in the 1 position permit alteration of the electron density at the reaction center by a change of *para* substituents on the aromatic ring. A combination of availability of starting meterials and practicality of synthesis led to the choice of substituted propiophenones as the carbonyl compounds employed in the syntheses of a series of tertiary enamines. A careful study of the hydrolysis of these enamines over a pH range of 17 log units allows formulation of a complete, detailed mechanism for their decomposition to propiophenones and secondary amines.

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Experimental Section

Enamines I–VI were made according to the procedure outlined by Stork.[5] Ketone (1 equiv), 1.5–2 equiv of amine, and a catalytic amount of *p*-toluenesulfonic acid were refluxed in toluene under a Dean–Stark water trap. About 400 ml of solvent and 2 g of catalyzing acid were used per mole of ketone. The secondary amines, except for dimethylamine, were distilled prior to use.

1-(4-Morpholino)-1-phenyl-2-methylethylene (I). After refluxing 10 days the solvent was removed and the residue vacuum distilled to give 24.3 g (53%) of I: bp 160–160.5° (14 mm); $n^{23.2}$D 1.5523.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.96; H, 8.53; N, 6.98.

1-(4-Morpholino)-1-(*p*-methylphenyl)-2-methylethylene (II). After refluxing 8 days a crystalline product was obtained upon removal of solvent. The crystals were filtered, recrystallized from methanol, and dried *in vacuo* over P_2O_5 to give 15.2 g (42%) of II. Two successive recrystallizations from methanol gave a white solid, mp 54.0–57.0°.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 78.07; H, 8.00; N, 6.39.

1-(4-Morpholino)-1-(*p*-chlorophenyl)-2-methylethylene (III). After refluxing 7 days the reaction mixture was cooled, neutralized with a freshly prepared solution of sodium methoxide, and washed with water. The organic layer was dried with anhydrous potassium carbonate and the solvent removed.[6] The resulting solid was twice recrystallized from methanol and dried *in vacuo* over P_2O_5 to give 12.7 g (54%) of a white solid (III), mp 43.2–44.2°.

Anal. Calcd for $C_{13}H_{16}ClNO$: C, 65.67; H, 6.78; Cl, 14.91; N, 5.89. Found: C, 65.82; H, 6.81; Cl, 14.69; N, 5.75.

1-(4-Morpholine)-1-(*p*-nitrophenyl)-2-methylethylene (IV). The reaction mixture was worked up as with the *p*-Cl derivative after refluxing for 5 days. Several recrystallizations of the solid orange product (mp <50°) from methanol and from ethanol did not separate the enamine from *p*-nitropropiophenone. Only the ketone was obtained from column chromatography of the mixture on Florisil and neutral alumina (Woelm) columns. A comparison of nmr peak areas showed that the ratio of enamine to ketone was about 4:1. Satisfactory kinetic evaluation of the enamine was obtained from the mixture.

1-Piperidino-1-phenyl-2-methylenethylene (V). The reaction mixture was refluxed for 2 weeks, the solvent removed, and the residue

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vacuum distilled to give 14.6 g (48%) of V: bp 139–139.5° (10 mm); $n^{26.8}$D 1.5487.

Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.74; H, 9.71; N, 6.93.

1-Piperidino-1-(*p*-chlorophenyl)-2-methylethylene (VI). After refluxing 5 days the reaction mixture was worked up following the procedure used for the corresponding morpholine enamine. Upon removal of solvent an oil was obtained. This was vacuum distilled to give 22.1 g (58%) of VI: bp 174.5–175.5° (12.5 mm); $n^{26.0}$D 1.5592.

Anal. Calcd for $C_{14}H_{18}ClN$: C, 71.30; H, 7.69; Cl, 15.03; N, 5.94. Found: C, 71.51; H, 7.89; Cl, 15.15; N, 5.72.

Enamines VII–IX were made according to the procedure of White and Weingarten.[7] To 500 ml of benzene were added 0.1 mol of ketone, 0.3 mol of amine, and 0.055 mol of titanium tetrachloride in an additional 100 ml of benzene. When reaction was complete, the reaction mixture was filtered, solvent removed, and the residue vacuum distilled.

1-Pyrrolidino-1-phenyl-2-methylethylene (VII). Vacuum distillation gave 3.4 g (18%) of VII: bp 139.5–140° (13 mm); $n^{28.0}$D 1.5503.

Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15, N, 7.48. Found: C, 80.85, 81.91; H, 9.01, 8.83; N, 6.70, 7.33.

This enamine was found to be more unstable than the others. It was assumed to be of sufficient purity to make satisfactory kinetic evaluations.

1-(N,N-Dimethylamino)-1-phenyl-2-methylethylene (VIII). Vacuum distillation gave 5.8 g (36%) of VIII: bp 117–118° (35 mm); $n^{22.0}$D 1.5332.

Anal. Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.59. Found: C, 82.07; H, 10.52; N, 8.73.

1-Piperidino-1-(*p*-methylphenyl)-2-methylethylene (IX). Vacuum distillation gave 8.9 g (41%) of IX: bp 162–163° (12.5 mm); $n^{22.0}$D 1.5437.

Anal. Calcd for $C_{15}H_{21}N$: C, 83.66; H, 9.83; N, 6.51. Found: C, 83.40; H, 9.69; N, 6.72.

N,N-Dimethylisobutenylamine (X). A sample donated by Eastman Chemical Products, Inc., was purified by distillation and a fraction boiling at 87–88° was used, $n^{20.0}$D 1.4216 (lit.[8] $n^{19.6}$D 1.4212).

***p*-Nitropropiophenone (XI).**[9] A 500-ml erlenmeyer flask containing 200 ml of ether and 50 ml of a 50% aqueous KOH solution was cooled in an ice bath. The mixture was stirred with a Teflon magnetic stirrer as 16.8 g (0.14 mol) of N-nitroso-N-ethylurea was added over a 2-hr period. After the final addition the mixture was allowed to stand for about 20 min. Most of the ether was decanted into a 200-ml erlenmeyer flask containing 3 g of KOH. More ether was added to the generating flask and this decanted as well. At no time is all the ether decanted. The ethereal solution of diazoethane sat over KOH for about 10 min. It was then slowly poured into a stirred solution of 6.6 g (0.044 mol) of *p*-nitrobenzaldehyde in 150 ml of ether. The reaction mixture was allowed to stand overnight at room temperature. A few milliliters of glacial acetic acid was added to ensure no remaining diazoethane. The reaction mixture was washed with 100 ml of saturated sodium bisulfite solution. The organic layer was dried over anhydrous magnesium sulfate and the ether removed. The crystals were washed with cold ethanol and dried *in vacuo* over P_2O_5 to give 4.4 g (57%) of IX, mp 87–89° (lit.[9] mp 87–89).

N-Nitroso-N-ethylurea (XII). The preparation was carried out according to Arndt's procedure for N-nitroso-N-methylurea.[10] The yield of dried product was 105 g (60%).

Infrared spectra were taken on a Perkin-Elmer Model 337 spectrophotometer. The propiophenone enamines show a characteristic band at 1635 cm^{-1}. Proton magnetic resonance spectra were taken on a Varian Model A-60. Chemical shifts are reported in parts per million downfield from tetramethylsilane. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The hygroscopic nature of enamines accounts for much of the error in the analyses. Solutions of enamines were prepared in ethanol just prior to use in kinetic studies. Reactions were run in aqueous solutions containing 3% ethanol. The kinetic experiments were carried out on a Cary Model 11 or Model 14 recording spectrophotometer. Except where otherwise noted reaction rates were measured at 25.00 ± 0.04°. The ionic strength was maintained at 0.20 by the addition of KCl. The molar absorbtivity of the reaction products from each enamine was compared with that found for a solution of the expected carbonyl product indicating that complete hydrolysis does occur. Because of the rapid rate of enamine hydrolysis encountered under certain conditions, the Cary Model 11 was modified so that solutions could be mixed by injection.[11] This allowed the measurement of reactions having half-lives as short as 0.9 sec.

First-order kinetics were observed throughout the entire pH range for all investigated enamines. The observed rate constants were calculated from slopes of plots of log $(A_t - A_\infty)$ or log $(A_\infty - A_t)$ *vs.* time. Points up to 90% conversion were used in the calculations. The symbol M^{-1} is employed for all second-order rate constants although those that represent observed first-order rate constants divided by the activity of the hydrogen or hydroxide ion concentrations as calculated from the antilog of pH measurements and from $pK_w = 14.00$ actually possess units of activity^{-1} sec^{-1}. These second-order rate constants may be converted to the molar concentration scale by multiplying them by 0.74, the mean ion activity of HCl and KOH in 0.20 *M* KCl.[12] Catalytic constants, ρ values, ω values, and all intercepts were calculated by the method of least squares. The estimated error in the observed rate constants is about 3% except when the observed hydrolysis rate is greater than 1×10^{-1} sec^{-1} where the error is estimated to be about 8%. There is a 5% error in the calculated energies and entropies of activation. The error in these values for the morpholine enamine is 14% because of its faster rate of hydrolysis.[13]

Results

The pH–rate profiles for the hydrolysis of the morpholine, dimethylamine, piperidine, and pyrrolidine enamines of propiophenone are presented in Figure 1. The points represent observed first-order rate constants; in regions where general acid catalysis is observed these represent values obtained by extrapolation to zero buffer concentration. A dashed line is drawn through the points calculated for rate-limiting formation of immonium ion. A solid line is drawn through the points calculated for its rate-limiting decomposition.

Hydrolysis in Basic and Neutral Solutions. For the morpholine enamine, k_{obsd} is independent of hydrogen ion concentration above pH 8. A run on the pH stat at pH 9.7 showed that neither hydrogen nor hydroxide ions are consumed in the overall reaction. Rate constants obtained by following the decrease in absorption of the enamine (220 mμ) are identical with those obtained by following the increase in absorption of propiophenone (244 mμ) (Figure 2), indicating no significant accumulation of any intermediate species. Figure 3 shows the effect of buffer concentration on the observed rate constants at two pH values; general acid catalysis is clearly indicated. The significant rate of hydrolysis at zero buffer concentration indicates the involvement of water as a general acid catalyst. The hydrolysis of the morpholine enamines of *p*-methyl-, *p*-chloro-, and *p*-nitropropiophenone also exhibit general acid catalysis at pH 10.38. When the rate constant obtained by extrapolation to zero buffer concentration is plotted against the σ value for the substituent,[14] a ρ value of -1.29 is obtained (Figure 4).

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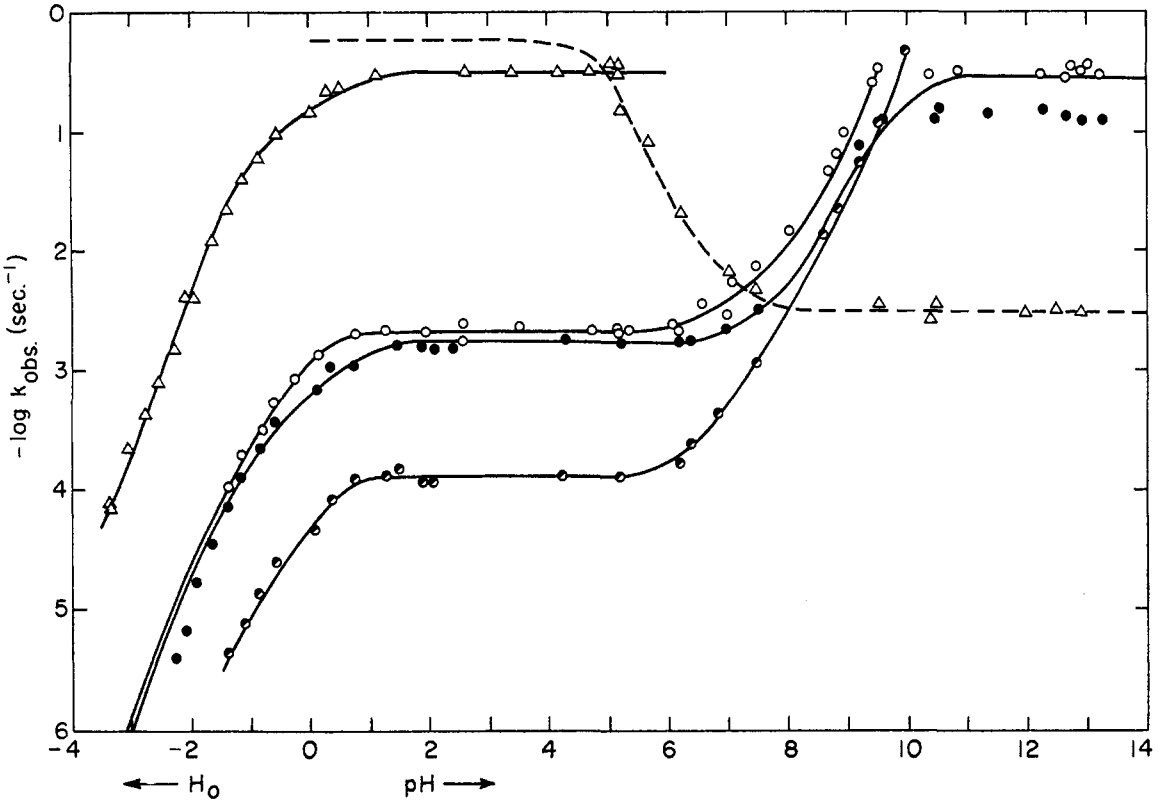

Figure 1. pH–rate profile for the hydrolysis of several propiophenone enamines at 25°: △, morpholine; ○, dimethylamine; ●, piperidine; ◐, pyrrolidine.

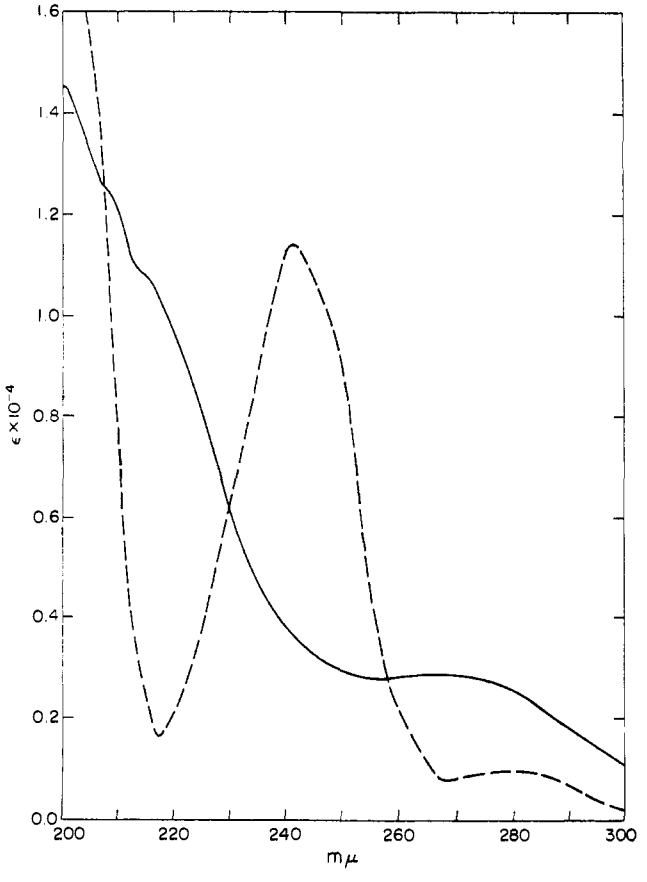

Figure 2. Absorption spectra of the morpholine enamine of propiophenone (solid line) and propiophenone (dashed line) in absolute ethanol at 6×10^{-5} *M*.

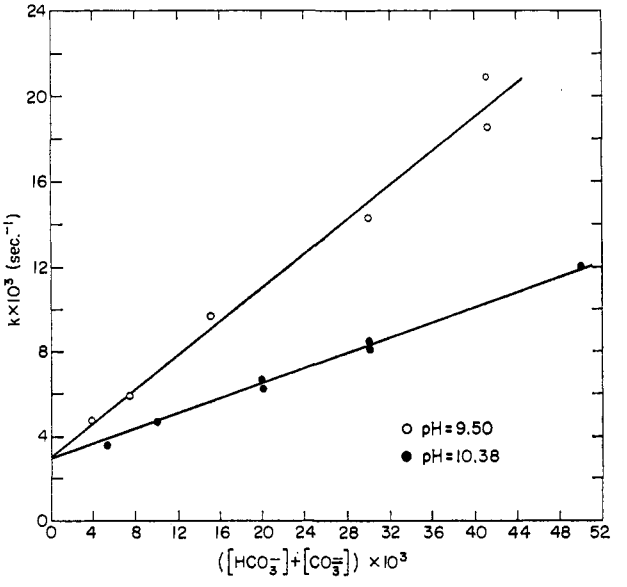

Figure 3. Observed first-order rate constants for the hydrolysis of the morpholine enamine of propiophenone as a function of total buffer concentration at 25°.

As the pH is decreased from 8 to about 5, the value of k_{obsd} extrapolated to zero buffer concentration for the hydrolysis of the morpholine enamine increases indicating the involvement of hydrogen ion in the rate equation. The linear relationship between k_{obsd} and general acid concentration is also found when the morpholine enamine is hydrolyzed at pH 7.48 and 7.00 using N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid (TES) as general acid and at pH

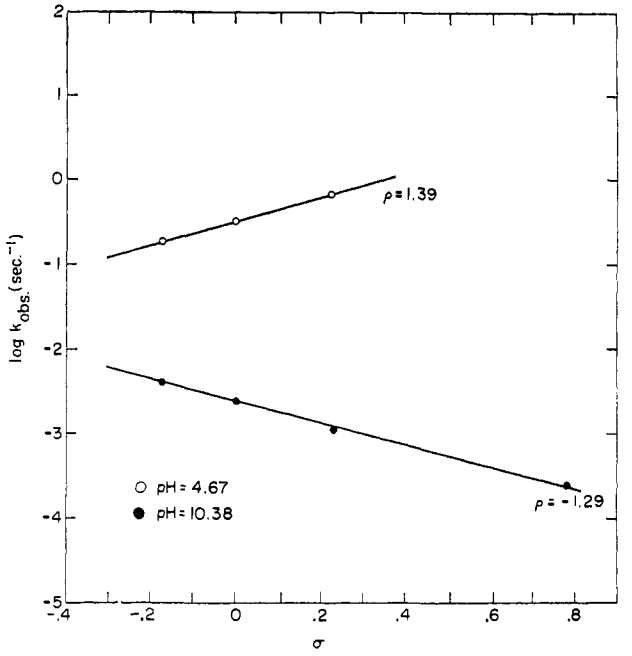

Figure 4. Logarithms of the observed first-order rate constants for the hydrolysis of *para*-substituted morpholine enamines of propiophenone as a function of the Hammett σ constant.

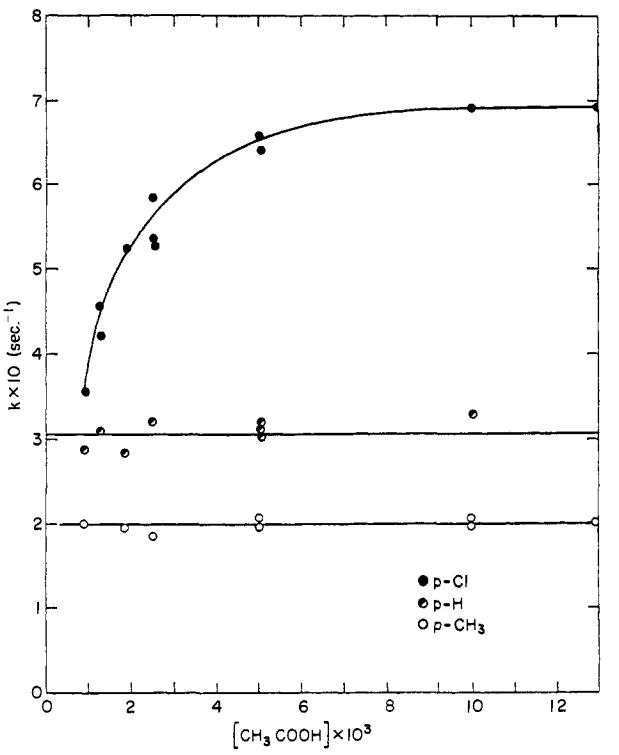

Figure 5. Observed first-order rate constants for the hydrolysis of the morpholine enamines of *p*-chloro-, *p*-hydro-, and *p*-methylpropiophenone as a function of general acid concentration at pH 4.67 and 25°.

6.18 using 2-(morpholino)ethanesulfonic acid (MES). When the pH is decreased to 5.58 with MES buffer or to 5.19 with succinic acid buffer, the linear relationship between observed rate constant and general acid concentration is no longer observed. The rate of hydrolysis is dependent on general acid concentration at low concentrations, leveling off and becoming essentially independent of general acid concentration as the concentration is increased. Such a leveling off of a rate *vs.* buffer concentration plot may be attributed to a change in rate-limiting step from one that is subject to general acid catalysis to one that is not. Below about pH 5 the rate of hydrolysis is independent of general acid concentration at all buffer concentrations.

The change in rate-limiting step from one that is subject to general acid catalysis to one that is not occurs at a much higher pH in the case of the dimethylamine, piperidine, and pyrrolidine enamines of propiophenone. At pH 10.36 the rate of hydrolysis of the dimethylamine enamine is linearly related to the general acid concentration while at pH 9.55 and below k_{obsd} is independent of general acid concentration. At pH 10.36 the rate of hydrolysis of the piperidine enamine of propiophenone is dependent on general acid concentration only at low concentrations and levels off as the concentration is increased, the rate of hydrolysis of the piperidine enamine of *p*-chloropropiophenone is linearly related to general acid concentration, and the rate of hydrolysis of the piperidine enamine of *p*-methylpropiophenone is independent of general acid concentration. The general acid catalyzed reaction exhibits a negative ρ value and the nongeneral acid-catalyzed reaction exhibits a small positive ρ value (<0.2).

Above about pH 10 the rates of hydrolysis of the dimethylamine and piperidine enamines are independent of pH and dependent on [HA]. The rate of hydrolysis of the pyrrolidine enamine is too rapid to be measured in this pH region. That the calculated rate constants (calculated for rate-limiting decomposition of immonium ion) in Figure 1 for the piperidine enamine do not correspond to the observed rate constants in strongly basic solution (where immonium ion formation is rate limiting) is attributed to the change in rate-limiting step that occurs about pH 10. From about pH 10–6 the rate of hydrolysis of the dimethylamine, piperidine, and pyrrolidine enamines is dependent on hydrogen ion concentration and independent of [HA]. The product of the observed rate constant and the hydrogen ion concentration is a constant from about pH 8 to 9.5 for the hydrolysis of the dimethylamine (1.1×10^{-10} M^{-1} sec^{-1}) and pyrrolidine (3.8×10^{-11} M^{-1} sec^{-1}) enamines.

Hydrolysis in Acidic Solutions. From about pH 1 to 6 the rate of hydrolysis of the three enamines is independent of both general acid and hydrogen ion concentrations. The same is true for the morpholine enamine from about pH 1 to 5. At pH 4.67 the rate of hydrolysis of both the *p*-CH$_3$ and unsubstituted morpholine enamines of propiophenone is independent of general acid concentration while the rate of hydrolysis of the *p*-chloro derivative is dependent on general acid concentration at low buffer concentration with the rate leveling off with increasing general acid concentration (Figure 5). Using the value obtained for the rate of hydrolysis of the *p*-chloro-substituted enamine at the higher buffer concentrations, a ρ value of 1.39 is obtained (Figure 4).

As the pH is decreased below unity, an increase in acidity causes a decrease in the observed rate of hydrolysis for all four enamines. Values of ρ have been obtained in acid solutions for *para*-substituted deriv-

atives of the morpholine enamine. At pH 1.10, $\rho = 1.53$. In solutions where $H_0 = 2.28$, $\rho = 2.20$ and an additional increase in acidity to $H_0 = -3.32$ has no further effect on the ρ value. Linear plots of log $k_{obsd} - H_0$ *vs.* log a_{H_2O} were obtained from rate constants observed for the hydrolysis of the morpholine and piperidine enamines in >3 *M* sulfuric acid solutions. The slope of the line, ω, is 1.4 and 3.2 for the morpholine and piperidine enamines, respectively. Similar plots were attempted in perchloric and hydrochloric acids. However, straight line slopes were not obtained from first-order plots when the reaction was carried out in perchloric acid, and the product spectra from the hydrolysis of the enamine in hydrochloric acid suggested that this acid reacts with the enamine, most probably by nucleophilic attack of chloride ion on the immonium ion.

Evidence for Buildup of Immonium Ion. Two consecutive reactions are observed during the course of hydrolysis of the piperidine enamine of propiophenone below pH 10. It is the k_{obsd} for the second reaction that is plotted in Figure 1. The initial reaction is very rapid; its rate increases as the pH is decreased below 10 and is subject to general acid catalysis. When the enamine is hydrolyzed in phosphate buffer in the pH range 6.3–7.3 the initial reaction is not observed although it is observed in this pH region with TES buffer. The initial reaction is barely discernible in the pH range 0–6. Below pH 0 it is more pronounced and its rate decreases slightly with increasing acidity. The dimethylamine and morpholine enamines exhibit similar initial rapid reactions. To delineate the nature of this initial reaction uv spectra were taken during the course of hydrolysis of the piperidine enamine at several pH's. In each set of spectra two species are seen, a strongly absorbing species at 244 mμ (ϵ 11,500) attributed to propiophenone and a less strongly absorbing species at about 270 mμ (ϵ 5500 in 5.0 *M* H_2SO_4).

The catalytic requirements and pH dependence of the initial reaction are accommodated by attributing it to a rapid buildup of immonium ion as described by eq 7. Attributing the species absorbing at about 270 mμ to immonium ion is substantiated by the observation that salicylideneethylamine has an absorption band at 273 mμ in acidic methanol.[11] The pH dependence of the initial reaction in strongly acidic solutions may be attributed to the departure of the activity of water from unity since under such conditions eq 7 reduces to $k_{obsd} = K_a k_{H_3O^+} a_{H_2O}$.

Further evidence for the postulation of a rapid buildup of immonium ion was obtained by following the hydrolysis of the propiophenone enamines in 5.0 *M* H_2SO_4 by nmr. The spectrum taken immediately after addition of the acid solution to the piperidine enamine showed a small doublet centered at 1.51 ppm with respect to tetramethylsilane and a larger triplet centered at 1.17 ppm. A second spectrum was taken immediately after completion of the first; the doublet had almost completely disappeared and the area under the triplet had increased. There was no evidence of the doublet in the third spectrum and no apparent change in the triplet. Several hours later no further change in the spectrum was observed. The solution was stored for several days, and the spectrum taken at the end of this time showed two triplets, one centered at 1.17 ppm and one centered at 0.73 ppm. The doublet centered at 1.51 ppm is attributed to the methyl group of the N-protonated enamine and the triplet at 1.17 ppm to the methyl group of the immonium ion. The late-appearing triplet at 0.73 ppm may be ascribed to the methyl group of propiophenone since the nmr spectrum of propiophenone in 5.0 *M* H_2SO_4 shows a single triplet occurring at this same field strength. Similar nmr studies of the other three propiophenone enamines gave no evidence for the existence of the N-protonated enamine; *e.g.*, the spectrum obtained immediately after adding the morpholine enamine to 5.0 *M* H_2SO_4 shows only two triplets, one at 0.73 ppm which increases with time and one at 1.17 ppm which decreases with time.

Acid Ionization Constants. Attempts to measure the pK_a's of the propiophenone enamines were unsuccessful because of the rapid formation of immonium ion at a higher pH than that at which the enamine would be fully N-protonated. An approximate pK_a of 5.0 was obtained for the morpholine enamine of propiophenone by observing the change in molar absorptivity at zero time with a change in pH. At pH 6.2 the enamine is fully unprotonated with evidence for some N-protonation at 6.0 and an increasing amount at 5.9. Approximate pK_a's could not be determined for the other propiophenone enamines because of their rapid hydrolysis rates in basic solutions, but in view of the steric and inductive effects of the phenyl group, the pK_a of a propiophenone enamine should be less than the pK_a of the corresponding isobutyraldehyde enamine. The morpholine, piperidine, and pyrrolidine enamines of isobutyraldehyde have been reported to have pK_a's of 5.5, 8.5, and 8.7, respectively.[15] The pK_a of the dimethylamine of isobutyraldehyde was found to be 7.85.

Preferred Geometric Isomer. The ir and nmr product spectra and vpc analysis indicate that only one geometric isomer is obtained from the syntheses of the propiophenone enamines. The uv spectrum of the morpholine enamine of propiophenone is given in Figure 2. The other propiophenone enamines exhibit similar spectra. Styrene[16] and propiophenone display a characteristic band at 244 mμ. In benzamide this band shifts to 225 mμ due to cross-conjugation.[17] The absence of a band between 225 and 244 mμ indicates that the enamine has its phenyl group twisted out of the plane of the double bond. When molecular models of the two possible geometrical isomers are studied, keeping the phenyl group and double bond in different planes, it appears that the steric requirement of the phenyl group is less than that of the amine. This steric factor suggests that the isomer with the methyl and phenyl groups on the same side of the double bond is the preferred geometrical isomer. *cis*-1-(4-Morpholino)-1,2-diphenylethylene has been reported to be thermodynamically more stable than the corresponding *trans* isomer.[18]

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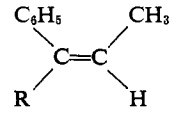
Table I. Rate and Equilibrium Constants for Enamine Hydrolysis[a]

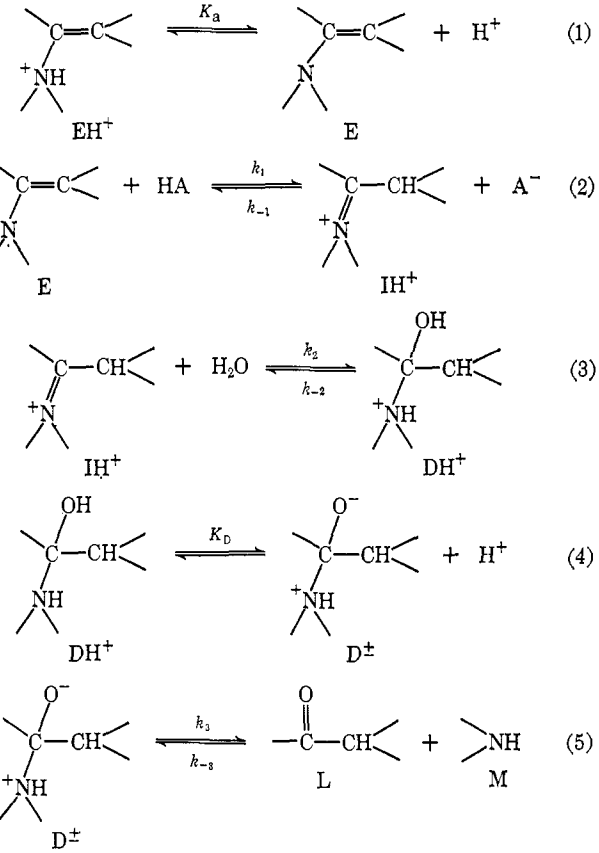


R	$k_{H_3O^+} \times 10^{-5}$ M^{-1} sec^{-1}	$k_{H_2O}[H_2O] \times 10^2$ sec^{-1}	Log K_1	$k_2' \times 10^{-3}$ M^{-1} sec^{-1}	k_3K_D/k_{-2}, M	$k_2^b \times 10^3$ sec^{-1}	E_2, kcal M^{-1}	$\Delta G_2^{\neq}$, kcal M^{-1}	$-\Delta S_2^{\neq}$, gibbs M^{-1}
	0.30	0.31			1.8	320 (566)	10.6	20.4	35
	14	14	9.76	5.0	1.2	1.74 (3.14)	11.4	23.3	42
	30	30	>9.85	11	1.3	2.26 (4.23)	10.8	23.6	45
		>80	>10.32	3.8	1.0	0.132 (0.266)	12.8	25.0	43

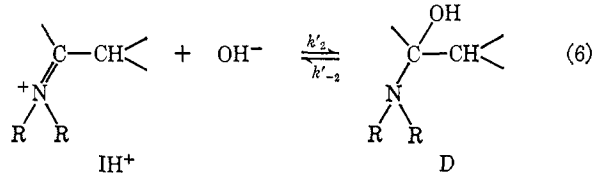
[a] 25.0° except for values in parentheses in k_2 column which are at 35.0°. [b] The second-order rate constants used to calculate the thermodynamic parameters were obtained by dividing the k_2 value by 55.

Discussion

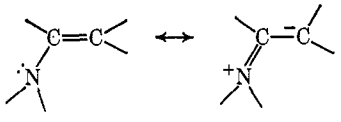
From a consideration of the pH–rate profiles and catalytic requirements for the hydrolysis of the morpholine, dimethylamine, piperidine, and pyrrolidine enamines of propiophenone, the following general mechanism is proposed for the hydrolysis of enamines.



In basic solutions IH^+ is also subject to attack by hydroxide ion (eq 6). Values for the rate and equilibrium constants are collected in Table I.



Hydrolysis in Strongly Basic Solutions (pH >10). Inspection of the pH–rate profiles in Figure 1 shows that above pH 10 the rate of hydrolysis of the propiophenone enamines (with the possible exception of the pyrrolidine enamine whose hydrolysis rate is immeasurably fast in this pH region) is independent of hydrogen ion concentration. General acid catalysis is observed and *para*-substituted derivatives of the morpholine and piperidine enamines exhibit negative ρ values indicating that the rate of hydrolysis is decreased by electron withdrawal from the reaction center. These observations give evidence for a rate-limiting proton transfer from a general acid to the enamine in this pH region. An enamine has two basic centers, the nitrogen atom and the carbon atom β to the nitrogen atom.



Since protonation of the nitrogen atom would be expected to take place by a diffusion-controlled reaction, protonation of the β-carbon atom of the free enamine (eq 2) must be the slow step of the reaction. (The N-protonated enamine should not undergo direct C protonation.) The rate equation can be expressed as

$$\text{rate} = [E]\Sigma k_1[HA] = [E_{tot}]k_{obsd}$$

The fraction of the enamine in the unprotonated form is dependent on the pH of the solution and the pK_a of the enamine

$$[E_{tot}] = [E] + [EH^+]$$

$$K_a = \frac{[E][H^+]}{[EH^+]}$$

Combination of the last three equations yields

$$k_{obsd} = \frac{K_a}{K_a + [H^+]}(k_{HA}[HA] + k_{H_3O^+}[H_3O^+] + k_{H_2O}[H_2O]) \quad (7)$$

Above pH 10 eq 7 reduces to

$$k_{obsd} = k_{HA}[HA] + k_{H_2O}[H_2O] \quad (8)$$

Equation 8 agrees with the lack of dependence of k_{obsd} on hydrogen ion concentration in the pH >10 region.

The rate of formation of immonium ion, as indicated by the value of $k_{H_2O}[H_2O]$, increases in the order morpholine < piperidine < dimethylamine < pyrrolidine enamine of propiophenone (Table I). The rate of C protonation increases with the basicity of the amine component of the enamine accounting for the slowest rate for the weakly basic morpholine enamine compared to the piperidine and other enamines of more than 100 times greater basicity. The rate of C protonation also depends upon the ease with which hybridization of the nitrogen atom can be changed from about sp^3 in the enamine to about sp^2 in the immonium ion. Bond oppositions are engendered in six-membered rings and relieved in five-membered rings as the hybridization is changed from sp^3 to sp^2. Consequently, formation of a double bond exocyclic to a six-membered ring is resisted while formation of a double bond exocyclic to a five-membered ring is accelerated relative to the acyclic analog.[19]

Hydrolysis in Neutral and Moderately Basic Solutions (pH 6–10). From pH 10 to pH 8 the hydrolysis of the morpholine enamine of propiophenone can still be described by eq 8. As the pH is decreased below 8, an increase in hydrogen ion concentration increases the rate of hydrolysis as predicted by eq 7. At pH 5.58 the linear relationship between the rate of hydrolysis and general acid concentration observed in more basic solutions is no longer valid. At low buffer concentrations, general acid catalyzed formation of immonium ion is still rate limiting. As the concentration of catalyst is increased, the rate of immonium ion formation increases linearly with increasing amount of catalyst until it reaches the rate of the next slowest step in the reaction sequence. At this point this step becomes rate limiting and since it is not catalyzed by general acids the overall rate of hydrolysis levels off with a further increase in buffer concentration.

The new rate-limiting step is consistent with uncatalyzed attack of water on the rapidly built up immonium ion (eq 3). At pH 4.67 uncatalyzed water attack is rate limiting for the hydrolysis of the morpholine enamines of propiophenone and *p*-methylpropiophenone even at very low concentrations of general acids. The hydrolysis of the *p*-chloro-substituted enamine, however, still exhibits rate-limiting formation of immonium ion at low buffer concentrations. This is not surprising since of the three enamines in Figure 5 the ratio of the rate of immonium ion formation to the rate of water attack on the immonium ion is smallest for the *p*-chloro-substituted derivative because of electron withdrawal from the reaction site. Thus the change in rate-limiting step occurs at a lower pH for this compound.

For the hydrolysis of the piperidine enamine of propiophenone a leveling off of the rate *vs.* buffer concentration plot occurs at pH 10.4 while for the dimethylamine enamine a leveling off is observed between pH 9.6 and 10.4 indicating a change in rate-limiting step at a slightly lower pH for the latter enamine.

(19) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 266, and references therein.

As the pH is decreased from 10 to about 6 the rate of hydrolysis of the dimethylamine, piperidine, and pyrrolidine enamines of propiophenone decreases markedly with increasing acidity and is not subject to catalysis by general acids. As in the case of the morpholine enamine, the nongeneral acid catalyzed reaction is attributed to rate-limiting attack of water on immonium ion (eq 3). Since, in the case of the hydrolysis of the dimethylamine, piperidine, and pyrrolidine enamines, this step is rate limiting in basic solutions, a contribution from hydroxide ion attack must be considered (eq 6). The rate equation can be expressed as

$$\text{rate} = (k_2 + k_2'[OH^-])[IH^+] \qquad (9)$$

Since the concentration of water is constant it does not appear in the rate equation but is considered as part of k_2.

The observation of a rapid buildup of immonium ion in acidic and weakly basic solutions precludes the possibility of a steady-state assumption for this species under these conditions. However, an equilibrium exists among unprotonated, N-protonated, and C-protonated enamines at all pH values where C protonation (immonium ion formation) is not rate limiting. Thus

$$[E_{tot}] = [E] + [EH^+] + [IH^+]$$

$$[E_{tot}] = \left(\frac{1}{K_1[H^+]} + \frac{1}{K_1K_a} + 1\right)[IH^+] \qquad (10)$$

where $K_1 = [IH^+]/[E][H^+]$ and $K_a = [E][H^+]/[EH^+]$. By combining eq 9 and 10 and rearranging, the observed rate constant can be expressed as

$$k_{obsd} = \frac{k_2K_1[H^+] + k_2'K_1K_w}{1 + [H^+]/K_a + K_1[H^+]} \qquad (11)$$

where K_w is the ion-product constant for water. The $[H^+]/K_a$ term of eq 11 can be ignored since it is small in comparison with $K_1[H^+]$. Thus the concentration of N-protonated species is never significant compared to the sum of the concentrations of the unprotonated and C-protonated species.

At pH 10.36 the hydrolysis of the piperidine enamine of propiophenone exhibits a very small ρ value (<0.2). At this hydrogen ion concentration eq 11 reduces to

$$k_{obsd} = \frac{k_2'K_1K_w}{1 + K_1[H^+]} \qquad (12)$$

and $K_1[H^+] = 0.25$. Since the equilibrium constant for C protonation, K_1, is aided by electron donation and the rate constant for hydroxide ion attack, k_2', is aided by electron withdrawal, the overall rate of reaction is little affected by substituent effects.

In strongly basic solution eq 11 reduces to

$$k_{obsd} = k_2'K_1K_w \qquad (13)$$

Equation 11 was derived from an equilibrium expression but there is no evidence for a rapid buildup of immonium ion in strongly basic solutions and, consequently, no reason to eliminate a steady-state assumption for this species. In this pH region, both the equilibrium and steady-state assumptions result in eq 13. From the values given in Table I for the piperidine enamine $k_{-1}[H_2O] = 2.4 \times 10^{-4}$ sec^{-1} and when $A^- = OH^-$ in eq 3, $k_{-1} = 2.4 \times 10^3\ M^{-1}$ sec^{-1}. Since

these values are less than those tabulated for k_2 and k_2', respectively, the conditions for eq 13 do not occur in this case; the decomposition of immonium ion is not rate limiting when it is at a steady-state level. When the immonium ion is at a steady state its formation is rate limiting; only when the immonium ion concentration builds up is its decomposition rate limiting.

The product of the observed rate constant and the hydrogen ion concentration is a constant from about pH 8 to 9.5 for the hydrolysis of the dimethylamine and pyrrolidine enamines. Under these conditions, eq 11 reduces to

$$k_{obsd} = k_2'[OH^-] \quad (14)$$

so that the product of the observed rate constant and hydrogen ion concentration is constant and equal to $k_2'K_w$.

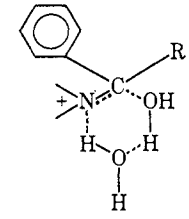
Hydrolysis in Moderately Acidic Solutions (pH 1–6). The pH–rate profiles in Figure 1 indicate that the rate of hydrolysis of the dimethylamine, piperidine, and pyrrolidine enamines of propiophenone is independent of hydrogen ion concentration from about pH 1 to about pH 6. The same is true for the morpholine enamine from pH 1 to 5. The reaction is also not subject to general catalysis in this pH range where immonium ion is the predominant species present. Water attack on the immonium ion is the predominant pathway for the reaction, the contribution of hydroxide ion attack being negligible, *i.e.*, $k_2K_1[H^+] \gg k_2'K_1K_w$ in eq 11. Since $[H^+]/K_a$ can be ignored, and $K_1[H^+] \gg 1$ in moderately acidic solutions, eq 11 reduces to

$$k_{obsd} = k_2 \quad (15)$$

The rate constant for water attack, k_2, increases in the order pyrrolidine ($pK_a = 11.1$)[15] < piperidine ($pK_a = 11.1$)[20] < dimethylamine ($pK_a = 10.8$)[20] ≪ morpholine ($pK_a = 8.7$).[21] Except for the pyrrolidine enamine, this is the order that would be predicted from a consideration of the relative basicities of the amine component of the enamines. The decreased reactivity of the pyrrolidine enamine may be explained by the observation that as the hybridization of a ring atom is changed from sp^2 to sp^3, bond oppositions are engendered if that atom is in a five-membered ring but relieved if it is in a six-membered ring. Consequently, a reaction involving destruction of a double bond exocyclic to a five-membered ring is retarded relative to the reaction involving the six-membered ring analog.

Thermodynamic parameters (Table I) were obtained for the hydrolysis of the propiophenone enamines at pH 4 where eq 3 is rate limiting. Below about pH 5 the hydrolysis of the propiophenone enamines becomes formally similar to the hydrolysis of Schiff bases since the acidity is sufficient to cause both rapid buildup of the enamine immonium ion $>C{=}N^+R_2$, and to protonate the imino nitrogen of the Schiff base, $>C{=}N^+(H)R$. For both classes of compounds the rate-limiting step in moderately acidic solutions is the attack of water on the positively charged imine linkage.[22–24]

The entropies of activation for the propiophenone enamines are about 10 gibbs/mol more negative than those for a series of substituted benzylidene-1,1-dimethylethylamines.[25] It is possible that the more negative activation entropies can be attributed to formation of a cyclic transition state, I, with the enamines but not with the Schiff bases. A cyclic



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transition state has the advantage of leading to a product in which the proton is on the nitrogen atom rather than on the less basic oxygen atom. A catalyst, therefore, is not required in order to remove a proton from the water molecule. Thus rate-limiting attack of water on the immonium ion intermediate of a propiophenone enamine is uncatalyzed (eq 3) while rate-limiting water attack on N-protonated benzylidene-1,1-dimethylethylamine is subject to general base catalysis.[22]

While this work was in progress a series of papers appeared in which the hydrolysis of the morpholine, piperidine, and pyrrolidine enamines of isobutyraldehyde was studied.[26–28] Protonation of the β-carbon atom is still rate limiting for the morpholine and piperidine enamines around pH 2.[28] Only in the case of the pyrrolidine enamine from about pH 2 to 5 is rate-limiting attack of water observed. Unlike the propiophenone enamines, water attack on this isobutyraldehyde enamine is subject to general base catalysis. That rate-limiting formation of immonium ion predominates in the case of the isobutyraldehyde enamines while decomposition of that species is rate limiting over a wide range of pH for the propiophenone enamines may be ascribed to conjugation stabilization that accelerates protonation of the β-carbon atom and retards the rate of reaction of the aromatic immonium ion relative to the corresponding aliphatic species. A study of the hydrolysis of a series of primary and secondary 2-cyanoenamines shows that immonium ion formation is the rate-limiting step down to pH 2 where carbinolamine formation becomes rate limiting.[29] That immonium ion formation is rate limiting throughout almost the entire pH range may in part be attributed to conjugation stabilization of the cyanoenamines.

Hydrolysis in Strongly Acidic Solutions (pH <1). Below about pH 1 an increase in acidity causes a marked decrease in the rate of hydrolysis (Figure 1). Since the observed rate constants obtained by following the increase in absorption of propiophenone at 244 mμ are identical with those obtained by following the de-

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(23) R. B. Martin, *J. Phys. Chem.*, **68**, 1369 (1964).
(24) P. Y. Sollenberger and R. B. Martin in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1968, p 349.
(25) R. K. Chaturvedi and E. H. Cordes, *J. Amer. Chem. Soc.*, **89**, 1230 (1967).
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(27) E. J. Stamhuis and W. Maas, *Rec. Trav. Chim.*, **82**, 1155 (1963).
(28) W. Maas, M. J. Janssen, E. J. Stamhuis, and H. Wynberg, *J. Org. Chem.*, **32**, 1111 (1967).
(29) J. K. Coward and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 5329 (1969).

crease in absorption of immonium ion at 270 mμ, there is no buildup of any intermediate species and a steady-state approximation can be made for the carbinolamine intermediate. From eq 1–5 we obtain

$$\text{rate} = \frac{-\mathrm{d}[\mathrm{IH}^+]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{L}]}{\mathrm{d}t} = k_3[\mathrm{D}^\pm] = \frac{k_3k_2K_\mathrm{D}[\mathrm{IH}^+]}{k_{-2}[\mathrm{H}^+] + k_3K_\mathrm{D}}$$

The concentration of water is considered as part of k_2. In strongly acidic solutions, however, the activity of water is no longer unity. In such solutions the observed rate constant may be expressed as

$$k_\mathrm{obsd} = \frac{k_3K_2K_\mathrm{D}a_{\mathrm{H_2O}}{}^\omega}{[\mathrm{H}^+] + k_3K_\mathrm{D}/k_{-2}} \qquad (16)$$

where $K_2 = k_2/k_{-2}$. From eq 16 it is evident that in weakly acidic solutions where $k_3K_\mathrm{D}/k_{-2} \gg [\mathrm{H}^+]$ and $a_{\mathrm{H_2O}} = 1$, the observed rate constant is simply equal to k_2, as is the case from about pH 1 to 6. As the pH is decreased below unity, the hydrogen ion concentration term in the denominator of eq 16 can no longer be neglected, and below about pH 0 the activity of water becomes less than unity. When $H_0 < -1.3$, the acidity of the solution is such that $(h_0) \gg k_3K_\mathrm{D}/k_{-2}$ and eq 16 reduces to

$$k_\mathrm{obsd} = k_3K_2K_\mathrm{D}a_{\mathrm{H_2O}}{}^\omega/(h_0) \qquad (17)$$

indicating that carbinolamine decomposition has become rate limiting.

The change in rate-limiting step from attack of water on immonium ion to decomposition of carbinolamine to propiophenone and amine is evidenced by the ρ values obtained in solutions of varying acidity. For the morpholine enamines we obtain at pH 4.67, $\rho = 1.39$, at pH 1.10, $\rho = 1.53$, and at both $H_0 = -2.28$ and -3.32, $\rho = 2.20$. When the acidity of the solution is sufficient to cause an equilibrium to prevail in eq 3, thereby making carbinolamine decomposition to carbonyl compound and amine rate limiting, the ρ values no longer increase with increased concentration of hydrogen ions and the overall rate is more dependent on electron density at the reaction site.

The pH dependence observed in strongly acidic solutions indicates that the N-protonated carbinolamine looses a proton before it undergoes rate-limiting decomposition to carbonyl compound and amine. Otherwise the acid inhibition would have to be attributed solely to the departure of the activity of water from unity.[23,24] The N-protonated carbinolamine may lose a proton in a rapid reversible step to form either the neutral carbinolamine or the carbinolamine zwitterion. It has been proposed that for reactions in which protons are liberated in acid solutions, a plot of log $k_\mathrm{obsd} - H_0$ *vs.* the logarithm of the activity of water will result in a straight line, the slope of this line, ω, indicative of the role of water in the reaction mechanism (eq 16 and 17): $\omega < 0.0$, water is not involved; $+1.2 < \omega < +3.3$, water acts as a nucleophile; $\omega > +3.3$, water acts as a proton transfer agent.[30,31] The slope of such a plot might determine whether the neutral or zwitterionic carbinolamine is the reactive species since water would act as a proton transfer agent in the decomposition of the neutral species but would not be involved in the decomposition of the zwitterion. The values of ω obtained at greater than 3 *M* H_2SO_4 are 1.4 and 3.2 for the morpholine and piperidine enamines, respectively. The observed ω values are consistent with the appearance of water as a nucleophile in a preequilibrium step according to eq 17 and do not allow for its additional appearance as a proton transfer agent. Thus water does not appear to be involved in carbinolamine decomposition suggesting that it is the carbinolamine zwitterion that undergoes rate-limiting decomposition. The observed pH dependence in strongly acidic solutions can be accommodated by the combined effects of acid inhibition of carbinolamine zwitterion formation and the departure of the activity of water from unity.

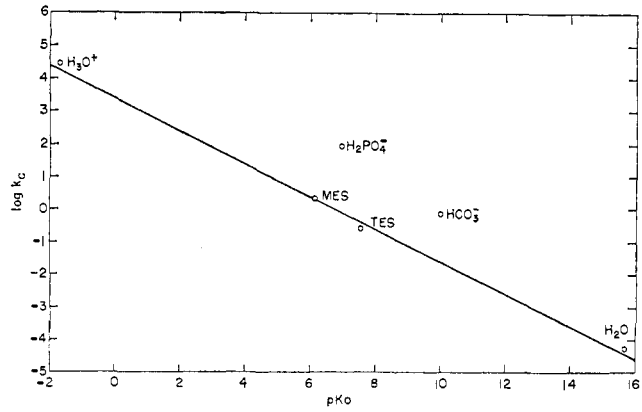

Figure 6. Brønsted plot of catalytic coefficients of various acids in the C protonation of the morpholine enamine of propiophenone. The slope, α, is 0.50.

Bifunctional Buffers. The monobasic phosphate ion and bicarbonate ion accelerate the rate of hydrolysis of those enamines that undergo rate-limiting protonation of the β-carbon in the pH regions governed by these buffers to a greater extent than would be predicted from their general acid strengths (Figure 6). For example, the hydrolysis of the morpholine enamine of propiophenone undergoes a transition from rate-limiting formation of immonium ion to rate-limiting decomposition of that species at about pH 5.5. When phosphate buffer is used, the change in rate-limiting step as indicated by a leveling off of the rate *vs.* [HA] plot is seen to occur at as high a pH as 7.3. That this leveling off should be attributed to a transition in rate-limiting step rather than to complexing of the catalyst to itself or to substrate is evidenced by the fact that rate *vs.* phosphate buffer concentration plots obtained for the hydrolysis of the morpholine enamine of *p*-nitropropiophenone do not level off. The pH at which the change in rate-limiting step occurs for this enamine is presumably not close enough to the pH region of phosphate buffer for acceleration of C protonation by this buffer to result in a change in rate-limiting step. The possibility that phosphate buffer is causing the formation of a product other than propiophenone is ruled out by a comparison of the ultraviolet absorption spectrum of the product with that of propiophenone.

Unusual catalytic effects have been observed for bifunctional buffers in other systems but these can generally be explained by the ability of the buffers to act as amphoteric catalysts.[24] For example, the

(30) (a) J. F. Bunnett, *J. Amer. Chem. Soc.*, 83, 4956 (1961); (b) *ibid.*, 83, 4968 (1961); (c) *ibid.*, 83, 4973 (1961); (d) *ibid.*, 83, 4978 (1961).
(31) R. B. Martin, *ibid.*, 84, 4130 (1962).

monobasic phosphate ion and bicarbonate ion exhibit an unusual catalytic effect in iminolactone hydrolysis, affecting the nature of the products rather than the rate of hydrolysis.[32] The unusual catalytic behavior is explained by the ability of these buffers to promote a concerted cyclic proton shift in the neutral carbinolamine intermediate. If the nitrogen atom of the enamine were protonated, a similar cyclic proton shift might be a possible explanation for the acceleration of β-carbon atom protonation. This, however, is not the case since the pK_a of the morpholine enamine of propiophenone is considerably less than the pH of the regions in which the unusual catalytic effect is observed, and the observation of general acid catalysis by these buffers requires the N-protonated species to be catalyzed by the basic component of the buffer. The basic component of the bicarbonate buffer system is the carbonate ion which is not bifunctional and consequently cannot participate in a concerted cyclic proton shift. It appears that another explanation is required for acceleration of β-carbon atom protonation of enamines by these bifunctional buffers.

Enamine Basicity. There is considerable disagreement in the literature as to whether enamines are stronger or weaker bases than the corresponding saturated amines. This disagreement results from the fact that an enamine has two possible sites for protonation. In all cases where basicity measurements are known to refer to protonation of the nitrogen atom of the enamine, enamines are found to be weaker bases than the corresponding saturated amines.[15,33] The decreased basicity may be attributed to the electron-withdrawing effect of the double bond and delocalization of the free nitrogen electron pair by resonance. Those cases in which enamines have been reported to be stronger bases than the corresponding saturated amines are situations in which C protonation of the enamine is compared with N protonation of the saturated amine.[34] It is evident from the fact that $K_a > 1/K_1$ that the N-protonated enamine is a weaker base than is the C-protonated species (immonium ion). This inequality also indicates that though formed more slowly the C-protonated species is more stable thermodynamically. It is the greater stability of the C-protonated species that is responsible for its eventual buildup during enamine hydrolysis. An nmr investigation of several aliphatic enamines has also shown that the N-protonated enamine is formed more rapidly but the immonium ion is more stable.[35]

Enamines are normally synthesized in hydrocarbon solvents so that inferences regarding the rate-limiting step in the formation reaction must be made with caution. From observations on synthesis rates from cyclic ketones[5,36] and other considerations it appears likely that carbinolamine dehydration (reverse of eq 3) is the rate-limiting step in the synthesis of many enamines.

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(35) J. Elguero, R. Jacquier, and G. Tarrago, *Tetrahedron Lett.*, **51**, 4719 (1965).

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Ground States of σ-Bonded Molecules. XI.[1] Conformational Analyses by MINDO/2 Method[2]

Nicolae Bodor[3] and Michael J. S. Dewar

Contribution from the Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712. *Received December 4, 1969*

Abstract: The MINDO/2 method has been used to predict relative stabilities of the conformers of some alicyclic hydrocarbons, including methyl-substituted cyclohexanes, decalins, and steroids. The results seem to agree well with the available evidence.

Recent work in these laboratories[1,4] has led to the development of a semiempirical SCF MO treatment, including all the valence electrons, which provides good estimates both of molecular geometries and heats of formation. This (MINDO/2) is a development of the original MINDO method,[5] using an improved method of parametrization. In its latest[1] form, MINDO/2 has given surprisingly good estimates of the differences in energy between such pairs of conformational isomers as the eclipsed and staggered forms of ethane, the boat and chair forms of cyclohexane, and the *cis* and *trans* forms of 1,3-butadiene; it therefore seems to offer a promising approach to the general problem of conformational isomerism in alicyclic systems. Here we report some preliminary applications of this kind to a number of cycloparaffin derivatives including a few simple steroids; to our knowledge, no all-valence-electron SCF MO treatment has previously been applied to molecules of this size.

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(2) This work was supported by the Air Force Office of Scientific Research through Grant No. AF-AFOSR-1050-67.

(3) Robert A. Welch Postdoctoral Fellow. On leave of absence from The Chemical-Pharmaceutical Research Institute, Cluj, Romania.

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