Mechanism of Enamine Reactions. IV.[1a] The Hydrolysis of Tertiary Enamines in Acidic Medium[1b]

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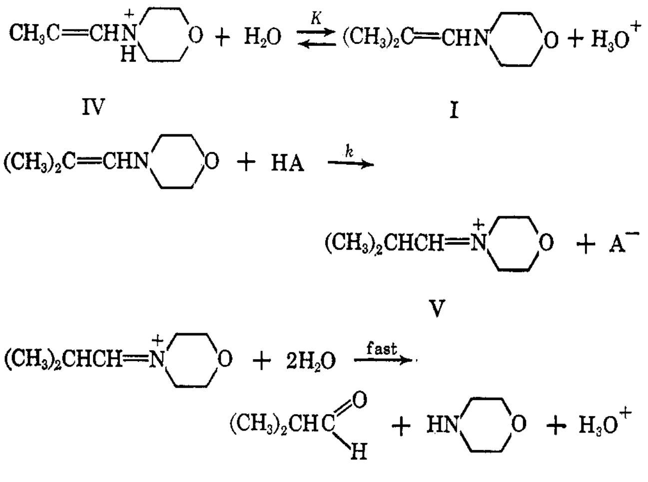
The rates of hydrolysis of 1-N-morpholino-1-isobutene (I), 1-N-piperidino-1-isobutene (II), and 1-N-pyrrolidino-1-isobutene (III) have been investigated in aqueous solutions of strong acids. The results lead us to propose a mechanism in which the rate-determining step varies with the pH of the solution. The reactivity of these enamines toward hydrolysis is discussed. It appears that the reactivity is influenced by the inductive effect of the cyclic amino part of the molecule and the difference in tendency in the formation of an exocyclic double bond of the cyclic systems.

In a previous paper[2] we reported the results of a study of the hydrolysis of tertiary enamines in basic, neutral, and, for 1-N-morpholino-1-isobutene (I), also in weakly acidic aqueous solutions.

A mechanism (Scheme I) was proposed in which the rate-determining step consisted of a proton transfer to the β-carbon atom of the enamine. The free base was shown to be in a mobile equilibrium with its N-protonated conjugate acid. The general expression for the first-order rate constant k was

SCHEME I



$$k = \frac{K}{K + a_{H_3O^+}}(a_{H_3O^+}k_{H_3O^+} + k_{HA}c_{HA} + k_{H_2O}c_{H_2O}) \quad (1)$$

In aqueous solutions of strong acids eq 1 reduces to 2, being independent of the acidity of the solution.

$$k = Kk_{H_3O^+} \quad (2)$$

Since both K and $k_{H_3O^+}$ have been determined,[2] the following rate constants of hydrolysis are predicted in acid solutions for compounds I–III.

1-N-morpholino-1-isobutene (I)	$k = 1.05 \times 10^{-3}$ sec^{-1}
1-N-piperidino-1-isobutene (II)	$k = 0.62 \times 10^{-3}$ sec^{-1}
1-N-pyrrolidino-1-isobutene (III)	$k = 11.8 \times 10^{-3}$ sec^{-1}

From the data in our previous paper[2] it is easily shown that eq 2 should describe the hydrolysis in solutions below pH 4 for I, pH 6 for II, and pH 7 for III if no other acids than H_3O^+ and H_2O are present.

From a study of the hydrolysis of these enamines with strong acids it appeared, however, that (2) is valid only in a limited pH range and on further acidification must be replaced by a more complicated equation.

Results

The hydrolysis of the enamines was followed spectrophotometrically at 25°. The decrease in ultraviolet absorption could be described by the kinetics of a first-order reaction. However, contrary to our expectation the rate constant, k (eq 2), was dependent upon the acidity of the aqueous enamine solutions.

A few first-order rate constants for the hydrolysis of I, II, and III at different concentrations of strong acids are collected in Table I.

TABLE I

FIRST-ORDER RATE CONSTANTS IN AQUEOUS PERCHLORIC ACID OF I, II, AND III AT 24.84°

	$k \times 10^4$ sec^{-1}		
Acidity, M	I	II	III
0.001			3.1
0.005			2.9
0.01	1.04	5.0	2.9
0.05			1.7
0.10	1.06	3.1	0.99
0.55	0.95		0.071
1.00	0.84	0.065	
3.12	0.22		
6.01	0.0049		
Predicted from eq 2	1.05	6.2	118

The results clearly show that the rate of hydrolysis cannot be described by eq 2 except in the case of I and II around pH 2.

The first-order rate constants measured in the case of III, however, were much smaller than expected from eq 2, even in solutions of low acidity. Therefore, a few measurements on III were carried out in a weakly acidic medium using acetate buffers. The results are given in Figure 1.

The values for k (corrected for buffer contributions) are found to be 7.2×10^{-4} sec^{-1} at pH 4.94 and 3.9×10^{-4} sec^{-1} at pH 4.41 and, thus, are again clearly pH dependent.

The situation is summarized in Figure 2, where the observed first-order rate constants, corrected for contributions of acids other than H_2O and H_3O^+, are compared with the rate constants calculated from the first and third terms of eq 1.[2]

Obviously the drawn lines in Figure 2 represent the rate of protonation of the enamines. The fact that the rate of hydrolysis becomes smaller in acid media indi-

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[1] (a) Part III: E. J. Stamhuis, W. Maas, and H. Wynberg, *J. Org. Chem.*, **30**, 2160 (1965). (b) Abstracted from the Ph.D. Thesis of W. Maas, University of Groningen, 1966 (in Dutch).

[2] E. J. Stamhuis and W. Maas, *J. Org. Chem.*, **30**, 2156 (1965).

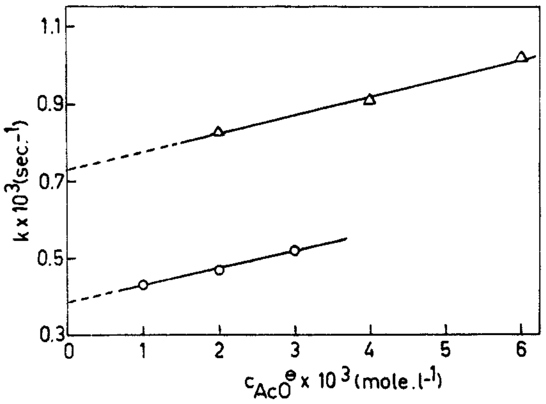


Figure 1.—First-order rate constants for the hydrolysis of 1-N-pyrrolidino-1-isobutene in acetate buffers (24.84°).

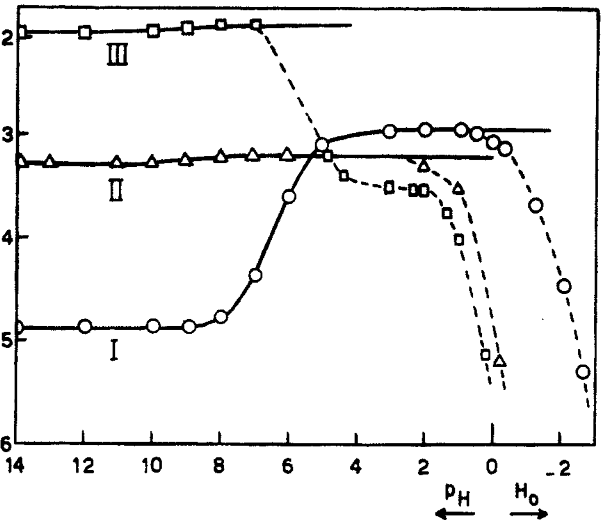


Figure 2.—Observed *vs.* calculated rates of hydrolysis of enamines (24.84°). Drawn lines: calculated log k values for I, II, and III. Observed values: ○ for I, △ for II, and □ for III. Values are corrected for buffer contributions.

cates that the immonium ions formed when the enamine is protonated on the β-carbon atom must be present as reaction intermediates.

The existence of the immonium ion V was proved by ultraviolet and nmr spectroscopy. A freshly prepared solution of I in a 6 *M* aqueous solution of perchloric acid showed an ultraviolet absorption maximum at 1960 A due to the conjugate acid IV.[2] After storage for 24 hr the absorption maximum was situated at 2150 A. The wavelength of the absorption maximum is 20 A smaller than the wavelength of the absorption maximum of I, consistent with the presence of the immonium ion V.[3,4]

The nmr spectrum of the freshly prepared solution of I in 6 *M* aqueous perchloric acid showed two absorptions situated at τ 8.08 and 8.17 and a doublet at τ 8.69. After 1 day the solution gave an nmr spectrum that showed no absorption at τ 8.08 and 8.17, but doublets at τ 8.69 (J = 7 cps) and τ 8.88 (J = 8 cps). According to the results of Elguero and co-workers[5] for the same enamine and of Leonard and Paukstelis[6] for III the absorption at τ 8.08 and 8.17 must be ascribed to the methyl groups of the conjugate acid IV. The doublet at τ 8.69 is ascribed to the methyl groups of the immonium ion V and the doublet at τ 8.88 to the isobutyraldehyde resulting from hydrolysis. The latter assumption was checked by dissolving isobutyraldehyde in 0.1 *N* aqueous hydrochloric acid. The nmr spectrum of this solution showed a doublet at τ 8.94 (J = 8 cps).

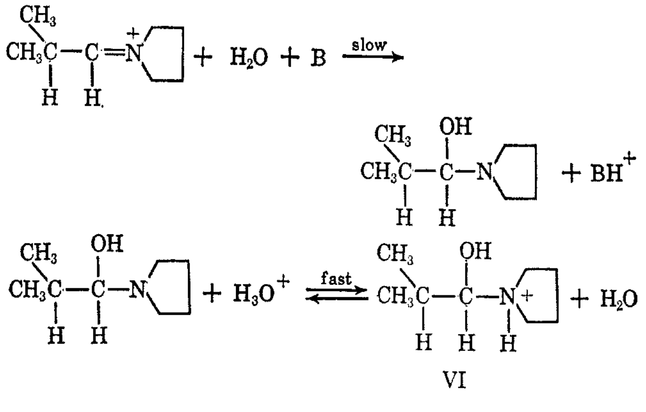
Discussion

Mechanism.—The decreasing rate of the hydrolysis of the enamines and the presence of the immonium ions as reaction intermediates show that a change in the rate-determining step occurs when the acidity of the medium increases. This change occurs for the compounds I and II around pH 2, but for III already around pH 6.

The protonation of the β-carbon atom of the enamine is no longer rate determining but may be considered to proceed in a fast equilibrium before the rate-determining step.

The mechanism of the hydrolysis of immonium ions may be evaluated best from the hydrolysis of III. This enamine shows a decrease of k in the pH region from about pH 7 to 2. We confine ourselves to this phenomenon first. Catalysis by base is the most plausible explanation. From the observation that the rate decreases with decreasing pH (catalysis by OH^- ions) and from the action of acetate ions (Figure 1), this catalysis appears to be a general base catalysis. The initial product of the reaction with water is an α-amino alcohol, which in the acid solution will subsequently be protonated in a rapid equilibrium according to the reactions shown in Scheme II. This mechanism is similar to that of the hydration of carbonyl compounds,[7] proposed by Bell and De B. Darwent[8] except for the fact that in the latter reaction general acid catalysis occurs as well as general base catalysis (Scheme III). In our case, however, we are convinced that acid catalysis, leading to a doubly charged ion may be excluded.

SCHEME II



From the results obtained in the acetate buffer solutions and the dilute solutions of perchloric acid the values for the catalytic coefficients of the Brønsted bases in the hydrolysis of the immonium ion, derived from 1-N-pyrrolidinoisobutene, at 24.84° are as fol-

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(3) G. Opitz, H. Hellmann, and H. W. Schubert, *Ann.*, **623**, 117 (1959).

(4) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

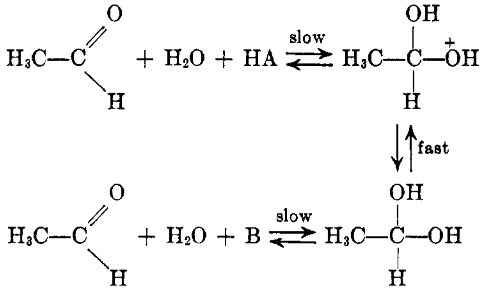
(5) J. Elguero, R. Jacquier, and G. Tarrago, *Tetrahedron Letters*, 4719 (1965).

(6) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963).

(7) In many reactions immonium ions behave in the same way as carbonyl compounds: J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

(8) R. P. Bell and B. de B. Darwent, *Trans. Faraday Soc.*, **46**, 34 (1950).

Scheme III



lows: $k_{OH^-} = 4 \times 10^5$ l. mole^{-1} sec^{-1}, $k_{OAc^-} = 4 \times 10^{-2}$ l. mole^{-1} sec^{-1}, $k_{H_2O} = 5.5 \times 10^{-6}$ l. mole^{-1} sec^{-1}.

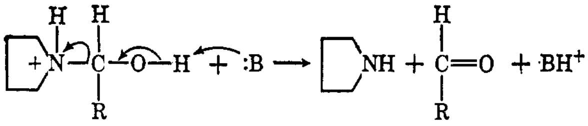
As can also be calculated from these rate constants the rate of hydrolysis around pH 2 becomes pH independent since the hydrolysis is completely due to the action of water, the contribution of the OH^- ions clearly being negligible owing to their very low concentration. This mechanism explains the variation of k with pH in the range of pH 7–2. The decrease of the reaction rate at pH values lower than 2 can only be explained by another change of the rate-determining step.

After hydration of the immonium ion the solution contains a protonated α-amino alcohol (VI). This species contains two acidic hydrogen atoms, the nitrogen proton and the oxygen proton, resulting in two acid–base equilibria shown in Scheme IV.

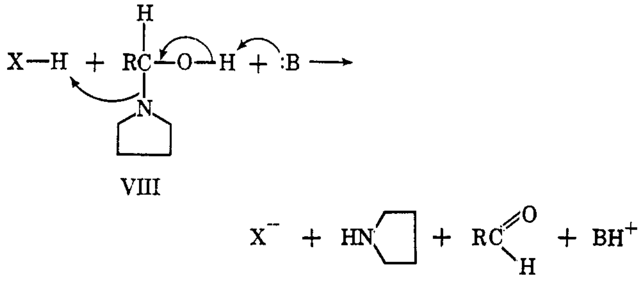
At first sight VIII might seem to be a more stable species than the zwitterionic species VII. But an estimate of the acidification of the OH group caused by the neighboring positive nitrogen atom[9] leads to a pK_a value of the OH function in VI of about 8 or 9 which is in the same order of magnitude as pK_a for the reaction VI ⇆ VIII.[10] Consequently we may assume that both VII and VIII exist in small, but nonnegligible, concentrations.

The rate-determining reaction might be a reaction of any of the three species VI, VII, or VIII as shown in steps a–c.

(a) a slow reaction of the N-protonated amino alcohol with a base

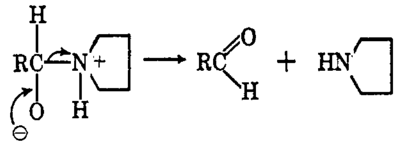


(b) a slow reaction of the amino alcohol with a base



VIII

(c) a slow reaction of the ammonium alcoholate zwitterion



VII

The reaction of species VI can only explain the observed pH dependence if the active base were the OH^- ion. In view of the fact that the concentration of OH^- is extremely small, it is unlikely that water under these circumstances would not contribute appreciably to the over-all reaction. The pH dependence of reactions b and c are both explained by the decreasing concentrations of VII and VIII with decreasing pH, so that here water may be the other reagent. Of reactions b and c the latter is by far the most probable one since the removal of the proton from the oxygen atom as in VII results in a considerable driving force to expel the strongly basic pyrrolidine. Besides, a reaction of type b would be expected to proceed much faster with VI than with VIII.

The decrease of the observed reaction rate in acidic media has also been observed in the hydrolysis of Schiff bases by Cordes and Jencks.[11] They explained this decrease by assuming a change of rate-determining step from the hydration of the protonated Schiff base to the reaction of the amino alcohol *via* the zwitterion. The mechanism of hydrolysis of enamines just outlined is exactly analogous to the mechanism of Cordes and Jencks[12] for the hydrolysis of Schiff bases.

Considering our own data and the results of Cordes and Jencks we conclude that the hydrolysis of α-amino alcohols proceeds *via* a slow reaction of the ammonium alcoholate zwitterion.

The mechanism of the hydrolysis of simple tertiary enamines in moderately concentrated aqueous solutions of strong acids may now be summarized by Scheme V.

Structure and Reactivity.—Owing to differences in reactivity of the enamines that were investigated, the rate-determining step in solutions with pH between 1 and 6 is dependent on the structure of the enamine. The experimental results compiled in Figure 2 show that the enamines I and II follow a different pattern. These are only apparent differences, however, and the general reaction scheme is the same.

For the second-order rate constants of the Brønsted acids H_3O^+ and H_2O of the protonation of the β-carbon atom of I, II, and III (reaction 4) the following values

	I	II	III
$k_{H_3O^+}$, l. mole^{-1} sec^{-1}	3.1×10^2	1.4×10^5	8.4×10^6
k_{H_2O}, l. mole^{-1} sec^{-1}	2.7×10^{-7a}	0.97×10^{-5}	1.7×10^{-4}

have been obtained,[2] with *a* determined in the present work. From these data the order of reactivity is seen to be pyrrolidino > piperidino >> morpholino.

The difference between the pyrrolidine enamine containing a five-membered ring and the piperidine enamine containing a six-membered ring may be explained by a different tendency to form an exocyclic double bond. When an exocyclic double bond is formed, the hybridization of the nitrogen atom is changed from sp^3 to sp^2, which is favored in the five-

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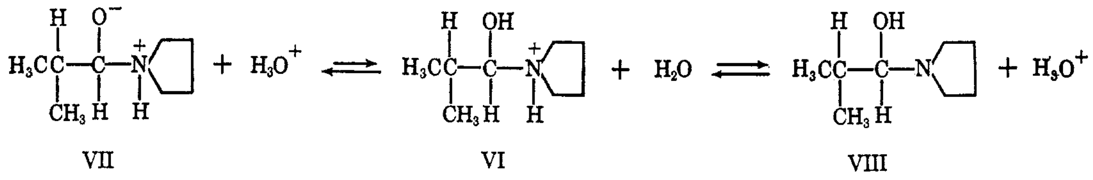
[9] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 222.

[10] For a detailed argument see ref 1b, pp 79, 80.

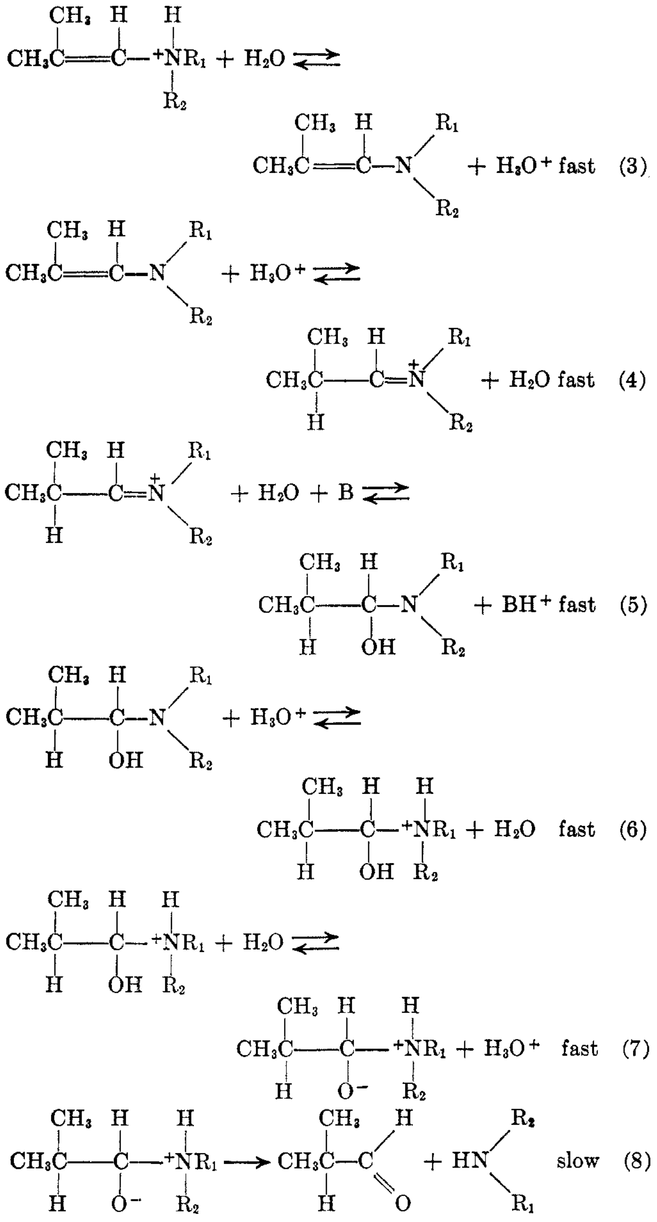
[11] E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **85**, 2843 (1963).

[12] W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

SCHEME IV



SCHEME V



I, R_1, R_2 = morpholino
II, R_1, R_2 = piperidino
III, R_1, R_2 = pyrrolidino

membered ring, but hampered in the six-membered ring.[13]

The greater reactivity of the piperidine enamine as compared with the morpholine analog may be explained by the electron-attracting influence of the oxygen atom of the morpholine ring, which reduces the electron density of the β-carbon atom. This effect also makes morpholine a much weaker base than piperidine.[14]

In weakly acidic solutions the rate of hydrolysis of III is determined by the rate of hydration of the immonium ion (reaction 5). Since this ion is stabilized by the favorable exocyclic double bond, a higher rate of hydration can be expected for the corresponding piperidine intermediate. The immonium ion derived from the morpholine enamine will be highly reactive toward water. The inductive effect of the oxygen atom and energetic unfavorable exocyclic double bond will result in a rapid addition of water which leads to the amino alcohol.

Since the first-order rate constant of this reaction for the immonium ion, derived from III is $k = 0.30 \times 10^{-3}$ sec^{-1}, this means that the first-order rate constants of the hydration of the immonium ions of I and II will be larger. The protonation of the enamines I and II, producing these immonium ions, proceeds with rates that are only slightly larger, 1.05×10^{-3} sec^{-1} and 0.62×10^{-3} sec^{-1}, respectively.[2] It is therefore reasonable to suggest that the hydration of the immonium ions of I and II proceeds at a higher rate than the formation of these ions from the enamines. This indicates that in weakly acidic solutions reaction 5 will not become rate determining in the case of I and II. Figure 2 shows that this is actually the case.

In moderately strong acidic solution a change in rate-determining step from reaction 5 to reaction 8 for III occurs, as has been mentioned above. Figure 2 clearly shows also a change in the slow step for the enamines I and II. This can only be explained by assuming a slow decomposition of the zwitterions, derived from I and II (reaction 8). In these acidic solutions the order of reactivity, derived from Figure 2 is morpholino > piperidino > pyrrolidino.

The difference in reactivity between the morpholine and the piperidine enamine is caused by the inductive effect of the oxygen atom of the morpholine ring, which acts as an acidifying agent on the hydroxyl group of the α-amino alcohol (reaction 7), causing a larger concentration of the zwitterion and as a consequence a faster decomposition. Since the position of the equilibrium in reaction 5 is further to the right for I than for II, the concentration of the ammonium alcohol in reaction 7 will be higher for I than for II.

In the pyrrolidine and piperidine enamines the inductive effects of the ammonium group are about equal. Here the difference in reactivity is mainly caused by the different positions of the equilibria in reaction 5. As has been pointed out already, this is due to the difference in stability of the exocyclic double bond in the immonium ions, derived from II and III.

Formation of Enamines I, II, and III.—According to the principle of the microreversibility the mechanism of the formation of enamines from carbonyl compounds and secondary amines must be the reverse of the mechanism of the hydrolysis.

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[13] H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957).

[14] H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1959).

The first step in the formation of enamines will be the addition of the amine to the carbonyl group. This addition will take place without the aid of an acid catalyst, which is in accordance with the mechanism of the addition of amines to carbonyl compounds, as proposed by Swain and Worosz.[15] The resulting zwitterion is rapidly converted to the α-amino alcohol.

The reaction of the amino alcohol to produce the immonium ion (the reverse of reaction 5) will be general acid catalyzed. It is in this reaction step that the catalytic influence of the frequently used p-toluenesulfonic acid will be found. Marchese[16] obtained evidence that in the formation of enamines the active catalyst is not p-toluenesulfonic acid but ammonium ions formed from the secondary amine and p-toluenesulfonic acid.

The observation of Marchese[16] that the morpholine enamine is formed faster than the piperidine enamine can be seen in this light. The greater electron-attracting power of the morpholine group as compared with the piperidine group would make the loss of a water molecule in the reverse reaction (5) for the morpholino intermediate more difficult if the same catalyst were active. However, the stronger acidity of the morpholinium ion than the piperidinium ion makes the former a more powerful catalyst, which effect obviously dominates.

Conclusion.—The hydrolysis of enamines and consequently also their formation takes place in a series of reactions all of which appear to be equilibria. A number of reactions may become rate determining each in a certain pH region. This picture is further complicated by the fact that changes in reactivity of the cyclic amine part cause appreciable shifts in the equilibria involved. However, considering well-known effects of inductive action and exocyclic double bond formation the seemingly large differences illustrated in Figure 2 are explained in a natural way. Extrapolation of the results obtained in this study to other compounds should take into careful consideration the shifts in a number of equilibria *and* the influence on rates caused by varying substituent effects.

Experimental Section

The enamines were synthesized from isobutyraldehyde and the secondary amines as described earlier.[2] The solvent water for the kinetic experiments was purified by demineralization and subsequent distillation in an all-silica apparatus. Proanalyse grade chemicals were used in preparing the solutions of the strong acids and the acetate buffer solutions.

The buffer solutions were prepared in the usual way, maintaining the ionic strength at 0.100 M by adding sodium chloride. The pH measurements were made on a Radiometer pH meter, Type TTT 1a, provided with a glass and a calomel electrode. The concentration of acid was determined by titration with an aqueous solution of sodium hydroxide using phenolphthalein as an indicator. The rate measurements were carried out following the decrease of the ultraviolet absorption in the range of 2000–2150 A using silica cells with a path length of 1 cm as described in a previous paper.[3] The instrument used was a Zeiss PMQ II spectrophotometer.

The first-order rate constants were determined graphically from plots of log ($E_t - E_\infty$) against time (t) except the rate constants for the hydrolysis of I in 6 M $HClO_4$, II in 1 M $HClO_4$, and III in 0.54 M $HClO_4$. In these cases, since the reactions proceeded very slowly, the first-order rate constants were determined by the Guggenheim method.[12]

Nmr spectra were run on a Varian A-60 spectrophotometer. The spectra of I in 6 M aqueous perchloric acid and of isobutyraldehyde in 0.1 N aqueous hydrochloric acid were recorded from about 2% solutions of these compounds, using a solution of tetramethylsilane in carbon tetrachloride as an external reference.

Registry No.—I, 2403-55-6; II, 673-33-6; III, 2403-57-8.

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(15) C. G. Swain and J. C. Worosz, *Tetrahedron Letters*, 3199 (1965).

(16) J. S. Marchese, Ph.D. Thesis, University of Maryland, 1964.

The Reaction of Perchloryl Fluoride with Selected Amines

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Perchloryl fluoride reacts with piperidine in aqueous solution to give N-perchlorylpiperidine which decomposes slowly and can be hydrolyzed to the enamine, Δ^2-piperidine, isolated as the trimer tripiperideine. In contrast, the same oxidizer reacts with 2,6-dimethylpiperidine, 2,2,6,6-tetramethylpiperidine, and 2,2,6,6-tetramethylpiperidin-4-one in solution to form the corresponding N-fluoro derivatives. This, presumably, is due to steric effects of the α-methyl groups. Tertiary amines such as N-methylpiperidine and triethylamine are oxidized to the enamines, N-methyl-Δ^2-piperidine and diethylvinylamine, which were isolated, respectively, as condensation products with chloranil and 2,3-dichloronaphtho-1,4-quinone. Aqueous triethylenediamine, with perchloryl fluoride, undergoes an oxidative fragmentation reaction resulting in the formation of formaldehyde and piperazine.

Gaseous perchloryl fluoride (ClO_3F) reacts strongly with most aliphatic and nonaromatic heterocyclic amines, and contacting the undiluted amines with perchloryl fluoride often results in violent, uncontrollable oxidations and/or explosions. However, these violent reactions can be moderated by either extreme dilution of the perchloryl fluoride with an inert gas or by dissolution of the amines in inert solvents, thereby permitting the isolation and identification of the products of the reactions.

Earlier studies[2] of the reactions of perchloryl fluoride with primary and secondary aliphatic amines indicate that the intermediate reaction products are extremely unstable and usually decompose to mixtures of unidentifiable dark tars. In our present work we have studied the reactions of perchloryl fluoride with piperidine, alkyl-substituted piperidines, and selected tertiary amines.

In general we found that the N-unsubstituted piperidines studied will form N-perchloryl and N-fluoro derivatives which are sufficiently stable for characteri-

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(1) Research Laboratories, U. S. Army Edgewood Arsenal, Edgewood Arsenal, Md.

(2) Unpublished observation at this laboratory.